Paediatric drug development: an opportunity for academia to close the gap

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an opportunity for academia to close the gap

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Voor Sara, Emile en Julie
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LIST OF ABBREVIATIONS

ABPM  Ambulatory blood pressure measurement
ACE  Angiotensin converting enzyme
ACEI  Angiotensin converting enzyme inhibitor
ADR  Adverse drug reaction
ADME  Absorption, distribution, metabolism, and excretion
AE  Adverse event
ARB  Angiotensin-II receptor blocker
ATC  Anatomical Therapeutic Chemical classification
AVP  Arginine vasopressin
BB  Beta(-adrenergic) blocker
BP  Blood pressure
BPCA  Best Pharmaceuticals for Children Act
BUN  Blood urea nitrogen
CCB  Calcium channel blocker
CI  Confidence interval
Cmax  Maximum concentration
DBP  Diastolic blood pressure
dDAVP  1-deamino-8-D-arginine-vasopressin
DDD  Daily defined dose
EFPIA  European Federation of Pharmaceutical Industries and Associations
EMA  European Medicines Agency
ESPGHAN  European Society for Paediatric Gastroenterology, Hepatology, and Nutrition
ESRD  End-stage renal disease
EU  European Union
FDA  Food and Drug Administration
FDAAA  FDA Amendments Act
FDAMA  Food and Drug Administration Modernization Act
FDASIA  FDA Safety and Innovation Act
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>FP7</td>
<td>7th Framework Programme</td>
</tr>
<tr>
<td>GER</td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>GRIP</td>
<td>Global Research in Paediatrics</td>
</tr>
<tr>
<td>H₂-RA</td>
<td>Histamine H₂-receptor antagonist</td>
</tr>
<tr>
<td>ICH</td>
<td>International Council on Harmonisation</td>
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<tr>
<td>IMI</td>
<td>Innovative Medicines Initiative</td>
</tr>
<tr>
<td>INN</td>
<td>International Nonproprietary Names</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional review board</td>
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<tr>
<td>ITCC</td>
<td>Innovative Therapies for Children with Cancer</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td>Liquid chromatography coupled with tandem mass spectrometry</td>
</tr>
<tr>
<td>LVH</td>
<td>Left ventricle hypertrophy</td>
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<tr>
<td>MA</td>
<td>Marketing Authorisation</td>
</tr>
<tr>
<td>M&amp;S</td>
<td>Modelling and simulation</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NASPghan</td>
<td>North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition</td>
</tr>
<tr>
<td>NDC</td>
<td>National Drug Code</td>
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<tr>
<td>NHLBI</td>
<td>National Heart, Lung and Blood Institute</td>
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<tr>
<td>NIHDI</td>
<td>National Institute of Health and Disability Insurance</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the counter</td>
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<tr>
<td>PBPK</td>
<td>Physiologically based pharmacokinetic modelling</td>
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<td>Pharmacodynamics</td>
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<td>Paediatric Committee</td>
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<td>Paediatric intensive care unit</td>
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<td>Paediatric investigation plan</td>
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<td>Pharmacokinetics</td>
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<td>Prescription only medication</td>
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<td>PPI</td>
<td>Proton pump inhibitor</td>
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<td>PPP</td>
<td>Private-public partnership</td>
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<td>PREA</td>
<td>Pediatric Research Equity Act</td>
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<td>PUMA</td>
<td>Paediatric Use Marketing Authorisation</td>
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<tr>
<td>RAAS</td>
<td>Renin angiotensin aldosterone system</td>
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<td>RCT</td>
<td>Randomized controlled trials</td>
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<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>SPC</td>
<td>Supplementary Protection Certificate</td>
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<tr>
<td>$T_{\text{max}}$</td>
<td>Time to $C_{\text{max}}$</td>
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<td>US</td>
<td>United States</td>
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<td>WHA</td>
<td>World Health Assembly</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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<tr>
<td>WP</td>
<td>Work package</td>
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CHAPTER 1

PREFACE TO THIS THESIS
‘It is worth considering that every infant treated with a drug without double-blind, randomized placebo-controlled trial-confirmed efficacy is participating in an experiment:
an experiment where $n = 1$,
with no institutional review board oversight,
no informed consent,
and no possibility that the results of the experiment can benefit any other infant.’
Correctly labelled, safe and effective medicines for children in age-appropriate formulations: it is an item of increasing importance. It matters to all health professionals involved in care for children at home or in the hospital, and to researchers in academia, industry and the regulatory agencies. Awareness that children may respond to drugs differently at one age than another, as well as differently from adults, has spread beyond the paediatric profession, to be recognized by the regulatory authorities. During the previous two decades, important legislations for paediatric drug development came into force. This PhD project was designed at a time of many changes in this legislative framework for paediatric drug development but also at a time in which half of the medicines is still lack evidence-based information on specific use in children. The legislations resulted in major changes in the drug development process, that have markedly expanded our knowledge of dosage, safety and efficacy of pharmaceutical use in children. Though, there are still significant gaps in our knowledge, not only in the newer drugs but also in the older drugs in current practice. Some of these gaps have been partially tackled during this thesis term, but the majority of questions are still valid today.

To understand the current knowledge gaps, it is essential to understand how drug development was designed in the past, and what the regulations have tried to remediate. This will be described in the next chapter, followed by the chapter on the outline and specific aims of this thesis. Subsequently, the different papers that identify some of the gaps in our current knowledge will be discussed consecutively (from chapter 4 to 7). However, this thesis will not only report on lack of knowledge, but will also describe how we can gain more knowledge in paediatric pharmacology in an efficient and effective way. We will need a multidisciplinary framework with other experts in drug development: advances in juvenile animal models and in modelling and simulation can contribute to a more efficient paediatric drug development process. However, the advances in non-clinical (preclinical) studies, will not eliminate the need for clinical trials in paediatrics. These clinical trials in children have many challenges for the future: consideration of re-evaluation of off patent drugs, inclusion of children with comorbidities, better information to the patients, etc. There is a task for academia to raise and tackle these new challenges, through collaboration with the regulatory authorities and pharmaceutical industry. In practice, we will do this by developing our SAFE-PEDRUG consortium, as will be described in this thesis. Moreover, it is our task,
as paediatricians and clinical pharmacologists, to defend the interests of the most important stakeholders: the patients, their parents and their patient organisations; during all phases of paediatric drug development. This will contribute to the availability of high quality medicines for use in children, that have been ethically researched and that were appropriately authorised.
CHAPTER 2

PAEDIATRIC DRUG DEVELOPMENT
1 LABELLING OF MEDICINES
Before any new medicine can be manufactured and marketed, it must receive a marketing authorisation (MA, or license). This authorisation was introduced in most European countries in the Sixties (e.g. the law on medicinal products of March 25, 1964 in Belgium). The licensing process was established as a response to major cases of drug toxicity that were found in foetuses and neonates exposed to certain drugs, in the late 1950s and early 1960s. These included phocomelia (in the developing foetus) caused by thalidomide and the grey baby syndrome (in the neonate) caused by chloramphenicol.

The aim of the licensing system is to ensure that medicines are examined for efficacy, safety, and quality. Pharmaceutical companies apply for a product licence for a particular drug, and in their submission they include the indication, dose, route of administration, and age group of patient for which this applies. These data should result from extensive trials looking at different dosage regimes, pharmacokinetics, and drug toxicity and are mentioned in the ‘Summary of Product Characteristics’ (SmPC; in Europe) or ‘Product label’ (in The United States) of the drug. It is worth considering that many drugs used in children have not had the advantage of these formal clinical trials, as will be discussed in the next section. It is remarkable that the above-mentioned dramatic findings with thalidomide and chloramphenicol triggered major steps forward in regulatory processes to protect the public, but did not result in requirements to study medicines adequately in the paediatric population.

2 ‘THERAPEUTIC ORPHANS’
The phrase ‘therapeutic orphans’ was used to describe children in 1963 by dr. Harry Shirkey. This phrase refers to the lack of medicines available for use in children: studies showed that over 50% of the medicines used for children have not been tested for use in this specified age group. Consequently, many drugs used to treat children are used off-label or unlicensed. The term ‘off-label’ use refers to use of a drug that is not included in the package insert (approved labelling) for that drug. This may involve using the medicine in a different age group, for a different indication, for a contraindication, at a different dose, or by a different route to that recommended. An example of off-label use of drugs include the use of
bronchodilator salbutamol by inhalation in infants, which is not licensed for this age group\textsuperscript{26,30}. Unlicensed medicines are \textit{where the medicine has been modified from that specified in its product license or the use of imported drugs}\textsuperscript{11,25,29}. An example of unlicensed use is crushing a tablet to prepare a suspension\textsuperscript{15,25}. Roughly half of drugs used in children are off-label or unlicensed, and the number is much higher in the advanced care settings and the neonatal population\textsuperscript{3-5,7,8,10,15,22,26,28,29,31,32,35,36}. Magalhães et al report in their most recent systematic review of papers published from 1994 to 2012 that prescriptions ranged from 12,2\% to 70,6\% for off-label and from 0,2 to 47,6\% for unlicensed drugs, depending on definition and setting\textsuperscript{32}.

During the past two decades, awareness has been growing that it is more ethical to evaluate medicines in children than to treat children off-label with drugs that have not been tested in this population\textsuperscript{37-39}. The public perception of clinical trials as experiments has led to a misleading distinction being made between clinical practice and clinical research\textsuperscript{40,41}. Often it seems more acceptable (to doctors, parents, and institutional review boards (IRBs)) to use untested medications on children as “routine clinical care” rather than enrol eligible children in a relevant clinical trial, in which the effects of interventions can be monitored and analysed\textsuperscript{40}. In the past, there has been a general reluctance about involving children in trials because of the fear of harming children by exposing them to uncertain treatment effects\textsuperscript{37}. Additionally, there has been little stimulus for pharmaceutical companies to study drugs in children because of several methodological, logistical, ethical and financial reasons\textsuperscript{41-44}. First, there is the complexity of paediatric clinical trials: potential risks specific to children, that are not usually of concern when considering studies in adults, including discomfort, pain, fear, inconvenience and separation from parents or familiar surroundings\textsuperscript{40,45}. Second, technical difficulties including the need for frequent blood sampling and the inability to measure endpoints such as pain and quality of life in very young children have been cited as a holdback to testing drugs in children\textsuperscript{37,41}. Other excuses for failure to do paediatric drug studies are the difficulty of patient recruitment, greater risk of liability, and the high cost of the studies\textsuperscript{2,27,37,40,41}. The high costs are a major disincentive for the pharmaceutical industry to fund trials in children, particularly when the market size at the end of an expensive research and development programme is often small\textsuperscript{40,41,46,47}.
The practice of off-label prescribing does not necessarily mean ‘off-knowledge’ prescribing. Dosage regimens are sometimes based on paediatric clinical trials and published experience in children\textsuperscript{20,22,25,48}. Additionally, these off-label dosage regimens may be recommended in clinical practice guidelines or pharmacotherapeutic handbooks\textsuperscript{22,49} but it should be noted that these may show remarkably variable dosing regimens for the same drug\textsuperscript{50-52}. A recent policy statement of the ‘American Academy of Pediatrics’ states that \textit{off-label prescribing does not necessarily imply an improper, illegal, contraindicated or investigational use}\textsuperscript{33} and \textit{that it is in the best interests of the child if no other treatment with at least a comparable benefit-risk ratio is available}\textsuperscript{36}. However, when assessment of the risks and benefits has not been done at the population level by the regulatory authorities, i.e. there is no paediatric labelling, higher requirements are placed on the prescriber when making the individual risk-benefit assessment for the patient\textsuperscript{36,53}. Obviously, such an assessment can only be performed if the data on the safety and efficacy of the medicinal product exist and are available to the prescriber, preferably directly on the product leaflet\textsuperscript{29,36,53}.

Off-label use of drugs was shown to be associated with a lack of efficacy due to subtherapeutic dosing and a greater risk of drug toxicity\textsuperscript{43,53-56}. Studies examining the aspect of adverse drug reactions (ADRs) linked to off-label and unlicensed use have found differing results. However, many suggest a greater adverse drug reaction risk associated with off-label and unlicensed drug use in children\textsuperscript{3,11,29,32,34,57-61}. This may result from a failure to understand the impact of developmental, physiological, or metabolic influences on a drug's pharmacokinetics\textsuperscript{36,43,55}, which will be discussed in the next section of this chapter.

3 PHARMACOKINETICS AND PHARMACODYNAMICS: ‘CHILDREN ARE NOT SMALL ADULTS’.

3.1 Pharmacokinetic and pharmacodynamic differences
Drug action relies on two processes: pharmacokinetics and pharmacodynamics. As stated above, to facilitate rational drug therapy in children, the developmental patterns of PK and PD processes involved need to be elucidated\textsuperscript{62,63}. 

15
The study of pharmacokinetics (hereafter abbreviated as PK) focuses on the processes of absorption, distribution, metabolism, and excretion. It provides a link between the prescribed dosage regimen and the profile of drug concentration over time: ‘what the body does to the drug’\textsuperscript{64,65}. Many differences in PK parameters between paediatric and adult patients have been identified: these differences are most extreme in neonates and infants and they are not always predictable\textsuperscript{64}. Drug absorption is affected by age, dose, formulation, route of administration, as well as, e.g., interacting food or other drugs\textsuperscript{55}. Specific issues are gastric acid production, gut permeability, including first-pass effects and the ontogeny of intestinal transporters, and skin permeability\textsuperscript{55,66}. For example, the relative systemic exposure of infants and children to topically applied drugs (e.g. corticosteroids, iodine antiseptics) may exceed that in adults, probably due to greater extent of cutaneous perfusion and higher ratio of total body surface area to body mass\textsuperscript{66}. Differences in the distribution of the drug relate to body composition, blood flow, protein binding, and membrane permeability\textsuperscript{39,55,65}. For example, the decreased drug-binding capacity to plasma proteins in neonates may result in a higher unbound cefazolin fraction in this age group\textsuperscript{67}. Metabolism of many drugs is dependent on hepatic blood flow and activity of drug-metabolising enzymes and transporters. Hepatic blood flow is reduced in neonates, and increases with increasing cardiac output over time\textsuperscript{45}. Due to ontogeny, the capacity of drug-metabolising enzymes and transporter changes in neonates and infants\textsuperscript{45,55}. Finally, as for excretion, renal elimination capacity (glomerular filtration rate, GFR) increases in the first 2 weeks of life to reach adult values at the end of infancy\textsuperscript{45,55,66,68}. At birth, glomerular filtration is the main pathway of renal drug elimination since tubular functions (secretion, absorption) are immature in neonatal life\textsuperscript{69}. This may result in a reduced clearance of drugs eliminated primarily by glomerular filtration (such as tobramycin)\textsuperscript{45}.

Age-associated changes in the absorption, distribution, metabolism, and excretion of drugs culminate in different PK and increased variability and thus serve as the determinants of age-specific dose requirements\textsuperscript{66}. The study of developmental PK investigates this variability and allows to recommend drug-dosing regimens and provides us with knowledge to prescribe paediatric drug therapies safely and effectively\textsuperscript{63}. Additionally, it is important to consider that the prominent variability in PK in paediatrics can be further aggravated by interfering environmental factors such
as pathological processes and treatment modalities, and genetic polymorphisms\textsuperscript{45,63,65,69,70}. These genetic polymorphisms are investigated in the evolving field of pharmacogenetics and pharmacogenomics\textsuperscript{71}.

\textbf{Pharmacodynamics} (hereafter abbreviated as PD) comprises the physiological and biological response to the administered drug\textsuperscript{72}. PD analysis aims to investigate the relationship between the drug dosage regimen and the response, both therapeutic and toxic: \textit{‘what the drug does to the body’}\textsuperscript{64,65,73}. Whereas differences in PK in paediatric patients have been studied by many groups, there has been far less work on differences in paediatric patients in relation to PD\textsuperscript{72,74,75}. The variability in PD (drug response) between individuals is often as wide as or wider than the variability in PK\textsuperscript{64}. Age-dependent variations in receptor number, receptor affinity, or post-receptor activation processes can manifest as a change in the potency, efficacy, or therapeutic range of a drug or in adverse effects\textsuperscript{75,76}. An example is diazepam producing sedation in adults and in some cases agitation in children\textsuperscript{14,75}.

3.2 Dose scaling and extrapolation

Children are not small adults, but are a heterogeneous group, ranging from preterm neonates to post-pubertal adolescents\textsuperscript{37}. Children have complex physiological, developmental, psychological and pharmacological characteristics that differ from adults and these features are also different across the neonate to adolescent age range\textsuperscript{37}. Hence, the simple downscaling of the adult dose, using functions related to body weight, height, or age may be insufficient for correct dosing in children\textsuperscript{14,40,56,72,77}. Such simple dose scaling approaches are questionable when complex absorption and disposition processes are encountered and can fail to predict exposure accurately, particularly in the very young\textsuperscript{77}. A general tendency is to normalize the adult dose by body weight on a linear scale (in mg/kg). This approach is however not correct for all age groups, because dose requirement is not always linearly related to body weight\textsuperscript{69,77,78}. When dose adjustment is based on age (i.e., preterm neonates, term neonates, infants, toddlers, children, and adolescents), the rapid changes in rates of organ maturation, body composition, blood flow, ontogeny of drug elimination and transport mechanisms occurring in developing children within each age group are not considered. Normalizing by body surface area (mg/m\textsuperscript{2}) has been reported to lead to
overdosing in neonates and infants, partly because of the inaccuracy of the formula to calculate body surface area or the unpredictability of low drug metabolizing enzyme activity at birth\textsuperscript{77,79}. On the other hand, no differences in drug metabolism may exist between children, adolescents and adults\textsuperscript{77}. It is clear that dose selection in children does not encompass correcting the adult dose per kg, age or m\textsuperscript{2} but is all about identifying the right covariates at the specific time in a child’s development. Nowadays, information about paediatric dose requirement and essential covariates can be generated from in silico techniques such as population based simulation and physiologically based pharmacokinetic models (as discussed in chapter 8)\textsuperscript{80}.

Efficacy and safety in adults cannot be extrapolated to children as the disease presentation itself may have a different natural history from adults and children may also suffer from diseases which do not occur in adults\textsuperscript{37,57}. A poor or incomplete understanding of the natural history and pathophysiology of many paediatric conditions may result in incorrect use of medicines and may lead to trial failures in research\textsuperscript{81,82}. The treatment of symptomatic gastroesophageal reflux disease is one such example\textsuperscript{81}. The current disease understanding is that neonates likely do not have acid-mediated gastroesophageal reflux disease (GERD), although they have some signs and symptoms of GERD including regurgitation and irritability\textsuperscript{81-86}. Therefore, in neonates, infants and children less than 18 months, the medical utility of proton pump inhibitors (PPIs) is unclear and may be limited to subpopulations such as those with erosive esophagitis\textsuperscript{81}. As a result, efficacy in children cannot be blindly extrapolated from adults efficacy and PD endpoints should be wisely selected for research in children\textsuperscript{81,82}.

4 PAEDIATRIC MEDICINES INITIATIVES

The development of safe and effective child-specific treatments requires high quality trials investigating PK and PD in children\textsuperscript{87}. During the last three decades, the United States (US) and the European Union (EU) have introduced strong paediatric initiatives to improve the paediatric situation, mostly through legislative measures aimed at increasing the number and quality of studies in children\textsuperscript{88}. These legislative changes have been introduced in response to scientific studies, documenting the extent of off-label and unlicensed drug use in paediatric patients\textsuperscript{74}. This section will not only focus
on initiatives that stimulate the number of clinical trials, but also on the initiatives to harmonise the conduct of clinical trials worldwide (ICH E11) and to improve the ethics of clinical trials (EU Directive 2001/20/EC).

4.1 Worldwide initiatives to stimulate paediatric clinical trials

4.1.1 The US legislation

The US Federal Government was the first to take initiative and issued in 1997 the Food and Drug Administration Modernization Act (FDAMA)[37,43,89]. The FDAMA encouraged studies of certain therapies being used in paediatrics by providing an exclusivity incentive provision[43]. It provided an additional 6 months of marketing exclusivity (i.e., no generics can be approved), if the sponsor voluntarily conducted the studies requested by FDA in the written request, submitted them in the specified time frame, and the studies fairly responded to the written request[43]. This provision was reauthorised in 2002 as the Best Pharmaceuticals for Children Act (BPCA) and was reauthorised again in 2007 as part of the Food and Drug Administration Amendment Act (FDAAA)[89]. Meanwhile, the FDA issued a regulation in 1998 that mandated paediatric assessment of new drugs (or already marketed drugs under certain circumstances), which was later codified as the Pediatric Research Equity Act (PREA) of 2003 and was also reauthorised in 2007 under the FDAAA[89]. Figure 2.1 shows that the US legislation has been reauthorised every five years, emerging each time with a new name and modifications[88]. The paediatric labelling process in the US progressed from the FDAMA encouraging the pharmaceutical industry to conduct paediatric studies in the 1990s, to a combined ‘carrot-and-stick’ approach of voluntary incentives and mandatory regulation[43,89]. In 2012, the FDA Safety and Innovation Act (FDASIA) came into force, reauthorising and strengthening the two complementary federal laws (BPCA and PREA) (table 2.1)[89]. The major changes in the FDASIA Act of 2012 is the permanence of the exclusivity law, consideration of the labelling of medical devices and the emphasis on the need to include neonates in more studies[37,90,91].
Figure 2.1: Time frame of the US and EU paediatric regulations\textsuperscript{37,88,90,92,93}. US: United States; EU: European Union; FDA: Food And Drug Administration.
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<th>USA</th>
<th>Europe</th>
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<td>Public Health Need (off-label or approved uses of a drug)</td>
<td>New drug or approved uses of the product, except orphan designation*</td>
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<td></td>
<td>PREA</td>
<td>New drug, new indication, new formulation, new route of administration</td>
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<td>Off-patent medicine</td>
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<td><strong>Reward</strong></td>
<td>6 months ‘Pediatric Exclusivity’</td>
<td>6 months SPC extension</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>10 years of data protection (PUMA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 additional years of market exclusivity*</td>
</tr>
<tr>
<td><strong>Decision Authority</strong></td>
<td>FDA</td>
<td>FDA</td>
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<td></td>
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<td>EMA (opinion: PDCO)</td>
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</tbody>
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FDA: Food and Drug Administration; EMA: European Medicines Agency; NA: not applicable; PDCO: Paediatric Committee; PUMA: Paediatric use marketing authorisation; SPC: Supplementary Protection Certificate.

* The Orphan Drug Act (1983) provides incentives (exclusivity and tax credits) for developing drugs with an orphan designation (<200 000 patients per year) in the US. This act is not targeted specifically at paediatric patients.

*in addition to 10 years awarded under the EU’s Orphan Regulation
4.1.2 The European Paediatric Regulation

Based on the experience of the US, the Paediatric Regulation (N°1901/2006\textsuperscript{99} and amendment N°1902/2006\textsuperscript{100}) entered into force on January 26, 2007\textsuperscript{56,95,101,102}. This is a regulation which means that it supersedes national laws and it should be directly implemented throughout Europe without the need for transposition into national laws (as opposed to a European directive)\textsuperscript{95,103}. Due to this Paediatric Regulation, drug development in Europe is no longer possible without considering the effects of the future use of the drug in children. For any application for medicines approval, pharmaceutical companies must include either the results of all studies performed in compliance with a paediatric investigation plan (PIP) or a decision on a waiver or a deferral that has been reviewed and agreed by an expert committee at the European Medicines Agency (EMA), the Paediatric Committee (PDCO)\textsuperscript{99}. This is the case for all new medicines (article 7), and for new indications, new pharmaceutical forms and new routes of administration of authorised medicines (article 8)\textsuperscript{56,95}. Generic products, homeopathic and herbal products are exempted from this obligation. The submitted PIP includes information concerning the timing and measures proposed to obtain a paediatric indication, in all paediatric subsets affected by the condition. In practice, a PIP defines the required clinical trials, the necessary age-appropriate formulations and forms and the need for juvenile animal studies\textsuperscript{95}. A PIP should be submitted early in development, upon completion of the PK studies in adults, and is reviewed by the PDCO. The PDCO, established in July 2007, is an expert body including members appointed by the EU member states, two members from Norway and Iceland (of the European Economic Area) and six members representing health professionals and patients associations\textsuperscript{56,97,99,104}. The PDCO can grant a waiver if: 1) the disease or condition only occurs in adults; 2) the medicine is likely to be unsafe or ineffective in children, or 3) the medicine does not offer a significant therapeutic benefit in children. Waivers can be granted for the whole paediatric population (full waiver) or some subsets only (partial waiver)\textsuperscript{95,99}.

When an agreed PIP is completed and all the information has been submitted to the regulatory authorities, the medicinal product will be granted an extra 6 months patent protection (extension of the duration of its Supplementary Protection Certificate [SPC]), which represents the financial reward to pharmaceutical companies. This extension is
granted whether or not the data support a paediatric indication\textsuperscript{95,103}. There is much debate among stakeholders on whether this financial incentive is sufficient. In the US, the 6-month patent extension awarded to companies completing agreed paediatric research was shown to be powerful and sufficient\textsuperscript{53}; though this was only the case for blockbusters such as medicines used in the treatment of gastroesophageal reflux or type 2 diabetes\textsuperscript{105}. The economic value of the reward depends on the turnover of the product concerned. In the case of blockbuster products the amount may be considerable, while for niche products the effect is small\textsuperscript{18,105}. Professor J. Ramet stated in his reflection paper that this situation for Europe might be different, as the European medicines market is different from the American market and Europe has almost a decade of paediatric research to catch up\textsuperscript{53}.

It is estimated that 20-35\% of all recognised diseases are rare, the prevalence of which is defined to be equal to or lower than 5 in 10000 persons in Europe\textsuperscript{106-108}. Several issues (such as the scarcity and geographical dispersal of eligible research subjects and the small market for excessively expensive, newly developed treatments) render the development and provision of drugs for the diagnosis, prevention and treatment of rare diseases a precarious enterprise\textsuperscript{106}. In the EU, a specific regulatory framework was created in 2000 to encourage the development of ‘orphan drugs’ for the diagnosis, prevention and treatment of rare diseases (including the provision of financial incentives)\textsuperscript{106,107}. Products that have been designated as \textit{orphan medicinal products} benefit from a 10-year period of market exclusivity but are not commonly protected by patent\textsuperscript{107,108}. As a result, the reward of an extension of the related SPC is not available. The financial incentive chosen for these products in the Paediatric Regulation consists of an additional two year added to the ten years of market exclusivity granted in the EU to orphan medicines\textsuperscript{95,109}.

The EU Paediatric Regulation also created a new type of MA to give an incentive to medicinal products that have been on the market in the EU states for some time and therefore are no longer covered by a patent\textsuperscript{88,95}. This \textit{Paediatric Use Marketing Authorisation (PUMA)} procedure permits application for authorisation of a paediatric indication for an existing medicinal product that is no longer covered by intellectual property rights\textsuperscript{99}. Up until now, only two drugs received a PUMA: buccal midazolam for
the treatment of prolonged, acute, convulsive seizures in paediatric patients\(^{110}\) and oral propranolol for the treatment of proliferating infantile haemangioma\(^{111}\).

The vast majority of pharmaceutical companies develop medicines at a global level: it is therefore important to consider not only EU but also other regions’ expectations or plans for paediatric development. In order to understand the differences between PIPs and written requests for the same drug and to avoid unnecessary duplication, monthly teleconferences are held between FDA scientists and the EU PDCO members. The Japanese authorities and Health Canada have joined as observers initially, but are now active participants\(^{97,112}\).

The Paediatric Regulation has now been in force for 8 years. At the end of 2012 (five years after the implementation of the Regulation) the European Commission undertook a public consultation. Most agree that The Regulation has created a new landscape for paediatric research in Europe\(^{103}\), though there are some difficulties:

- The insurmountable back log of studies that need to be carried out\(^{32,113}\). By the end of 2012 the EMA had agreed 600 PIPs\(^{18,88}\). Unfortunately, this resulted in only a slight increase in the number of paediatric trials. As of January 2010, the proportion of paediatric trials as a percentage of all clinical trials in Europe increased only moderately (from 7.9% in 2006 to 9.0% of all trials in 2012)\(^{18}\). By the end of 2012 only 33 of the 600 approved PIPs have been completed\(^{18}\). This may be due to the high attrition rate during the drug development process\(^{114}\), but also due to the fact that paediatric trials requested by EMA can be deferred for years until adult development. Paediatric medicines development is generally performed once safety and efficacy data have been obtained in adults, and only when the development in adults has been successful. Therefore, deferrals can be granted by the PDCO (either of the initiation of studies and/or their completion) because the PDCO wants to prevent that delaying MA until all paediatric studies are completed would delay approval in the adult population by several years. The 5-year report of the EMA with the PDCO states that at that moment (5 year after introduction of the Paediatric Regulation) 63% of new medicines intended for both adults and children had a deferral in the agreed PIP\(^{115}\). A deferral on average delays the performance of paediatric trials by 3–5 years\(^{56}\), which leads to considerable delays in making
medicines available to children. However, this situation is better than the time before the Paediatric Regulation in which most drugs were not evaluated in children.

- The PIPs received by the EMA mainly concern medicines targeting adult diseases, which is in line with economic profit expected by companies. An analysis by Olski et al showed that most of the paediatric developments will be performed in endocrinology, oncology, infectious diseases and cardiovascular diseases, which relates to the economic importance in the adult market.

- The number of products being developed for the adult market, coupled with the relative scarcity of paediatric patients with the same condition, can create significant feasibility issues for the conduct of the paediatric trials. Examples of this are drugs for treatment of type 2 diabetes or melanoma.

- Clinical trials before market authorisation tend to be small and provide a very limited safety database. The unique risk for long-term adverse developmental effects cannot adequately be addressed before MA of the product.

Although much still needs to be done, developments to date indicate that with concerted efforts and appropriate resources, change is possible but slow. One must realise that the European Paediatric Regulation created a new framework, where each stakeholder is on a learning curve.

4.1.3 ‘Better Medicines for Children’ Resolution of the World Health Assembly

In May 2007, the World Health Assembly (WHA) – the highest governing body of the World Health Organization (WHO, with all of the 194 member states having a seat) - adopted the ‘Better Medicines for Children’ resolution 60.20. Importantly, this resolution was endorsed by almost all governments of the world. This resolution raises the concern on the lack of access to essential medicines of assured quality for children, as well as of the insufficient investment in clinical trials of drugs for children. In December 2008, the WHO has launched a global campaign, ‘Make Medicines Child Size’, to reach the Better Medicines for Children resolution’s goals.
4.1.4 Paediatric medicines initiatives in other countries across the globe

The problem of off-label prescribing is global: it concerns all children of the world, those in the developing world and those in the developed world, even in the richest countries.\textsuperscript{36,43,87,123} Next to the above-mentioned EMA, FDA, and WHO initiatives, only a few individual countries have taken paediatric medicines initiatives. These have been less extensive and weaker, with modest results,\textsuperscript{37,88} although most of the countries have endorsed the WHA Better Medicines for Children Resolution.\textsuperscript{88} Japan and Canada grant incentives for paediatric drug development but currently do not include any requirement or obligation for paediatric drug evaluation in their legislation.\textsuperscript{37,88} In the other countries, the initiatives are even weaker.\textsuperscript{37,88} Unfortunately, the pharmaceutical industry does not appear to be interested in transferring the benefits of approved paediatric appropriate medicines in the US and EU to other countries.\textsuperscript{37,88} This may be due to lack of economic incentives and the high costs associated with amending the labels of existing medicines with new paediatric data or registering new medicines.\textsuperscript{37}

Over 89% of children live in low and low-to-middle income countries.\textsuperscript{36,37,123} Clinical trials of children’s medicines in the developing world are needed to provide treatments for neglected diseases that are encountered in this part of the world.\textsuperscript{36} However, there is a disproportionately small number of trials in children in low income countries: only about a quarter of the 604 trials of medicinal products in children published in 2007 were conducted in these countries.\textsuperscript{37} In addition to the lack of necessary clinical trials in lower and lower to middle income countries, a growing number of those that are performed in these countries are a result of global redistribution of clinical trials; from high-income to low-to-middle income countries.\textsuperscript{36,122,124} Such trials are primarily intended to provide data for regulatory approval of a medicine in the competitive markets of the developed countries, especially in the areas providing lucrative incentives for the development of medicines for children (US and EU).\textsuperscript{122} This is because less developed countries have characteristics which make them attractive for such clinical trials, including high prevalence of diseases, commonly in treatment-naïve form, and lower trial costs.\textsuperscript{122} Such trials will need our attention, as they run the risk of leading to exploitation, particularly if the population from which the trial subjects come do not have access to the medicine once it is approved.\textsuperscript{88,122}
4.2 ICH E11: harmonizing the development of paediatric medicines

The International Council for Harmonisation (ICH), formerly International Conference on Harmonisation, includes members of Europe, US, Japan, Canada and Switzerland, accompanied by observers such as Brazil, India and Mexico. The framework of the ICH has issued a group of recommendations for the development of paediatric medicines in July 2000: the ICH E11. This ICH E11 is currently being updated. The objective of this document is to align the procedures for clinical trials required to evaluate the safety, quality and efficacy of medication. The ICH E11 document describes the procedures that professionals must take in order to put medications on the paediatric market. Most famous is the ICH E11 classification of children by age. ICH E11 discusses following age categories: the premature (less than 36 weeks of gestation), the newborn (between 0 and 27 days), the infant (between 28 days and 23 months), the child (between 2 and 11 years) and the adolescent (older than 12 years). Interestingly, adolescence has a variable upper limit that depends on the context. ICH E11 notes that the age is 16 to 18 years depending upon the region. Each of the age subgroups has its own characteristics which may require separate trials. However, in many instances disease incidence and severity may be age-dependent, but not in agreement with the current ICH classification. Additionally, these conventional subgroups do not fully coincide with maturation of some organs. The system of different age groups disregards the evidence that multiple physiological processes involved in PK and PD develop beyond the proposed age boundaries. The ICH E11 therefore states that a flexible approach is necessary to ensure that studies reflect current knowledge of pediatric pharmacology.

5 KEY CONCEPTS IN PAEDIATRIC DRUG RESEARCH

5.1 Age-appropriate formulations

The potential impact of the formulation of a medicine is often underestimated. An appropriate drug formulation is the basis of an efficient drug therapy for children and should allow administering medicines to children accurately and safely. As stated earlier in this text, the paediatric population represent a vulnerable group and comprises a wide range of developmental levels, physiological particularities, and age related abilities. The pharmaceutical companies are not always able to provide a
formulation for a single drug substance, comprising all ages, developmental stages and specificities of children’s health. Unfortunately, the development of commercially available appropriate formulations for children has been slow. The unavailability of appropriate formulations often results in drug manipulation by parents and carers and in extratemporaneous preparation or compounding by the pharmacist. If compounding or manipulation is likely to be required, it is preferable that data are generated by industry, approved by the competent authorities and provided in the Summary of Product Characteristics. Examples of commercial oral solids that do have information related to converting the tablet/capsule into an oral liquid for paediatric or geriatric use in the US include benazepril hydrochloride, clonazepam, lisinopril, enalapril, losartan potassium, and rifampin. Most prescribing information from the manufacturer, however, does not address this issue. Without appropriate supporting evidence of quality, drug manipulations or compounding should be avoided if possible. Both the EMA and the WHO published guidelines on the development of medicines for paediatric use. However, limited knowledge is currently available on the (sociocultural) acceptability of different dosage forms, administration volumes, and taste. It is well known that unpleasant taste of medicines is a major reason for compliance and adherence issues in children.

Besides the active compounds, drug formulations may also contain excipients as cosolvents, preservatives, sweeteners or colorants. Examples are propylene glycol, benzyl alcohol, ethanol, aspartame and polyethylene glycol. Excipients have always been considered inactive and inert agents, and for this reason, their importance has been largely underestimated. However, excipients have been associated with specific toxicity and can expose children, infants and neonates to significant safety risks. Thus, it is important to consider every compound of a drug formulation as a substance with the potential of producing drug toxicity: identification of acceptable intake limits and specific information about excipients to prescribers and patients are mandatory. Until tailored excipient-free formulations or other strategies for dose-flexible formulations become available, compounding practices for drug formulations should be evaluated to guarantee correct dosing, product stability and safety.
5.2 Ethical considerations in conducting paediatric research

Historically, children have been seen as vulnerable subjects who should be protected from the risks of research\textsuperscript{146}. The result has been a paucity of safety and effectiveness data that has made the use of - off-label - therapeutic agents a virtually uncontrolled experiment, whenever they have been prescribed for children\textsuperscript{146,147}. More recently, paediatric research has come to be a moral imperative\textsuperscript{146,148}. There are multiple ethical challenges in this\textsuperscript{147}. Concerns about the protections for children enrolled in research, has led to the development of regulations or guidelines specific to research involving children\textsuperscript{146}.

5.2.1 Ethical framework

Research must adhere to ethical principles. There are a number of general statements (ethical codes and legislations) that guide medical research in human subjects; notably the Nuremberg Code, the Declaration of Helsinki\textsuperscript{149}, and the Council of Europe’s Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine\textsuperscript{150-154}. These principles are also echoed and referred to in the ICH E6 guideline on Good Clinical Practice\textsuperscript{154,155}.

5.2.1.1 EU Directive 2001/20/EC and Regulation EU N°536/2014

Directive 2001/20/EC\textsuperscript{156} (further, the Clinical Trials Directive) of April 2001 was one of the milestones for the ethical conduct of clinical trials\textsuperscript{151}. Its objective is to coordinate clinical trials over the entire territory of the EU and to reinforce the ethical frame within which these trials must be conducted\textsuperscript{126}. The Clinical Trials Directive discusses the concept of consent and assent, the issue of financial incentives, the importance of minimising discomfort, fear and pain, and the volume limits for safe blood sampling. All EU member states were bound to implement this directive into national law before May 1, 2004, with the freedom to adopt stricter provisions than those set down in the text of the directive (as long as the standards of protection and time limits captured in the directive were not violated)\textsuperscript{148,151}. By consequence, there exists considerable variety among the national laws that implement the Clinical Trials Directive and these domestic requirements in the EU member states have to be taken into account when conducting a trial in a specific EU member state\textsuperscript{148}. In Belgium, this Directive was
implemented in the ‘Law concerning experiments on the human person’ (article 7) of May 7, 2004\textsuperscript{157}.

In 2014, the Clinical Trials Directive was reviewed and adopted by the European legislation makers in the new Regulation EU N°536/2014\textsuperscript{158}. Interestingly, it has taken the legal form of a regulation ensuring that the rules for conducting clinical trials are identical throughout the EU\textsuperscript{158}. This regulation is expected to be implemented no earlier than May 28, 2016\textsuperscript{158,159}. Until then the current Clinical Trials Directive will apply\textsuperscript{158,159}. The new legal rules specifically mandate a closer coordination of clinical trial applications assessments across EU Member States, supported by much closer collaboration between the national competent authorities and the ethics committees within each Member State\textsuperscript{159}.

5.2.2 Ethical concerns in paediatric research

5.2.2.1 Preventing unethical research

The protection of minor research subjects is extensively addressed in the Clinical Trials Directive. First, it is a well-known principle that the interests of the patient always prevail over those of science and society. Second, the Clinical Trials Directive states that minors should only be involved in research if there is a necessity to do so\textsuperscript{151}. Consequently, minors should only be involved in research when similar results cannot be obtained by research in competent adults or by other research methods. Third, it prohibits incentives or financial inducements to simulate research participation, except for compensation\textsuperscript{151,157}. Finally, it requires that an ethics committee with paediatric expertise endorses the research protocol\textsuperscript{151,157}. The Belgian Law stipulates that Ethics Committees that assess and endorse paediatric protocols, must include at least two doctor-specialists in paediatrics, or take advice from two doctor-specialists in paediatrics on the clinical, ethical and psychosocial aspects of the protocol\textsuperscript{157}.

5.2.2.2 Counterbalancing risks and burdens

Clinical trials entail risks and burdens\textsuperscript{148}. Procedures have been made to review the acceptability of risks and burdens in paediatric clinical trials, in which research ethics committees play a prominent role\textsuperscript{148}. The enrolment of children in a clinical investigation must not only be considered scientifically necessary, but also show an appropriate balance of risk and potential benefit\textsuperscript{146,148}. Therapeutic research (research
that is likely to generate a direct benefit for the subject involved) is often distinguished from non-therapeutic research (research that is not likely to generate a direct benefit for the subject involved)\textsuperscript{148}. While proportionality can be regarded as a general principle, exceptions are possible. Very small risks and burdens (often defined as ‘minimal risks’ and ‘minimal burdens’) for example can be deemed acceptable without a proportionate compensation in the form of a direct benefit to the research subject\textsuperscript{148}. In practice, deciding upon risks is a precarious enterprise. It is difficult to measure benefit, risk and burden and to assess their proportionality in a reliable way\textsuperscript{148}. The risks should be considered in conjunction with the severity of the condition or diseases to be studied and the risks and benefits of alternative therapies\textsuperscript{160}. Clinical trials must be designed to minimise pain, fear, discomfort, and any other foreseeable risk in relation to the disease and development\textsuperscript{157}.

The Clinical Trials Directive provides a counterbalance to the risks and burdens involved in paediatric research by requiring that the research generate a direct benefit\textsuperscript{157}. This direct benefit is defined broadly as “some direct benefit” that can be either an individual benefit (to the research subjects) or a group benefit (to the group of patients)\textsuperscript{151,157}. In the case of group benefit, no additional requirements (on risk and burden) are applicable\textsuperscript{151}. However, when it comes to national implementation of the Clinical Trials Directive, in many European countries, non-beneficial research is subjected to a strict minimal risk and minimal burden threshold. At the same time, in other countries there is no explicit distinction between therapeutic and non-therapeutic research and proportionality between risks and benefits is not linked to specific risk thresholds\textsuperscript{148}. In this respect, the Belgian Law provides that research risks may not be disproportionate to the expected benefits\textsuperscript{157}.

To evaluate the safety and efficacy of medicines and to determine best prescribing practice, comparative effectiveness trials are needed. Comparators (placebo or active) are necessary to differentiate the effects of the test intervention from confounding variables, including natural disease progression and placebo effect\textsuperscript{161}. As for placebo-controlled trials in children, which is considered the ‘gold standard’ for the assessment of the effect size of prospective new medicines, strict rules exist\textsuperscript{14,162}. These are described in the additional guidance on the Clinical Trials Directive\textsuperscript{163}. The principle of clinical equipoise has to be satisfied, in other words there should be true uncertainty
with regard to the effect of the two treatments, i.e. new drug and placebo\textsuperscript{162,163}. This means that all existing information should be collected, that could make the use of placebo unnecessary\textsuperscript{14}. Furthermore, other trial designs should be considered if appropriate\textsuperscript{163}. The use of placebo is not acceptable if the method of administration of the therapy is invasive or causes the patient unnecessary discomfort\textsuperscript{162}. In conclusion, the use of placebo in clinical trials needs careful consideration and good scientific justification\textsuperscript{160}. When there are proven effective therapies, use of placebo can be considered if both the new treatment and placebo are given as an add-on to the standard of care treatment(s)\textsuperscript{161}. Also the use of an active comparator in a paediatric trial requires special attention with regard to age-appropriate formulation, developmental pharmacology, and off-label and unlicensed medications\textsuperscript{161}.

5.2.2.3 Fair distribution of decisional power and responsibilities
From a legal point of view, children cannot consent and the consent of the parents or a legal representative is necessary. The European Clinical Trials Directive clearly sets out that informed written consent must be obtained, and in the case of children, ‘must represent the minor’s presumed will’\textsuperscript{14}. It should respect the child’s right to participate and decline participation\textsuperscript{14}. ‘Assent’ is used to define the agreement that can be given by a legally non-competent child. It is mentioned in an additional guidance on the Clinical Trials Directive\textsuperscript{163}, in the European Convention\textsuperscript{150}, and in US regulations and guidelines\textsuperscript{164}, but most interestingly not in the European Clinical Trials Directive\textsuperscript{156} itself\textsuperscript{14}. The concept of informed consent and assent will be discussed more in detail in chapter 8.

5.3 Specific paediatric populations
There are subpopulations of children that deserve special attention and that will require out-of-the box thinking and novel ideas, if we are to progress at a similar pace as for the general paediatric population\textsuperscript{165}.

5.3.1 Neonates
Neonates are widely considered a vulnerable population that is deserving of special protections in the research setting\textsuperscript{166}. They differ from children and adults in their disease presentation and their drug response\textsuperscript{167}. It is known that the largest developmental changes in PK and PD are likely to occur in the age range younger than
1 year and that these changes are the most striking during the first weeks of life\textsuperscript{50,168,169}. Drug dosing in neonates is challenging and should be based on integrated knowledge concerning the physiological characteristics of the neonate, PK and PD parameters of the drug, and the specific diseases to be treated (or the medical interventions such as extracorporeal membrane oxygenation or whole-body cooling)\textsuperscript{50,55,76}. Furthermore, formulations - including its excipients – need attention in neonatal drug development\textsuperscript{39,55,89}.

It is surprising, and also disappointing, that many medicines are still not studied in the most vulnerable population\textsuperscript{32,88,169,170}. In general, the younger the patient and the more critical and rare their disease, the more likely children will need a treatment involving off-label and or unlicensed drugs\textsuperscript{39,166}. In recent years, legislative efforts in both the US and Europe have begun to turn the tide against off-label use in children, but the effects of this legislation on the development of neonatal studies have been much more modest\textsuperscript{55,116,167,169,170}. In Europe, the analysis of PIP opinions agreed between January and October 2008 revealed that the proportion of PIPs that included neonates was 26\%\textsuperscript{56,112}. A similar analysis of PIP opinions between March and December 2011 showed an increase to 32\%\textsuperscript{112}. This increase is not reflected in any changes of authorisation as completion of most of these planned trials are deferred. That is, they can take place after the adult development\textsuperscript{167}.

Neonatal research is governed by the same ethical protections provided to older paediatric population: neonates must be enrolled only when their involvement is scientifically necessary to answer an important question about the health or welfare of neonatal subjects\textsuperscript{166}. Obtaining parental permission might be challenging at a time when in many cases both parents are under profound emotional stress because of serious illness or malformation of the baby\textsuperscript{166,171}.

While existing guidelines recommend minimising the volume of blood drawn from all children for research purposes, neonates are particularly vulnerable to anaemia from repeated blood sampling\textsuperscript{91,166}. Limits for trial-related blood loss are recommended in the Recommendations for Implementation of Directive 2001/20/EC\textsuperscript{160,172}. Per individual, the trial-related blood loss (including any losses in the manoeuvre) should
Chapter 2

not exceed 3% of the total blood volume (or 2.4ml/kg) during a period of four weeks and should not exceed 1% of the total blood volume at any single time\textsuperscript{172,173}.

5.3.2 Adolescents

Adolescence is the period of transition from childhood to adulthood with numerous physical, physiologic, cognitive and behavioural changes\textsuperscript{135,174-176}. Physical changes during puberty can result in unpredictable pharmacological parameters that may not change in a consistent relationship with age, or developmental stage, making it difficult to scale drug treatment based on studies of prepubescent children or adults\textsuperscript{174,177}. Recruiting adolescents into clinical trials is therefore essential to ensure that research results and clinical characterisation will be applicable for that age group\textsuperscript{177}. Though, adolescents are often not adequately represented in paediatric clinical trials, and this is particularly true for paediatric cancer trials\textsuperscript{177-179}.

Research in adolescents can be challenging, as adolescents belong to the paediatric age group but may have the capacity to make adult decisions in many other areas of their lives. The need for assent, as already discussed, is paramount. An adolescent may cease to be a minor and become legally competent during a prolonged trial. This must be recognised and informed consent must be sought as soon as possible when this occurs. There needs to be protection of confidentiality, and the disclosure of information to parents and other health professionals, needs to be transparent to the adolescent\textsuperscript{160}. Additionally, the inclusion of female adolescents with childbearing potential in clinical trials is particularly challenging\textsuperscript{177}. Moreover, it is important to consider (non)compliance or (non)adherence in this age group. Developmental milestones normally experienced during adolescence include the eagerness to fit in with one’s peers and the need to exercise autonomy and independence. This may result in varied and conflicting adherence to prescribed regimens\textsuperscript{174,177,179,180}. All the above-mentioned findings are reported to contribute to the exclusion of adolescents from clinical trials and should be addressed in order to improve the recruitment and participation of adolescents in children\textsuperscript{177}.

5.3.3 Critically ill children

The paediatric intensive care unit (PICU) patient population compromises patients from different age groups: infants, children and adolescents. They are an important group to
consider as many drugs used every day in the PICU evolved without adequate study\textsuperscript{165}. It has been reported that a number of disease states in the critical care unit can lead to PK and PD changes in adults\textsuperscript{181,182}. In addition, in children, it is has been shown that in this population maturational physiological changes of childhood can be further modulated by pathophysiological processes (cardiopathy, sepsis, renal or hepatic failure) and treatment modalities (extracorporeal membrane oxygenation, renal replacement therapy) applied in critical care\textsuperscript{45,70,76,183,184}. Therefore, clinicians must not only be aware of age-related changes in PK and PD but should also consider various drug-disease and drug-drug interactions\textsuperscript{183-185}. Furthermore, critically ill patients are more likely to suffer an ADR because of this altered drug metabolism. Studies of the PK, PD and toxicity of drugs in critically ill neonates, infants and children are essential\textsuperscript{3,47}.

Because of the high population heterogeneity and the relatively low number of admissions per single centre, patient recruitment is often challenging. As for ethics of clinical trials in the PICU, in addition to scientific necessity and the appropriate balance of risk and benefit, parental permission and child assent are important ethical components\textsuperscript{165}. Emotions associated with the critical illness of their child might make it very difficult for parents to give an informed parental consent. Additionally, the patient (child who is admitted to a PICU) is often not capable of assent given his or her critical clinical condition\textsuperscript{165}.

5.3.4 Obese children

With the epidemic of childhood obesity, it is not uncommon for prescribers to puzzle over an appropriate drug dose for an obese child\textsuperscript{186,187}. Defining the optimum therapeutic dose of a drug relies on an understanding of PK and PD\textsuperscript{186}. Both these processes can be affected by body composition and the physiological changes that occur in obese children. Although it is reasonable to assume that increases in fat mass alter the distribution of lipophilic drugs and increases in lean mass alter drug clearance, good quality and consistent clinical data supporting these assumptions are lacking for the majority of drugs\textsuperscript{186}. What impact obesity has on physiology relevant to drug disposition, such as protein binding (specifically $\alpha_1$-acid glycoprotein), liver and renal function remains unclear\textsuperscript{180,186}. Additionally, very little has been reported on the impact of obesity on PD, although the few reports that have emerged suggest that obese patients may exhibit an altered response on pharmacotherapy\textsuperscript{188}. These relatively few
clinical studies that have evaluated the impact of obesity have often been limited by poor design and insufficient sample size\textsuperscript{186,188}. Moreover, clinical studies conducted during drug development rarely include (or are required to include) obese subjects\textsuperscript{186}. The absence of age and weight appropriate PK and PD data has left dosing practices at the discretion and experience of the care provider\textsuperscript{189}. Dosing regimens are often expressed in mg/kg. As stated before, this linear mg/kg-based dosing is subject to debate even in normal-weight children between 0 and 18 years, but an overdose may be anticipated if the dosing is based on mg/kg body weight in overweight and, particularly, obese and morbidly obese children\textsuperscript{187}. Dose adjustments according to dosing scalars such as lean body weight, or ideal body weight have been proposed and used but no single approach is thought to cover all circumstances\textsuperscript{186,189,190}.

5.4 Paediatric cancer trials as a paradigm for paediatric clinical research

As stated by Massimi et al, paediatric oncology is a challenging field in paediatric medicine. Cancer in children is rare in comparison to adults\textsuperscript{191}. The rarity of cancer in children limits the new substances that can be tested clinically in patients and childhood cancer is very different from cancer in adults, in terms of the types of cancer that affect different age groups\textsuperscript{191,192}. Other considerations in the development of new treatments in paediatric tumours is their effect on growing children and adolescents, the use of multi-agent chemotherapy and the need for extensive supportive care\textsuperscript{192}.

Paediatric cancer trials offer a paradigm for paediatric clinical research\textsuperscript{40}: paediatric oncology is the area where treatments have achieved outstanding results through rigorous protocols (using medicines off-label)\textsuperscript{193}. The participation of children with cancer in clinical trials has become increasingly common since the 1970s, and is very likely responsible for the large increases in cancer survival observed since then\textsuperscript{37,40,192,194}. This was achieved essentially through prospective clinical studies performed by paediatric oncology networks and cooperative groups because pharmaceutical companies were not committed to developing their drugs in the paediatric population\textsuperscript{103}. In many cases, no application for MA was made to the authorities\textsuperscript{14}. Since January 2007, the start of the Paediatric Regulation, only a few cancer medicines were authorised with a full paediatric indication\textsuperscript{88}. In accordance with
the Paediatric Regulation, the PDCO adopted a list of conditions that occur exclusively in adult populations (such as adenocarcinoma of the pancreas or adenocarcinoma of the colon). Twenty of the 35 conditions listed are related to oncology. Therefore, all classes of medicinal products intended to treat these conditions do not require a PIP. Based on this list of malignancies that do not occur in children, pharmaceutical companies may be tempted to systematically ask for a waiver for most of their compounds under development in adult malignancies. The PDCO confirmed that, from April 2008 to April 2012, paediatric development was waived in 197 adult oncology conditions (out of 313 conditions in total; 63%). As a result, compounds of potential interest to children could be missed. Recently, in July 2015, the EMA reviewed the class waiver list and updated and/or revoked 23 class waivers. In this way, it will be possible for the PDCO not only to consider the adult indication but also to link the mechanism of action of the drug to paediatric tumour biology. This evaluation based on mechanism of action for cancer drugs will hopefully contribute to a new paradigm shift in paediatric clinical research. An important initiative to stimulate this new concept is the European consortium for Innovative Therapies for Children with Cancer (ITCC), created in 2003 to develop new drugs, both at the preclinical and clinical levels, in malignant solid tumours and leukaemias. This network identifies relevant biological targets in paediatric tumour biology, using a large biobank of tumour samples; evaluates anticancer drugs in relevant paediatric tumour models; and runs phase I and early phase II trials through a network of 36 clinical investigation centres.

6 PAEDIATRIC CLINICAL PHARMACOLOGY

Professor K. Hoppu (University of Helsinki) defines paediatric clinical pharmacology as a scientific discipline that involves all aspects of the relationship between drugs and humans during growth, development and maturation. In view of the new legislative measures, the demand for expertise in paediatric clinical pharmacology has never been greater. Although clinical pharmacology was born as an independent discipline in the beginning of the 1970s and led to a rapid improvement in adult medicine, paediatric clinical pharmacology has not kept pace. The development of the capacity to critically appraise paediatric pharmacology data involves synthesizing knowledge (e.g. pharmacology, epidemiology, and clinical research design), skills (e.g. PK, statistics, and grant writing) and attitudes (e.g. ethics). Historically, there has been a lack of training
programs in paediatric clinical pharmacology\textsuperscript{17,200}. Paediatric clinical pharmacologists have been self-taught and have designed their own training, frequently training in paediatrics before undertaking adult clinical pharmacology training. This is not ideal however as ‘children are not small adults’, and have their very own pharmacologic characteristics. A survey in 2005 showed the presence of only 18 paediatric clinical pharmacologists in Europe\textsuperscript{36}. To the best of our knowledge, there are no more recent data. A major training effort to build capacity for the various areas of expertise is needed and is to some extent underway. In Europe, the new paediatric networks are expected to become a major resource for training\textsuperscript{36}. An additional important 7\textsuperscript{th} Framework Programme (FP7)-funded initiative called Global Research in Paediatrics (GRIP) will focus on international paediatric clinical pharmacology education and training\textsuperscript{39,74,76}.

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Paediatric drug development


CHAPTER 3

OUTLINE AND AIMS OF THIS THESIS
1 GENERAL OBJECTIVE

The field of paediatric clinical pharmacology has existed for only about two decades and is obviously a rather young discipline. As discussed in detail in the previous chapter, regulations have stimulated paediatric clinical trials and the performed paediatric trials have elucidated beautiful knowledge but much still needs to be done and several important issues remain to be addressed:

1. Did the legislations result in appropriate clinical trials? Were those trials able to provide correct evidence and information for use in children?
2. Does this result in an appropriate labelling for children? In other words, do we have drugs labelled and formulated for the patients we treat in daily practice?
3. If we have evidence on efficacy and safety of a drug including correct labelling, do we use this knowledge in daily practice?

The aim of this doctoral thesis is to provide insights into the current situation of drug use in children by evaluating possible gaps in knowledge, notably gaps between the available paediatric data in literature on one hand and the labelling and prescriptions in daily practice on the other hand. The focus in this thesis was on four ‘cases’: the case of desmopressin, antihypertensives, the first generation H₁-antihistamines, and proton pump inhibitors. All four are frequently prescribed in paediatrics. We hereby aim to integrate different aspects of paediatric clinical pharmacology: both observational (by literature review and pharmacoepidemiological research) and interventional (pharmacokinetic) research. The research questions focusing on different levels of the drug evaluation and marketing process are indicated in figure 3.1 of this chapter.

Finally, the current – difficult - situation of drug development in children was the starting point of the development of a paediatric drug research unit. The evaluation of the feasibility of this research unit was an important part of this PhD and will be described in the last part of this thesis.
2 COMPOUND SPECIFIC OBJECTIVES

2.1 Desmopressin
Desmopressin (1-deamino-8-D-arginine-vasopressin, dDAVP) is a synthetic vasopressin analogue. Desmopressin is currently the only pharmacological treatment to receive a grade A, level 1 recommendation for use in nocturnal enuresis. Desmopressin oral lyophilisate was marketed in 2005 before the implementation of the Paediatric Regulation and was labelled based on minimal pharmacokinetic and pharmacodynamics studies. Our paediatric trial with desmopressin investigates whether these minimal studies suffice for correct use and dosing in children. More specifically, our study explores the stated bioequivalence of two oral formulations of desmopressin: tablet and oral lyophilisate (chapter 4).

2.2 Antihypertensives
Antihypertensives were the type of drugs that have been likely to fit with the FDA and EMA legislations about one decade ago: hypertension is prevalent in the paediatric population, and at that time some of the newer antihypertensives were under...
development for adult indication, there was widespread off-label prescription and there was a lack of paediatric formulations. Moreover, antihypertensives were block-busters, meaning that six months of marketing exclusivity likely would be an incentive. Consequently, the legislations have resulted in antihypertensive trials investigating particularly angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in children\textsuperscript{4}. The major question is whether these trials resulted in adequate paediatric data. In other words: Did these trials result in a decrease in off-label prescribing? Did they provide PK/PD data in the population we treat in daily practice? Do we have long term safety data? Are age-appropriate formulations available now?

Part of these questions are investigated in our study focusing on the management of hypertension in children. It is based on a review of the literature and the Summary of Product Characteristics of antihypertensives. This study evaluates the labelling status and availability of age-appropriate formulations of these frequently used antihypertensives in children (chapter 5, section 5.1).

The second section within this chapter focuses specifically on the group of ACEIs, through review of the published papers on efficacy and safety of ACEIs in children (chapter 5, section 5.2).

2.3 First generation H\textsubscript{1}-antihistamines

As stated before, during the past decades, much attention has been paid to off-label and unlicensed drug use in children: many – in fact, most of the - drugs in paediatrics are prescribed off-label or unlicensed with possible underdosing and overdosing as a result. First generation H\textsubscript{1}-antihistamines are prescribed on-label in the paediatric population for a variety of indications: allergic rhinitis, urticaria, and last but not least itch. They are most often sold over the counter and used without any medical supervision\textsuperscript{5}. With the study focusing on first generation antihistamines, we want to investigate the situation of old drugs in children: is their use supported by evidence from clinical trials? The study investigates the availability of evidence for this use in children. The hypothesis of our investigation is that there is limited evidence of efficacy (chapter 6).
2.4 Proton pump inhibitors

Consumption of acid suppressants, such as H$_2$-receptor antagonists and proton pump inhibitors, has increased markedly in the last two decades. This is a worldwide observation in adults$^6-10$. The prescription of the acid suppressants was also initiated in the paediatric population during the last decade. Importantly, this prescription in children is currently only advocated for the specific indication of gastroesophageal reflux disease (GERD), as clearly indicated in the current international guidelines$^6$. Infants may show symptoms of GERD. However, the available randomised controlled trials with PPIs in infants show that PPIs and placebo produce similar improvement in crying, despite the fact that acid suppression only occurred in the PPI group$^{11-17}$. Based on clinical experience, the hypothesis is that there is an increase in prescriptions of acid suppressant despite the lack of evidence for their use. This will be investigated in chapter 7. Pharmaco-epidemiological studies of drug usage in children are invaluable in determining whether medicines are prescribed rationally or not in paediatric patients$^{18}$. The reported pharmaco-epidemiological study is an analysis of the Belgian prescription database, Pharmanet.

3 DEVELOPMENT OF A NEW PAEDIATRIC DRUG RESEARCH APPROACH

Our findings in the above-mentioned papers were the starting point for the development of a paediatric drug research unit. We are convinced that improved availability of appropriately labelled, safe and effective medicines for children in age-appropriate formulations will only be acquired by a significant increase in high quality clinical trials in children. This will require a collaboration of different experts and stakeholders in the field of paediatric clinical pharmacology$^{19}$. Chapter 8 describes the development of our SAFE-PEDRUG consortium.

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CHAPTER 4

PHARMACOKINETICS OF DESMOPRESSIN ADMINISTERED AS TABLET AND ORAL LYOPHILISATE FORMULATION IN CHILDREN WITH MONOSYMPTOMATIC NOCTURNAL ENURESIS


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ABSTRACT
Desmopressin 120µg oral lyophilisate and 200µg tablet are considered bioequivalent, based on extrapolation of studies in a limited number of adults, and on one dose-finding study of desmopressin oral lyophilisate in children. However, no comparative pharmacokinetic study was executed confirming this statement. No data are available on the influence of food intake on the bioavailability of desmopressin tablet in a paediatric setting, although studies in adults have documented that food intake results in a significantly lower desmopressin plasma concentration. In this study, we analysed plasma concentrations of desmopressin oral lyophilisate and tablet with concomitant food intake. 23 children with monosymptomatic nocturnal enuresis (mean age 12,7 years) were recruited. Two tests were performed on two separate days in identical conditions with a standardised food and fluid intake. Desmopressin was administered as desmopressin tablet or desmopressin oral lyophilisate immediately after a meal. Desmopressin plasma concentration was measured at 1 hour, 2 hours and 6 hours post dosing. No significant difference in plasma concentration of 120µg desmopressin oral lyophilisate and 200 µg tablet was demonstrated, even with concomitant food intake. A significant difference in variability was found, identifying a smaller variance for desmopressin oral lyophilisate plasma concentrations at all time points. Conclusion: This study demonstrates comparable plasma levels for desmopressin oral lyophilisate, despite the lower dose. The dosage for desmopressin oral lyophilisate is more predictable due to the significantly smaller variance. Therefore, desmopressin oral lyophilisate seems more suitable, especially in the younger age group for whom time interval between dinner and drug-administration is limited.
1 INTRODUCTION

Paediatric pharmacokinetic studies are essential to guide correct paediatric dose regimens, which results in higher response rates and a lower prevalence of side effects. The European Regulation, introduced by the European Medicines Agency in 2007, aims to stimulate these paediatric clinical trials for any new drug, for existing drugs in a new indication, or in a new formulation, by offering 6 months of patent prolongation by the request to deliver a paediatric investigational plan (PIP) with an appropriate paediatric formulation. On the other hand, off-patent drugs can receive a market exclusivity of ten years, called a paediatric use marketing authorisation (PUMA), when tested for an exclusive paediatric indication\(^1\). These initiatives resulted in new pharmacokinetic and pharmacodynamic (PK/PD) data of industry driven protocols but those studies give insufficient answers to specific paediatric needs, especially for drugs patented prior to the Paediatric Regulation. This is documented in the case of desmopressin: the oral lyophilisate formulation was marketed before the implementation of the Paediatric Regulation. This formulation that completely fulfilled the EMA criteria of a paediatric adapted formulation was labelled for children of 5 years or older in the enuresis nocturna indication on the basis of minimal PK/PD studies and did not receive a full paediatric investigational plan.

Bedwetting or nocturnal enuresis – the leakage of urine while sleeping in children aged 5 years or older- is a frequent problem\(^2\). Overall nocturnal enuresis prevalence varies from 6 to 10% of children aged 7 years and these figures are similar worldwide\(^3\). A spontaneous annual cure-rate of 15% has been generally accepted\(^4\), even though recent evidence has shown that 1% of adults still wet their beds\(^3\). Enuresis is a disease with a major impact on the well-being and functioning of the child, both directly as a result of enuresis and indirectly as a result of its psychological consequences such as poor self-esteem\(^5\). Consequently, treatment for bedwetting is not only justified but is mandatory.

Monosymptomatic enuresis is defined as enuresis in children without any other lower urinary tract symptoms and without a history of bladder dysfunction\(^2\). It constitutes a heterogeneous disorder, which can be caused by one or more pathophysiological mechanisms\(^3\). Nocturnal polyuria (nocturnal urine output exceeding 130% of expected
Pharmacokinetics of desmopressin in children

bladder capacity\(^2\)) is one of those factors that can play a role in the persistence of bedwetting after the age of 5 years\(^6\). A primary cause of nocturnal polyuria has been identified as a relative deficiency of the antidiuretic hormone arginine vasopressin (AVP) during the night, resulting in high nocturnal diuresis and reduced concentration of urine\(^7\). Desmopressin (1-deamino-8-D-arginine-vasopressine, dDAVP) is a synthetic vasopressin analogue: it retains the antidiuretic properties of vasopressin, but avoids the unwanted vasopressor and uterotonic effects\(^8\). dDAVP is currently the only pharmacological treatment to receive a grade A, level 1 recommendation for use in nocturnal enuresis from the International Consultation on Incontinence\(^9\). The only serious adverse event reported with desmopressin is symptomatic hyponatremia with water intoxication\(^4\). The higher incidence of hyponatremia in patients treated with nasal spray has been claimed to be related to its higher and unpredictable bioavailability\(^10\).

Both oral formulations, the tablet and oral lyophilisate formulation, reach a maximum plasma concentration within 2h. Tablets have an average bioavailability of 0.08-0.16% in adults, the oral lyophilisate has an average bioavailability that is approximately 60% higher than the tablet\(^11\). None of the available desmopressin formulations have been demonstrated to require a size dependent dosing regimen, which is exceptional in paediatric pharmacotherapy. Efficacy and safety of desmopressin in children was evaluated for the enuresis nocturna indication in tablet doses of 0.2, 0.4 and 0.6 mg\(^12\). The oral lyophilisate formulation offered an alternative in clinical practice for children who are unable to swallow a tablet. The labelling of this formulation was supported by a limited number of data in children and mainly concentrated on small age spectrum of 6 to 12 years. Bioequivalence between 120 µg oral lyophilisate desmopressin and 200 µg tablet formulation was documented in adults. This was extrapolated to children, because of the reassuring PK/PD data from the dose finding study. To the best of our knowledge, the only paediatric trial evaluating the correlation between pharmacokinetics and pharmacodynamics is this dose finding study but this is only for the oral lyophilisate formulation. There is a relationship to be expected between plasma levels and pharmacodynamics as suggested in this study\(^6,13\). No cross-over with desmopressin tablet formulation in the same patient was performed\(^5\).
Our study compared the pharmacokinetic profiles of tablet and oral lyophilisate formulation of desmopressin through a prospective cross-over study. In this study design, a meal was included, in contrast to the available pharmacokinetic (adult) studies. All former studies were conducted in the artificial fasting setting (participants did not eat since at least two hours) although food influences on absorption of desmopressin have already been demonstrated in adults by Rittig et al. Knowing that oral desmopressin has to be taken at least one hour before the last void, our design is more appropriate in young children, seeing that in real life the interval between evening meal and sleeping time is never more than two hours.

The primary endpoint of this study is to confirm bioequivalence for desmopressin tablet 200 µg and oral lyophilisate 120 µg in the non-fasting state. Secondary endpoint is size dependency of desmopressin dosing.

2 MATERIALS AND METHODS

2.1 Patients
In order to be eligible for this study, patients had to be between 5 and 18 years old and suffering from monosymptomatic nocturnal enuresis, partially responding to desmopressin tablet or nasal spray. Twenty-three patients were selected in a tertiary enuresis centre. Exclusion criteria were desmopressin hypersensitivity, any clinically significant disease likely to interfere with the evaluation, abnormalities of the oral cavity, and use of antibiotics, diuretics or any drug affecting desmopressin plasma concentration. Written informed consent was obtained from all parents and/or legal guardian; while children of appropriate intellectual maturity signed an assent form. The study was conducted in accordance with ICH guidelines of Good Clinical Practice and approval was obtained from our local Ethics Committee (EC 2009/653).

2.2 Study drugs
Desmopressin (dDAVP) was provided as tablets containing 200 µg of dDAVP as desmopressin acetate (Desmotab®, Ferring N.V., Aalst, Belgium) and oral lyophilisate containing 120 µg of dDAVP as desmopressin acetate (Minirin® Melt, Ferring).
2.3 Drug administration

The formulations were compared in a two-period cross-over design, as this is the preferred design for bioequivalence studies of two formulations\textsuperscript{15}. dDAVP was administered on two separate days, with an interval of two weeks between both treatments. On arrival, the volunteers had been fasting since the morning. Patients treated with desmopressin tablets took their last dose more than 30 hours before the start of the study. At noon, a standardised 510 Kcal meal was administered. This was immediately followed by desmopressin administration. To maintain hydration, 8 hours of insensible loss was compensated at 5 hours post-desmopressin-administration by oral water administration.

2.4 Laboratory assessments and safety profile

At one hour, two hours and six hours post-desmopressin-administration, blood was sampled for pharmacokinetic analysis. Plasma concentrations of desmopressin were determined by using a validated LC-MS/MS method with a range of 2.00-100 pg/ml. All spontaneously reported adverse events were recorded, as well as those routinely questioned at the end of each study day.

2.5 Statistics

Statistical evaluation was performed using statistical software SPSS version 19. Wilcoxon matched pair signed-rank test was selected to compare the plasma concentrations, which were not normally distributed. Levene’s test was used to assess significant differences in variability. Spearman’s rank correlation coefficient was employed for assessing the correlation between weight corrected dose and plasma concentration. The level of significance was set at P<0.05.

3 RESULTS

Four girls and nineteen boys were eligible for the study. The mean age of the included patients was 12.7 years (range: 7-18 y; 95% confidence interval (CI): 11.5-13.9). The mean weight of the included patients was 50.1 kg (range: 24.0-81.8kg, 95% CI: 43.53-56.73). One boy was excluded from paired statistical analysis since he did not succeed in taking the tablet formulation properly due to mental disability, while administering
the oral lyophilisate formulation was no problem. All other included patients completed both (tablet and oral lyophilisate) tests under identical circumstances.

The plasma desmopressin concentration at various intervals after dDAVP 120 µg oral lyophilisate and 200µg tablet are shown in figure 4.1. This figure clearly shows the differences in variance between the two different formulations, as confirmed by the Levene’s test (table 4.1).

![Boxplots of Plasma dDAVP Concentration](image)

**Figure 4.1:** Plasma dDAVP concentrations after single doses of dDAVP administrated as tablet and oral lyophylisate.

Boxplots illustrate median values and first quartile on each side. Whiskers indicate 10th and 90th percentile.

**Table 4.1**: Levene’s test for homogeneity of variance.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>1h post dosing</th>
<th>2h post dosing</th>
<th>6h post dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tablet</td>
<td>Oral lyophilisate</td>
<td>Tablet</td>
</tr>
<tr>
<td>Variance</td>
<td>23.50</td>
<td>5.93</td>
<td>13.41</td>
</tr>
<tr>
<td>Test of homogeneity of variances : p-value</td>
<td>P=0.020</td>
<td>P=0.041</td>
<td>P=0.007</td>
</tr>
</tbody>
</table>
Correlation testing – by Spearman’s rank correlation coefficient - indicates a significant positive correlation between plasma concentrations of dDAVP and dose corrected by weight at 2h and 6h post dosing in the oral lyophilisate group. This is not the case for the tablet formulation (table 4.2). This is reported graphically in figure 4.2 and 4.3. The Spearman correlation coefficient provides a measure of association between dose corrected by weight and plasma correlations, which are significant and markedly higher in the 2h post dosing and the 6h post dosing group (table 4.2).

**Table 4.2:** Two-tailed correlation test by the Spearman’s rank correlation coefficient Rs.

<table>
<thead>
<tr>
<th>Correlation</th>
<th>1h post dosing</th>
<th>2h post dosing</th>
<th>6h post dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tablet</td>
<td>Oral lyophilisate</td>
<td>Tablet</td>
</tr>
<tr>
<td>Tablet dose/weight</td>
<td>Rs = 0.120</td>
<td>p-value: 0.613</td>
<td>Rs = 0.206</td>
</tr>
<tr>
<td>Oral lyophilisate dose/weight</td>
<td>Rs = 0.393</td>
<td>p-value: 0.096</td>
<td>Rs = 0.499</td>
</tr>
</tbody>
</table>
Figure 4.2: Correlation of dose corrected by weight to plasma concentrations at 2 hours post dosing

Figure 4.3: Correlation of dose corrected by weight to plasma concentrations at 6 hours post dosing
3.1 Side effects and laboratory safety profile

One patient experienced nausea and vomiting 5 hours post-dDAVP-administration. Assessment of serum sodium demonstrated no hyponatremia: serum sodium was 136 mmol/L. This patient was one of the youngest participants (9 years old) and had the highest dDAVP plasma level with desmopressin oral lyophilisate (13.05 pg/ml) at 1 hour post dosing time. There were no other notable safety events.

4 DISCUSSION

Pharmacokinetic and pharmacodynamics studies are essential to define therapeutic range, minimising side effects and optimising response rates. It has already been shown that children are not small adults\textsuperscript{16}. Consequently, extrapolation from adult clinical trials is impossible without validation by a paediatric study. It is generally believed that sublingual desmopressin is absorbed in the mouth and the esophagus\textsuperscript{17} but this is - as such – not yet proven by proper studies. Our study (evaluating both oral formulations, with food intake) gives further but indirect evidence for the buccal absorption, given that lower doses of melt result in equal concentrations to those of the tablet formulation. This is the first study in children assessing and confirming the claimed bioequivalence for pharmacokinetic characteristics between desmopressin tablet 200 µg and desmopressin oral lyophilisate 120 µg\textsuperscript{11,18}. In this study, no statistical differences in the plasma concentrations at 1, 2 and 6 hours post dosing were observed, even when administered in combination with food. Plasma concentration of desmopressin has a large variability: in some patients the plasma concentration is below the detection limit. This is well described in the limited literature, but so far there are no data to correlate the range difference with the different pharmacodynamic effects. We acknowledge that the design with only three plasma concentration samples does not allow to calculate exact maximum concentration (C\textsubscript{max}), time to C\textsubscript{max} (T\textsubscript{max}) and bioavailability due the few time-points, a choice made to limit blood sampling in children for obvious reasons. The population approach using non-linear mixed effect modeling to obtain pharmacokinetic parameters would be the preferred approach when dealing with sparse (and unbalanced) data as it would permit further exploration of the influence of different covariates to explain the variability\textsuperscript{19}. However, for ethical reasons, we restricted the number of blood samples to 3 fixed sampling time points. For population PK in this number of patients (23), we should have staggered the sampling time points.
In the absence of proper clinical trials with the lyophilisate formulation for nocturnal enuresis, these data are crucial for clinical practice and guidelines, as volume of prescriptions for the lyophilisate formulation is markedly exceeding the prescription of the tablet.

Bioequivalence is indicated by the study results however an adequate pharmacokinetic analysis is not possible given the sparse samples. When we fine-tune our analysis, significant differences are identified. The significantly smaller variance at all three sampling times is important in daily practice, indicating that pharmacokinetics of desmopressin oral lyophilisate are much more predictable than the tablet formulation. The interpretation of this observation is extremely important considering the safety discussion for desmopressin over the last years. There is an obvious correlation between doses and pharmacodynamic effect in the tubulus, although this correlation is complex: dose is correlated to duration of action, rather than to maximal concentrating capacity\textsuperscript{6}. The similar PK levels of tablet and oral lyophilisate formulations are reassuring. Higher plasma levels for the oral lyophilisate group were expected after the observation of significantly longer duration of action and indices of shorter time to reach maximal diuresis and a higher concentration capacity in the previous pharmacodynamics study\textsuperscript{20}.

Our results show a significant dose-concentration correlation in the oral lyophilisate group when we normalise dose for size (body weight), in contrast to the tablet group. This is the first documentation of such a size-dependency for this peptide in children from 5 to 18 years old. Besides, parenteral dosing of most other peptides is also size-dependent and there is even for desmopressin a documented size-effect, since young children and neonates with diabetes insipidus need significantly lower doses than juvenile patients\textsuperscript{21}.

We suggest that the lack of evidence for a size effect in the tablet and the spray, should be attributed to the poor predictability of their bioavailability, thereby masking every size effect. This observation is important since the number of patients treated in the age group of 5 to 8 years is fast increasing, which might on one hand suggest some prudence in uptitrating desmopressin dosage in young children, but on the other hand...
offers a rationale for uptitrating in adolescents who do not reach maximal anti-diuresis and maximal concentrating capacity.

Despite the limited number of patients and sampling, this study design allows us to conclude that desmopressin oral lyophilisate 120 µg has less variance, compared to the stated bioequivalent dose of 200 µg tablet, indicating more predictable pharmacokinetic characteristics. Full interpretation to this observation can only be given, if we could correlate pharmacokinetic data with concentrating capacity and antidiuretic effect. The finding of a size-dependency indicates that a full pharmacokinetic and dynamic program (looking for age, size, sex, puberty differences) is necessary in children, not only for every new drug, but also for every new formulation.

As we do not have complete pharmacokinetic data of all our study patients, we cannot make a correlation between PK and PD. This is the purpose of our future research. To straighten the finding of the correlation between dose adjusted for weight and plasma levels, we would need more children in the young age group (especially younger than 5) and more children in the high size group. However, in these children we have the ethical burden that children < 5 years are not considered to have pathologic enuresis nocturna (and have no indication for the treatment with dDDAVP) and in the older children, only limited children have the monosymptomatic form of enuresis nocturna.

In conclusion: In this study, evidence is provided for superior pharmacokinetic characteristics of dDAVP oral lyophilisate, particularly smaller variability in plasma concentration and a better prediction of plasma concentrations. It remains to be explored how information on variability can be used to develop an optimal dosage regimen of the drug in an individual patient.

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SECTION 5.1: MANAGEMENT OF HYPERTENSION IN CHILDREN AND ADOLESCENTS

De Bruyne P, Vande Walle J

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Acta Clin Belg 2014; 70(2): 87-94
ABSTRACT

Hypertension has been recognized as an important health issue in the paediatric population over the past years. This emphasizes the need for an organised and effective plan for diagnosis and management. This review provides information to guide physicians through a structured approach to 1) screen children for hypertension during routine visits; 2) use normative blood pressure tables for diagnosis and classification; 3) perform a clinical evaluation to identify the presence of risk factors, comorbidities and/or target organ damage; and 4) initiate an individualized plan of care that includes follow-up blood pressure measurement, therapeutic lifestyle changes and - if necessary - pharmacological therapies.
1 INTRODUCTION AND PURPOSE

There is growing evidence that mild blood pressure (BP) elevations in children and adolescents are much more common than it was thought before. Recent reports indicate that hypertension now affects between 3% and 5% of the pediatric population. This makes hypertension one of the most common chronic diseases of childhood, especially in adolescence. Longitudinal studies have made it clear that BP abnormalities during childhood do translate into adult hypertension. Where there was in the past a predominance of secondary hypertension in children, associated with renal disorders and/or drug therapy, there is now an increasing frequency of essential hypertension.

There are two major reference frames for the management of hypertension in children: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents from the National Heart, Lung and Blood Institute (NHLBI) and the revised guidelines of the European Society of Hypertension. It should be noted that these pediatric guidelines are much more expert than evidence based, since they are supported by only few observational and interventional trials in contrast with the adult guidelines. The remoteness of incident cardiovascular events from BP values many years beforehand makes the relationship of BP values with events hardly feasible. Consequently, many of the classifications and recommendations in children are based on statistical considerations, and result from assumptions rather than the results of experiments or result from extrapolations from evidence obtained in adults.

Increased BP at pediatric age is an underestimated problem in primary and secondary care in Belgium. Major attention to this topic is only given in very subspecialized pediatric nephrology and cardiology journals. Therefore there is a need to translate these international guidelines into a Belgian setting.

2 DEFINITION AND CLASSIFICATION OF HYPERTENSION

Diagnostic criteria for elevated BP in children are based on the concept that BP in children increases with age and body size, making it impossible to utilize a single BP level to define hypertension, as done in adults. The definition of elevated BP for children is based on percentiles derived from population studies of healthy children. Extensive pediatric normative data on auscultatory clinic measurements have been
provided for the United States, based on more than 70000 children, from the Task Force for Blood Pressure in Children\textsuperscript{5-7}. A few national studies were undertaken in Europe, but were unable to overrule the Task Force for Blood Pressure as reference\textsuperscript{1}, even for the European setting\textsuperscript{8}, since they included less patients, and differences were only mild and therefore hardly clinical relevant.

Normal BP in children is defined as systolic blood pressure (SBP) and diastolic blood pressure (DBP) less than 90\textsuperscript{th} percentile for age, sex and height, whereas hypertension is defined as SBP and/or DBP persistently 95\textsuperscript{th} percentile or more, measured on at least three separate occasions with the auscultatory method. Children with average SBP or DBP 90\textsuperscript{th} percentile or more but less than 95\textsuperscript{th} percentile are classified as having high-normal blood pressure. Adolescents with BP 120/80 mmHg or more even if less than 90\textsuperscript{th} percentile are also considered as having high-normal BP\textsuperscript{1,6}. Redwine et al showed that having high-normal BP is a higher risk of developing hypertension\textsuperscript{2,3}. Additionally, the Fourth Report provides criteria for staging the severity of hypertension in children and adolescents in stage 1 hypertension and stage 2 hypertension, which can be used clinically to guide evaluation and management\textsuperscript{1,3,6}. Children with stage 2 hypertension should be evaluated and treated more quickly and/or intensively than those with a lower degree of BP elevation (table 5.1)\textsuperscript{1}.

3 DIAGNOSTIC EVALUATION

3.1 Blood pressure measurement

Patients with hypertension may show symptoms such as headache, malaise, nose bleeding and palpitations but hypertension is predominantly an asymptomatic condition, which can only be diagnosed by routine measurement of BP\textsuperscript{3}. Children above three years of age who are seen in a medical setting should have their BP measured\textsuperscript{3,6,9}. Younger children should have their BP measured in special circumstances: history of prematurity, congenital heart disease, known renal disease or urologic malformations, malignancy, solid-organ transplant, other systemic illnesses and drugs known to be associated with elevated BP\textsuperscript{6}. The diagnosis of hypertension should be based on multiple office BP measurements, taken on separate occasions over a period\textsuperscript{1}. Although office BP should be used as reference, BP values obtained out of office may improve the evaluation in untreated and treated individuals\textsuperscript{1}.
Table 5.1: Classification of hypertension in children and adolescents

<table>
<thead>
<tr>
<th>Systolic or diastolic blood pressure (if systolic and diastolic categories are different, categorize by the higher value)</th>
<th>Frequency of BP measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Recheck at next scheduled physical examination</td>
</tr>
<tr>
<td>High-normal blood pressure</td>
<td>Recheck in 6 months</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>Recheck in 1-2 weeks or sooner if symptomatic; if persistently elevated on 2 additional occasions, evaluate or refer to a paediatric nephrologist/cardiologist within 1 month</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>Evaluate or refer to a paediatric nephrologist/cardiologist within 1 week or immediately if the patient is symptomatic</td>
</tr>
</tbody>
</table>

BP: blood pressure

3.1.1 Office or clinic blood pressure

Office BP measurement has provided the basis for the present knowledge of the potential risk associated with hypertension and has guided management for many years. The available reference values for defining BP classes have been obtained by the auscultatory method (Korotkoff sounds-based measurement). These BP standards, including the 50th, 90th, 95th and 99th percentiles by gender, age, and height are publicly accessible on https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf. Oscillometric devices, which do not measure SBP and DBP directly but calculate BP from pressure oscillations detected in the arm cuff, have been introduced more recently. It should be noticed that values obtained by the oscillometric method are generally higher than values obtained by the auscultatory method. Few oscillometric devices have been successfully validated using an established protocol. The continuously updated data available on monitor validation for children is found at www.dableducational.org. Another important issue to consider in the measurement
of BP in children, is that appropriate cuff size can vary substantially among children of the same age. The cuff bladder should have a width that covers approximately two-thirds of the upper arm and a length that encircles at least 80% of the upper arm, preferably 100%\textsuperscript{6}. Preferably, BP is measured at the right arm, after the patient has been sitting for 5 minutes, feet on the floor and right arm supported with cubital fossa at heart level\textsuperscript{6}. The right arm is preferred in repeated measures of blood pressure for consistency and comparison with standard tables and because of the possibility of coarctation of the aorta, which might lead to false (low) readings in the left arm\textsuperscript{6}. Moreover, a four extremities BP check is mandatory in a child with hypertension to evaluate for coarctation of the aorta, which is one of the causes of secondary hypertension\textsuperscript{10}. If the leg BP is lower than the arm BP (in supine position\textsuperscript{11}) – or if femoral pulses are week or absent, coarctation of the aorta may be present\textsuperscript{6}.

### 3.1.2 Ambulatory blood pressure

Although office BP is still the reference for the diagnosis of hypertension, ambulatory BP measurement (ABPM) is now increasingly recognized as being indispensable to the diagnosis and management of hypertension, in children of 5 years or older\textsuperscript{6,9,12}. It has contributed significantly to ‘unmask’ BP phenomena, unlikely to be identified by office BP\textsuperscript{1,6}. These have included the dipping and non dipping patterns of nocturnal BP, BP values in the hypertensive range in the office but not out-of-office (white-coat hypertension)\textsuperscript{1,3,12} or, vice versa, in the normotensive range in the office but not out-of-office (masked hypertension)\textsuperscript{1,12}. Reference values provided by the German Working Group on Pediatric Hypertension are currently considered the best available data for paediatric ABPM\textsuperscript{13,14}. ABPM is often used in randomized clinical trials of BP-lowering drugs (in adults) to compare antihypertensive efficacy between therapeutic agents and to assess 24-hour BP control, including improvement in nocturnal dipping with treatment. Use of ABPM, therefore, provides additional information on circadian BP control that may alter selection and dosage of an antihypertensive\textsuperscript{12}.

### 3.1.3 Home blood pressure

Concerning home BP measurements, evidence in children and adolescents is limited. In children, home BP has superior reproducibility than office BP has and is similar to that for ABPM. Home monitoring for 6-7 days with duplicate morning and evening
measurements is recommended. Home BP in children is lower than daytime ambulatory BP, probably due to a high level of physical activity during the day.

3.2 Evaluation for risk factors and for secondary hypertension

In order to identify possible causes of hypertension, the first investigations in the child with hypertension should include: a complete (family) history, physical examination, blood exam, urinalysis and ultrasound of kidney and heart.

Primary hypertension often clusters with other risk factors. Considerable advances have been made in recent years in identifying conditions often associated with and considered responsible for high BP in children and adolescents. Overweight is probably the most important of the conditions associated with elevated BP in childhood and accounts for more than half of the risk for developing hypertension. Birth size and postnatal growth have also been recently implicated in the development of high BP and adult cardiovascular disease. Furthermore, dietary habits early in life, and particularly high salt intake, have been implicated as factors favoring higher BP values. Studies on racial differences showed that African-American children had a higher prevalence of overweight/obesity and left ventricle hypertrophy (LVH) than non-African-American children. Sleep disorders including sleep apnea are associated with hypertension, coronary disease, heart failure and stroke in adults. Although limited data are available, they suggest an association of sleep-disordered breathing and higher BP in children. Consideration of these associated risk factors and appropriate evaluation in those children in whom the hypertension is verified, are important in planning and implementing therapies.

Sustained hypertension in children and adolescents is classified as secondary when a specific cause can be found, which can sometimes be corrected with specific intervention. The most common causes of secondary hypertension differ according to the age of the children. In very young children (<6 years), hypertension is most often the result of renal parenchymal diseases such as glomerulonephritis, renal scarring, polycystic kidney, renal artery stenosis and renal dysplasia. Hypertension is present in approximately 50% of children with chronic kidney disease. Both high BP and increased proteinuria are predictors of the progression of renal disease among children with chronic kidney disease. The most common cardiovascular cause of hypertension
is coarctation of the aorta and Turner’s syndrome. In all ages, following rare but identifiable causes of hypertension should be considered: endocrine diseases (hyperthyroidism, Cushing’s syndrome, primary hyperaldosteronism) and some endocrine tumors (pheochromocytoma and neuroblastoma), and food or drugs that raise BP (liquorice, oral contraceptives, steroids, non-steroidal anti-inflammatory drugs, cyclosporin)\textsuperscript{16}.

3.3 **Evaluation of target-organ damage**

Once hypertension is confirmed, organ damage evaluation should include heart, great vessels and kidney, due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease\textsuperscript{1,3}. Subsequently, evaluation of organ damage is also useful as an intermediate endpoint for monitoring treatment protection\textsuperscript{1}. Neurologic and ophthalmologic clinical evaluation are indicated in severe hypertension\textsuperscript{1}. The most useful and relevant way (and primary tool) to evaluate target-organ damage is by assessing left ventricular mass using echocardiography\textsuperscript{3,5,6,9,16}. Left ventricular hypertrophy (LVH) can result from prolonged exposure of the left ventricle to increased afterload caused by increased systemic BP\textsuperscript{3}. The prevalence of LVH in children and adolescents with arterial hypertension has been found to be around 20 – 41\%\textsuperscript{18}. Identification of LVH may suggest the need for more urgent and more aggressive treatment of hypertension\textsuperscript{3,5}.

4 **ANTIHYPERTENSIVE TREATMENT**

4.1 **When to initiate antihypertensive treatment**

As in adults, also in children, the decision to initiate antihypertensive treatment should not be taken on BP levels alone, but should consider the presence or absence of target organ damage, other (cardiovascular) risk factors or diseases such as obesity, renal diseases or diabetes\textsuperscript{1}. It should be stressed that if the patient is symptomatic, immediate referral and treatment are indicated\textsuperscript{19}. In children with proven secondary hypertension, specific treatment of the underlying disease must be initiated immediately after detection\textsuperscript{1}. In children with primary hypertension, antihypertensive therapy should first target the risk factors for BP elevation (i.e. overweight, increased salt intake, low physical activity)\textsuperscript{1}.
4.2  Goal of treatment

4.2.1  Blood pressure target in the general hypertensive population
Paediatric BP targets are commonly defined population based, in the absence of prospective long-term studies linking children BP levels to cardiovascular outcomes. The 95th percentile is commonly used as a cutoff for defining hypertension in children and adolescents without renal comorbidity. The recommendations of the European Society of Hypertension states that this provides a rationale for targeting children and adolescents with primary hypertension to a BP below the 95th but also mentions that is probably wiser and safer to aim at a BP below the 90th percentile\(^1\).

4.2.2  Blood pressure target in renal disease
The international guidelines advocate to target a BP <50th percentile in hypertension associated with renal disease. This statement is to some extent supported by the prospective randomized ESCAPE trial\(^17\): strict BP control aiming for a 24-h target below the 50th percentile of mean arterial pressure by the addition of other antihypertensive agents to angiotensin converting enzyme inhibitor (ACE) therapy resulted in a better 5-year renal survival, despite a return of proteinuria toward pretreatment values. Analysis by achieved BP levels showed similar renal outcomes with any 24-h BP below the 75th percentile, contrasting with significantly reduced 5-year renal survival in patients exceeding the cutoff level. Proteinuria appears to be an important modifier of the renoprotective efficacy of intensified BP control. Admittedly, only a minority of patients in the different studies reached values < 50 percentile\(^1\).

4.3  Therapeutic strategies

4.3.1  Life style changes
Non pharmacological treatment of hypertension includes weight loss, aerobic exercise, restriction of salt intake and stress reduction\(^5\). While these therapies may be effective in reducing the BP to the targeted levels, pharmacologic therapy will need to be considered if they do not\(^5\). Life style changes should not only precede but also accompany pharmacological treatment\(^1\).
4.3.2 Pharmacological therapy

4.3.2.1 Therapeutic orphans

A major issue related to the use of antihypertensive medications in young people is the availability of safety and efficacy data\(^3\). Historically, few drug trials were conducted in children, with the consequence that many drugs had to be used empirically, without the benefit of specific paediatric efficacy, safety, or dosing information\(^3\). Besides, there is lack of suspensions or other age appropriate drug formulations\(^20\). In 2007, the European authorities implemented the European Regulation after realising that children also have the right to be treated with drugs that have been studied in children\(^1\). The goal of this Regulation of Medicinal Products for Pediatric Use is to increase the availability of medicines authorised for children, as well as to improve the information on the use of medicinal products in the paediatric population\(^1\). The Paediatric Regulation requires manufacturers to study medications in children to be able to market them in Europe. Despite this initiative, reliable paediatric data obtained from controlled studies with older compounds with expired patent protection are still not available\(^1,6\). Hopefully, the Paediatric Use Marketing Authorisation will help resolve this problem, at least in part\(^1\). For the time being, the present recommendations on pharmacotherapy in hypertension are based on few industry-sponsored studies, and mostly on single-center case series, collective clinical experience, expert opinion and extrapolation from data obtained in adults\(^1\).

Like in adults, choice of antihypertensive agents can include angiotensin converting enzyme inhibitors (ACEIs), angiotensin-II receptor antagonists (ARBs), calcium antagonists, beta-blockers and diuretics (table 5.2)\(^1,5,6\). Although many individual antihypertensive compounds have been studied in the paediatric age group, no paediatric studies comparing different agents have been conducted\(^3,5,6,21\). This situation leaves the prescriber without evidence-based guidance for choice of drug\(^3,5\). The etiology of the hypertension, the anticipated benefits for the child, and the potential adverse effects should guide the choice of medication\(^5\). Certain co-morbidities that favor certain classes of drugs include the use of an ACEI or an ARB in patients with diabetes and microalbuminuria or proteinuric renal disease. Calcium channel blockers are also a good option in patients with diabetes or metabolic syndrome because they improve insulin sensitivity. Beta-blockers and calcium channel blockers should be
considered in patients with migraine. In general, black children and adolescents do not respond well to ACEIs at standard doses. Severe symptomatic hypertension should be treated with intravenous antihypertensive drugs\textsuperscript{6}.
Table 5.2: Recommended initial doses adapted from Lurbe et al\textsuperscript{1}, Kavey et al\textsuperscript{3} and Flynn et al\textsuperscript{20}. The maximum recommended dose should not be exceeded.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Starting oral dose</th>
<th>Interval</th>
<th>Maximum daily oral dose</th>
<th>Labeling for hypertension in children with dosing advise in Belgium\textsuperscript{22}</th>
<th>Availability of paediatric formulation in Belgium\textsuperscript{22}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone\textsuperscript{e}</td>
<td>0.3mg/kg/day</td>
<td>Once daily</td>
<td>2mg/kg up to 50mg</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td>0.5 – 2 mg/kg/dose</td>
<td>Once to twice daily</td>
<td>6mg/kg</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td>Not available in Belgium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>1mg/kg/day</td>
<td>Once to twice daily</td>
<td>3.3mg/kg up to 100mg</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Beta-adrenergic blockers</strong></td>
<td>Atenolol</td>
<td>0.5 – 1 mg/kg/day</td>
<td>Once to twice daily</td>
<td>2mg/kg up to 100mg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>1 – 2 mg/kg/day</td>
<td>Twice daily</td>
<td>6mg/kg up to 200mg</td>
<td>&gt; 6y</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Propanolol</td>
<td>1mg/kg/day</td>
<td>Twice to three times daily</td>
<td>16mg/kg up to 640mg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>Amlodipine</td>
<td>0.06 mg/kg/day</td>
<td>Once daily</td>
<td>0.3mg/kg up to 10mg</td>
<td>&gt; 6y</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td>2.5mg/day (no dose referenced to weight available)</td>
<td>Once daily</td>
<td>10mg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Extended-release nifedipine</td>
<td>0.25 – 0.5 mg/kg/day</td>
<td>Once to twice daily</td>
<td>3mg/kg up to 120mg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitors</strong></td>
<td>Captopril</td>
<td>0.3 – 0.5mg/kg/dose</td>
<td>Twice to three times daily</td>
<td>6mg/kg up to 450mg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
<td>0.08 mg/kg/day</td>
<td>Once daily</td>
<td>0.6mg/kg up to 40mg</td>
<td>&gt; 20kg</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Dosage Range</td>
<td>Frequency</td>
<td>Max Dose</td>
<td>Age限制</td>
<td>禁忌症</td>
<td>可能副作用</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>-----------</td>
<td>----------</td>
<td>----------</td>
<td>-------</td>
<td>-----------</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>0.1 mg/kg/day</td>
<td>Once daily</td>
<td>0.6mg/kg up to 40mg</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>0.08mg/kg/day</td>
<td>Once daily</td>
<td>0.6mg/kg up to 40mg</td>
<td>&gt; 20kg</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 – 6 mg/day</td>
<td>Once daily</td>
<td>20mg</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Angiotensin-II receptor blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>0.16 – 0.5 mg/kg/day</td>
<td>Once daily</td>
<td>32mg</td>
<td>&gt; 6y</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Irbesartan</td>
<td>75 – 150mg/day (no dose referenced to weight available)</td>
<td>Once daily</td>
<td>300mg</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>0.75 – 1.4 mg/kg/day</td>
<td>Once daily</td>
<td>1.4mg/kg up to 100mg</td>
<td>&gt; 6y and &gt; 20kg</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Valsartan</td>
<td>1.3 mg/kg/day</td>
<td>Once daily</td>
<td>2.7mg/kg up to 150mg</td>
<td>&gt; 6y</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

* Standard dose of chlortalidone has been decreased in adults because of side effects. Use in children should also be cautious with use of the lowest effective dose and monitoring of serum electrolytes.
4.3.2.2 Monotherapy versus combination therapy

It is reasonable that in children, treatment should be started with a single drug administered at a low dose in order to avoid rapid fall in BP. If BP does not decrease sufficiently after a few weeks, usually four to eight weeks, an increase to the full dose should be initiated. Once the highest recommended dose is reached, or if the child experiences side effects from the drug, a second drug from a different class should be added.

4.3.2.3 Beta-adrenergic blockers (BBs)

Beta-adrenergic antagonists reduce the effect of endogenous catecholamines on beta-adrenergic receptors. Although BBs were among the first and most widely used antihypertensive medications in children, there are limited studies evaluating BBs in children. Characteristics that distinguish one BB from another include cardioselectivity, alpha-adrenergic activity, hydrophilic and lipophilic properties and intrinsic sympathicomimetic activity. The variability of pharmacologic properties of drugs in this group and characteristics of each individual drug influence the selection of medication.

There is limited information on efficacy and safety of the newer vasodilating beta-blockers like carvedilol (non-selective β-blocker with α1-blocking property) and nebivolol (selective β₁-blocker that has vasodilatory properties through the NO mechanism) for the treatment of hypertension in children.

Possible side effects attributable to BBs include bradycardia, anorexia, asthma exacerbations, night terrors, heart block, fatigue, cold extremities, and sexual dysfunction.

It is important to note that BBs are associated with changes in carbohydrate and lipid metabolism; and can inhibit the warning signs of hypoglycaemia. For patients with labile glycemic control, β-adrenergic antagonists, including those that are cardioselective, should be avoided. BBs are not considered first line therapy in adolescents because of their interference with physical activity.

4.3.2.4 Calcium channel blockers (CCBs)

Calcium channel blocking antihypertensives are a heterogeneous group of compounds that inhibit the influx of extracellular calcium into the cellular membrane of the smooth
muscle and other contractile cells by blocking the transmembrane transport of calcium. This results in reduced contractility and arteriolar smooth muscle tone in a dose-dependent fashion. Dihydropyridines are the major class of CCBs used to treat essential hypertension in children because of their relative selectivity for arteriolar smooth muscle\(^5\). These include amlodipine, isradipine, felodipine, nicardipine and nifedipine. They have shown efficacy in treating hypertension in children. Nicardipine and isradipine have been described to cause cerebral vasodilation and must be used cautiously in children with intracranial pathology if at all\(^{25,26}\). On theoretical grounds this should be extended to all calcium channel blockers\(^{25}\). The most common adverse effects reported with the use of CCBs include peripheral edema, dizziness, flushing, nausea, headache, and postural hypotension. Other reported adverse events include gingival hyperplasia, chest pain, nausea, and vomiting, and reflex tachycardia seen with nifedipine. Side effects are seen more commonly as maximum dosages of the drugs are reached\(^5\).

The non-dihydropyridines are rarely used for the treatment of essential hypertension in children and adolescents because of their effects on cardiac conduction and contractility\(^5\).

4.3.2.5 Angiotensin-converting enzyme inhibitors (ACEIs)

ACE inhibitors act on the renin-angiotensin system by preventing the conversion of angiotensin I to angiotensin II. Angiotensin II is a vasoconstrictor that also causes aldosterone secretion\(^5,21\). In addition, ACE inhibitors cause a decrease in bradykinin metabolism, which is thought to play also a role in the antihypertensive effects of these medications\(^{21}\). ACE inhibitors are widely used in the management of both primary and secondary hypertension in paediatric patients. In general, they have few adverse effects in standard doses and have convenient dosing schedules to improve adherence\(^5\).

The side effects of ACE inhibitors in children do not differ from those seen in adults. They include hypotension, cough, hyperkalemia and elevated creatinine\(^5,21\). Monitoring of serum electrolytes and creatinine are recommended with initiation of therapy and periodically to monitor the potassium and creatinine. Other adverse reactions include angioedema, headache, anemia, tachycardia, vertigo, dyspnea, rash and leucopenia\(^5\).
ACEIs are contraindicated during pregnancy and should be used cautiously in those of child-bearing age\textsuperscript{21}. Maternal use during pregnancy is associated with profound fetal hypotension, growth restriction, pulmonary and renal hypoplasia, anuria and neonatal death\textsuperscript{5}.

4.3.2.6 Angiotensin-II receptor blockers (ARBs)

ARBs act on the renin-angiotensin system by blocking the binding of angiotensin II to the AT1-subtype of the angiotensin-II receptors in blood vessels and other tissues. Unlike ACE inhibitors, ARBs have minimal effect on bradykinin metabolism\textsuperscript{21}. Data on the effects of ARBs in hypertensive children have accumulated recently. Several studies have demonstrated the efficacy of ARBs in the treatment of hypertension in children. The ARBs irbesartan, candesartan, valsartan, and losartan have shown to lower SBP and DBP. Irbesartan, candesartan and losartan have also shown to decrease proteinuria by over 50\% as well. ARBs are generally well tolerated, with a favorable side effect profile. Side effects reported include rhinitis, urinary and gastrointestinal infections, headache, dizziness, blurred vision, fatigue, anemia and hyperkalemia. Other adverse reactions reported include rash and pruritus, hyperglyceridemia, leucopenia and thrombocytopenia. Although cough and angioedema occur in patients with ARBs, they are observed less frequently than in patients treated with ACEIs.

The same precautions should be taken in pregnancy and in women of child-bearing age as with ACEIs. Similar congenital malformations seen with ACEI exposure during pregnancy have been reported\textsuperscript{5}.

4.3.2.7 diuretics

Diuretics are used primarily as a second medication when adequate BP has not been attained with monotherapy especially in adolescents and in children with renal disease with high volume states. There is a paucity of studies examining the use of diuretics for essential hypertension in children. The two types primarily used are thiazides and loop diuretics. \textit{Thiazide diuretics} exert their effect on the distal tubule in the kidney to decrease sodium and water reabsorption and increase potassium secretion in an ion exchange mechanism by inhibiting the sodium-chloride membrane transporter. With long term use, the thiazides produce vasodilation. Their efficacy is dependent on the glomerular filtration rate. They are most efficacious when the GFR is >50ml/min and
ineffective when the GFR is <30ml/min. Thiazide diuretics produce elevations in blood glucose and insulin levels. Loop diuretics exert their effect at the ascending limb of the loop of Henle by decreasing the reabsorption of sodium and water by inhibiting the sodium-potassium-chloride membrane transporter. They also increase renal blood flow by reducing renovascular resistance. Loop diuretics are more potent than thiazides but their efficacy also decreases as GFR is reduced. They are used primarily in patients with underlying renal disease, fluid retention and renal insufficiency (30-50ml/minute)\textsuperscript{1,21}.

Common side effects of diuretics relate to their effects on fluid and electrolyte balance. Therefore serum electrolytes and creatinine should be monitored. Hypokalemia, volume contraction ± hypotension, anorexia, nausea and vomiting, pancreatitis and elevated uric acid levels have been reported as well as ototoxicity with the use of loop diuretics\textsuperscript{5}.

No clinical trials were found to support spironolactone’s role in paediatric hypertension, although it is used in the treatment of hypertension secondary to diseases characterized by mineralocorticoid excess and as concomitant therapy in children taking medications that increase aldosterone secretion such as CCBs and vasodilators\textsuperscript{21,24}.

4.3.2.8 Other antihypertensive agents

No paediatric studies have been conducted for direct vasodilators, centrally acting agents or alpha-1 receptor antagonists, despite their long history of clinical use in the pharmacological management of hypertension in children\textsuperscript{1}.

5  LONG TERM FOLLOW-UP

As in adults, antihypertensive therapy in children and adolescents must be monitored closely, both for efficacy and for potential adverse effects. BP should be measured in the office every 2 to 4 weeks until good control is achieved. Once control is achieved, then office BP measurement every 3 to 4 months is appropriate. Periodic laboratory monitoring may also be required, particularly if a diuretic or agent affecting the renin-angiotensin system is prescribed, or if the hypertensive child or adolescent has underlying renal disease as the cause of their hypertension\textsuperscript{3}. Since nocturnal and/or
circadian rhythm of BP are probably directly correlated with long term target damage, 24 hours BP measurement for monitoring is highly recommended\(^{18}\).

Adherence to treatment is an important long-term issue in the treatment of hypertension in children and adolescents, because most patients have so few symptoms. In adolescents, this situation is particularly difficult because they often do not like to take their medications and do not like to be perceived as different from their peers. If BP control can be achieved with a single drug that is taken once a day, this improves the likelihood of compliance and this should be taken into consideration when the initial agent is chosen. The adverse effect profile of the medication may also affect adherence\(^{3}\).

6 CONCLUSION

Although most of the adverse outcomes of hypertension occur in adulthood, there is now more clear recognition of the relationship between childhood and subsequent adult BP and identification of subclinical end-organ damage in children, adolescents, and adults. This should increase the focus by paediatricians and general practitioners on detection of hypertension and reinforce the efforts to achieve BP reduction via non-pharmacological and pharmacological treatments in children with hypertension.

REFERENCES


6. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation,
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SECTION 5.2:
THERAPEUTIC EFFICACY
AND SAFETY OF ACE INHIBITORS
IN THE HYPERTENSIVE PAEDIATRIC
POPULATION: A REVIEW

Snaeuwaert E, Vande Walle J, De Bruyne P

Accepted by Archives of Disease in Childhood
ABSTRACT

PURPOSE. Since 1997, strong incentives have been introduced worldwide to improve access to safe and effective medicines addressing the therapeutic needs of children. Angiotensin-1 converting enzyme (ACE) inhibitors, the most prescribed antihypertensive drugs in the paediatric population, are one of the prototype drugs targeted by the legislation initiatives. Our purpose in assembling this review is to evaluate and describe the current evidence for the efficacy and safety profile of ACE inhibitors in the paediatric population.

METHODS. The authors made a descriptive review of the literature from 1980 to 2015, using following search terms: hypertension, child, paediatric, ACE (inhibitors), renin-angiotensin aldosteron system, captopril, lisinopril, enalapril, ramipril and fosinopril.

RESULTS. A total of 16 studies evaluating efficacy and safety of ACE inhibitors were included in this review. The included studies demonstrate that ACE inhibitors have the potency to decrease the systolic and/or diastolic BP with an overall favourable safety profile in a short-term period. More important, the incentives resulted in an improvement of the overall availability of paediatric labelling, dosing and safety information for ACE inhibitors. However, they failed to fulfil several of paediatric needs: absence of long-term safety data on growth and maturation, absence of commercially available child-friendly formulations and incomplete evaluation of the entire paediatric hypertension population.

CONCLUSION. Additional efforts are needed to close the gap between the availability of drugs that are labelled and indicated for paediatric use and the actual drug usage in children, especially in young children, neonates and children with severe hypertension, renal transplantation or severe renal impairment.
Hypertension is increasingly recognized as an important disease in childhood. Hypertension is diagnosed in childhood, according to the National High Blood Pressure Group 2004, when an average systolic (SBP) and/or diastolic blood pressure (DBP) is found to be on the 95th percentile or above for age, gender and height on at least three separate occasions\(^1\). It is widely accepted that early identification and treatment of hypertensive children may possibly prevent the development of established hypertension and its complications in adulthood\(^2,3\).

Angiotensin-1 converting enzyme (ACE) inhibitors have the power to restore the balance between two endogenous systems that are predominantly affected in the pathogenesis of hypertension in childhood: the renin–angiotensin system (RAS) and the kallikrein–kinin system. Blocking of ACE induces a decrease in systemic vascular resistance, an increase in renal plasma flow and stimulates salt excretion, making ACE inhibitors potent antihypertensive therapies. Furthermore, ACE inhibitors have demonstrated in adulthood to have a renoprotective potency in adulthood by (a) firstly inducing vasodilatation of the efferent arteriole and decreasing the filtration pressure, and thus the degree of proteinuria. Secondly, they , and by (b) suppressing suppress local growth and inflammatory factors, with subsequently leading to a reduction of glomerular hypertrophy, sclerosis, tubulointerstitial inflammation and fibrosis. Since hypertension in childhood is most frequently secondary to a renal parenchymal disease, ACE inhibitors are recognized as very useful antihypertensive therapies in the paediatric population. Adverse effects that patients treated with ACE inhibitors can encounter are hypotension, cough, hyperkalaemia, acute kidney injury, foetal anomalies and angioedema. Neutropenia, rash and nephrotic-range proteinuria are adverse events especially related to the sulphydryl-group of captopril. In patients with volume depletion, bilateral renal artery stenosis or unilateral renal artery stenosis in a single kidney, an ACE inhibitor can induce an important drop in glomerular filtration rate (GFR)\(^4\).

ACE inhibitors are one of the prototype drugs targeted by strong incentives introduced worldwide to improve access to safe and effective medicines addressing the therapeutic needs of children\(^5\). In 1997, the United States (US) launched the pioneering
legislation who aimed to promote drug licensing and labelling for children: the ‘Food and Drugs Administration (FDA) Modernization Act’, followed by the ‘Best Pharmaceuticals for Children Act’ in 2002, the ‘Research Equity Act’ in 2003, and the FDA Amendments Act and the FDA Safety and Innovation Act in 2012. In 2007, the European Union’s (EU) Paediatric Regulation and the World Health Assembly of Resolution WHA60.20 followed, based on the US experience. These incentives resulted in an increased number of published clinical trials in hypertensive children. In 2014, the first comprehensive Cochrane review about pharmacological interventions in hypertensive children has been published evaluating randomised controlled trials with antihypertensive therapies, including ACE inhibitors. However, only four trials evaluating enalapril, lisinopril and fosinopril were included and the review was not believed to be robust enough to provide firm recommendations for first-line agents in children with hypertension.

As a consequence in clinical practice, the selection of the most appropriate ACE inhibitor therapy in children remains a challenge and many clinical questions continue to exist. Our purpose in assembling this review was to evaluate and describe all the current evidence for the efficacy and safety profile of ACE inhibitors in the paediatric hypertensive population and with it, to formulate the remaining questions.

2 MATERIALS AND METHODS
A literature search was performed in PubMed, including abstracts from 1980 to April 2015. Search terms included hypertension, child, paediatric, ACE (inhibitors), RAS and kallikrein-kinin system, and following drugs: captopril, lisinopril, enalapril, ramipril and fosinopril. We then continued with the `snowball method' by looking for references in recent publications and reviews. All intervention studies and observational studies on efficacy and safety of ACE inhibitors in hypertensive children (0-18 years) were included in this review. Trials not published in English, editorial pieces and opinions were excluded. The studies were analysed and following information was collected: design, number of patients, age, ACE inhibitor, dose, formulation, intervention, primary and secondary end-points, antihypertensive and adverse events. To assess the risk of bias of the included studies, we used the Newcastle-Ottawa Scale (NOS) for cohort studies, evaluating the selection of the study groups; the comparability of the groups; and the
ascertainment of the outcome of interest. The Cochrane Collaboration’s tool for assessing risk of bias was used to evaluate for randomized studies, scoring sequence generation, allocation concealment, blinding, incomplete or selective outcome reporting and others.

3 RESULTS

A total of 16 studies evaluating efficacy and safety of ACE inhibitors in the paediatric hypertensive population were included in this review (see table 5.3). To explore the differences between ACE inhibitors, the studies were grouped according to the evaluated ACE inhibitor: captopril (7), lisinopril (3), enalapril (2), fosinopril (1) and ramipril (3). Most of the studies were cohort studies with retrospective or prospective data collection. So far 4 double-blind RCT’s (randomized clinical trials) have been published. Three of them (lisinopril, enalapril and fosinopril) were developed according to a type C design, including initial randomization, followed by 2 or more active treatment arms (e.g., low, medium, and high dosage), a second randomization to double-blind withdrawal to placebo, and an open-label ‘safety’ phase. The ESCAPE trial, evaluating the time to 50% decrease in GFR or progress to end-stage renal disease (ESRD) in intensified versus conventional BP control with ramipril treatment, used a prospective open-label RCT design. The quality of the included RCT was very variable. Using the Cochrane Collaboration’s tool, the risk of bias was low for sequence generation, blinding and incomplete outcome data in only 2/5 trials. Information about allocation concealment was only available for 1 study. Assessment of selective outcome reporting was considered low in all included RCT. Three of the included studies were supported by the industry. Except for the prospective cohort studies of ramipril, the risk of bias (NOS ≥6) in the cohort studies were considered to be high.

Different definitions of hypertension were used in the studies. Two of the studies defined hypertension as a diastolic blood pressure (DBP) of ≥95th percentile for age, gender and height on repeated measurements, according to the ‘Fourth Report’. In contrast, a systolic blood pressure (SBP) of ≥95th percentile was used in 2 studies, and a SBP or DBP of ≥95th percentile was used in 3 studies. Soergel et al., Seeman et al. and Wühl et al. defined hypertension as 24-hour mean systolic or diastolic
arterial pressure \( \geq 95\text{th percentile} \) for age, gender and height.\(^{21,22,24,25}\) The proportion of children with primary or secondary hypertension varied highly between studies. Additionally, the fosinopril trial included children with high-normal SBP or DBP, which were not included in other trials\(^ {19,20}\). In contrast, captopril and ramipril were exclusively evaluated in children with hypertension secondary to renal disease\(^ {9-13,21,22,24}\). The glomerular filtration rate (GFR) ranged from 11 to \( >90\text{mL/min/1.73m}^2 \) and two studies included also children on dialysis\(^ {11,26}\). Children with a GFR of \( <30\text{mL/min/1.73m}^2 \) were excluded in 5 studies\(^ {15,17-20,26}\). Except for the study of Mirkin et al. and Callis et al., children with severe hypertension were always excluded from the studies\(^ {12,26}\).

The age range of the patients included varied from premature infant to adolescents. Most of the studies were performed in children \( \geq 3\text{ years} \). No RCT has been performed in children \( <6\text{ years} \). Captopril was the only ACE inhibitor evaluated in neonates and premature infants (\( >25\text{ weeks of gestational age} \)). All included studies applied a weight-based dose strategy for dose determination and a dose-ranging study design was used in 4 trials\(^ {15,17-20}\). Only few reports documented the formulation of the ACE inhibitor used in the study: suspension forms were evaluated for enalapril and tablets were used in 9 studies\(^ {9,12,15-20,22-24}\). The follow-up period of the participants varied widely from 3 days to 6.1 years.

Beside the ESCAPE trial, all studies used blood pressure (BP) as their primary outcome variable. In contrast, the ESCAPE trial used the time to 50% decrease in GFR or progress to end-stage renal disease in intensified versus conventional BP control with ramipril\(^ {24}\). The majority of the studies used SBP with or without the combination of DBP, as their primary outcome variable\(^ {9-14,16-22}\). Only the lisinopril RCT used DBP as their primary outcome variable\(^ {15}\). Most of the studies determined BP auscultatory, 24 hours ambulatory blood pressure measurement (ABPM) was used in 4 studies\(^ {18,21,22,24,25}\).

### 3.1 Therapeutic efficacy

#### 3.1.1 Captopril

Captopril, the first ACE inhibitor studied in the paediatric population, has been evaluated in 7 small studies including children with hypertension due to renal disease\(^ {9-14,26}\). Mirkin et al. published the largest prospective study of 73 children treated with captopril, and a significant reduction in BP was found, with a normalisation of the DBP
Chapter 5

and SBP after 6 months in respectively 45% and 53%\textsuperscript{12}. Similar BP reduction was found in four other studies\textsuperscript{10-13,26}. Captopril was shown to be an effective antihypertensive agent in neonates (n=20) of more than 25 weeks of gestational age with a greater potency than in older children\textsuperscript{9,14}.

3.1.2 Lisinopril
Efficacy of lisinopril has been evaluated in one RCT of 115 hypertensive children that found a clear dose-related response of -0.28 mmHg per unit increase in dose ratio in sitting DBP in the middle and high dose group\textsuperscript{15}. Lisinopril administration in hypertensive children has also been evaluated in a retrospective study and was found to result in a decrease in both SBP and DBP\textsuperscript{16}. The efficacy of lisinopril has also been evaluated children with a renal transplant in a 30 day pharmacokinetic study and was also found to decrease both SBP and DBP with ≥ 6 mmHg in respectively 85% and 77%\textsuperscript{23}.

3.1.3 Enalapril
The efficacy of enalapril has been studied in two large double-blind RCT’s, evaluating respectively 110 and 281 hypertensive children\textsuperscript{17,18}. Wells et al. found a linear dose-response ratio, more specifically a decrease of 0.3 mmHg in DBP per unit increase in dose ratio, and a significant mean difference in DBP of 6.1 ± 2 mmHg between the three groups of enalapril compared to placebo\textsuperscript{17}. Schaefer et al. compared valsartan with enalapril in an active-controlled RCT, and found that both drugs were equally effective in reducing BP compared to baseline. In the subgroup of children which had a 24 hours ABPM, valsartan was found to provide a significant greater mean arterial SBP reduction than enalapril\textsuperscript{18}.
Table 5.3: An overview of all included studies evaluating captopril, lisinopril, enalapril, fosinopril and ramipril.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Patients</th>
<th>Dose, formulation</th>
<th>Study design</th>
<th>Outcome</th>
<th>Effect</th>
<th>Quality of study (NOS; Cochrane Collaboration’s tool)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinaiko et al.\textsuperscript{11}</td>
<td>Captopril</td>
<td>n = 10</td>
<td>Dose: 0.5-2.0 mg/kg, max. 6 mg/kg/d</td>
<td>Duration: 12m Design: prospective cohort, no control population. Initially dose titration protocol, followed by dose determination according to magnitude and duration effect in dose titration</td>
<td>Primary: ND Secondary: ND</td>
<td>Reduction in mean SBP and DBP ≥10 mmHg in all patients after 1, 2 or 3 doses respectively 10-77 mmHg, 2-67 mmHg or 0-67 mmHg No correlation dose and magnitude of BP reduction (p=0.37)</td>
<td>Selection 0/6 Comparability 0/2 Outcome 0/5</td>
</tr>
<tr>
<td>Mirkin et al.\textsuperscript{12}</td>
<td>Captopril</td>
<td>n = 73</td>
<td>Dose: 0.3 mg/kg to max. 2 mg/kg 8q Dose reduction in renal impairment Formulation: tablet or crushed tablet dissolved in water (&lt;30</td>
<td>Duration: 3 m (n=30), 3-6 m (n=10), 6-12 m (n=19), &gt;12 m (n=14) Design: prospective cohort, no control population</td>
<td>Primary: ND Secondary: ND</td>
<td>Reduction in SBP &amp; DBP (p&lt;0.001) Normalisation SBP &amp; DBP after 6 m in 53% and 45% of patients respectively</td>
<td>Selection 0/6 Comparability 0/2 Outcome 0/5</td>
</tr>
<tr>
<td>Study</td>
<td>Drug</td>
<td>n</td>
<td>Age</td>
<td>Definition</td>
<td>Population</td>
<td>Dose</td>
<td>Duration</td>
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<tr>
<td>Sinaiko et al.10</td>
<td>Captopril</td>
<td>34</td>
<td>premature infants to adolescents</td>
<td>ND</td>
<td>3 groups of children with secondary HT: renal disease, neonates, postTx</td>
<td>0.01-2 mg/kg/d, in neonates 0.01-0.5 mg/kg/d</td>
<td>ND</td>
</tr>
<tr>
<td>Callis et al.26</td>
<td>Captopril</td>
<td>42</td>
<td>1-17y (mean 11.2y)</td>
<td>ND</td>
<td>ND</td>
<td>0.3-3mg/kg/d</td>
<td>1.5-6.1 years (mean 3.2 years)</td>
</tr>
<tr>
<td>Bouissou et al.(^{13})</td>
<td>Captopril</td>
<td>n = 25</td>
<td>Population: ESRD treated with haemodialysis</td>
<td>Population: severe HT due to renal disease (10 on dialysis, 10 renal Tx)</td>
<td>Mean decrease of DBP from 106 to 86 mmHg</td>
<td>After mean follow-up of 38 months all obtained normal blood pressure</td>
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<td></td>
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<td>Age: 1.5-18 y</td>
<td>cohort, no control group</td>
<td>Dose: initial 1.3mg/kg/d, sustained 2.2 mg/kg/d</td>
<td>Duration: 2-40 m, mean 15 m</td>
<td>Primary: SBP, DBP, Secondary: cardiomegaly, tolerance</td>
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<td></td>
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<td>Definition: &gt;97.5 percentile of BP; &gt;10 mmHg &gt;97.5 percentile; &gt;30 mmHg &gt;97.5 percentile of BP</td>
<td>Design: retrospective cohort, no control group</td>
<td>Formulation: ND</td>
<td>Clinical: compared to initial BP, a SBP and DBP lowering of 26% at day 2 to 65% at 6 m was registered</td>
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<td></td>
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<td>Population: severe HT due to renal disease (10 on dialysis, 10 renal Tx)</td>
<td>Compared to initial BP, a SBP and DBP lowering of 26% at day 2 to 65% at 6 m was registered</td>
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<tr>
<td></td>
<td></td>
<td>Selection 0/6</td>
<td>Comparability 0/2</td>
<td>Isolated use of captopril was ineffective in 13% of cases</td>
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<td></td>
<td></td>
<td>Outcome 0/5</td>
<td></td>
<td>No relation between blood pressure response and aetiology, degree HT or plasma renin concentration</td>
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<td></td>
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<td></td>
<td></td>
<td>Normalisation of cardiomegaly in 3/5 patients</td>
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<tr>
<td>Study</td>
<td>Intervention</td>
<td>n</td>
<td>Gestational Age</td>
<td>Age at Diagnosis</td>
<td>HT Duration</td>
<td>Dose</td>
<td>Formulation</td>
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<tr>
<td>O'Dea et al.</td>
<td>Captopril</td>
<td>11</td>
<td>27-43w</td>
<td>2-84 days</td>
<td>23±7.5 days</td>
<td>Initial 0.13 (0.05) mg/kg/d, sustained to 0.85 (0.13) mg/kg/d, at day 21. 0.48 (0.19) mg/kg/d</td>
<td>Tablets in water</td>
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<tr>
<td>Tack et al.</td>
<td>Captopril</td>
<td>9</td>
<td>25-41w</td>
<td>10-72 days</td>
<td>49±28 days</td>
<td>Captopril started at 123±108 days (range 10 to 269 days) postnatal age</td>
<td>0.3mg/kg, maintenance dose 0.2±0.02mg/kg</td>
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<tr>
<td>Study</td>
<td>Drug</td>
<td>Participants</td>
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<tr>
<td>Soffer et al.15</td>
<td>Lisinopril</td>
<td>n = 115</td>
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<td>Age: 6-16 y</td>
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<td></td>
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<td>Definition: &gt; 95th percentile DBP</td>
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<td></td>
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<td>Population: mainly secondary HT, GFR&gt; 30mL/min/1.73m²</td>
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<td>3 different doses (&lt;50/&gt;50kg):</td>
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<td>- Low: 0.02 mg/kg (0.625/1.25mg)</td>
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<td>- Middle: 0.07 mg/kg (2.5/5mg)</td>
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<td>- High: 0.61 mg/kg (20/40 mg)</td>
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<td>Formulation: tablets</td>
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<td></td>
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<td>Duration: dose ranging (2 w) + randomized washout (2 w)</td>
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<td>Design: prospective, double-blind randomized, placebo-controlled, industry driven</td>
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<td></td>
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<td>Primary: DBP</td>
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<td></td>
<td></td>
<td>Secondary: SBP</td>
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<td>Increasing doses resulted in greater reductions in sitting DBP (low, -7.6 mmHg; medium, -9.3 mmHg; high, -16.4 mm Hg)</td>
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<td>↓ 0.28 mmHg in sitting DBP/unit ↑ in dose ratio (p&lt;0.01), similar findings for sitting SBP</td>
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<td></td>
<td>Mean difference in DBP between lisinopril and placebo 6.19 ± 1.86 mmHg; low dose = placebo</td>
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</table>

<table>
<thead>
<tr>
<th>Raes et al.16</th>
<th>Lisinopril</th>
<th>n = 59</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Age: 0.2-17.6 y</td>
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<tr>
<td></td>
<td></td>
<td>Definition: &gt; 95th percentile DBP or SBP</td>
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<tr>
<td></td>
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<td>Population: Primary HT (1), renal disease (58)</td>
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<tr>
<td></td>
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<td>Dose: mean 0.105 mg/kg , range 0.1-0.5 mg/kg</td>
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<td>Formulation: tablets, capsules with crushed tablets in young children</td>
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<td></td>
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<td>Duration: 2±1.8 y</td>
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<td></td>
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<td>Design: retrospective</td>
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<td></td>
<td></td>
<td>Primary: BP</td>
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<td></td>
<td>Secondary: height</td>
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<td></td>
<td></td>
<td>↓ SBP of 19 mmHg</td>
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<td></td>
<td></td>
<td>↓ DBP of 18 mmHg</td>
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<tr>
<td></td>
<td></td>
<td>Growth unaffected</td>
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<td></td>
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<td>Other antihypertensive necessary in 12 of 59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1/6</td>
<td>0/2</td>
<td>1/5</td>
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<table>
<thead>
<tr>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
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<tbody>
<tr>
<td>unclear</td>
<td>unclear</td>
<td>unclear</td>
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<tr>
<td>Incomplete outcome</td>
<td>Selective outcome</td>
<td>low</td>
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<tr>
<td>uncertain</td>
<td></td>
<td>Others high</td>
</tr>
<tr>
<td>Study</td>
<td>Drug</td>
<td>n</td>
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<tr>
<td>------------------</td>
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</tr>
<tr>
<td>Trachtman et al.</td>
<td>Lisinopril</td>
<td>13</td>
</tr>
<tr>
<td>Wells et al.</td>
<td>Enalapril</td>
<td>110</td>
</tr>
<tr>
<td>Schaefer et al.</td>
<td>Enalapril or Valsartan</td>
<td>n = 281</td>
</tr>
<tr>
<td>Li et al.\textsuperscript{19} + extrapolation by Menon et al.\textsuperscript{20}</td>
<td>Fosinopril</td>
<td>n = 253</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Age: 6-16 y</td>
<td></td>
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<tr>
<td>Definition HT: &gt; 95th percentile DBP or SBP; high normal BP: 90-95 percentile of DBP or SBP</td>
<td></td>
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<tr>
<td>Population: HT, high normal BP + associated condition (diabetes mellitus, renal disease in 20.9%)</td>
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<tr>
<td>Three different doses fosinopril:</td>
<td></td>
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<tr>
<td>- Low: 0.1 mg/kg, &gt; 60kg 10 mg</td>
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<tr>
<td>- Middle: 0.3 mg/kg, &gt; 60kg 20 mg</td>
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<tr>
<td>- High: 0.6 mg/kg, &gt; 60kg 40 mg, (max 40 mg)</td>
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<tr>
<td>Formulation: tablet</td>
<td></td>
<td></td>
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<tr>
<td>Duration: dose ranging (2 w), randomized washout (2 w), open label safety study (52 w)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design: prospective, double-blind randomized, placebo-controlled</td>
<td></td>
<td></td>
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<tr>
<td>Industry-driven</td>
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<tr>
<td>Primary: SBP</td>
<td></td>
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</tr>
<tr>
<td>Secondary: DBP, % &lt;90\textsuperscript{th} percentile DBP and SBP, safety, racial difference</td>
<td></td>
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<tr>
<td>3 doses equally effective in lowering SBP (low -10.9 mmHg, medium -11.3 mmHg, high -11.9 mmHg), no dose-response (p=0.53)</td>
<td></td>
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<tr>
<td>Withdrawal effect to placebo of 3.7 mmHg</td>
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<tr>
<td>40-60% reached BP control</td>
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<tr>
<td>13/-8.3 mmHg decrease in BP at week 52</td>
<td></td>
<td></td>
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<tr>
<td>No dose-response in non-black patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blacks: significant dose-response (p=0.03)</td>
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<tr>
<td>Sequence generation</td>
<td></td>
<td></td>
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<tr>
<td>low</td>
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<tr>
<td>Incomplete outcome</td>
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<tr>
<td>low</td>
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<tr>
<td>Allocation concealment</td>
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<tr>
<td>low</td>
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<tr>
<td>Selective outcome</td>
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<td>low</td>
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<tr>
<td>Others</td>
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<tr>
<td>high</td>
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<tr>
<td>Study</td>
<td>Drug</td>
<td>n</td>
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<td>------------------</td>
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<tr>
<td>Soergel et al.</td>
<td>Ramipril</td>
<td>14</td>
</tr>
<tr>
<td>Seeman et al.</td>
<td>Ramipril</td>
<td>31</td>
</tr>
<tr>
<td><strong>Definition</strong>: mean SBP and/or DBP ABPM ≥ 95th percentile</td>
<td><strong>Control population</strong></td>
<td><strong>Nighttime DBP and 8 mmHg nighttime SBP</strong></td>
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<tr>
<td><strong>Population</strong>: chronic kidney disease with HT or proteinuria, GFR&gt;30mL/min/1.73m²</td>
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</tbody>
</table>

**Wühl et al.**

+ continuation by Wühl et al. ²⁴

*(ESCAPE trial)*

<table>
<thead>
<tr>
<th><strong>Ramipril</strong></th>
<th><strong>Dose</strong>: ramipril 6 mg/m²</th>
<th><strong>Duration</strong>: 6m (interim), extension to 5y (final)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong>: tablets</td>
<td><strong>Design</strong>: prospective cohort study, multicentric study in interim study, randomized, open-label study for final analysis.</td>
<td><strong>Final study</strong>: primary: time to a decline of 50% in GFR or progression to ESRD. Secondary: BP, GFR, and urinary protein excretion.</td>
</tr>
<tr>
<td><strong>Population</strong>: secondary HT due to CKD (GFR ranges from 11-80mL/min/1.73m²)</td>
<td><strong>Interim 6m</strong>: BP, urinary protein</td>
<td><strong>Effect equally for day/night &amp; systolic/diastolic</strong></td>
</tr>
<tr>
<td><strong>Exclusion</strong>: renal artery stenosis, renalTx, unstable condition</td>
<td><strong>Interim (6m)</strong></td>
<td><strong>Linear correlation initial MAP &amp; change in MAP during therapy</strong> <em>(r=0.51, p&lt;0.0001)</em></td>
</tr>
<tr>
<td></td>
<td><strong>Selection 2/6</strong></td>
<td><strong>Incomplete outcome low</strong></td>
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<td></td>
<td><strong>Final (5y)</strong></td>
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</table>
To assess the risk of bias of the included studies, the Newcastle-Ottawa Scale (NOS) was used for cohort studies, evaluating selection of the study groups; the comparability of groups; and ascertainment of the outcome of interest. The Cochrane Collaboration’s tool for assessing risk of bias was used to evaluate for randomized studies, scoring sequence generation, allocation concealment, blinding, incomplete or selective outcome reporting and others.
3.1.4 Fosinopril
Fosinopril has been studied in one placebo controlled RCT with 253 children with hypertension or a high normal BP. The three evaluated doses of fosinopril were found to be equally effective in lowering SBP\textsuperscript{19,20}. However, a significant dose response was found in black children, which was absent in non-black children, indicating that black children may need higher doses per body weight\textsuperscript{20}. In this study population, 40-60\% of the children reached BP control and a decrease of -13/-8.3 mmHg in BP was reached at 52 weeks follow-up.

3.1.5 Ramipril
Soergel et al. and Seeman et al. prospectively followed respectively 14 and 31 children taking ramipril and found a significant decrease in both SBP and DBP and nocturnal dipping\textsuperscript{21,25}. In the interim analysis of the ESCAPE trial, evaluating 352 children with chronic kidney disease after 6 months treatment with ramipril, a significant decrease in mean SBP of 11.6 mmHg and a greater decrease in SBP was shown in children with a GFR of <40mL/min/1.73m\textsuperscript{22}. In the final analysis of the ESCAPE trial, 385 children were randomized to intensified (<p50) or conventional (p50-p90) BP control to compare the time until they lose ≥50\% in GFR or they progress to ESRD. This primary endpoint was reached in respectively 41.7\% versus 29.9\% of the children. Intensified BP control was found to have a 35\% lower risk to lose ≥50\% in GFR or progress to ESRD\textsuperscript{24}.

3.2 Safety profile of ACE inhibitors
The short-term safety profile of lisinopril, enalapril and fosinopril in children 6-16 years was evaluated in detail, however long-term safety data are lacking. Ramipril and captopril are the only ACE inhibitors in which the safety profile has been evaluated over a period of ≥5 years. All the adverse events (AE), included in the studies evaluating ACE inhibitors, are summarized in table 5.4. Since the study design (retrospective versus prospective), the duration of follow-up and the characteristics of the study populations (age, co-morbidities, renal function) were very different, comparison between the different ACE inhibitors is difficult.
Table 5.4: Summary of all adverse events reported in the included studies.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Drug</th>
<th>Hyperkalaemia</th>
<th>Increased creatinine and/or BUN</th>
<th>Cough</th>
<th>Dizziness, vertigo, headache, postural symptoms, hypotension</th>
<th>Gastro-intestinal</th>
<th>Others</th>
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</thead>
<tbody>
<tr>
<td>Sinaiko et al.</td>
<td>10</td>
<td>Captopril</td>
<td>/</td>
<td>/</td>
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<td>/</td>
<td>/</td>
<td>Neutropenia (2)</td>
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<td></td>
<td>73</td>
<td>Captopril</td>
<td>Potassium significantly elevated, but &lt;5mmol/L</td>
<td>- BUN significantly increased from 22.9-29.8 mg/dL to 31.5-39.1 mg/dL (p&lt;0.001)</td>
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<td></td>
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<td></td>
<td></td>
<td>- Creatinine increased from 1.11 mg/dL to 1.3 mg/dL (p&lt;0.05)</td>
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<td></td>
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<td></td>
<td>- 19/50 had increase of creatinine &gt;50%, 5/19 did had bilateral renal artery stenosis (of unilateral in single kidney)</td>
<td></td>
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</tr>
<tr>
<td>Mirkin et al.</td>
<td>34</td>
<td>Captopril</td>
<td>/</td>
<td>- In 62% of study population increase in creatinine</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- mean increase in serum creatinine from 1.1 (0.1) to 1.7 (0.2) mg/dL in renal</td>
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<td></td>
<td>/</td>
<td>/</td>
<td>Hypotension (1) in patient with renal artery stenosis and heart failure</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>Study (Author)</td>
<td>Patients</td>
<td>Treatment</td>
<td>Mean Increase in K+</td>
<td>Hypertension</td>
<td>Renal Function</td>
<td>Other</td>
<td>Adverse Effects</td>
<td></td>
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</tr>
<tr>
<td>Callis et al.</td>
<td>42</td>
<td>Captopril</td>
<td>Mean 5.3±0.7 mmol/L</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>Pruritus and rash (1), ageusia (12), leukopenia (2)</td>
<td></td>
</tr>
<tr>
<td>Bouissou et al.</td>
<td>25</td>
<td>Captopril</td>
<td>Mean increase of 1.6 mmol/L, non-severe hyperkalaemia</td>
<td>/</td>
<td>/</td>
<td>Transient vomiting (1)</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>O’Dea et al.</td>
<td>11</td>
<td>Captopril</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>Hypotension with oliguria (1) in ? (dose 0.5 mg/kg/d)</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>Tack et al.</td>
<td>9</td>
<td>Captopril</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>Hypotension with &gt;40% reduction in BP from baseline (9), oliguria (4)</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>Soffer et al.</td>
<td>115</td>
<td>Lisinopril</td>
<td>Hyperkalemia (1)</td>
<td>Increased creatinine and blood urea nitrogen (2)</td>
<td>Cough (1), not related lisinopril</td>
<td>Headache (4), dizziness (2)</td>
<td>Abdominal pain, diarrhoea, nausea and vomiting (2)</td>
<td></td>
</tr>
<tr>
<td>Raes et al.</td>
<td>59</td>
<td>Lisinopril</td>
<td>/</td>
<td>/</td>
<td>Cough (1)</td>
<td>Hypotension (7), headache (1), vertigo (2)</td>
<td>Death (5) (non-lisinopril related), anaemia (1), headache, tachycardia, dizziness, hypovolaemia and dyspnoea (1), tachycardia (1)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>ACE Inhibitor</td>
<td>Adverse Effects</td>
<td>Observations</td>
<td></td>
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<td>-------------------------------------------------------------------------------</td>
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<tr>
<td>Trachtman et al. 23</td>
<td>13</td>
<td>Lisinopril</td>
<td>- GFR decrease &gt;20% (1)</td>
<td>Dizziness (2), Nausea (2), stomach ache, Gastroenteritis with hospitalization (1),</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Wells et al. 17</td>
<td>110</td>
<td>Enalapril</td>
<td>No difference in pre- and post potassium</td>
<td>- Slight increase BUN and/or creatinine (5), Dizziness (4), headaches (2), Chest pain, increased blood pressure, hypotension, diarrhoea, cough, dyspnoea, pruritus, rash, and blurred vision (1),</td>
<td></td>
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<tr>
<td>Schaefer et al. 18</td>
<td>281</td>
<td>Enalapril, Valsartan</td>
<td>Potassium &gt; 5.5mmol/l (4), Potassium &gt; 6 mmol/l (4)</td>
<td>/</td>
<td></td>
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<tr>
<td>Li et al. 19 + extrapolation by Menon et al. 20</td>
<td>253</td>
<td>Fosinopril</td>
<td>Hyperkalaemia (1)</td>
<td>/</td>
<td></td>
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<tr>
<td>Soergel et al. 21</td>
<td>14</td>
<td>Ramipril</td>
<td>/</td>
<td>/</td>
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</tr>
<tr>
<td>Seeman et al. 25</td>
<td>31</td>
<td>Ramipril</td>
<td>Did not change significantly, hyperkalaemia (2)</td>
<td>/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESCAPE trial 24</td>
<td>352, extension 385</td>
<td>Ramipril</td>
<td>Hyperkalaemia (18), severe hyperkalaemia (7)</td>
<td>Decreased GFR (50), Cough (4), Hypotension (2), dizziness (1), headache (1), Gastrointestinal symptoms (1), diarrhoea (2), Stomatitis (1), tonsillitis (2), urinary tract infection (1), nocturnal enuresis (1), fatigue (1), hair loss (2), leukopenia (3), death (1), respiratory tract infection (5), pericarditis (1), anaemia (1),</td>
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</table>

BUN = blood urea nitrogen, GFR = glomerular filtration rate, n = total number of patients. Caution has to be taken when comparing the different ACE inhibitors (see table S.3), since the study design and other study characteristics were very different.
Dizziness, vertigo, postural symptoms and headache were frequently reported as adverse events, especially in the enalapril and fosinopril trials. The incidence of hypotension in the captopril studies was remarkably high in contrast to the other ACE inhibitors. The incidence of increased creatinine and/or BUN varied among the different trials from absent to 62% in the study of Sinaiko et al. The ESCAPE trial, including only children with chronic kidney disease (GFR 11-80mL/min/1.73m²), reported an increase in creatinine in 50 of the 385 participants of the study population. The incidence of cough in the studies was widely different between the studies but was remarkably lower than in the adult studies, which report cough in almost 20% of the participants. Angioedema has not been reported in these studies.

Only a few serious AE were reported in the included studies: acute kidney injury in one child with an underlying renal artery stenosis receiving captopril and one child receiving enalapril, severe hypotension with oliguria in one neonate receiving captopril, haemorrhagic infarction in one neonate receiving captopril and avulsion fracture in one child receiving enalapril. No related deaths were reported after receiving ACE inhibitors.

4 DISCUSSION

Thanks to the initiatives of the USA, Europe and the WHO, an overall increase in clinical trials evaluating the efficacy and safety of ACE inhibitors occurred. Overall, ACE inhibitors have demonstrated to have the potency to decrease the systolic and/or diastolic BP with an overall favourable safety profile in a short-term period. More importantly, paediatric labelling by the FDA Reports was obtained for 3 of the 5 discussed ACE inhibitors in the paediatric hypertensive population: lisinopril (for children ≥6 years), enalapril (for children ≥1 month) and fosinopril (for children ≥6 years).

However, is it really true that the promising legislative initiatives and the improved paediatric labelling narrowed the gap between the availability of ACE inhibitors labelled and indicated for paediatric use and the actual drug usage in children? Welch et al. reported that still 25.5 to 33.1% of the children are receiving unlabelled or not indicated antihypertensive medications. Furthermore, they report that still 7% of all the prescribed antihypertensive drugs were prescribed “off-label” in children, with neither
Antihypertensives in children and adolescents

FDA-approved paediatric label information nor dosing recommendations in the Fourth Report. The risks of “off-label” use are generally accepted and recently highlighted by Wharton et al. which demonstrated that a quarter of the drugs that received new paediatric labelling obtained a new paediatric safety signal. Furthermore, the recently published Cochrane review evaluating the efficacy and safety of antihypertensive therapies, including ACE inhibitors, could only include 4 studies evaluating lisinopril (1), enalapril (2) and fosinopril (1) in the analysis. Since trials comparing an ACE inhibitor directly to placebo are lacking, ACE inhibitors were not included in the meta-analysis. Consequently, the Cochrane review failed to provide firm recommendations for ACE inhibitors in the paediatric hypertensive population. Therefore, we assumed to summarize all the current evidence available on ACE inhibitors in the paediatric population in this review, including also non-randomized studies. Although we recognize that the majority of these non-randomized studies were of low quality with high risk of bias, they are currently the only studies reporting about the use of ACE inhibitors in high-risk populations (neonates, young children, children with renal transplant, chronic kidney disease, ESRD, …) in contrast to the highly selected mild hypertensive population in RCT.

Although the efficacy and safety profile and labelling status of ACE inhibitors improved over time, they still do not meet with the true clinical relevance and several obstacles have to be conquered. Firstly, we have to realise that the efficacy of ACE inhibitors is only evaluated based on BP, a surrogate outcome variable, and the proof of efficacy of ACE inhibitors on hard outcome variables such as end-organ damage, cardiovascular morbidity or mortality in adulthood is completely lacking. Also the use of 24 hours ABPM in clinical trials were poor. Furthermore, the studies evaluated ACE inhibitors only in a short period and the long-term effect and safety of ACE inhibitors on growth, pubertal development and maturation is still unknown.

A second important limitation of these studies is the incomplete inclusion of the population of children with hypertension. Beside the studies of ramipril, captopril and Trachtman et al. most of the studies concentrated on mild hypertensive patients and children with comorbidities such as severe renal impairment, renal transplantation or severe hypertension were excluded. However, children with comorbidities are known to present with more severe and therapy resistant hypertension, which require higher
doses of ACE inhibitors or combination therapy to control the BP. Furthermore, the risk of adverse events (e.g. hyperkalaemia) is extremely higher in children with renal impairment, renal transplantation or in children taking concomitant transplant medication (e.g. tacrolimus, cyclosporine).

In addition to the previous remarks, the poor availability of labelled ACE inhibitors, indicated for the younger children (<6 years) and neonates has to be highlighted. Among the discussed ACE inhibitors, enalapril is the only ACE inhibitor with paediatric labelling for children younger than 6 years\textsuperscript{28}. To date, no ACE inhibitor has been evaluated by a proper conducted RCT in children younger than 6 years or neonates. For this age group, only studies with small study samples and/or poor design (retrospective, no control group) are available for captopril, lisinopril and ramipril (>3 years). The fact that there are no efficacy and/or safety studies for young children and neonates is unfortunate, as most of them will have secondary forms of hypertension that may require multiple medications to achieve adequate BP control. In contrast to the other studies, the prevalence of hypotension as AE was remarkably high in the captopril studies evaluating neonates and preterm born infants. This is not surprising, since neonates have a lower GFR (and thus a longer serum half-life) and the neonatal kidney is dependent on the angiotensin II post-glomerular efferent arteriole vasoconstriction to maintain blood pressure\textsuperscript{9,14,31}. Additionally, the deleterious effects of ACE inhibitors during the second and/or third trimester of pregnancy are well described: renal tubular dysgenesis, foetal anuria leading to oligohydramnios, and the Potter sequence of facial dysmorphism, limb-positioning defect, and lung hypoplasia associated with skull ossification defect\textsuperscript{32}. The question if ACE inhibition should be avoided in the immature kidney remains unanswered.

At last, the incentives did not result in an improved availability of age-appropriate formulations. Until nowadays, no suspension for ACE inhibitors is commercially available, limiting consequently a safe and child-friendly administration of these medications in the paediatric population.

Therefore, a greater effort to improve paediatric labelling is necessary, with special attention for children <6 years, neonates and children with severe renal impairment, severe hypertension or renal transplant.
5 CONCLUSION

The recent legislative initiatives increased the availability of paediatric labelling of ACE inhibitors. Nevertheless, many drugs used by hypertensive children have an insufficiently mapped out efficacy and safety profile and lack paediatric labelling. Moreover, many clinical questions remain and consequently complicate the selection of the most appropriate and effective ACE inhibitor in hypertensive children. The legislative initiatives also failed to fulfil several of paediatric needs: absence of long-term safety data on growth and maturation, absence of commercially available child-friendly formulations and incomplete evaluation of the entire paediatric hypertension population. Additional efforts are needed to close the gap between the availability of drugs that are labelled and indicated for paediatric use and the actual drug usage in children, especially in young children, neonates and children with severe hypertension, renal transplantation or severe renal impairment.

REFERENCES


ABSTRACT

BACKGROUND AND AIMS. During the last decades, much attention has been paid to off-label and unlicensed prescriptions in paediatrics. However, on-label prescribing can also cause health issues. In this paper, the case of first generation H₁-antihistamines is investigated, notably the range of indications for which products are licensed in different European countries and the evidence base (or lack thereof) for each indication, as well as reported adverse drug reactions.

METHODS. Review of the Summary of Product Characteristics of first generation H₁-antihistamines with a focus on paediatric use. This is plotted against the evidence available in literature.

RESULTS. This investigation shows a large variability in labelled indications and licensing ages, when compared in five different European countries. Moreover, most of the indications are not based on clinical trials evaluating efficacy and safety of these drugs in children.

CONCLUSION. When considering the vaguely labelled indications in combination with the known safety issues of first generation H₁-antihistamines such as sedation, caution is warranted. With the first generation H₁-antihistamines as example, this article points to possible problems in children with on-label use of (older) drugs.
1 INTRODUCTION

Over the past two decades, there has been an increase in attention surrounding drug use in children. Most of the attention is directed towards unlicensed and off-label drug use in this population. Justifiably, as percentages of unlicensed and off-label drug prescriptions reach 66% in the hospital and 39% in the ambulatory setting\(^1\). The paediatric population is a heterogeneous group, ranging from preterm neonates to postpubertal adolescents. They have complex physiological, developmental, and psychological characteristics that differ from adults and these features vary across the neonate to adolescent age range. The simple extrapolation of efficacy and safety from adults to children is insufficient for correct pharmacotherapy in children as it can result in suboptimal therapy, unexpected responses and ADRs\(^2\). The development of effective and safe child-specific treatments therefore requires high quality trials in children\(^2\)-\(^4\).

On-label use of drugs in children might also confront health care professionals and consumers with potential risks. Although it is generally assumed that drugs are considered for labelling only if they have been proven efficacious and safe, many medications, in particular those introduced before 1985 have not been optimally studied in randomised, controlled trials\(^5\). In their day, they received authorisation out of lack of regulation of the required specifications and they remain on the market because the pharmacovigilance systems have not detected enough ADRs requiring their withdrawal\(^6\). A good example of this is the case of the first generation antihistamines such as alimemazine, cyproheptadine, diphenhydramine and dimenhydrinate. There is wide spread use of first generation H\(_1\)-antihistamines in children; they have been on the market for a long time and many of them have received over the counter (OTC) status\(^6\). Though, these first generation H\(_1\)-antihistamines are known to have the most major side effects. They have poor receptor selectivity for the H\(_1\) receptor, occupying muscarinic cholinergic, α-adrenergic, serotonin receptors, and ion channels\(^5\). Additionally, first-generation H\(_1\)-antihistamines are lipophilic, facilitating crossing of the blood-brain barrier into the central nervous system with drowsiness, cholinergic effects and impairment as a consequence\(^5\).

The aim of this analysis paper is to compare registered indications of marketed first generation H\(_1\)-antihistaminic drugs for children in several European countries and to
look for the evidence supporting these indications. Additionally, reported ADR of these drugs involving children will be evaluated.

2 METHODS
For this review, we focused on the first generation H₁-antihistamines with WHO Anatomical Therapeutic Chemical classification (ATC)-code R06, that are available in an oral single-drug preparation in five selected European countries (Belgium, France, Germany, the Netherlands, and the United Kingdom). Country specific drug databases and national formularies were searched for first generation antihistamines. They were listed using their International Nonproprietary Names (INN). Second, for each formulation, available on the market, the Summary of Product Characteristics (SmPC) was examined in detail. Their licensed indications, the accessibility on the market (OTC or prescription only medication, POM), and the age limit for paediatric use in the respective countries were listed and compared. Finally, these labelled indications were compared with the available evidence of efficacy and safety of oral first generation H₁-antihistamines in children. A literature review of clinical trials, case series and case reports of first generation H₁-antihistamines involving children was conducted. Four major databases namely Medline, Embase, Pubmed and Web of Science were searched. Medline and Embase were searched electronically via Ovid. Ovid’s age group classification was used to limit the results to the paediatric age groups. Pubmed and Web of Science were searched via their specific websites. Abstracts were read and evaluated; if relevant, full papers were obtained. Information regarding formulation, route of administration and comparison was gathered. As for safety, we not only evaluated the reported ADRs in the obtained papers. We also consulted the database of The Netherlands Pharmacovigilance Centre Lareb, one of the best organised pharmacovigilance offices in Europe, for reports of ADRs of first generation H₁-antihistamines in children.

3 RESULTS
3.1 Variability in indications
Sixteen different first generation H₁-antihistamines are marketed in single-drug preparation in the five evaluated countries (supplementary table 6.A). When comparing
the different INNs, the huge variability in registered indications, accessibility (OTC or POM) and licensing ages for paediatric use is striking. To demonstrate this variability and the (lack of) existing evidence more extensively, three examples will be discussed in the following paragraphs: the case of alimemazine, cyproheptadine and dimetindene maleate.

**Table 6.1:** Differences in licensed indications, licensing age and accessibility of alimemazine tartrate (trimeprazine tartrate), cyproheptadine and dimethindene maleate in children in the investigated countries.

<table>
<thead>
<tr>
<th>Licensed indication</th>
<th>Alimemazine tartrate</th>
<th>cyproheptadine</th>
<th>Dimethindene maleate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic conditions</td>
<td>B, F, and N</td>
<td>F, N, and UK</td>
<td>N</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Itch</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itch in chickenpox</td>
<td></td>
<td>UK</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>UK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine and vascular headache</td>
<td></td>
<td></td>
<td>UK</td>
</tr>
<tr>
<td>Insomnia</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premedication</td>
<td>F, and UK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma bronchiale</td>
<td>F, and N</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accessibility</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>POM</td>
<td>B, N, and UK</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>OTC</td>
<td>F</td>
<td>F, and UK</td>
<td>B</td>
</tr>
</tbody>
</table>

B: Belgium; F: France; N: The Netherlands; UK: The United Kingdom. The selected cases are not available in Germany.
POM: prescription only medication; OTC: over the counter

### 3.2 Case 1: Alimemazine

Alimemazine, also known as trimeprazine, is a first generation H<sub>1</sub>-antihistamine in the phenothiazine chemical class. There is a broad range of licensed indications and licensing ages for this drug in the different evaluated countries (table 6.1). The efficacy of alimemazine for children with sleep problems has been investigated in four small randomised controlled trials (table 6.2). These trials found conflicting results with some
Are first generation antihistamines effective in children?

reporting short-term improvement while on alimemazine\textsuperscript{15-19}. Alimemazine has been shown to have the sedative effect, necessary for the use as a premedicant in children\textsuperscript{20,21}. In addition, in a randomised placebo controlled trial with 15 children alimemazine caused relief of retching after Nissen fundoplication\textsuperscript{22}. In some countries, alimemazine is indicated for itch, allergic diseases, urticaaria, cough and asthma bronchiale. However, the clinical trials supporting these specific indications could not be located. Case reports described significant morbidity\textsuperscript{15,23-25} in children of 4 years and younger after alimemazine use and intoxication. All case reports were published more than ten years ago. Three out of eight ADRs after intake of alimemazine in the Lareb database were in children. Two of them were 2 year or younger\textsuperscript{14}.

3.3 Case 2: Cyproheptadine

Cyproheptadine is an antihistamine of the piperidine chemical class with antiserotoninergic characteristics. Small prospective studies evaluated cyproheptadine in children with allergic conditions including primary acquired cold urticaria\textsuperscript{26} and mite-induced allergic rhinitis\textsuperscript{27}. In each of these trials, the active comparator (ketotifen, and loratadine respectively) showed similar or better results when compared to cyproheptadine (table 6.3). The lack of a placebo control group in the both above-mentioned studies makes it difficult to determine if cyproheptadine had a positive therapeutic effect. In the United Kingdom, cyproheptadine is indicated for prophylaxis of paediatric migraines (table 6.1). However, clinical data concerning its efficacy were limited to a retrospective chart review in 30 children\textsuperscript{28}. No trials supporting the use of cyproheptadine in itch (caused by chickenpox) and anaphylaxis could not be located. An important side effect of cyproheptadine is increased appetite. This side effect is the reason for the frequent off-label use of cyproheptadine as an appetite stimulant. We could locate two chart reviews evaluating this effect: in children aged 7 months to 6 years\textsuperscript{29} and in children aged 9 months to 20 years\textsuperscript{30}. Reported (side) effects in these chart reviews were – next to increased appetite - somnolence, irritability, and abdominal pain. Three out of five side effects of cyproheptadine at Lareb were reported in children; each in a different age group.
3.4 Case 3: Dimethindene maleate

The third example is the case of dimethindene maleate, a first generation antihistamine of the alkylamine chemical class. This drug is indicated for a wide variety of pruritic conditions (table 6.1). In some countries it is used in the treatment of itch in the context of a varicella infection. In Belgium, it is available OTC with an approved use in infants one month and older. In the neighbouring country The Netherlands, it is a prescription only medication, indicated for children aged 1 year and older. Only one trial\textsuperscript{31} examined the use of this antihistamine in alleviating the pruritus in varicella infection. A randomised placebo controlled trial in 126 patients showed improvement in severity of itching in the treatment group. However, neither the method of randomisation nor the blinding process was described in this paper (table 6.4)\textsuperscript{32}. Although there were no published case reports of safety issues in children with this drug; 7 out of 9 reports of ADRs in the Lareb were in children, all of them less than 4 years of age\textsuperscript{14}. 
<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Investigational product</th>
<th>Comparator</th>
<th>Primary outcome</th>
<th>Key result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richman, 1985 18</td>
<td>22 patients with severe awaking problems (mean age 22 months)</td>
<td>Double blind, randomised controlled trial</td>
<td>Oral alimemazine</td>
<td>placebo</td>
<td>Sleep questionnaires: composite score</td>
<td>Moderate improvement, no permanent effect on sleep</td>
</tr>
<tr>
<td>Simonoff and Stores, 1987 19</td>
<td>18 patients (age 7 to 39 months) with night waking</td>
<td>Double blind, randomised controlled trial</td>
<td>Oral alimemazine</td>
<td>Placebo</td>
<td>Parental sleep diary (duration and time)</td>
<td>Significantly fewer awakenings, less awake at night, and more night time sleep</td>
</tr>
<tr>
<td>Patel et al, 1990 21</td>
<td>90 patients (age 2 to 12 years) scheduled for anaesthesia</td>
<td>Double blind, randomised controlled trial</td>
<td>Midazolam</td>
<td>Diazepam-droperidol and alimemazine</td>
<td>Anxiolysis on arrival in the anaesthetic room</td>
<td>Anxiolysis was significantly greater in the midazolam group compared with the trimeprazine group.</td>
</tr>
<tr>
<td>France et al, 1991 16</td>
<td>45 patients (age 7 to 27 months) with sleep problems</td>
<td>Double blind, randomised controlled trial</td>
<td>Oral alimemazine</td>
<td>Placebo and extinction group</td>
<td>Daily Sleep diary (duration and time)</td>
<td>Abrupt reduction in sleep disturbance with alimemazine</td>
</tr>
<tr>
<td>Mitchel et al, 1997 20</td>
<td>85 children scheduled to undergo anaesthesia for adenoidectomy and/or tonsillectomy, older than 6 months</td>
<td>Double blind, randomised controlled trial</td>
<td>Oral midazolam</td>
<td>Oral alimemazine and placebo</td>
<td>Anxiety, crying and distress on arrival in the anaesthetic room</td>
<td>More patients were calm and quiet following midazolam than following trimeprazine, with both premedicant agents comparing favourably with placebo</td>
</tr>
<tr>
<td>France et al, 1999 17</td>
<td>12 patients (age 6 to 27 months) with sleep problems</td>
<td>Double blind, randomised controlled trial</td>
<td>Oral alimemazine, two different doses</td>
<td>Placebo</td>
<td>Daily sleep diary (duration and time)</td>
<td>No clinically significant effects of the low dose detected, whereas the effects of the high dose were not consistently replicated across nor within patients</td>
</tr>
<tr>
<td>Antao et al, 2005 22</td>
<td>12 patients (age 8 months to 15 year)</td>
<td>Double blind, randomised controlled trial</td>
<td>Oral alimemazine</td>
<td>Placebo</td>
<td>Number of retching episodes</td>
<td>Significant decrease in number of retching episodes with alimemazine compared to placebo.</td>
</tr>
</tbody>
</table>
### Table 6.3: Table summarising the available studies with cyproheptadine in children

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Investigational product</th>
<th>Comparator</th>
<th>Primary outcome</th>
<th>Key result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visitsunthorn et al, 1995</td>
<td>6 patients (age 4 to 9 years) with cold urticaria</td>
<td>Double blind cross over study</td>
<td>Cyproheptadine</td>
<td>Ketotifen</td>
<td>Clinical symptoms</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Lewis et al, 2004</td>
<td>30 patients (age 3 to 18 years) diagnosed with migraine</td>
<td>Chart review</td>
<td>Cyproheptadine</td>
<td>No comparator</td>
<td>Headache frequency</td>
<td>Overall positive response rate for cyproheptadine was 83%</td>
</tr>
<tr>
<td>Wu et al, 2012</td>
<td>49 patients (age 2 to 12 years) with perennial allergic rhinitis</td>
<td>Double blind, randomised controlled trial</td>
<td>Loratadine</td>
<td>Cyproheptadine</td>
<td>Total symptom score</td>
<td>Significantly greater reduction in symptom scores in the loratadine group</td>
</tr>
<tr>
<td>Rodriguez et al, 2013</td>
<td>80 patients (age 9 months to 20 years) with dyspeptic symptoms</td>
<td>Chart review</td>
<td>Cyproheptadine</td>
<td>No comparator</td>
<td>Resolved dyspeptic symptoms</td>
<td>Response to therapy was reported in 55% of patients.</td>
</tr>
<tr>
<td>Sant’Anna et al, 2014</td>
<td>127 patients (age 7 months to 6 years) with poor weight gain</td>
<td>Chart review</td>
<td>Cyproheptadine</td>
<td>No comparator</td>
<td>Weight change</td>
<td>A significant improvement in weight was observed compared to baseline</td>
</tr>
</tbody>
</table>

### Table 6.4: Table summarising the available studies with dimethindene maleate in children

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Investigational product</th>
<th>Comparator</th>
<th>Primary outcome</th>
<th>Key result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Englisch and Bauer, 1997</td>
<td>128 patients (age 1-6 years) with chickenpox</td>
<td>Double blind, randomised controlled trial</td>
<td>Oral dimethindene maleate</td>
<td>Placebo</td>
<td>Itching severity score</td>
<td>Dimethindene maleate group showed significant reduction of itching severity score compared with placebo.</td>
</tr>
</tbody>
</table>
4 DISCUSSION
Licensed indications may lead to the misconception that these indications are evidence based, even more if they have an OTC status. However, our review shows that the on-label indications for first generation H₁-antihistamines are often not supported by clinical trials in children. The efficacy of orally administered antihistamines in paediatric patients are generally extrapolated from adults or older paediatric patients⁶,³³, which does not match with the current ‘Better Medicines for children’ policy³⁴. As stated before, this is clinically relevant because ‘off-knowledge’ use of drugs in children might result in underdosing, overdosing and ADRs.

The European Union Paediatric Regulation, implemented in 2007, created a new type of marketing authorisation to give an incentive for medicinal products that have been on the market in the EU states for some time and therefore are no longer covered by a patent. A successful application results in 10 years of data and market protection³⁴. This Paediatric Use Marketing Authorisation (PUMA) could be a solution for the lack of knowledge on efficacy and safety of off-patent drugs in children. However, up until now only two drugs received a PUMA³⁵.

Although some first generation antihistamines may be associated with less sedation than others, sedation associated with this group of antihistamines is so common that these antihistamines have been termed by the US Food and Drug Administration (FDA) as ‘sedating antihistamines’. First generation antihistamine-induced sedation has been described to occur in more than 50% of patients receiving therapeutic doses which may adversely affect a child’s learning abilities³⁶-³⁹. Yet, many of the first generation antihistamines are available to the consumer OTC, as sleeping aids underscoring their soporific effects. Moreover, the high accessibility on the market and thus the widespread use of first generation antihistamines in paediatrics has been accompanied by frequent intoxication. Typically, children ingesting large quantities of first generation antihistamines experience marked sedation, lethargy, and anticholinergic-like symptoms including dry mouth, tachycardia, and hyperactivity with potential progression to acute psychosis³⁷. There is probably an underreporting of these side effects to the pharmacovigilance systems, as most clinicians see these side effects as an already-known problem. Paediatric pharmacovigilance will be essential to reduce
ADRs with these antihistamines, through better detection and prevention of the ADRs\textsuperscript{40,41}. Education of health professionals about the importance of pharmacovigilance has been shown to be effective in increasing reporting of ADRs\textsuperscript{41,42}. Unfortunately, we did not obtain information on the actual use of these antihistamines in the evaluated countries which would help to assess the possible impact of these ADRs.

Before the treatment with any antihistamine is started, the child and family should be counselled on the appropriate use. That is age of licensed use, frequency and dosing, clinical effects and possible side effects\textsuperscript{43}. Moreover, based on the lack of evidence of efficacy and the safety problem of the first generation H\textsubscript{1}-antihistamines, Schad et al\textsuperscript{44} stated that the paediatric use of first generation antihistamines should even be restricted to two uncommon situations. First in children with urticaria or dermatitis whose pruritus is so severe that sedation is a benefit rather than a risk and second if there is anaphylaxis requiring intravenous antihistamine as adjunctive therapy to epinephrine.

In conclusion, this case of first generation H\textsubscript{1}-antihistamines demonstrates that on-label prescriptions in children are not free from risks. A broad range of vague indications, as a result of lack of evidence brings a lack of clarity for clinicians, pharmacists and patients. Obviously, this problem is not restricted to the first generation antihistamines. This article argues for a wider discussion on evaluation of labelled indications for children in general.
**Supplementary table 6.A**: Overview of the first generation H₁-antihistamines available in Belgium, France, Germany, the Netherlands and the United Kingdom, in oral single drug formulation, with ATC-code R06. The table shows labeled indications, ages and accessibility on the market.

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>FORMULATION</th>
<th>INDICATION</th>
<th>LICENSING AGE</th>
<th>OTC/POM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alimemazine tartrate (Trimeprazine tartrate)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>Tablet</td>
<td>Symptomatic treatment of various allergic manifestations: rhinitis, conjunctivitis, urticaria. Adjuvant symptomatic treatment of itching skin conditions (eczema, prurigo ...).</td>
<td>&gt;12y</td>
<td>POM</td>
</tr>
<tr>
<td>France</td>
<td>Drops</td>
<td>Occasional insomnia. Transient insomnia. Symptomatic treatment of various allergic manifestations: rhinitis (seasonal or perennial), conjunctivitis, urticaria. Symptomatic treatment of uncomfortable dry cough, more specifically at night. Premedication before general anaesthesia.</td>
<td>&gt;1y (antihistamine, and as premedication) &gt;2y (antitussive) &gt;3y (sleep medication)</td>
<td>POM</td>
</tr>
<tr>
<td></td>
<td>Syrup</td>
<td>Occasional insomnia. Transient insomnia. Symptomatic treatment of various allergic manifestations: rhinitis (seasonal or perennial), conjunctivitis, urticaria. Symptomatic treatment of uncomfortable dry cough, more specifically at night.</td>
<td>&gt;1y (antihistamine) &gt;2y (antitussive) &gt;3y (sleep medication)</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>Occasional insomnia. Transient insomnia. Symptomatic treatment of various allergic manifestations: rhinitis (seasonal or perennial), conjunctivitis, urticaria. Symptomatic treatment of uncomfortable dry cough, more specifically at night.</td>
<td>&gt;6y</td>
<td>POM</td>
</tr>
<tr>
<td>Germany</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Tablet</td>
<td>Allergic conditions due to release of histamine such as hay fever, perennial allergic rhinitis, urticaria and other dermatoses based on allergic (direct type), drug exanthemas, allergic dermatoses and as adjuvant for bronchial asthma of allergic origin.</td>
<td>&gt;2y</td>
<td>POM</td>
</tr>
<tr>
<td>Country</td>
<td>Formulation</td>
<td>Indications</td>
<td>Age</td>
<td>Accessibility</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------</td>
<td>---------------</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>Oral solution, tablet</td>
<td>Management of urticaria and pruritus.</td>
<td>&gt;2y</td>
<td>POM</td>
</tr>
<tr>
<td></td>
<td>Oral solution, tablet</td>
<td>Premedication as a sedative before anaesthesia</td>
<td>2-7y</td>
<td>POM</td>
</tr>
<tr>
<td>Chlorphenamine maleate</td>
<td>Belgium</td>
<td>Tablet Symptomatic treatment of various allergic manifestations: hay fever and pollinosis, allergic rhinitis and conjunctivitis, acute urticaria. Adjuvant for drug allergy, serum sickness, angioedema, pruritus, insect bites, contact dermatitis, atopic dermatitis.</td>
<td>&gt;6y</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td>France</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>NA</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>The Netherlands</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>The United Kingdom</td>
<td>Syrup For the symptomatic relief of hay fever, vasomotor rhinitis, urticaria, angioedema, reactions to food or medicines, serum reactions, and insect bites. Symptomatic relief of itch associated with chickenpox.</td>
<td>&gt;1y</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>For the symptomatic relief of hay fever, vasomotor rhinitis, urticaria, angioedema, reactions to food or medicines, serum reactions, and insect bites. Symptomatic relief of itch associated with chickenpox.</td>
<td>&gt;6y</td>
<td>OTC</td>
</tr>
<tr>
<td>Clemastine hydrogen fumarate</td>
<td>Belgium</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>France</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Formulation</td>
<td>Indications</td>
<td>Age</td>
<td>Status</td>
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<td>-------------------------------</td>
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<td>-----------------------------------------------------------------------------</td>
<td>-----</td>
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</tr>
<tr>
<td>The Netherlands</td>
<td>Tablet</td>
<td>Prevention and symptomatic treatment of allergic conditions based on release of histamine, such as hay fever, perennial allergic rhinitis, urticaria and other dermatoses due to allergy (direct type) such as prurigo and insect bites; drug exanthemas and as an adjuvant for other forms of eczema. Prevention of adverse events during hyposensibilisation treatment, due to allergy. Adjuvant for allergic asthma.</td>
<td>&gt;1y</td>
<td>POM</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>Tablet</td>
<td>Allergic rhinitis, including hay fever and perennial rhinitis, vasomotor rhinitis. Allergic dermatoses, including pruritus, atopic eczema and contact dermatitis. Angioneurotic oedema, drug allergy.</td>
<td>&gt;1y</td>
<td>OTC</td>
</tr>
<tr>
<td>Cyclizine hydrochloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Belgium</td>
<td>NA</td>
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<tr>
<td>France</td>
<td>NA</td>
<td></td>
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</tr>
<tr>
<td>Germany</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Tablet</td>
<td>Prevention and treatment of motion sickness. Prevention and treatment of nausea vomiting.</td>
<td>&gt;6y</td>
<td>OTC</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>Tablet</td>
<td>Prevention and treatment of nausea and vomiting including: motion sickness, nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period, vomiting associated with radiotherapy. Relief of vomiting and attacks of vertigo associated with Meniere’s disease and other forms of vestibular disturbance.</td>
<td>&gt;6y</td>
<td>OTC</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Tablet</td>
<td>Symptomatic treatment of various allergic manifestations: rhinitis (seasonal or perennial), conjunctivitis, urticaria.</td>
<td>&gt;6y</td>
<td>OTC</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Formulation</td>
<td>Use</td>
<td>Age</td>
<td>Availability</td>
</tr>
<tr>
<td>------------------</td>
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<td>----------------------------------------------------------------------</td>
<td>-----</td>
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</tr>
<tr>
<td>The Netherlands</td>
<td>Tablet</td>
<td>Treatment of acute and chronic allergies: dermatoses based on allergy such as urticaria, angioneurotic edema, dermatitis, insect bites or insect stings; allergic conditions such as allergic rhinitis (rhinitis vasomotorica), hay fever, serum sickness and allergic drug reactions. Adjunctive therapy to adrenaline and other standard measures for the relief of anaphylactic reactions.</td>
<td>&gt;2y</td>
<td>POM</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>Tablet</td>
<td>Treatment of acute and chronic allergic and pruritic conditions, such as dermatitis, including neurodermatitis and neurodermatitis circumscripta; eczema; eczematoid dermatitis; dermatographism; mild, local allergic reactions to insect bites; hay fever and other seasonal rhinitis; perennial allergic and vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; urticaria; angioneurotic oedema; drug and serum reactions; anogenital pruritus; pruritus of chicken pox. Adjunctive therapy to adrenaline and other standard measures for the relief of anaphylactic reactions. In migraine and vascular headache.</td>
<td>&gt;2y</td>
<td>OTC</td>
</tr>
</tbody>
</table>

**Dexchlorpheniramine maleate**

<table>
<thead>
<tr>
<th>Country</th>
<th>Formulation</th>
<th>Use</th>
<th>Age</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>NA</td>
<td>Symptomatic treatment of allergic manifestations: rhinitis (seasonal or perennial), conjunctivitis, urticarial.</td>
<td>&gt;6y</td>
<td>OTC</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Tablet</td>
<td>Symptomatic treatment of allergic conditions: allergic conditions of the respiratory tract such as hay fever, perennial allergic rhinitis; allergic skin conditions: urticarial; other hypersensitivity reactions: drug allergy, food allergy, allergic conjunctivitis.</td>
<td>&gt;6y</td>
<td>POM</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>NA</td>
<td>Symptomatic treatment of allergic manifestations: rhinitis, conjunctivitis, urticaria. Symptomatic relief of pruritus in some dermatologic conditions.</td>
<td>&gt;6y</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>Temporarily or occasional aid to promote induction of sleep.</td>
<td>&gt;16y</td>
<td>OTC</td>
</tr>
</tbody>
</table>

**Diphenhydramine hydrochloride**

<table>
<thead>
<tr>
<th>Country</th>
<th>Formulation</th>
<th>Use</th>
<th>Age</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Tablet</td>
<td>Symptomatic treatment of allergic manifestations: rhinitis, conjunctivitis, urticaria. Symptomatic relief of pruritus in some dermatologic conditions.</td>
<td>&gt;6y</td>
<td>OTC</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Country</th>
<th>Formulation</th>
<th>Uses</th>
<th>Age</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Tablet</td>
<td>Prevention and treatment of motion sickness.</td>
<td>&gt;2y</td>
<td>OTC</td>
</tr>
<tr>
<td>Germany</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>Tablet</td>
<td>Prevention of allergic conditions, e.g. hay fever, vasomotor rhinitis, stings, urticaria, angioneurotic oedema, drug sensitivity, contact dermatitis and photosensitivity.</td>
<td>&gt;12y</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td>Tablet, syrup</td>
<td>Relief of temporary sleep disturbance.</td>
<td>&gt;16y</td>
<td>OTC</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>Tablet</td>
<td>Prevention and symptomatic treatment of motion sickness.</td>
<td>&gt;2y</td>
<td>OTC</td>
</tr>
<tr>
<td>France</td>
<td>Capsule</td>
<td>Prevention and treatment of motion sickness.</td>
<td>&gt;15y</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td>Syrup</td>
<td>Prevention and treatment of motion sickness.</td>
<td>&gt;2y (for motion sickness)</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short term symptomatic treatment of nausea and vomiting (not associated with fever).</td>
<td>&gt;6y (for nausea and vomiting)</td>
<td>OTC</td>
</tr>
<tr>
<td>Germany</td>
<td>Syrup</td>
<td>Prevention and symptomatic treatment of nausea and vomiting, especially in motion sickness.</td>
<td>&gt;6kg</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td>Dragees</td>
<td>Prevention and symptomatic treatment of nausea and vomiting, especially in motion sickness.</td>
<td>&gt;6y</td>
<td>OTC</td>
</tr>
<tr>
<td></td>
<td>Slow release capsule</td>
<td>Prevention and symptomatic treatment of nausea and vomiting, especially in motion sickness.</td>
<td>&gt;14y</td>
<td>OTC</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>Tablet</td>
<td>Anti-emetic in the prevention and treatment of motion sickness; irradiation sickness, postoperative vomiting, drug-induced nausea and vomiting, and the symptomatic treatment of nausea and vertigo due to Meniere’s disease and other labyrinthine disturbances.</td>
<td>&gt;2y</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Dimetindeenmaleaat**
<table>
<thead>
<tr>
<th>Country</th>
<th>Formulation</th>
<th>Indications</th>
<th>Duration</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Tablet, drops</td>
<td>Symptomatic treatment of pruritus of various origins: urticaria, food allergy, drug allergy, eczema, chickenpox, insect bites, pruritus senilis. Symptomatic treatment of allergic rhinitis: hay fever, or perennial rhinitis.</td>
<td>&gt;1m</td>
<td>OTC</td>
</tr>
<tr>
<td>France</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>drops</td>
<td>Symptomatic treatment of allergic conditions due to release of histamine such as hay fever, perennial allergic rhinitis, urticaria and other dermatoses based on allergic (direct type).</td>
<td>&gt;1y</td>
<td>POM</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxylamine succinate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>tablet</td>
<td>Occasional insomnia.</td>
<td>&gt;15y</td>
<td>OTC</td>
</tr>
<tr>
<td>Germany</td>
<td>Oral solution</td>
<td>Short term treatment of sleep disturbance.</td>
<td>&gt;1y</td>
<td>OTC</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketotifen fumarate</td>
<td></td>
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</tr>
<tr>
<td>Belgium</td>
<td>Oral suspension</td>
<td>Prevention of: Extrinsic bronchial asthma, chronic bronchitis with allergic component, infant wheezing, allergic rhinitis.</td>
<td>&gt;6m</td>
<td>POM</td>
</tr>
<tr>
<td></td>
<td>Capsule, slow release tablet</td>
<td>Prevention of: Extrinsic bronchial asthma, chronic bronchitis with allergic component, infant wheezing, allergic rhinitis.</td>
<td>&gt;3y</td>
<td>POM</td>
</tr>
<tr>
<td>France</td>
<td>Capsule, oral solution, tablet</td>
<td>Symptomatic treatment of seasonal allergic rhinoconjunctivitis.</td>
<td>&gt;4y</td>
<td>POM</td>
</tr>
<tr>
<td>Country</td>
<td>Formulation</td>
<td>Indication</td>
<td>Age</td>
<td>Prescribing Authority</td>
</tr>
<tr>
<td>----------------</td>
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<td>-----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Germany</td>
<td>Syrup</td>
<td>Adjuvant for prevention of allergic asthmatic symptoms in combination with other anti-inflammatory drugs in patients with allergic condition. Symptomatic treatment of allergic rhinitis and allergic skin conditions if non-sedation oral antihistamines or – for allergic rhinitis – local antihistamines or local glucocorticoids are not indicated.</td>
<td>&gt;6m</td>
<td>POM</td>
</tr>
<tr>
<td></td>
<td>Capsule</td>
<td>Adjuvant for prevention of allergic asthmatic symptoms in combination with other anti-inflammatory drugs in patients with allergic condition. Symptomatic treatment of allergic rhinitis and allergic skin conditions if non-sedation oral antihistamines or – for allergic rhinitis – local antihistamines or local glucocorticoids are not indicated.</td>
<td>&gt;3y</td>
<td>POM</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Syrup, tablet, drops</td>
<td>Prevention of bronchial asthma with allergic cause. Prevention and treatment of allergic rhinitis and allergic dermatoses.</td>
<td>&gt;6m</td>
<td>POM</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>Elixir, tablet</td>
<td>Symptomatic treatment of allergic conditions including rhinitis and conjunctivitis.</td>
<td>&gt;3y</td>
<td>POM</td>
</tr>
<tr>
<td><strong>Meclozine hydrochloride</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>tablet</td>
<td>Prevention and symptomatic treatment of nausea, vomiting and vertigo associated with motion sickness.</td>
<td>&gt;12y</td>
<td>OTC</td>
</tr>
<tr>
<td>France</td>
<td>tablet</td>
<td>Symptomatic treatment of vertigo. Prevention and treatment of motion sickness.</td>
<td>&gt;15y</td>
<td>POM</td>
</tr>
<tr>
<td>Germany</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Tablet</td>
<td>Motion sickness.</td>
<td>&gt;3y</td>
<td>OTC</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>Tablet</td>
<td>Prevention and treatment of motion sickness. Prevention of nausea and vomiting of sickness and in particular travel sickness.</td>
<td>&gt;2y</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Oxomemazine</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Syrup</td>
<td>Symptomatic treatment of uncomfortable dry cough, more specifically at night.</td>
<td>&gt;2y</td>
<td>OTC</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
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<tr>
<td>---</td>
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</tr>
<tr>
<td>The Netherlands</td>
<td>Syrup</td>
<td>Cough.</td>
<td>&gt;2y</td>
<td>POM</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Pimethixene

| Belgium | NA | | |

| France | Syrup | Symptomatic treatment of uncomfortable dry cough, more specifically at night. | >2y | POM |
| Germany | NA | | |
| The Netherlands | NA | | |
| The United Kingdom | NA | | |

### Promethazine hydrochloride

| Belgium | NA | | |

| France | Syrup | Symptomatic treatment of various allergic manifestations: rhinitis (seasonal or perennial), conjunctivitis, urticaria. | >1y | OTC |
| Tablet | Symptomatic treatment of various allergic manifestations: rhinitis (seasonal or perennial), conjunctivitis, urticaria. Occasional insomnia and transient insomnia. | >15y | OTC |
| Germany | Tablet | Restlessness and agitation with underlying psychiatric disease. Nausea and vomiting. | >2y | POM |
| The Netherlands | Tablet, syrup | Prevention and symptomatic treatment of allergic conditions based on release of histamine, such as hay fever, perennial allergic rhinitis, urticaria and other dermatoses due to allergy (direct type) such as prurigo and insect bites; drug exanthemas and as an adjuvant for other forms of eczema and allergic asthma. Motion sickness. | >2y | POM |
### The United Kingdom

<table>
<thead>
<tr>
<th>Tablet, elixir</th>
<th>Symptomatic treatment for allergic conditions of the upper respiratory tract and skin including allergic rhinitis, urticaria and anaphylactic reactions to drugs and foreign proteins. As an adjunct in preoperative sedation in surgery and obstetrics As an antiemetic. For short term use: paediatric sedative.</th>
<th>&gt;2y</th>
<th>OTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet</td>
<td>As a night-time sleep aid, for the correction of temporary disturbances of sleep pattern where there is difficulty in going to sleep or staying asleep, caused for example by specific dislocation of normal routine.</td>
<td>&gt;16y</td>
<td>OTC</td>
</tr>
</tbody>
</table>

### Promethazine teoclate

<table>
<thead>
<tr>
<th>Belgium</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>NA</td>
</tr>
<tr>
<td>Germany</td>
<td>NA</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>NA</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

ATC-code: anatomical therapeutic chemical classification code; NA: not available (in oral single drug formulation); ND: no data; OTC: over the counter; POM: prescription only medication.
REFERENCES


32. Tebruegge M, Kuruvilla M, Margarson I. Does the use of calamine or antihistamine provide symptomatic relief from pruritus in children with varicella zoster infection? Arch Dis Child 2006; 91(12): 1035-6.


CHAPTER 7

CHANGES IN PRESCRIPTION PATTERN OF ACID SUPPRESSANT MEDICATIONS BY BELGIAN PAEDIATRICIANS: ANALYSIS OF THE NATIONAL DATABASE (1997-2009)

De Bruyne P, Christiaens T, Vander Stichele R, Van Winckel M

Published in the Journal of Pediatric Gastroenterology and Nutrition
ABSTRACT

OBJECTIVES. To examine the trend in the prescribing of proton pump inhibitors (PPIs) and histamine H$_2$-receptor antagonists (H$_2$-RAs) for children in Belgium from 1997 to 2009 to encourage discussion regarding appropriate clinical use.

METHODS. Monthly claim based data for PPIs and H$_2$-RAs were obtained from the national Health Insurance database (Pharmanet 1997-2009).

RESULTS. The total monthly volume of all reimbursed antireflux medication, prescribed by Belgian paediatricians increased 7-fold from 20782 daily defined doses (DDDs) in January 1997 to 142912 DDDs in June 2009. During this study period reimbursed volume of H$_2$-RAs increased from 2575 to 38996 DDDs and of PPIs from 3472 to 103926 DDDs per month.

CONCLUSIONS. PPI use has increased substantially in children. Utilisation does not seem to commensurate with prevalence of GERD in children. This study encourages clinical discussion regarding well-considered use of these drugs in children.
Chapter 7

1 INTRODUCTION

Consumption of acid suppressants, such as histamine H\textsubscript{2}-receptor antagonists (H\textsubscript{2}-RAs) and proton pump inhibitors (PPIs), has been increasing markedly in the last two decades. This is a worldwide observation in adults\textsuperscript{1-5}. The prescription of these acid suppressants was also initiated in the paediatric population, in the last decade. This prescription in children is advocated in current paediatric guidelines, only for the indication of gastroesophageal reflux disease (GERD)\textsuperscript{1}, which refers to the troublesome persistent symptoms or complications resulting from reflux of gastric contents\textsuperscript{1,6-10}. There is little knowledge on the prevalence of GERD in children\textsuperscript{11}. On the basis of a large claim database that uses ICD-9 codes, GERD was diagnosed in 12.3% of North American infants and in 1% of other paediatric age groups (aged 1-17 years)\textsuperscript{11,12}. The incidence of childhood presentation (age <5years) of GERD in another North American retrospective cohort study by Chitkara et al was estimated to be 0.9/1000 person years\textsuperscript{13}.

It is important to distinguish gastroesophageal reflux disease (GERD) from gastroesophageal reflux (GER). GER is defined as the passage of gastric contents into the esophagus and is a normal physiological phenomenon in healthy infants and children\textsuperscript{7-11,14}. Nevertheless, frequent or copious regurgitations are worrying parents and are frequently brought to the attention of a health care professional\textsuperscript{7,15-20}. The use of acid suppressants in this uncomplicated GER indication is off-label, and not advocated by guidelines, as is the case for the widely used prokinetic agents (such as metoclopramide and domperidone) and mucosal surface antacids\textsuperscript{1,9,17}.

From the perspective of a tertiary paediatric gastroenterology department, we noticed a recent increase of the use of acid suppressants, particularly the PPIs. We set out to perform a retrospective observational drug utilization study of these drugs in children, to quantify this trend. The aim of this study was to describe the longitudinal evolution of the prescription rate of acid suppressants by Belgian paediatricians, over the last decade, and to investigate drug registration and reimbursement policies associated with abrupt changes in trends.
2 MATERIALS AND METHODS

2.1 Data collection with regard to medication utilisation

We investigated the prescription pattern of paediatricians (certified specialists in Belgium). From January 1997 to June 2009, we collected data on the use of H2-RAs, PPIs and cisapride with respective ATC-classes A02BA01/02/03/04/07, A02BC01/02/03/04/05 and A03FA02. Over the time of the study, the number of children (between 0 and 16 years old) in Belgium has been stable at 1.95 million children, representing a stable 20% of the population21,22. Birth rate has evolved from 10.9 in 2000 to 10.1 per 1000 inhabitants in 200923. The acid suppressant drugs were all prescription-only-medication in Belgium during this period, restricted to indications for adults, with patients paying only 25% of the fixed price of these medications. The remaining 75% is paid to the pharmacist by the insurer.

We used an administrative claim database, the Pharmanet database, from the Belgian National Institute of Health and Disability Insurance (NIHDI) covering almost the entire Belgian population (98% in 2009)22,24, in universal population-based public health insurance25. This completely anonymous database collects dispensing data of reimbursed medications from all community pharmacies in Belgium, since 1996. Over-the-counter (OTC) products (such as metoclopramide, domperidone and alginates) and products bought in a hospital pharmacy (such as cisapride since 2005) are not included in this database. As the database includes nearly all Belgian citizens, it provides the opportunity to investigate all the prescriptions made by paediatricians, without bias by socio-economic status of the patient, affiliation to an insurance company, or geographical location.

The collected data consist of all reimbursed acid suppressants identified by National Drug Codes (NDCs) and month of reimbursement. Reimbursed volume is expressed in daily defined doses (DDDs); this is the assumed average maintenance dose per day for a drug used for its main indication in adults, as stated by the World Health Organization. The version 2010 of the ATC/DDD methodology was used. Another presentation of volume is the number of DDDs per 1000 inhabitants per day. The DDD/1000 inhabitants/day is a measure of how many people in every thousand Belgians are taking the standard dose of a drug every day, it may provide a rough estimate of the
proportion of the study population treated daily with a particular drug or group of
drugs\textsuperscript{26}. Since 2004, the Pharmanet database also registers the age group of the patient
for which the drug is bought.

2.2 Collection of data on regulatory events regarding acid
suppressants in Belgium

We consulted the Belgian State Monitor, the official publication of the Belgian
government, for information on reimbursement policies. Further information was
sought on the website of the Belgian Centre for Pharmacotherapeutic Information
(BCFI/CBIP), which is a non-profit, non-governmental organisation providing
independent information on drugs and promoting rational prescribing, intended to
health professionals. In addition, we reviewed the literature, and particularly the
articles of Van Driel et al on prescription pattern of acid suppressants in adults in
Belgium\textsuperscript{2,4}.

2.3 Statistical analysis

To estimate the change in acid suppressant consumption, an interrupted time-series
design was used to analyse prescription volume, taking into account monthly sales
volumes from January 1997 to February 2001 as the pre-intervention period, March
2001 to April 2003 as the intervention period and April to June 2009 as the post
intervention period\textsuperscript{27}. Segmented lineair regression analysis was used in each time
segment (preintervention period and postintervention period) to compare the
differences. Linear regression has two parameters, the level (the intercept) and the
slope. In each time segment, changes in level and the slope were calculated to quantify
the change. All statistical analysis was conducted in SPSS software, version 19.

2.4 Ethical questions

All data in Pharmanet are completely anonymous. No individual patient records were
involved. The protocol of the study was submitted to the NIHDI before retrieving the
data.
3 RESULTS

3.1 Regulatory events regarding acid suppressant agents in Belgium

Several developments may have influenced the prescription pattern for acid suppressant drugs (table 7.1). The first important event was the withdrawal of cisapride, a gastrointestinal prokinetic agent that was prescribed to over millions of children with GERD worldwide in the nineties\(^9,17\). Since 1993, there have been several reports of fatal cardiac arrhythmias or sudden deaths with cisapride use\(^9,17,28\). This led to the withdrawal of cisapride from the European and USA markets in 2000\(^9,17\). Afterwards, in Belgium, cisapride could only be prescribed within very restricted programs\(^1\), and since 2005, cisapride is no longer available in Belgian community pharmacies.

\(\text{H}_2\)-RAs and PPIs came to the Belgian market in the beginning of the nineties and were reimbursed only after prior approval by the sickness fund of the patient, based on the report of an endoscopic examination. Though, it was shown before that approximately 10\% of patients tried to circumvent this by declining reimbursement and by paying the whole expense of the drug\(^29\). Between March 2001 and April 2003, two new reimbursement measures were taken by the Belgian government, both shifting access from ‘restricted’ to ‘open benefit’ (i.e. an endoscopic examination was no longer required). Consequently, a prior approval was no longer required to obtain reimbursement of these medicines. In 2001, the first measure made the cheaper \(\text{H}_2\)-RAs available without authorisation. In 2003, the expiry of the patent of omeprazole, and the price reduction of rabeprazole created opportunities for new cost-saving measures. This reimbursement policy of April 2003 made the cheapest PPIs (omeprazole and rabeprazole) available without restrictions\(^2,4\). In July 2005 restrictions were again tightened for PPIs, by an a posteriori control system: physicians prescribing PPIs had to document in the Health Record an endoscopy report or a report with the patient’s history and the results of a clinical examination and keep this available for possible inspection later on\(^2\).

Table 7.1 shows the relevant consecutive events that took place during the observed period. We emphasise that the reimbursement measures mentioned were in the first place issued for the adult patient, but were also applicable for children. Van Driel et al
demonstrated the influence of these policies on the volume of acid suppressants, prescribed for adult patients\textsuperscript{2,4}.

**Table 7.1**: Overview of the reimbursement measures and other events concerning acid suppressant medications for adults in Belgium (1997-2009).

<table>
<thead>
<tr>
<th>Year</th>
<th>Reimbursement policies</th>
<th>Registration policies</th>
<th>Other events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Withdrawal of cisapride and stop production. Available cisapride prescribed within restriction programs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Cimetidine and ranitidine ‘open benefit’ Rabeprazole introduced at low price</td>
<td>Rabeprazole introduced</td>
<td>Patent omeprazole expires</td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td>Esomeprazole introduced</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Omeprazole and rabeprazole ‘open benefit’ in exchange for lower prices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Sharpened reimbursement policy for proton pump inhibitors (with a posteriori control)</td>
<td></td>
<td>Cisapride no longer available</td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td>Patent lansoprazole expires</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td>Patent pantoprazole expires</td>
</tr>
</tbody>
</table>

### 3.2 Prescription pattern of acid suppressants

There was a remarkable increase in acid suppressant prescriptions by Belgian paediatricians from 1997 to 2009. The total monthly volume of all reimbursed antireflux medication increased 7-fold from 20782 DDDs in January 1997 to 142912 DDDs in June 2009. During the study period the reimbursed volume of \( \text{H}_2 \)-RAs increased from 2575 to 38996 DDDs and of PPIs from 3472 to 103926 DDDs. Monthly public expenditure for these medications increased from a total of €35 000 in January 1997 to a total of €65000 in June 2009, despite 60 % decrease of mean expenditure per DDD for all antireflux medication from 1997 through 2009 (€1.62 per DDD in 1997 to €0.64 per DDD in 2009).
Figure 7.1 shows the number of DDDs reimbursed for H₂-RAs, PPIs (divided into the group of omeprazole and rabeprazole and the group of the other PPIs) and cisapride. Before 2001, volumes of reimbursed H₂-RAs and PPIs were low. From 2001 on, volumes of H₂-RAs and particularly PPIs increased remarkably. Cisapride prescription volume decreased since the restricted indications in 2000 and further restriction policies in 2003 and 2005. H₂-RAs had their biggest increase in the first half of the study period. After 2003, PPIs took the upper hand. In 2005, there was a remarkable temporary increase and subsequent drop in reimbursed volume in 2005, potentially provoked by hoarding. Though, there was little impact on the overall trend.

![Figure 7.1](image)

**Figure 7.1**: Monthly reimbursed volume of H₂-receptor antagonists, proton pump inhibitors (omeprazole/rabeprazole and others) and cisapride in defined daily doses prescribed by Belgian paediatricians. Indicated moments are the first reimbursement measure in March 2001 and the second reimbursement measure in April 2003. The grey lines plotted on the graph represent the spline model, constructed in function of the segmented regression analysis. PPI: proton pump inhibitor.

The first reimbursement measure in March 2001 boosted the prescription volumes of (cheaper) H₂-RAs but soon a steady rise in reimbursed volume of the PPIs started. After
the second reimbursement measure, the cheapest PPIs continued to grow, at the expense of the other PPIs, as was intended by this policy (table 7.2). There were significant differences in both intercept and slope of the regression line of the consumption data of both H₂-RAs and PPIs, before and after the intervention period.

Table 7.2: Changes in reimbursed prescription volume of the PPIs omeprazole and rabeprazole, the other PPIs and all H₂-receptor antagonists

<table>
<thead>
<tr>
<th>Product</th>
<th>Period</th>
<th>Slope (95% CI)</th>
<th>Intercept pre (95% CI)</th>
<th>Intercept post (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂-receptor antagonists</td>
<td>Pre</td>
<td>87.1 (64.9 – 109.3)</td>
<td>8706 (8055 – 9358)</td>
<td>27619 (26370 – 28869)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>182.5 (153.9 – 211.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole/rabeprazole</td>
<td>Pre</td>
<td>56.0 (42.5 – 69.5)</td>
<td>5844 (5447 – 6240)</td>
<td>20173 (16749 – 23597)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>879.9 (801.6 – 958.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other PPIs</td>
<td>Pre</td>
<td>30.5 (26.5 – 34.5)</td>
<td>1392 (1274 – 1509)</td>
<td>3505 (3052 – 3958)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>50.1 (39.8 – 60.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interrupted time series showing the significant changes in mean prescription volume as well as the trend of the change for the product groups (the PPIs omeprazole and rabeprazole, the other PPIs and all H₂-receptor antagonists) before and after the intervention period March 2001 – April 2003.
CI: confidence interval; PPI: proton pump inhibitor.

From 2004 on, Pharmanet database includes the age category of the patient for whom the prescription is intended. It was impossible to provide a reliable estimation of consumption of acid suppressants in infants younger than 1 year, as the age categories in the Pharmanet database are not granular enough (0 to 2 years). In addition, for more than a third of the prescriptions, issued by paediatricians, the age of the patient was not mentioned. For those prescriptions where age was mentioned and in the category of 0 to 2 years, only the consumption of PPIs increased (by almost a factor 2) between 2004 and 2008 (table 7.3).
Table 7.3: Monthly reimbursed volume in daily defined dose per 1000 inhabitants per day of histamine H₂-receptor antagonists and proton pump inhibitors, prescribed by all prescribers and by paediatricians.

<table>
<thead>
<tr>
<th>Year</th>
<th>Histamine-2-receptor antagonists</th>
<th>Proton pump inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All prescribers for all inhabitants</td>
<td>Paediatricians for children aged 2 years and younger</td>
</tr>
<tr>
<td>1997</td>
<td>4.96</td>
<td>0.08</td>
</tr>
<tr>
<td>2004</td>
<td>7.93</td>
<td>0.51</td>
</tr>
<tr>
<td>2008</td>
<td>13.13</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Over the study period, availability of different products, packages and formulations - each indicated by a specific National Drug Code (NDC) - increased 10-fold. The number of NDC’s (national drug codes) of a specific product indicates the number of different packages and formulations on the market. The amount of NDCs went from 34 in January 1997 to 359 in June 2009. The huge increase in the total amount of NDCs indicates the increase in different packages and formulations, due to the introduction of generics. Nearly all of these represent capsules in adults’ doses. During the study period only the cimetidine and ranitidine oral suspension was a formulation suitable for children. There are no paediatric formulations of proton pump inhibitors on the Belgian market. However, anecdotal reports from pharmacist report on the practice of mixing omeprazole pellets from capsules in baby food.

4 DISCUSSION

To the best of our knowledge, this study is the first observational drug utilisation study on paediatric use of acid suppressants in children, performed in a national claims database with universal coverage. Our analysis of acid suppressants over a period of more than twelve years shows that there was a substantial increase in prescribed drug volume and expenses; while the study population was stable. These results concern nearly all reimbursed acid suppressant prescriptions, dispensed by community pharmacies and made by Belgian paediatricians. Throughout this study period, several developments may explain this increase. From 2000 on, serious restrictions to prescribe cisapride – an important player on the antireflux market - were issued until the drug
was withdrawn from the market in 2005\textsuperscript{28}. The graphs suggest that the prescription restrictions of cisapride led to an increase in prescription of the acid suppression drugs, namely PPIs and H\textsubscript{2}-RAs, from 2001 on. After the first measure of March 2001, the consumption of H\textsubscript{2}-antihistamines increased as soon as the prior approval restrictions were dropped, but not at the expense of PPI consumption. In the same period, when PPIs were still subjected to prior approval, prescriptions rose slowly.

In April 2003, the first PPIs (omeprazole and rabeprazole) were made available without restriction, in exchange for substantial price reductions. In the adult population potential savings by these price reductions were counteracted by a soaring consumption volume, mainly in the PPIs, and for the indication of esophagitis. The abolition of prior approval for H\textsubscript{2}-RAs and omeprazole in exchange for price reductions was a drug policy measure to curb expenditures in the adult population. However, this provoked in the paediatric population an unintended spectacular growth in consumption of acid suppressant drugs from 0.14 in 1997 to 2.12 DDDs in 1000 inhabitants per day in 2008. Two thirds of this use consisted of PPIs. In children and infants the use of the more expensive PPIs (still under a priori control) was rather exceptional. It is possible that paediatricians preferred to use omeprazole, (which was available without restrictions and the need for documentation) to stay below the radar of a priori control in the off-label indication. The policy of a posteriori control, issued in 2005, seems to have had little deterring effect.

Marketing strategies by pharmaceutical companies were not directed at use in infants because these molecules are not approved for this age group and legally off-label. But – as Hassall stated in a recent commentary - the term acid reflux as used in the marketing of PPIs to adults has probably trickled down to adolescents and children, and in more recent years, to infants\textsuperscript{30}. This may have blurred the dividing line between gastroesophageal reflux and GERD in children\textsuperscript{18,30}. OTC medication was not included in our study database. It can be presumed that some of the prescriptions of OTC medication of the past (for example of domperidone) have faded into PPI prescriptions, after they switched to ‘open benefit’.

Our database shows that a large volume of the PPIs, prescribed by paediatricians, are used in children of 2 years of age and younger. This increase observed in our Belgian
study is consistent with the prescription patterns described by Barron et al, Chen et al and Blokpoel et al\textsuperscript{7,31,32}. These studies showed a similar increase in PPI prescriptions, in a population which anyhow didn’t have these particular reimbursement measures. This overdiagnosis of GER is not unimaginable in the infant age group as excessive crying or irritability and regurgitations are the most common reasons for parents seeking professional help for their infants in the first 3 months of life. It is not surprising that many irritable infants may have also regurgitations. Many children are being given acid suppressing drugs and motility agents in the belief that reflux is the cause of crying\textsuperscript{19,30}. Though, the available RCTs with PPIs in infants show that PPIs and placebo produce similar improvement in crying, despite the finding that acid suppression only occurs in the PPI-group\textsuperscript{7,8,12,20,31,33,34}. It should also be noted that, in Europe, none of the available PPIs are labeled for infants under 12 months of age\textsuperscript{1,7,8}. The current Paediatric Gastroesophageal Reflux Clinical Guidelines of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) clearly state that GER should be treated in the first place by reassuring and guiding the parents\textsuperscript{1}. The future will show whether highlighting these guidelines during scientific paediatric meetings and in local medical press is able to change prescription attitudes as we know that there is a possible discrepancy between physicians’ clinical impressions, interpretation of medical literature and behavior\textsuperscript{14}.

A limitation of the study is that we only have information on the volume prescribed by paediatricians, and not on the prescription volume by general practitioners for children. By consequence, our data are possibly an underestimation, certainly not an overestimation. Second, this is an observational study in a claims database; covering an entire population. This is a strength but has the disadvantage of being less detailed: the prescription data are not linked to clinical diagnosis or to individuals. Consequently, only the number of prescriptions but not the number of treated patients could be identified. Third, the duration of therapy of each patient could not be identified. However, it is most unlikely that an increase in mean duration of therapy was sufficiently important to explain the reported huge rise in PPI prescriptions. The use of DDDS in children is another limitation, as DDD is the standard dose for adults.
Unfortunately, we could not correct this unit for age or for weight, as these details of the patients were not mentioned in the database.

In conclusion, there was a remarkable increase in prescriptions of antireflux medication by paediatricians during the last decade, more particularly of PPIs. This is similar to the rising acid suppressant prescriptions in adults. The withdrawal of cisapride might have contributed partly to the early rise but cannot fully explain the recent ‘PPI boost’, which is most prominent in infants. This finding contrasts with the evidence that PPIs offer little benefit for excessive crying and irritability. Other causes for the rise of the acid suppressants might be a larger availability of acid suppressants on the market (generics, etc), the reimbursement conditions (omission of restricted reimbursement), mentality change: parents seem to be less tolerant of irritable, crying children and marketing: the marketing strategy to promote PPIs for the treatment of acid reflux may have trickled down to children and infants. The current guidelines indeed state that infants with uncomplicated gastroesophageal reflux do not need medication, but reassuring and guiding of parents. Future investigation into the reasons for not following the guidelines and for the growing prescription rate of PPIs in infants is imperative.

ACKNOWLEDGEMENTS

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REFERENCES


CHAPTER 8

SAFE-PEDRUG: DEVELOPMENT OF A NEW PAEDIATRIC DRUG RESEARCH APPROACH
1 INTRODUCTION: IMPORTANCE OF COLLABORATION

Improved availability of appropriately labelled, safe and effective medicines for children in age-appropriate formulations will require a significant increase in high quality clinical trials in children. For this, we will both need the development of a national or international infrastructure and a strong collaboration with the different stakeholders in paediatric drug development; notably for the exchange of knowledge and to overcome recruitment problems\(^1\)-\(^7\). This was emphasized by MacLeod in his paper on the improvement of drug treatment for children: *The most pressing challenge remaining is mobilisation of a critical mass of caregivers, pharmacologists, pharmacists, and other child health professionals prepared to employ their skills on behalf of children and youth who need access to better pharmacotherapy.* (Figure 8.1)\(^8\). This need for collaboration was also identified by the EMA through the Paediatric Regulation; as will be discussed later in this chapter.

![Synergistic relationships to ameliorate drug therapy for children (adapted from MacLeod\(^8\))](image-url)

**Figure 8.1**: Synergistic relationships to ameliorate drug therapy for children (adapted from MacLeod\(^8\))
The traditional clinical trial stakeholders identified are the regulatory authorities, pharmaceutical industry and academia. Each of the main stakeholder group is currently adapting to the new developing world of paediatric pharmacology: all of them are expanding their expertise in the different aspects of paediatric preclinical and clinical research. For example, experts in modelling and simulation have been working in industry and academia for years. During recent years, this specific expertise is being markedly expanded in the group of national and international regulatory authorities; this in order to improve and facilitate review of clinical trial protocols and to give sound scientific advice to the investigators. It can be expected that all will continue to develop their expertise in the coming years, which will be important for paediatric pharmacology. The specific task of the academia in this collaboration will be to give scientific advice for new regulations to the authorities and to deliver innovative tools to the industry. Additionally, retaining and fostering public and political interest in paediatric medicines will be pivotal for success. Nowadays, the importance of a strong collaboration with other stakeholders such as patient organisations, child health professionals, and government and funding agencies is increasingly recognized (figure 8.1). An example of this are the representatives of patients organisations being a member of the PDCO at the EMA. Unfortunately, such collaborations are currently rather scarce and should be developed and consolidated in the future.

2 THE SAFE-PEDRUG PROJECT: BUILDING CAPACITY FOR RESEARCH AND DEVELOPMENT OF MEDICINES FOR CHILDREN

2.1 Management and workflow
The need for collaboration with the different stakeholders in Belgium and Europe was a starting point for our SAFE-PEDRUG project: a consortium of experts in paediatrics, pharmaceutical sciences, veterinary medicine and ethics. This consortium is composed of experts of three different Belgian universities which are actively involved in research and clinical care of children: Ghent University, Vrije Universiteit Brussel and KULeuven. The planning of this project was started in November 2011; the project itself was initiated in January 2014 with funding by the Agency for Innovation by Science and Technology in Flanders (now managed by the Research Foundation – Flanders (FWO)). At the core of the consortium is the project team that provides strategic leadership.
This team is composed of the chairs of each work package (WP) of the project as presented in figure 8.2. Crucial in the project is the identification of the needs of the paediatric population (WP 1) and the generation of paediatric PK and PD knowledge before the actual human trials are performed. For this, we explore the value of the porcine juvenile animal model (WP 3) and PK modelling (physiologically-based pharmacokinetic modelling) (WP 4). For the evaluation of this approach, three case compounds were selected: desmopressin, lisinopril, and fluoroquinolones. The results of these models are plotted against human paediatric data (WP 2). Furthermore, PK and PD in neonates and critically ill children will be explored in WP 5 and WP 6 respectively. Last but not least, the ethics of paediatric clinical trials and the concept of consent and assent will be explored by the ethicists of our team (WP 8). Robust management and monitoring processes are in place to ensure that our studies are of high quality and deliver to time and target (WP 9).

2.2 Advisory Board and Stakeholder Group
The SAFE-PEDRUG consortium is supported by experts from national and international stakeholder groups (including industry, regulatory authorities, and patient organisations). These experts are represented in the Advisory Group and Stakeholder Group of our project and meet face-to-face every year. During preparation of the granting documents they had input in relevant issues and during the yearly meetings the progress of our project is reported and discussed. Their main task is to direct the research within the SAFE-PEDRUG consortium by identifying and prioritising appropriate research questions.
Figure 8.2: Workflow of the SAFE-PEDRUG project with the main data streams
WP: work package, ACE: angiotensin converting enzyme
3 PROGRESSION THROUGH THE SAFE-PEDRUG COLLABORATION

3.1 Building up scientific competence

Regulatory requirements to address paediatric drug development are now expected earlier in the overall drug development programs\textsuperscript{11}. Current European regulations expect submission of the paediatric investigation plan ‘no later than’ the completion of the relevant human pharmacokinetic studies in adults\textsuperscript{11,12}. As a result, paediatric development is expected to be more regularly integrated into the adult drug development program. However, this shift means that the benefit of full knowledge from both adult human clinical data and longer term adult animal data may not be available to aid in the design of the paediatric clinical trials. As experience with the PIP has grown, sponsors are increasingly developing their nonclinical strategy in an effort to overcome this limitation\textsuperscript{11}. Preclinical testing by modelling and simulation and juvenile animal models will be of great value for this.

3.1.1 Modelling and simulation in WP 3, WP 5 and WP 6

Modelling and simulation (M&S) are powerful tools that are now being used in drug development\textsuperscript{13}. To meet the objectives of the Paediatric Regulation, there is definitely a need for techniques that make optimal use of the limited opportunities for clinical research with a limited number of children. That is why methodologies such as M&S are recognized by industry, academia and regulators as promising techniques for increasing the quality of data and analyses in small populations\textsuperscript{14}. Modelling compromises the description of the behaviour of a system or process by a set of mathematical expressions that is usually a simplification of certain aspects of reality and focuses only on those factors and processes that are believed to be important\textsuperscript{15}. Simulation is then the application of this mathematical model usually over time to explore situations that have not been investigated experimentally, thereby extrapolation beyond the currently available experimental data\textsuperscript{15}.

Two basic areas of M&S application have emerged in recent years in paediatric clinical pharmacology research\textsuperscript{13}. One is a “bottom-up” application of M&S techniques, such as physiologically based pharmacokinetic (PBPK) modelling, to optimise trial designs, select dose level and dosing regimens, develop sampling schemes, and select outcome measures\textsuperscript{13,15,16}. This application of M&S is frequently based on adult data and uses
various extrapolation approaches that incorporate PK and PD data from preclinical species, in vitro experiments, and paediatric data from pilot studies or studies in older paediatric groups\textsuperscript{13,15}. This technique is used in WP 3. The second emerging area is a “top-down” application of M&S techniques that has been used even more frequently to analyse PK and PK–PD data from paediatric studies, especially using population based approaches to derive maximum information content from the limited data collected in paediatric studies\textsuperscript{13,15}. It allows the extrapolation of the influence of different covariates such as body weight and age to explain the variability in drug response\textsuperscript{17}. This modelling approach is used in WP 5 and WP 6. Although bottom-up and top-down modelling can be differentiated, more complex applications of modelling and simulation in drug development apply aspects of both of these modelling techniques\textsuperscript{15}.

It should be noted that in silico prediction of PK behaviour in paediatric patients is not intended to replace clinical studies. However, it provides a valuable aid to decision-making with regard to first-time dosing in children and study design\textsuperscript{18}. The clinical trial then becomes ‘confirmatory’ rather than ‘exploratory’\textsuperscript{18,19}. This may reduce the number of paediatric subjects required in a drug development program\textsuperscript{20}. Regulatory bodies increasingly encourage the use of M&S methods for all paediatric drug development programs, which is also reflected in a number of regulatory guidance documents, working groups and workshops\textsuperscript{14,15,18,21,22}.

Drug developers are now building teams of people who have training in M&S, but who often lack any paediatric clinical experience\textsuperscript{23}. We are convinced that a close collaboration between clinicians, pharmacists and pharmacometricians will not only decrease the invasiveness of clinical trials, but will increase the value of these investigations by combining a priori determination of the optimal dose to be studied and optimal sampling techniques to minimise the invasive procedures\textsuperscript{24,25}.

### 3.1.2 The porcine juvenile animal model in WP 4

Nonclinical animal studies play a central role in supporting drug development in both the paediatric and adult populations. The goals of these investigations are to characterize the absorption, distribution, metabolism, and excretion (ADME) and toxicokinetics in animals, as well as to identify potential target organs for toxicity. With
regard to paediatric drug development, an additional level of complexity is involved, as evaluation of human relevance not only involves considerations of cross-species applicability of findings but also the stages of growth and maturation as the child or animal ages\textsuperscript{11}. Juvenile animal studies can contribute to a thorough evaluation of potential drug related effects with direct dosing, thus providing information on both target organ toxicity and developmental effects\textsuperscript{11}. With the new legislations, there has been an increased interest in juvenile animal models to further support paediatric clinical trials\textsuperscript{26}. The FDA and the EMA issued guidelines regarding nonclinical safety evaluation of paediatric drug products\textsuperscript{11,27}. Both authorities conclude that the requirement and design of juvenile animal models should be on a case-by-case basis and only after careful consideration of all available data, the indication and the age and duration of treatment of the intended paediatric population\textsuperscript{26,27}. When a clear or scientifically based potential (safety) concern exists, juvenile animal studies might be valuable adjunct studies to address specific concerns or fill a data gap\textsuperscript{27}.

A recent report about the juvenile animal studies performed in the context of a PIP show the rat (65\%) and the dog (7\%) as the most frequent animals used\textsuperscript{26}. In our project the pig will be evaluated as a juvenile animal model. Over the years, pigs (\textit{Sus scrofa domestica}) became more of interest as alternative model due to anatomical, physiological and biochemical resemblances between adult pigs and humans\textsuperscript{28}. It has similarities with human beings with respect to cardiovascular system and renal function parameters\textsuperscript{28,29}. The pig model offers the advantage that the effect of medicines on growth and development can be evaluated in a practical timeframe of 6 months. The potential use of this animal model could be very broad, including PK/PD modelling, and toxicity testing\textsuperscript{28}.

### 3.1.3 Consideration of specific paediatric populations in WP 5 and WP 6

The importance and the challenges of considering neonates and critically ill children in paediatric drug development have been described in chapter 2. Both neonates and critically ill children differ from other children and adults in their drug response. These differences may be caused by changes in PK and/or PD\textsuperscript{18}. Besides maturational changes (and pharmacogenetics), treatment modalities (hypothermia, extracorporeal circulation) and environmental issues (microbiome, critical illness, comedication) may
further intensify the PK/PD variability. In WP 5 and WP 6 drug disposition in these special paediatric population will be investigated.

3.1.4 Advocacy for ethical aspects of paediatric clinical trials in WP 8: informed consent and assent

Consent and assent is an essential but also challenging element in paediatric clinical trial management. A local survey by our SAFE-PEDRUG group showed that the major issues for investigators regarding obtaining informed consent were: availability of both parents, time available for explanations and questions, and obtaining informed consent in a stressful environment. The availability of both parents was considered to be the most serious issue, indicating that the participants were not comfortable including children in a trial when only one parent was available to give permission. These issues will be further evaluated in WP 8 of the SAFE-PEDRUG project.

Ideally, the consent process should be a dynamic and continuous process obtained prior to enrolling a child in a trial. It requires an ongoing dialogue between the child, parents and investigators throughout their participation. Since children are unable to provide informed consent, paediatric research relies on parental permission to authorise the enrolment of children in research. The decision-making right of the parent applies until the minor child reaches the legal age of majority and is given the right to consent independently under local jurisdiction. The age of majority and definition of minor varies considerably by country and region. Also the requirement for permission from one or both parents is assigned by national regulations. For parental or proxy consent to be valid, four essential components must be fulfilled: the person granting permission must be mentally competent, have received appropriate information about the purpose and duration of the study and its risk and benefits, understand the information, and give consent voluntarily without coercion (i.e. free from pressure). The informed consent form is the conduit for summarizing the study and documenting disclosure about the study. The form describes the purpose, procedures, risks, alternative treatments and other details mandated by national and local regulations. It should be perceived as an adjunct for informing participants. However, forms have increasingly evolved into a detailed description of every event, often in language beyond the recommended level of ethics committees.
Assent is described as *knowing agreement whereby the child is presented with age-appropriate information and is given the opportunity to voice an opinion regarding participation*. The guidance on the implementation of the EU Clinical Trials Directive 2001/20/EC requires that a minor’s assent is ‘considered’, but is not a legal requirement. The guidance recommends that the child should participate in the informed consent process whenever appropriate. The minimum age requirements for assent has been widely debated and vary considerably. It is obvious that also developmental stage, intellectual capacities, psychological state and life experience contribute to a child’s ability to assent. Most studies recommend the use of age-appropriate language and conclude that children from 9 years old may be able to understand the benefits and risks of research. The ICH defers to ethics committees for interpreting local statutes on the minimum age for assent. In practice, ethics committees most often require assent by age 6 or 7. Content for the assent form should be appropriate for each age group or level of understanding. As such, one study may need more than one version of the assent form.

For several reasons, the signature of a document by no means guarantees a duly informed, well-considered, rational decision and it must be emphasized that ethics, law, and ethics committees do not establish ethical research conduct as such. Researchers and other health care professionals play a key role in the practical realisation of ethical research conduct. The challenge ahead is to foster ethical conduct in all involved. In addition, it would be unreasonable to expect from minors and their parents to just own the skills and know-how that are required to make well-considered decisions on participation in a clinical trial. However, at present, easily accessible support for minors and their parents in deciding on research participation is still largely lacking. Efforts should be made to employ the vast and unexplored potential of empowering all involved for the advancement of ethical conduct in paediatric clinical research. Practical support for the practical involvement of minors in decisions on research participation could be of great help in making the principle of respect for persons operational in the setting of paediatric research. In WP 8 of this project, we will investigate the possibility of using supportive materials for enhancing comprehension and making the trial progress more visible for the children. The materials may take the form of computer games, that can be individualised for...
educational levels languages and other specifics relevant to the targeted study population\textsuperscript{30}.

### 3.1.5 Optimisation of the PIP based model through paediatric preclinical investigations

As for the Paediatric Regulation, PIPs must be submitted around the end of Phase I of adult trials. However, in practice, the proposed paediatric trials tend to be amended and postponed (deferred) to the end of the drug evaluation process, as they are largely based on the results of adult trials. This top-down approach from adult to child – as presented in figure 8.3 - delays the availability of the drug for children. Based on our own results, we expect the feasibility of a paediatric drug research consortium focusing on a bottom-up approach. This involves appropriate paediatric clinical design for paediatric indications, based on evidence in early adult studies, but also paediatric PK/PD modelling and data from paediatric animal models. This approach can contribute to better prior paediatric PK and PD knowledge and speed up the start of the paediatric trials. Consequently, PIPs will no longer be an add-on to the adult drug development process. This will require devoted ‘paediatric teams’ within academia and industry. Our multidisciplinary team with specific expertise in paediatric drug research including physicians, pharmacometricians, and experts in pharmaceutical sciences and veterinary medicine will investigate this approach.
Figure 8.3: Timing of PIP development under the Paediatric Regulation\textsuperscript{12}
MA: marketing authorisation; PIP: paediatric investigation plan
3.2 Future perspectives

The SAFE-PEDRUG project is a work in progress. The work packages will be completed in the coming two years. One of the future goals is to join the Enpr-EMA network, which was one of the obligations of the Paediatric Regulation (article 44). It is a European network of existing national and European networks and centres with specific expertise in performing studies in children. This European Network was called Enpr-EMA for European Network of Paediatrics Research at the European Medicines Agency and was launched in March 2011. It now has 17 member networks, that can be divided into three main categories: national networks, disease-oriented networks, and other representing special activities or age-related networks (e.g. neonatology). The goals of these networks, usually not for profit, are to provide facilities and access to paediatricians, children and their families for the proper conduct of clinical trials in children. It is our aim to fulfil the recognition criteria of Enpr-EMA (research experience and ability; network organisation and processes; scientific competencies and ability to provide expert advice; quality management; training and educational capacity to build competencies and public involvement) in the next coming year.

3.3 Conclusion

This research initiative illustrates that a close collaboration of experts in the different fields of paediatric pharmacology, together with other stakeholders, can put a new perspective on the future of paediatric pharmacology. Exchange of ideas and knowledge can help to tailor paediatric clinical trials to the PK/PD-characteristics and the needs of children.

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CHAPTER 9

DISCUSSION AND FUTURE PERSPECTIVES
1 DISCUSSION

Although current legislations and initiatives are improving the scope, quantity and quality of trials in children, there are still deficiencies that need to be addressed to accelerate equitable access to evidence-based therapies. This was shown in the five studies in this doctoral thesis. The chosen cases were relevant as they concern drugs that are prescribed frequently in paediatrics.

1.1 Desmopressin

Studies in the appropriate patient population are mandatory for good information about the drug in this population. This is the case for desmopressin. Desmopressin (dDAVP, 1-deamino-8-arginine vasopressin) was first synthesized in 1967, as vasopressin analogue. Desmopressin was initially introduced for the treatment of central diabetes insipidus in 1972. Subsequently, in 1980, desmopressin was approved for the management of primary nocturnal enuresis in children. Being clinically employed for over 30 years, a range of formulations has been developed for the treatment of nocturnal enuresis: intranasal solution was introduced in 1972 and withdrawn from the market because of safety considerations, tablets were introduced in 1987 and an oral lyophilisate was introduced in 2005. The latter was labelled for children of 5 years and younger based on adult bioequivalence studies (between tablet 200µg and oral lyophilisate 120µg) and one dose finding study in children. Our study (chapter 4) questions the stated bio-equivalence of both formulations: tablet and oral lyophilisate showed different variability in plasma concentrations, with suggestion of need for weight dependant dosing with the oral lyophilisate formulation. In a next step, our pharmacokinetic study and data were further analysed by our colleagues of The Faculty of Pharmaceutical Sciences. This analysis confirmed our findings.

Bio-inequivalence is often undetected unless linked to serious inefficacy or safety issues. Most bioavailability and bioequivalence studies are generally done in healthy adult volunteers, which can lead to safety issues in drugs with a narrow therapeutic range. A level of uncertainty is added when these medications are used in children. This finding warrants for bio-equivalence studies in the treated population.
1.2 Antihypertensives

In children with hypertension, non-pharmacological measures are often recommended as first-line therapy, but a significant proportion of children will eventually require pharmacological treatment to reduce blood pressure. Until 1997, few antihypertensive agents were studied systematically in children, and very few were labelled for use in patients younger than 18 years. Off-label use, with all of its implied risks was often the only viable option available to physicians who treated children with hypertension. The legislation changes in the Unites States and Europe have led to the study and approval of antihypertensive agents for children. However, treatment for this conditions is still hampered by uncertainty about the efficacy and safety of antihypertensive medicines in children, as was shown in our study (chapter 5).

The first study (section 5.1) shows that there is still a backlog in labelling of antihypertensives. Diuretics and beta-blockers have been used in children for many years. However, there are few published clinical trials evaluating the use of these agents. Most diuretics and beta-blockers have a long history of safety and efficacy based on clinical experience in hypertensive children. Their patents expired before the enactment of the FDAMA, thus decreasing the likelihood of further large, randomised controlled trials of these agents. For those older compounds, in Europe, the PUMA was expected to resolve this problem, at least in part. Up until now, however, no antihypertensive has been granted a PUMA yet. Of the calcium channel antagonists, amlodipine has the most clinical trial data to support its use in paediatric patients. In the past decade, the number of studies evaluating ACEIs and ARBs in children has increased as the number of agents in the class has expanded and clinical experience with these agents has grown. This was induced by written requests in the US. The incentives in place for the completion of the ‘pediatric study plans’ are designed to encourage trial completion; sponsors are given exclusivity if the trials are completed, and the decision to grant exclusivity is not dependent on product safety or efficacy. Feasibility is, therefore, of far greater importance than optimal trial design.

Antihypertensive agents should be examined in clinical relevant settings. Many of our patients who fall within a labelled age group still receive an off-label (off-knowledge) prescription because those patients we treat most frequently (with cardiac or renal...
disease, after transplantation, with specific concomitant medication) were excluded from the labelling studies\textsuperscript{12}. The exclusion of these groups of children with complex diseases resulting in secondary hypertension may preclude the intelligent, well-informed use of agents in children in these diagnostic categories\textsuperscript{11}. Additionally, our more recent review (section 5.2), evaluating the clinical trials of the ACEs, showed that the rather recent trials induced by the US and European legislation failed to fulfil several of paediatric needs: there is still absence of long-term safety data on growth and maturation, and incomplete evaluation of the entire paediatric hypertension population\textsuperscript{13}. This is similar to the conclusion of the Cochrane review on pharmacological interventions for hypertension in children\textsuperscript{5}: there is sparse data informing the use of antihypertensives agents in children. An additional problem is that reported outcomes are limited to blood pressure and do not include evaluation of end organ damage\textsuperscript{5,7}. Furthermore, although initial data concerning the pharmacokinetics, effectiveness, and safety of antihypertensives in children are becoming available, the large-scale comparative trials as conducted in adults that show superiority of one drug or one therapeutic approach over another have not been conducted in children\textsuperscript{5,6}. This would most likely require multicompany trials which are not well accepted at the moment (most probably because of intellectual property issues) but should be considered. In conclusion, we need studies of the comparative effectiveness, long-term safety and effects on growth, development and neurocognitive development\textsuperscript{14}. Clinical trials are usually powered for efficacy and not safety, as the latter requires a greater number of patients\textsuperscript{15-17}. Because clinical trials provide evidence regarding the efficacy of a new medicine, postmarketing surveillance is essential following the widespread use of a medicine to detect less common ADRs\textsuperscript{15-19}. This surveillance is at the moment mostly dependent upon a passive system of ADR reporting by health professionals (preferably in central databases such as the EudraVigilance database)\textsuperscript{15,16,18,20}. Education of health professionals in relation to drug toxicity improves the reporting rate of suspected ADRs\textsuperscript{15}. Other (active) methods may be considered to detect and/or monitor long term safety issues more efficiently: large data resources (in electronic medical records) with record linkage\textsuperscript{21}, treatment registries\textsuperscript{22} and post authorisation safety studies\textsuperscript{23}. A post-authorization safety study is a study that is carried out after a medicine has been authorized to obtain further information on a medicine’s safety, or
to measure the effectiveness of risk-management measures and can be imposed in the marketing authorization as part of this risk management plan\textsuperscript{22,24}.

Additionally, our studies show there is a lack of suspensions or other age appropriate drug formulations: only the ARBs have an age-appropriate formulation\textsuperscript{25}. This is remarkable, as some clinical trials in children have been performed with age-appropriate formulations (suspension)\textsuperscript{26}. Those were extemporaneously compounded liquid solutions that were developed and tested for short-term stability and bioequivalence\textsuperscript{6,27-29}. Unfortunately those formulations are not commercially available at the moment\textsuperscript{6}.

1.3 First generation H\textsubscript{1}-antihistamines

Similarly to the use of off-label (off-knowledge) drugs, on-label drugs frequently confront health care professionals and consumers with potential risks. Although it is generally assumed that drugs are considered for labelling only if they have been proven efficacious and safe, many older medications, have not been optimally studied in randomised, controlled trials. This is clearly the case for first generation antihistamines. The first antihistamine for human use, phenbenzamine, was developed in 1942\textsuperscript{30}. Later diphenhydramine and numerous other preparations became available: many of the first generation H\textsubscript{1}-antihistamines have been in clinical use since the 1940s and 1950s\textsuperscript{30,31}, long before regulatory agencies existed. They were licensed before the era of randomised controlled trials and modern evidence-based medicine\textsuperscript{31} and they remain on the market because the pharmacovigilance systems have not detected enough ADRs requiring their withdrawal\textsuperscript{32} or risk minimization measures. This was the case for the approved paediatric indication of codeine for cough and/or cold\textsuperscript{33}. First generation H\textsubscript{1}-antihistamines are lipophilic molecules that easily cross the blood-brain barrier\textsuperscript{34}. They have poor receptor selectivity and, thus can have varying amounts of anticholinergic, anti-alpha-adrenergic and antiserotonin effects\textsuperscript{34}. Use of these medication may result in drowsiness, sedation, somnolence and fatigue leading to impairment of cognitive function, memory and psychomotor performance\textsuperscript{31,34}. Our study (chapter 6) showed that they are used ubiquitously in on-label OTC medications for allergy and cold symptoms, insomnia, itching, urticaria, motion sickness and diarrhoea. Our literature review showed that in many cases there is no evidence for
this labelling, resulting in the large variety of labelled indications we could observe in our study. Many consumers and health care providers assume that these medications are safe because they are sold on-label and OTC, yet their safety profiles are one of the least studied in the literature\textsuperscript{31,34}. This is probably because they were sold as OTC medications long before safety profiles of medicines were closely examined\textsuperscript{34}. This study draws the attention to the fact that in some older medicines on-label use may imply off-knowledge use and pleas for re-examination of the allowance of OTC sale now that we recognize more fully the dangers of this class of drugs and as modern non-sedating antihistamines are now available.

1.4 Proton pump inhibitors

Proton pump inhibitors have become some of the most frequently prescribed medications for treatment of adults and children\textsuperscript{35}. Omeprazole, the first PPI, was approved for human use in the US in 1988\textsuperscript{36}. In recent years, all PPIs have received approval for use in paediatric patients for the treatment of GERD, and some for the treatment of erosive reflux esophagitis and the eradication of \textit{Helicobacter pylori}. Pharmacokinetic knowledge has been elucidated quite extensively. Most of the studies with PPIs in the paediatric populations were stimulated by the Best Pharmaceuticals for Children Act after a written request of the FDA\textsuperscript{35} and – unfortunately – most have been done in subjects of 2 years and older\textsuperscript{36}. At the moment of our study (chapter 7) there was no labelling for infants in Europe. In Belgium, there are no age appropriate formulation for children of age 6 years or younger.

The study of chapter 7 shows that PPI use has increased substantially in children during the last decade. Proton pump inhibitors were the most prescribed drugs in this study. At the same time, there are no indications that the prevalence of GERD - which is the most important labelled indication - is increasing. The increase in prescriptions was higher than any probable increase in prevalence of GERD. We saw that a large volume of the PPIs prescribed by paediatricians, is used in children aged 2 years and younger. Many young children are been given acid-suppressing drugs and motility agents in the belief that reflux is the cause of crying in infants, although the available randomised controlled trials with PPIs in infants show that PPIs and placebo produce similar
improvement in crying, despite the fact that acid suppression only occurred in the PPI group\textsuperscript{37-43}.

The study in chapter 7 demonstrates that publication of scientific results of paediatric trials is not sufficient for a rational use of medicines in children. This was confirmed by a more recent study by Quitadamo et al\textsuperscript{44}: even the new ESPGHAN and NASPGHAN joint recommendations on the management of reflux in children\textsuperscript{45} could not change the prescription attitudes. This study suggests that PPIs in children are often over-used and prescribed in an inappropriate manner and pleas for continuous audit and educational programs in paediatric general practice\textsuperscript{46}. We see a role for the paediatric clinical pharmacologists to help valorising the results of paediatric clinical trials, from bench to bedside. Next to that, prescribing physicians and children’s parents should make an effort to achieve a more rational drug utilisation\textsuperscript{46}. It is not only necessary that the data on the use of a specific product in the paediatric population are assembled, but that these data are then also appropriately communicated to, and used by, paediatricians in their day-to-day practice for the benefit of their patients\textsuperscript{47}.

2 FUTURE PERSPECTIVES

Drug development takes place at the interface of three main stakeholders: pharmaceutical industry, regulatory authorities and academia. So far, the role of academia was rather limited. In the next few years, the academic world has to strengthen its position in drug development and further identify and defend the needs of the patients, especially those who have comorbidities, neonates, critically ill patients, etc.; if necessary against the mainstream of financial interests of industry and society. This will require discussions with government and industry for increased investment in paediatric drug research and gaining a place in relevant networks.

As was shown in the presented papers, extrapolation of adult knowledge to children is in many cases not defendable. Careful and high-quality observational and interventional studies in children are mandatory. Priorities for this research cannot solely be set within the pharmaceutical industry or indirectly through requirements set forth by regulatory agencies. Instead the academic community with the support of patients’ and parents’ advocates, needs to lead the way. Academia should defend the rights of patient populations that are under-represented in drug development, such as
children, unborn children, pregnant women, critically ill patients and the elderly. Therefore, it is mandatory that academia are involved in the early phases of drug evaluation.

2.1 Developing a new paediatric drug research approach

Academia can help to close the gaps in paediatric PK and PD knowledge; not only through conducting high quality clinical trials but also through exploration of promising techniques such as M&S and juvenile animal models, as described in chapter 8. Fine-tuning of those techniques to paediatrics may contribute to optimisation of the current PIP-based model, aiming at an earlier start of the paediatric trials (enabling long term follow-up of the patients).

This doctoral thesis is one of the first steps in our paediatric pharmacology research line. The SAFE-PEDRUG consortium aims at developing a paediatric drug research unit. The current project has already been an accelerant for paediatric drug development at our centre and has resulted in close and successful collaboration with our colleagues of pharmaceutical sciences and veterinary medicine. We are confident that our research will continue to provide new insights in paediatric PK and PD, as well as to improve the ethics of paediatric clinical trials. We aim to become a strong member of the Enpr-EMA network and other relevant networks in the future. In this way, we – as a mainly academic consortium – will be able to be fully involved in paediatric drug development.

2.2 Networking

Academia can be an initiator for collaborations of experts and other stakeholders; with the aim of better integration and utilization of efforts in paediatric drug development. Expert centres and networks should concentrate paediatric expertise and should measure up to high quality standards for designing and performing clinical trials.

Collaboration and networking should cross the borders of faculties and universities within academia and should involve networking with other stakeholders of paediatric drug development. Although different interest are at stake, large consensus exists among the different stakeholders on the urgent need to establish new modes of
collaboration among industry, academia, pharmaceutical industry, regulators and patients’ organisations\textsuperscript{51}.

Public-private partnerships (PPPs) involving both private for-profit companies and publicly funded non-profit institutions are a rather new instrument to implement collaborative efforts and to share financial efforts. Until recently, PPPs in the biomedical sector were mostly bilateral agreements, typically between a pharmaceutical company and an academic institution. Now larger consortia are built to tackle the major changes that the healthcare system, and more specifically paediatric drug development, faces. Academia should play an pivotal role in the task prioritisation of these research consortia. A recent European initiative is the Innovative Medicines Initiative (IMI). IMI was set up in 2008 (by the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA)) to enhance the competitiveness of the pharmaceutical sector in Europe for the benefit of patients and scientists: in this initiative industry investment is matched by funds from the European Union and the funds support other consortium members, including academic teams, small and medium-sized enterprises, and patients’ organisations\textsuperscript{51,52}. IMI now focuses on paediatric drug development as well. Key challenges of private-partnerships have to be considered such as management complexity, selection of research topics, intellectual property rights, and overlap between consortia\textsuperscript{53}.

Patient and health organisations can and should be involved in the network of drug development. Patients and families have the experience and skills that complement those of researchers. They know how it feels like to undergo the treatments with their various side effects. They have a good idea of which research questions are worth investigating, and when a research question should be framed differently\textsuperscript{54}. Caregivers should be involved in study design (invasiveness of tests, randomisation, acceptability of formulations, feasibility, etc), but also when priorities on therapeutic needs are considered\textsuperscript{55,56}. The fact that parents or patient groups are represented through advocacy organisations at the PDCO and scientific advisory committees is an initiative that should be further explored\textsuperscript{54-56}. This will improve patient empowerment and provide better ways to inform patients about clinical trials.
2.3 Centralization to improve transparency and efficacy

One of the focuses of future (paediatric) drug development is on centralization. An example of this is the new Clinical Trial Regulation (N°536/2014) that will aim to harmonize the clinical trial application process. Other initiatives for centralization that academia should make full use of in the future are the following:

2.3.1 Registries

We should aim for full transparency in paediatric drug research with registration of trials, publication of trial results, and centralisation of safety knowledge. The importance of clinical trials, and of registries collecting their data, has been well established by the scientific community. Registries keep track of research from its beginning, and, can disclose when it remains unpublished (or only positive endpoints are published). This publication bias distorts the evidence base on which health care decisions are made. Numerous national and international clinical trial registries have been set up in the last few years, the most influential of which is the US’ clinicaltrials.gov. They facilitate the systematic review of clinical data, prevent publication bias, and the unnecessary duplication of research efforts, permit the identification of gaps in the knowledge base and promote international collaboration and data sharing. The same applies to the large databases for reporting (pre and post authorization) adverse drug reactions.

As important as developing expertise, is the communication of the acquired knowledge to the patients, the prescribers, the authorities and other investigators. The above-mentioned registries can make trial information available to clinicians, investigators, and the public.

2.3.2 Datasharing and biobanking

Datasharing and expansion of high-quality biobanking will be an important undertaking for future drug development. Anonymous linking of clinical data may provide researchers with the opportunity to study multiple research questions. For instance, the combination of existing pharmacokinetic datasets from medical literature, may significantly reduce the need for prospective pharmacokinetic trials. An illustration of this is the paper of Michelet et al in which our desmopressin dataset was combined with another dataset for population pharmacokinetic modeling.
storage in biobanks for future research are interesting step forward, provided that there are sufficient assurances that stringent processes and standards for patient privacy/confidentiality are in place \(^{60}\).

### 2.4 Paediatric clinical pharmacology

Paediatric clinical pharmacology is a discipline that offers many opportunities because it covers exciting multidisciplinary areas such as paediatrics, clinical pharmacology, pharmacometrics, pharmacogenomics, etc. The research in this thesis showed that there is still much to learn in paediatric clinical pharmacology, through interventional and observational research. Paediatric clinical pharmacologists should not only be involved in paediatric clinical trials and drug development but also in the correct and safe use of medicines.

Promotion of *rational use of medicines* is an important task of paediatric clinical pharmacologists. The justification for promoting clinical trials in paediatric patients is to ensure that they receive medicines that have been scientifically tested for both efficacy and safety and that age-appropriate formulations are available. Once scientific evidence is obtained and published, there is an obligation to ensure that health professionals use this information \(^{47,62}\). Unfortunately, irrational use of medicines appears to be a problem in high-income countries as well as in low-income countries. It is in this area that paediatric clinical pharmacologists can play an important role. There is a crucial role locally in drug and therapeutic committees ensuring that medicines that are likely to benefit children are introduced onto hospital formulary. They can contribute nationally and in Europe to drug formularies (such as kinderformularium.nl or the British National Formulary for Children), national prescribing committees, paediatric pharmacology research units and regulatory bodies \(^{62,63}\).

Another focus for the paediatric clinical pharmacologists will be *paediatric pharmacovigilance* as drugs toxicity unfortunately remains a significant problem in children \(^{15,18,64}\). Drug toxicity can occur from medication errors and also from an ADR after single or repeated use of a drug \(^{15,65,66}\). Clinical trials are usually powered for efficacy and not safety, as the latter requires a greater number of patients \(^{15-17}\) and do not provide long term safety information. While clinical trials provide evidence
regarding the efficacy of a new medicine, postmarketing surveillance is essential following the widespread use of a medicine to detect less common ADRs\textsuperscript{15-19}. As stated before, safety data cannot be extrapolated from adults to children as the profile and severity of ADRs are often different in adults and children, and effects on growth and maturation cannot be observed in adults\textsuperscript{67}. This postmarketing surveillance is mostly dependent upon health professionals\textsuperscript{15,16,18}. Education of health professionals in relation to drug toxicity improves the reporting rate of suspected ADRs\textsuperscript{15}. Paediatric clinical pharmacologists can play a key role in this\textsuperscript{18}; not only for educating but also for taking initiatives for detection (through laboratory or clinical outlier data signalling) and prevention (through drug prescription and administration errors prevention strategies) of ADRs\textsuperscript{17,65}.

The above-mentioned goals will require good education and training in paediatric clinical pharmacology for (future) physicians and pharmacists; not only for those working in drug development (academia, industry or regulatory authorities) but also for those involved in direct patient care. Collaboration and joint efforts of medical and pharmaceutical faculties and societies, together with the other stakeholders in paediatric drug development will be necessary to achieve this goal.

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Prescribing in children is often based on extrapolation from trials in adults due to the lack of paediatric data. The paediatric population is a heterogeneous group, ranging from preterm neonates to post-pubertal adolescents. Their disease presentation may have a different natural history and they may suffer from diseases which do not occur in adults. Children have complex physiological, developmental, and psychological characteristics that differ from adults. These features are also different across the neonate to adolescent age range. This might result in suboptimal therapy, unexpected responses, and ADRs. Therefore, both in the US and the EU, regulations to stimulate paediatric trials came into force.

In chapter 2, we introduce paediatric drug development, with its concept of ‘children are not small adults’, off-label and unlicensed prescriptions and the worldwide medicines initiatives. Subsequently, we discuss specific considerations for paediatric clinical trials such as ethical challenges, specific paediatric populations, and the importance of paediatric clinical pharmacology as a subdiscipline. Chapter 3 summarizes the specific objectives of this thesis. As the different publications report on different drug classes, a brief introduction on those compounds is integrated in this chapter. Chapter 4 reports on a PK study with desmopressin in children. This paper questions the stated bioequivalence of two oral formulations of this drug in children. Chapter 5 explores the case of antihypertensives in children and adolescents. The review in section 5.1 shows that most of the antihypertensives used in children still lack a labelling and that the availability of age-appropriate formulations is minimal. The case of ACEIs is further explored in section 5.2. This review shows that long term safety, comparative studies and investigations in children with comorbidities are priorities for the future. In chapter 6, a review of the SmPCs and a literature review showed that the on-label use of some old antihistamines is off-knowledge. Given this lack of evidence for use and their negative safety profile, these drugs should be used with caution. Subsequently, chapter 7 focuses on the irrational use of acid suppressant drugs in children. This pharmaco-epidemiological study shows that the number of prescriptions
of PPIs in infants and young children has increased markedly during the last decade. In this paper, we discuss the possible causes for this increase.

In conclusion, although the worldwide medicines initiatives resulted in a slight increase in the number of paediatric clinical trials, there are still several gaps in the knowledge of paediatric PK and PD. We lack knowledge on efficacy and safety of off patent drugs and old on-label drugs. Even in the group of newer on-label drugs, the knowledge about the impact of comorbidity and knowledge about long term safety should be optimised. We are convinced that these issues can be tackled by optimising the current PIP-based model. Chapter 8 reports on the SAFE-PEDRUG initiative in which different faculties of Ghent University, together with The Vrije Universiteit Brussel and KULeuven, collaborate on this concept.
SAMENVATTING

Aangezien we veel pediatrische kennis over een geneesmiddel missen, is voorschrijven voor kinderen meestal gebaseerd op extrapolatie van volwassen studiegegevens. We weten dat de pediatrische populatie een heterogene groep is, variërend van premature neonaat tot postpubertaire adolescent. Pediatrische aandoeningen kunnen een andere natuurlijk verloop hebben dan bij volwassenen en daarnaast veranderen kinderen voortdurend op fysiologisch, ontwikkelings- en psychologisch vlak. Dit kan leiden tot suboptimale therapie of onverwachte werking van een therapie. Daarom hebben de Verenigde Staten en Europa regulaties uitgevaardigd om het uitvoeren van pediatrische klinische studies te bevorderen. In hoofdstuk 2, introduceren we het pediatrisch geneesmiddelenonderzoek. Vervolgens bespreken we specifieke overwegingen voor pediatrische studies zoals ethiek, specifieke populaties en het belang van pediatrische klinische farmacologie als subdiscipline. Hoofdstuk 3 geeft een overzicht van de specifieke doelstellingen van dit proefschrift. Omdat de verschillende publicaties verschillende geneesmiddelen bespreken, wordt hierbij een korte inleiding over deze compounds geïntegreerd. Hoofdstuk 4 bespreekt een PK studie met desmopressine bij kinderen en stelt de aangegeven bio-equivalentie van twee orale toedieningsvormen voor kinderen in vraag. Hoofdstuk 5 bespreekt antihypertensieve medicatie bij kinderen. In de eerste paper (deel 5.1) blijkt dat voor de meeste van de antihypertensiva een labelling en goede toedieningsvormen voor kinderen ontbreken. De groep van ACE-inhibitoren wordt verder onderzocht in deel 5.2. Deze studie toont dat lange termijnsveiligheidsonderzoek, vergelijkende studies en onderzoek bij kinderen met comorbiditeit prioriteiten voor de toekomst zijn. In hoofdstuk 6, toont een overzicht van de bijsluiters en een literatuurstudie dat on-label gebruik van een aantal oude antihistaminica ‘off-knowledge’ is. Gezien dit gebrek aan evidentie en het negatieve veiligheidsprofiel, moeten deze met voorzichtigheid worden gebruikt. Vervolgens onderzoekt hoofdstuk 7 het irrationeel gebruik van zuurremmers bij kinderen. Dit farmaco-epidemiologisch onderzoek toont dat het aantal voorschriften voor protonpompremmers bij jonge kinderen sterk is toegenomen tijdens de laatste tien jaar. In dit artikel bespreken we de mogelijke oorzaken voor deze toename. Samengevat, hoewel de wereldwijde initiatieven hebben geleid tot een lichte toename
van het aantal pediatrische klinische studies, zijn er nog duidelijk hiaten in onze kennis van pediatrische PK en PD. We missen kennis over de geneesmiddelen waarbij het patent verstreken is en over oude on-label geneesmiddelen. Zelfs in de groep van de nieuwe on-label geneesmiddelen, moet de kennis over de invloed van comorbiditeit en lange termijns veiligheid worden verbeterd. We zijn ervan overtuigd dat deze problemen kunnen worden aangepakt door het optimaliseren van het huidige PIP-model binnen de ‘Paediatric Regulation’. Hoofdstuk 8 bespreekt het SAFE-PEDRUG initiatief waarbij verschillende faculteiten van de Universiteit Gent, samen met de VUB en de KULeuven, samen werken aan dit concept.
CURRICULUM VITAE

1 PERSONAL DETAILS
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2 CURRENT POSITION
Scientific staff at the Department of Paediatrics and Medical genetics of Ghent University - Co-initiator of the IWT-SBO project: ‘Integrating multidisciplinary translational bottom-up approaches towards a new paradigm for paediatric investigations: the next step in ethical paediatric drug research.’ (Project number 130033).

3 OTHER FUNCTIONS AND MEMBERSHIPS
- Tutor and examiner Pharmacotherapy at Faculty of Medicine and Health Sciences of Ghent University
- Chair of the Pediatric Pharmacology (Pedfarm) workgroup of Ghent University Hospital
- Member of the Core Group of the bpcrn (Belgian Paediatric Clinical Research Network)
- Reviewer Ethical Committee Ghent University Hospital
- Member of the editorial team of kinderformularium.nl (Dutch paediatric formulary)
- Member of Physiology Subgroup of HESI (ILSI Health and Environmental Sciences Institute) DART (Developmental and Reproductive Toxicology) Project on Nonclinical neonatal pediatric models.
- Trainer clinical pharmacology and biopharmacy (Dutch Society of Clinical Pharmacology and Biopharmacy – site Ghent University)

4 EDUCATION - EXPERIENCE


International experience obtained during medical studies:
- Erasmus exchange program: internship internal medicine and orthopaedic surgery at Hôpital Claude-Bernard Bichat, Paris (France), Jan 17- Apr 10, 2005.


Training hospitals: Heilig Hart Hospital Roeselare (Belgium) and Ghent University Hospital Ghent (Belgium)

2012 – 2015: Appointment as IWT PhD student at the department of Paediatrics and Genetic Medicine of Ghent University, Ghent (Belgium). Doctoral Grant (SB-111279) for Strategic Basic Research of the Agency for Innovation by Science and Technology in Flandres: ‘From extrapolation to patientoriented drug research: the importance of a full paediatric pharmacokinetic and pharmacodynamics program’.

Including a nine month fellowship (Jan, 2015 – Sept, 2015) Clinical Pharmacology and Toxicology at the University of Toronto / Hospital for Sick Children Toronto, supervised by Prof. dr. Shinya Ito, Prof. dr. Gideon Koren and Prof. dr. Irena Nulman.

(FWO travel grant for long stay abroad, V4.059.15N)
Supplementary certificates:
- Investigator Site Personnel Training GCP training: Jan 23, 2016.

Doctoral training programme Ghent University 2012-2015
- Advanced Academic English: Writing Skills (2012)
- Project Management (2013)
- Communication Skills: Meeting Skills (2013)
- Personal effectiveness (2015)

Facultative courses:
- Summer School of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition ‘Challenges in paediatric gastroenterology’, Madrid (Spain), September 11-15, 2012.
- EUCROF/RIPPS/EMA Conference ‘Methodological approaches to overcome the challenges of drug evaluation in children’, Londen (UK), April 18, 2013.
- GRIP training course and 14th congress of the European Society for Developmental Perinatal and Paediatric Pharmacology: Salzburg (Austria), June 4-7, 2013.
- Postgraduate course ‘Pharmacotherapy’ held at the 24th annual meeting of the European Society of Paediatric and Neonatal Intensive Care: Rotterdam (The Netherlands), June 12-15, 2013.
- Course ‘Introduction to Pharmacokinetics’ (Kinesis), Breda (The Netherlands), November 13-15, 2013.
- Postacademic training ‘Analysis of Variance’, Institute for Continuing Education in Science of Ghent University, Ghent (Belgium), January-February 2014.
- RIPPS Conference ‘Methodological Approaches to Paediatric Pharmacoepidemiology & Pharmacovigilance’, Lyon (France), December 5, 2014.
- bpcrn GRiP (Global Research in Pharmacology) Roadshow, Brussels (Belgium), April 24, 2015.
- Interuniversity Pharmacokinetics Symposium, Leuven (Belgium), April 29-30, 2015.
- The Hospital for Sick Children Research Institute Retreat, Toronto (Canada), June 5, 2015.
- The Canadian Society of Pharmacology and Therapeutics: Annual Meeting, Toronto (Canada), June 7-10, 2015.
- The 15th biennial Congress of the European Society for Developmental Perinatal and Pediatric Pharmacology, Belgrade (Serbia), June 23-26, 2015.
- The 48th Congress of the European Society of Paediatric Nephrology. Brussels (Belgium), September 3-5, 2015.
- Second conference on Drug Development in Pediatric and Rare Diseases: Past Successes and Current Opportunities, Basel (Switzerland), February 2-3, 2016.
- Innovative Medicines Initiative (IMI) Workshop on Paediatric Clinical Trials, Brussels (Belgium), April 5, 2016.

Supervision of students for thesis together with a senior researcher:

5 PUBLICATIONS (ORCID ID: 0000-0002-3090-9755)

Publications in journals with peer review:


Book chapter:


Abstracts of oral and poster presentations:


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literature. 48th Congress of the European Society of Paediatric Nephrology. Brussels (Belgium), September 3-5, 2015. Poster.
Published in: Pediatric Nephrology 2015; 30: 1584.

Published in: Pediatric Nephrology 2015; 30: 1597.

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Curriculum Vitae


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