Use of non-steroidal anti-inflammatory drugs in porcine health management

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Abstract

Objective Treatment of inflammation and pain management is an important topic in the welfare of pigs. It is very difficult for veterinary practitioners to choose the most appropriate product for a certain problem. This review aims to summarise and discuss the characteristics of different non-steroidal anti-inflammatory drugs (NSAIDs), as well as paracetamol and metamizole, available for pigs in the European Union.

Methods The databases Pubmed, Google Scholar, CliniPharm CliniTox and European Medicines Agency were searched. Relevant terms (eg,'meloxicam', 'fever', 'swine', 'pig', 'inflammation', 'castration', 'pain') were used to search for original articles, reviews and books. Only peer-reviewed articles were used. References from studies were also analysed in order to find additional relevant studies.

Conclusion Studies which have investigated the efficacy of NSAIDs for different conditions, using different treatment regimens, are scarce. Most studies focused on the efficacy of NSAID-related pain alleviation in piglet castration, as well as the anti-inflammatory potential of NSAIDs in experimental inflammation models. Little research has been carried out on the use of metamizole, tolfenamic acid, paracetamol and sodium salicylate and their effect in pigs.

Introduction

Farm animal welfare is increasingly gaining importance in society. Veterinarians and the entire veterinary profession have a pivotal role in safeguarding animal welfare.[1] The World Organization of Animal Health (OIE) has implemented animal welfare standards since 2005 and new standards are continuously added. The prevention and alleviation of pain are very important aspects of animal welfare. Various conditions in farm animals, including pigs, may cause pain and inflammation, for example, parturition and especially dystocia, lameness and surgical interventions.[2] These conditions may also negatively impact (re)productive parameters.[3 4] Corticosteroids (dexamethasone), non-steroidal anti-inflammatory drugs (NSAIDs) and NSAID-like drugs (having only antipyretic and analgesic effects) can be used to alleviate pain, inflammation and fever in pigs. Opioids, which are very potent analgesic drugs, are to the authors' knowledge not registered for use in livestock animals in the European Union (EU).

There are five NSAIDs and two NSAID-like drugs approved for pigs in the EU: meloxicam, flunixin, tolfenamic acid, ketoprofen, sodium salicylic acid, and paracetamol and metamizole, respectively. Sodium salicylic acid and paracetamol are registered for oral administration, ketoprofen is registered for oral and parenteral administration, and the others are only registered for parenteral administration.

So far, there is no review paper summarising and discussing the use and efficacy of NSAIDs in pigs against specific clinical problems. All NSAIDs differ in analgesic, antipyretic and antiphlogistic potential and efficacy, which makes it difficult for pig veterinarians to select the most suitable product(s) for a certain condition.

The present paper reviews and discusses the characteristics of the different NSAIDs available for pigs in the EU, the main indications for use in pigs, and the potential interactions with other medicines commonly used in combination with NSAIDs in pig herd health. An introduction is given on the pathogenesis of inflammation, pain and fever and their most relevant causes in pig practice (ie, castration of

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piglets, periparturient period, lameness and infectious diseases). The current knowledge of parenterally used NSAIDs is then discussed, followed by the orally administered NSAIDs, commonly used at group level. Finally, some conclusions and future perspectives are provided.

The efficacy of NSAIDs in surgical interventions (table 1), during the periparturient period (table 2), in lame sows (table 3) and in inflammatory processes in pigs (table 4) is summarised in this review. A table showing the pharmacokinetics and pharmacodynamics of NSAIDs in pigs is presented in an online supplementary file. The mode of action of NSAIDs has already been discussed[5 6] and is outside the scope of this review.

Inflammation, fever and pain in pigs

Inflammation is a physiological reaction of the body towards damage of tissue, which results in fluidic and cellular alterations within the injured tissue. During the fluidic phase, the vessels have an increased permeability and thus plasma proteins and oedema fluid can enter the perivascular area. With this transudate, chemokines are released in the periphery of the injury and attract neutrophils and macrophages (cellular phase). These phases aim to dilute and eliminate the cause of inflammation and to repair the damaged tissue. By consequence these pathophysiological reactions lead to the cardinal signs of inflammation: heat (fever, due to inflammatory cytokines/prostaglandins), redness (due to vasodilatation), oedema/swelling (due to vasodilatation), pain (due to inflammatory cytokines/prostaglandins) and loss of function of the injured tissue.[7]

Inflammation processes commonly occur in pigs of different ages and can have a severe impact on animal welfare as they cause pain and illness. The periparturient period is a quite challenging and stressful time for sows: they are moved to the farrowing stable with different housing conditions and a different feed, they undergo hormonal changes, the parturition is a painful process, and there may be stress caused by the farmer handling their offspring. Post-partum dysgalactiae syndrome (PDS) is the most relevant disease in sows during that period and risk factors and prevalence vary between farms.[8–10] Sows can show severe clinical signs such as agalactiae/hypogalactiae, metritis or mastitis. However, subclinical cases are more prevalent, which makes detection and early treatment difficult. Castration and tail docking of piglets are painful interventions that are commonly practised worldwide. The European Food Safety Authority (EFSA) and the Federation of Veterinarians of Europe (FVE) strongly advise the use of anaesthesia and analgesia for castration in pigs of all ages and training of people performing surgical castration.[11 12] NSAIDs on their own are insufficient to reduce pain during invasive surgical interventions (ie, castration) and thus should only be used in association with appropriate (either local or general) anaesthesia. Nevertheless, surgical castration is still often performed without any anaesthetic and/or analgesic treatment. In the fatteners, locomotion problems and respiratory diseases are the most important. Lameness is a multifactorial problem and it is also important in breeding animals. It is often associated with the housing (floor and cages), but management, nutrition, genetics as well as infectious pathogens may also be involved. It can be easily recognised during a daily herd inspection. It occurs more on an individual level than on a herd level. Respiratory problems have various causes (infectious and non-infectious) and are typically herd problems and as such demand a herd level treatment. They can have a tremendous economic impact as they are associated with a reduction in performance and an increase in antimicrobial use.[13]

The practitioner or the farmer can recognise a sick animal by several methods, for example, measuring the rectal temperature of the animal, observing individual behaviour (feed and/or water intake, locomotion) or, up to a certain point, evaluating the expression of pain (vocalisation, posture of the animal). Body temperature in pigs is mostly measured rectally, and values depend on their weight and age. Pain is a very difficult sign to evaluate as it is mostly subjective. In addition, pigs, as prey animals, tend to hide pain as much as possible. In 2016, Di Giminiani *et al*[14] published a method to measure and monitor pain via a 'piglet grimace scale' in piglets during and after castration and tail-docking. In addition to the 'piglet grimace scale', observation of behaviour—that is, suckling, playing, vocalisation, scratching, tail wagging, body position, isolation—helps to assess pain in pigs.[14–16] This is called the 'behavioural pain score'.[17] In scientific publications, researchers also use physiological parameters to evaluate pain or stress, including temperature, heart rate, blood pressure or respiratory rate, and concentrations of hormones such as cortisol, adrenocorticotropic hormone (ACTH) or prostaglandin E_2(PGE_2). Using such a scaling system in practice is difficult as it is time-consuming and labour-intensive. With the fast evolving developments in precision livestock farming it might be possible to assess some of these parameters and welfare in an automated manner without the need for human intervention.[18]

NSAIDs are the drugs of first choice in pig practice to alleviate pain and manage inflammation. Their main characteristics and the indications for their use are discussed below.

Parenterally administered NSAIDs

Meloxicam

Main characteristics

Meloxicam is one of the more recently developed NSAIDs. Engelhardt *et al*[19] highlighted meloxicam as a preferential cyclo-oxygenase 2 (COX-2) inhibitor in his

Table 1 Overview of the efficacy of NSAIDs in surgical interventions in pigs

Substance	Dosage (mg/kg BW)	Route of administration	Timing	Surgery	Pain* (post-op)	Stress*	Skin temp	Growth/weight gain	Pre-weaning mortality	Wound healing	References
Meloxicam/paracetamol	1/100	Intra-arterial/rectal	1x at surgery	Catheter implant	Meloxicam ‹paracetamol	Meloxicam ‹paracetamol					17
Meloxicam	0.4	Intramuscular	18±4 min prior	Castration	↘	↘		=			24
Meloxicam	0.4	Intramuscular	1x after	Castration	↘		=	=	=		26
Meloxicam	0.4	Intramuscular	30 min prior	Castration, tail docking	↘	↘		=	(↘)		25
Meloxicam	30	Per oral (sows)	D4–D6 after farrowing/ surgery D5	Castration, tail docking	↘	↘	↗				28
Meloxicam	0.4	Intramuscular	15 min prior	Castration	=	=		=	=		29
Meloxicam	0.4	Intramuscular	±20 min prior	Castration, tail docking	=						15
Ketoprofen	3	Intramuscular	20 min prior	Castration	↘	↘					51
Ketoprofen	3	Intramuscular	10–30 min prior	Castration	↘	↘					52
Ketoprofen	3	Intramuscular	30 min prior	Castration	↘	↘		=	=		54
Flunixin/meloxicam/metamizole	2.2/0.4/50	Intramuscular	15–30 min prior	Castration	↘ / ↘ / (↘)	↘ / ↘ / (↘)		=			73
Flunixin/meloxicam	2.4/0.8	Intramuscular	30 or 0 min prior/at surgery	Castration	Flunixin ‹Meloxicam	Flunixin ‹Meloxicam	↘ / ↘	=		↘ / ↘	74
Tolfenamic acid/meloxicam	2/0.4	Intramuscular	1 hour prior	Castration	Tolfenamic acid ‹Meloxicam	Tolfenamic acid ‹Meloxicam				=	91
Tolfenamic acid/meloxicam/ ketoprofen	2/0.4/3	Intramuscular	10 min prior	Castration	(↘) / ↘ / (↘)	(↘) / ↘ / (↘)					16
Acetylsalicylic acid	22	Per oral	30 min prior	Castration	=			=			101

During invasive surgical interventions (ie, castration), NSAIDs should only be used in association with anaesthesia (local or general).
*Parameters for pain or stress evaluation depended on the study: prostaglandin E, cortisol, adrenocorticotropic hormone, vocalisation, grimace scale, behaviour.
↘, reduction; (↘), no significant reduction; =, no difference; ↗, increase.
BW, body weight; D, day; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2 Overview of the efficacy of NSAIDs in sows during the periparturient period

Substance	Meloxicam	Meloxicam	Meloxicam	Meloxicam/flunixin	Ketoprofen	Ketoprofen	Ketoprofen	Metamizole/flunixin
Dosage (mg/kg BW)	0.4	0.4	0.4	0.4/2	3	3	1	50/0.5
Route of administration	Intramuscular	Intramuscular	Per oral	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Timing	±90 min pp	<12 hour pp	At farrowing	1.5–24 hours post clinical PDS signs	During 3 days pp	<12 hours pp	<12 hours pp	At farrowing +24 hours later if needed
Healthy sows	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes/no
Feed refusal	=	=		Meloxicam=flunixin	↘			
Backfat					↗		=	
Constipation					↘			
Lying time	=							
Fever	=	=		Meloxicam=flunixin			↘	= / ↘
Piglet growth	(↗)	(↗)	↗	Meloxicam=flunixin	=		=	
Pre-weaning mortality	=	=	=	Meloxicam <flunixin		↘	=	
IgG level piglets (day 1)			↗					
Number weaned piglets/litter						↗		
References	30	32	31	33	55	57	56	75

↘, reduction; (↘), no significant reduction; =, no difference; ↗, increase; (↗), no significant increase.
BW, body weight; IgG, immunoglobulin G; NSAIDs, non-steroidal anti-inflammatory drugs; PDS, post-partum dysgalactia syndrome; pp, post-partum.

Table 3 Overview of the efficacy of NSAIDs in lame pigs

Substance	Meloxicam	Meloxicam	Meloxicam/flunixin	Ketoprofen	Ketoprofen	Ketoprofen	Ketoprofen/benzylpenicillin	Flunixin
Dosage (mg/kg BW)	0.4	0.4	1/2.2	3	6	2/4	3/20	2.2/4.4
Route of administration	Intramuscular	Intramuscular	Per oral/intramuscular	Intramuscular	Intramuscular	Per oral	Intramuscular	Intravenous
Timing	2 x in 24 hours		±28 hours and ±52 hours pi	3 d every 24 hours + 5 wk every 48 hours	16 hours pi	5 d	3/5 d	14 hours pi
Age or weight		±267 kg	±241 kg	2 y (210 kg)	11.7 d (4.5 kg)		Birth–5 wk	10 d
Cause	Non-infectious	Non-infectious	Experimental induced (amphotericin B)	OCD	Experimental induced (kaolin)	Non-infectious	Various	Experimental induced (kaolin)
MT			↗		↗			↗ < ↗
Pain sensitivity			↘		↘		↘	
Lameness*	↘	↘		↘		↘	↘†	
Standing time		↗						
Feed intake	↗							
Pregnant	yes	yes	no			Yes (<100 d)		
References	107	35	34	59	47	58	108	72

*Parameters for evaluation of lameness depended on study: standing time, stepping frequency, symmetry of leg movement.
†Antimicrobial treated group and antimicrobial + NSAID treated group showed similar results.
↘, reduction; ↗, increase.
BW, body weight; d, days; MT, mechanical nociceptive threshold; NSAIDs, non-steroidal anti-inflammatory drugs; OCD, osteochondrosis dissecans; pi, post induction; wk, weeks; y, years.

Table 4 Overview of the efficacy of NSAIDs in inflammatory processes in pigs

Substance	Dosage (mg/kg BW)	Route of administration	Timing	Age or weight (kg)	Experi-mental	Pathogen/disease	Rectal temperature	Clinical signs*	Food consumption	Combination with AM	References
Meloxicam	0.4	Intramuscular	1 hour prior	2 months (25-39)	Yes	LPS *Ec*	=	↘			36
Meloxicam/flunixin	1.5/5.5	Intramuscular	10 hours + 1 hour prior LPS	5 wk	Yes	PRRS + LPS *Ec*	=	=			37
Ketoprofen/flunixin	3/2	Intramuscular	8 hours + 32 hours post	11–12 wk (30–40)	Yes	*Ap*	↘ / =		↗ / =		60
Ketoprofen	3	Intramuscular	6 hours post	3 wk	Yes	*Hp*	↘	↗	↗	Enrofloxacin 7.5 mg/kg	61
Ketoprofen/ acetylsalicylic acid/ paracetamol	1.5/100 and 35/30	Per oral	2 hours prior (via water) or 2 hours post (bolus)	20.5–50.5	Yes	LPS *Ec*	Ketoprofen <Acetylsalicylic acid= paracetamol				62
Ketoprofen	0.5/1/2/4	Per oral	1 hour post	10 wk (21–35)	Yes	LPS *Ec*	↘	↘			63
Ketoprofen	6	Intramuscular	1 hour prior	10 wk (28.5)	Yes	LPS *Ec*	↘	↘		Gamithromycin 12 mg/kg	64
Ketoprofen	1.5	Per oral	3 d	14 wk (24–57)	No	Mild PRDC (*Mh*, *Bb*, *Hp*)	↘	↘	=	Doxycycline 10 mg/kg (5 d)	65
Ketoprofen	3.3	Per oral	3 d	40–43	No	Acute respiratory disease outbreak (*Ap* + SIV)	↘	=	=		109
Flunixin	2.2	Intravenous	10 min prior	9–10 months	Yes	*St*	=	↘			78
Flunixin	2	Intramuscular	24 h/3 d	7–8 wk (11.3)	Yes	LPS *Ec* + *Pm*	↘	↘	↗	Ceftiofur† 3 mg/kg (5 d)	77
Paracetamol	15	Per oral	Every 12 hours	Growing pigs	No	Respiratory disease (*Ss*, *Bb*, *Hp*, *Ap*, *Pm*)			=	Doxycycline 5 mg/kg	95
Acetylsalicylic acid	60	Per oral	3 d	Growing pigs (28)	No	Vaccination: foot-and-mouth disease	↘		(↗)		105
Acetylsalicylic acid	100	Per oral	5 d	3 months (31)	No	Acute PRDC (*Mh*, *Pm*)	↘			Doxycycline 10 mg/kg (5 d)	110

*Clinical signs depended on the study: tachypnoe, vomiting, behaviour, shivering, stance time, dyspnoe.
†Antimicrobial treated group and antimicrobial + NSAID treated group showed similar results.
↘, reduction; =, no difference; ↗, increase; (↗), no significant increase.
AM, antimicrobial drugs; *Ap*, *Actinobacillus pleuropneumoniae*; *Bb*, *Bordetella bronchiseptica*; BW, body weight; d, days; *Ec*, *Escherichia coli*; *Hp*, *Haemophilus parasuis*; LPS, lipopolysaccharide; *Mh*, *Mycoplasma hyopneumoniae*; NSAIDs, non-steroidal anti-inflammatory drugs; *Pm*, *Pasteurella multocida*; PRDC, porcine respiratory disease complex; PRRS, porcine reproductive and respiratory syndrome; SIV, swine influenza virus; *Ss*, *Streptococcus suis*; *St*, *Salmonella typhimurium*; wk, weeks; y, years.

pharmacological analyses. That characteristic made it a favourable gastrointestinal tolerance drug, compared with other NSAIDs at that time, which mostly inhibited both COX isoforms, COX-1 and COX-2. In another study, Engelhardt *et al*[20] pointed out that meloxicam has, besides the anti-inflammatory characteristics in soft tissue, also anti-arthritic characteristics in experimentally-induced joint diseases in rats. Meloxicam reduces bone and cartilage destruction, and inflammation-induced oedema development, due to antagonism of immunologically mediated consequences. Besides the anti-inflammatory effects, meloxicam shows analgesic effects on inflammation-related pain, but no central analgesic effects (no effect on heat-induced pain or mechanically-induced pain). In this same context, meloxicam does not have a central influence on body temperature regulation (caloric centre). By inhibiting thromboxane B_2 production through toxins, meloxicam is, however, able to reduce pyrogen-induced fever. A recent study showed that long-term use (63 days) of meloxicam (0.4 mg/kg daily, corresponding to recommended dose) in growing pigs did not lead to any known NSAID-related side effects (gastric or enteric ulceration) and did not have an effect on osteogenesis or chondrogenesis in growing pigs.[21]

The pharmacokinetics of meloxicam not only differ between species,[22] but might also be dependent on the age of the animal. Fosse *et al*[23] showed that the elimination half-life ($T_{1/2el}$) of meloxicam (0.4 mg/kg) in piglets (mean age 19.2 days) is short (2.7 hours), but comparable to $T_{1/2el}$ described in adult pigs (2.5 hours) reported on the label of the approved product. However, plasma clearance was slightly lower in piglets (0.061±0.008 L/kg/hour) than in adult pigs (45 kg, 0.091 L/kg/hour), which might be due to differences in the hepatic clearance. They also showed a weak accumulation of meloxicam in the exudate (maximum plasma concentration (C_{max}) 0.655 µg/mL vs 3.277 µg/mL in plasma). In a pilot study of the same group (not published), only exudate protein concentration of 5000–17 000 µg/mL (compared with the sponge model in horses: 40 000–90 000 µg/mL in exudate) was measured (different inflammation model: multi-perforated tubes or cages). This could explain the low accumulation of the product at the site of inflammation, as protein binding of NSAIDs in general is high. It is not clear whether this low concentration is due to the experimental model chosen or a specific characteristic of meloxicam when used in pigs. Nevertheless, the exudate PGE_2 concentrations were significantly lower in the meloxicam treated group compared to the placebo treated group.[23]

Indications

Castration

Meloxicam can mitigate postoperative pain, but not intraoperative pain. Therefore, combination with anaesthetics, sedatives and other analgesics is required, for example, lidocaine (local anaesthetic). The recommended time point of injection is 30 min before surgical intervention. Meloxicam should not be given to piglets <2 days of age. Reyes *et al*[17] compared meloxicam to paracetamol in 8- to 20-day-old piglets regarding postoperative pain. Piglets treated with meloxicam at a higher dose than the recommended dose (1 mg/kg, intra-arterial (ia), once at moment of surgery, no adverse effects noticed), showed a significantly lower behavioural pain score and were back to baseline values of overall pain scores after 24 hours. In 2010, Keita *et al*[24] demonstrated that castration with pre-surgical meloxicam (0.4 mg/kg, intramuscular (im) between 10 to 30 min before castration) treatment decreased cortisol values and pain-related behaviour in piglets postoperatively. This was confirmed in the study of Tenbergen *et al*,[25] although meloxicam treatment had no impact on growth performance in piglets. Piglets treated with lidocaine locally (between 3–30 min before castration) and meloxicam (0.4 mg/kg immediately after castration) presented a reduced pain perception during surgery and also after surgery.[26]

In order to reduce animal stress and tissue damage at the injection site, the first studies in swine were based on oral administration of meloxicam. The bioavailability was 87% in adult swine[27] and transmission of the product was shown from the sow to the piglet via the milk.[28] Additionally, Bates *et al*[28] showed that oral administration of meloxicam to the sow (dosage 30 mg/kg body weight (BW)) was able to reduce pain (lower PGE_2, lower plasma cortisol concentration) in 5-day-old piglets after castration. Further studies should be performed to assess transmammary transmission of meloxicam and the impact on piglets' behaviour and pain. As meloxicam is quite well metabolised (<3% of unchanged meloxicam in urine, and 17% in faeces after oral administration), it remains to be investigated how much really passes the blood–udder barrier, how high the initial dose in lactating sows has to be, and how long the sows have to be treated.

However, other studies showed that meloxicam has only a minimal effect on pain alleviation of anaesthetised piglets during castration, even when used together with local anaesthetics.[15 29]

Periparturient period

Meloxicam administration in healthy sows in the periparturient period (0.4 mg/kg im, once ±90 min after birth of last piglet) did not increase the total lying time of the sow. Theoretically, piglets could thus not increase their uptake of colostrum and milk. However, in a second study, the immunoglobulin G (IgG) concentrations in the piglets were higher, the pre-weaning growth of the piglets was better, but there was no effect on pre-weaning mortality.[30 31] The latter authors also showed that treated sows did not develop

mastitis. The underlying mechanisms for the positive effects still remain unclear. In contrast, Tenbergen *et al*[32] could not demonstrate a significant improvement in piglet growth after meloxicam administration (0.4 mg/kg im, once within 12 hours of farrowing) in the sow. Hirsch *et al*[33] treated sows suffering from mastitis with systemic antibiotics, oxytocin and either meloxicam or flunixin. Both NSAIDs were equally efficient in producing an improvement in clinical signs in the sow (milk flow, nursing behaviour, vaginal discharge and degree of inflammation of mammary glands). However, piglet mortality was significantly lower in diseased litters (diarrhoea, weakness, lameness, etc) from sows treated with meloxicam, compared to litters of flunixin-treated sows (14.0% and 31.7%, respectively).

Locomotion disorders

The effects of meloxicam on non-infectious locomotor disorders in pigs have not been thoroughly investigated. Pairis-Garcia *et al*[34] showed that meloxicam (1 mg/kg BW, per oral (po), 28.5 and 52.5 hours after induction) mitigated pain sensitivity in experimentally-induced (by ia injection of amphotericin B) lame sows. However, Conte *et al*[35] reported that meloxicam (0.4 mg/kg im) has only a short-term analgesic effect (increased standing time after feeding) and thus a marginal effect on pain mitigation in natural occurring lameness in sows. It seems that the severity of the lameness in relation to NSAID treatment may play a role. In addition, it is questionable whether meloxicam is able to accumulate sufficiently at the site of inflammation (the joint), depending probably on the severity of inflammation and thus the plasma proteins present in the tissue.

Systemic infectious diseases

In an experimentally induced infection model using lipopolysaccharide (LPS; endotoxin, component of the cell wall from Gram-negative bacteria which functions as an antigen and toxin, and thus induces inflammation at the place of release), Friton *et al*[36] demonstrated that meloxicam (0.4 mg/kg im administered once) significantly reduced concentrations of thromboxane B_2 and ameliorated the clinical score (rectal temperature, behaviour, vomiting, etc). Meloxicam had no adverse effect on the immune system response. This anti-endotoxin and anti-inflammatory effect of meloxicam could, however, not be demonstrated in an experimentally induced porcine reproductive and respiratory syndrome virus (PRRSV) multifactorial respiratory disease (LPS) model. There was no effect on fever or respiratory signs.[37] This reveals that every infection and treatment with NSAIDs should be examined individually and that infections with different pathogens may lead to different inflammation pathways.

Ketoprofen

Main characteristics

Ketoprofen acts as a peripheral and central NSAID[38 39] and is described as one of the most potent NSAIDs.[40] In humans, ketoprofen is mainly used for rheumatoid arthritis, osteoarthritis or musculoskeletal inflammation. In animals, ketoprofen is used across all species for different diseases; however, there are only a few studies of ketoprofen in pigs. In contrast to meloxicam, ketoprofen is a non-selective COX inhibitor. Beside the COX inhibition, ketoprofen may also inhibit the 5-lipoxygenase metabolite leukotriene B_4, an acute inflammatory response mediator.[41–43] This dual inhibition has been discussed elsewhere.[44–46] Moreover, as for all pyrazolone derivatives, ketoprofen is marketed as a racemic mixture of R(−) and S(+) enantiomers, where the R-enantiomer plays the dominant analgesic role in pigs.[47] For the sake of simplicity, the term ketoprofen will be used in this review. Moreover, as ketoprofen can also be administered orally, this part will be considered in this chapter too.

Bioavailability of ketoprofen in pigs is complete. T_{max} (time to maximum plasma concentration) for po and im administration (3 mg/kg) is 1 hour after injection. C_{max} varies between 5 µg/mL (po) and 7.5 µg/mL (im) and $T_{1/2el}$ is between 3 hours (im) and 3.5 hours (po). In one study the mean plasma concentration was at least 1 µg/mL (dose for alleviation of orthopaedic pain in humans) over approximately 10 hours after im or po injection (3 mg/kg) and over 12 hours if 6 mg/kg po was administered.[48] Tissue concentrations are important as the plasma concentrations are difficult to relate with efficacy of analgesic or anti-inflammatory potential. During anaesthesia, ketoprofen reduces the urinary flow in piglets; however, this effect might be counteracted by inhalation of nitric oxide.[49 50]

Indications

Castration

In 2010, Courboulay *et al*[51] claimed that ketoprofen (administered im 20 min before castration) had no direct effect of pain relief during castration, as behaviour during castration was comparable to non-treated animals, but lower cortisol concentrations could be detected after castration and also the piglets' behaviour after castration was comparable to the sham castrated ones. In a second trial, the use of lidocaine pre-surgically (10 min) was also tested and it might have decreased pain sensation during castration. However, the pre-surgical time point of ketoprofen administration has to be reconsidered, as T_{max} is around 1 hour. Schwab *et al*[52] confirmed these findings: there were no behavioural changes during castration, but the cortisol and ACTH concentrations were lower after castration compared with the placebo group. These results might be explained by the pharmacokinetic studies (6 mg/kg ketoprofen iv) of Fosse *et al*,[53] who showed that

the mean plasma concentration of ketoprofen was lower in 6-day-old piglets compared with 21-day-old piglets. The volumes of distribution were significantly larger in the younger ones and clearance was much higher. In a kaolin inflammation model involving approximately 12-day-old piglets, Fosse *et al*[47] could not detect an antipyretic effect of ketoprofen (probably due to the only slight increase of body temperature after kaolin stimulation); however, body temperature tended to be lower and skin temperature was lower after 2–12 hours. Ketoprofen treated piglets had significantly higher mechanical nociceptive thresholds for 12–24 hours after treatment; however, the analgesic effect of ketoprofen under clinical conditions such as castration remains unclear. Beside the analgesic effects of ketoprofen after castration, there seems to be no effect (3 mg/kg im 30 min before castration) on growth performance of piglets until weaning.[54]

Periparturient period

The first trials in post-partum administration of ketoprofen in healthy sows (3 mg/kg im during 3 days after farrowing) revealed a better body condition score, especially in sows with higher parity (6–9), and a decreased loss of backfat during the first 2 weeks of lactation.[55] The treated sows presented less constipation and feed refusal during lactation, but there was no effect on the weight gain of piglets from treated sows. This was confirmed by Claeyé *et al*,[56] who showed that in healthy sows, ketoprofen (1 mg/kg im) reduced rectal temperature by 0.43°C during the first 24 hours. There was no effect on weight gain or survival of the piglets. Homedes *et al*,[57] however, revealed a lower mortality rate of piglets between days 2 and 7 after farrowing and a higher number of piglets weaned per litter, when healthy sows were treated with ketoprofen (3 mg/kg im) within 12 hours after parturition. They hypothesised that this could be due to better milk production, although the piglets' weight gain was not recorded.

Locomotion disorders

Mustonen *et al*[58] examined lameness in sows in commercial farms and treated them daily with 2 or 4 mg/kg ketoprofen over 5 days. The lameness score significantly improved after 5 days in >50% of the treated group, and there were no adverse side effects (gastrointestinal irritation). In 2008, Oomah[59] presented a case report of osteochondrosis dissecans in a boar, where treatment with ketoprofen (3 mg/kg im over 5 weeks every 48 hours) resolved lameness completely. However, the boar became recumbent the day following withdrawal, was euthanised and lesions were found during necropsy.

Systemic infectious diseases

Most investigations have analysed the role of ketoprofen in infectious disease therapy, as it has potent antipyretic characteristics. Swinkels *et al*[60] compared treatment with ketoprofen (3 mg/kg im) to flunixin (2 mg/kg im) in an experimental *Actinobacillus pleuropneumoniae* model. The treatment was given twice, 8 and 32 hours after challenge. They demonstrated that ketoprofen had a highly significant antipyretic effect 2 hours post administration that lasted for about 8 hours. Feed and water consumption were also higher, whereas only food consumption 12–18 hours post infection was significantly higher in the ketoprofen treated group compared with the control group (infected, non-medicated). These effects were not so prominent in the flunixin-treated group. However, the typical fibrinous haemorrhagic pleuropneumonia lesions could not be prevented in both treatment groups. Viehmann *et al*[61] assessed the therapeutic effects of ketoprofen, in addition to an appropriate antibiotic treatment, in an experimental *Haemophilus parasuis* infection study. The pigs showed a quicker decrease of body temperature and enhanced higher daily weight gain compared with the group treated with antibiotics only. In an *Escherichia coli* LPS-induced inflammation model, Salichs *et al*[62] and Mustonen *et al*[63] examined the antipyretic and antiphlogistic effect of oral ketoprofen administration. Ketoprofen prevented rectal temperature from rising after infection or brought it back close to the baseline within the first 2 hours after injection. Moreover, total clinical scores (general behaviour, respiratory rate, locomotion) were lower compared with control groups. Wyns *et al*[64] confirmed these positive effects in a comparative study of in vitro and in vivo LPS challenge and subsequent ketoprofen and antibiotic (gamithromycin) therapy. Mustonen *et al*[63] demonstrated that there was no additional therapeutic effect in the endotoxin model when treating pigs with a higher dose of ketoprofen (4 mg/kg compared with 2 mg/kg). Salichs *et al*[65] treated fattening pigs from a commercial farm showing mild porcine respiratory disease signs with ketoprofen over 3 days, combined with 5 days of antibiotic treatment with doxycycline. Treated animals showed a faster improvement of clinical parameters (rectal temperature, depression, sneezing and cough) and less weight loss. However, no conclusion could be made for treatment in severe porcine respiratory disease complex (PRDC).

Flunixin

Main characteristics

Flunixin is widely used in post-surgical pain release in equine and canine medicine and in visceral pain release in colic treatment in horses. In 2006, Buur *et al*[66] were the first to analyse the pharmacokinetics of flunixin in swine (18–26 kg) after iv administration of 2 mg/kg. $T_{1/2el}$ was 7.76 hours. The volume of distribution in swine was quite large (1.8 L/kg) despite the plasma protein binding capacity of >98%. Buur *et al*[67] investigated the drug interaction between sulfamethazine

(sulfonamide) and flunixin. They demonstrated a drug interaction, but no clinically significant changes that would modify tissue disposition, as there was no significant change in free drug concentrations in the in vivo experiments. Increased free drug concentrations could be the cause of displacement of plasma proteins. The pharmacokinetics resulting from the different ways of administering flunixin have also been evaluated in 42-week-old gilts.[68] There was no difference in T_{max} and $T_{1/2el}$ between po and im administration. However, the mean C_{max} in im and po administration was 3.748 µg/mL and 0.946 µg/mL, respectively. Additionally im administration led to a continued flunixin concentration >0.2 µg/mL (EC_{50} of flunixin evaluated in horses) for up to 8 hours, whereas po administration showed only effective drug concentrations over 4 hours. Therefore, Pairis-Garcia *et al*[68] claimed the po administration route was more practical compared to im administration. Howard *et al*[69] analysed the impact of breed and sex on pharmacokinetic parameters of flunixin in swine. They noticed that after iv flunixin administration, clearance and volume of distribution at steady state differed significantly between breeds, but not between sexes. Furthermore, they observed changes in gene expression involved in drug metabolism, which may explain differences in the pharmacokinetic parameters between breeds.[70] In a recent follow-up study the same authors identified alterations in genes involved in porcine liver metabolism after flunixin administration.[71]

Only one study in piglets examined the pharmacokinetic and pharmacodynamic parameters of flunixin.[72] Therefore, a kaolin-induced inflammation model has been used in order to evaluate mechanical nociceptive thresholds in 10-day-old piglets. The IC_{50} for the 2.2 mg/kg and 4.4 mg/kg flunixin treated groups were 6780 µg/mL and 2630 µg/mL, respectively. Moreover, only the high-dosage group showed a long lasting effect in antinociception (34 hours). The calculated ED_{50} for this precise model was 6.6 mg/kg, which is much higher than the current marketed dose (2.2 mg/kg), but apparently provides a better analgesic effect, at least in piglets.

Indications

Castration

In 2009, Langhoff *et al*[73] reported that surgically castrated piglets treated with flunixin showed decreased cortisol concentrations 30 min, 1 hour and 4 hours after castration and significantly reduced pain-related behaviour compared to the control group. Reiner *et al*[74] did not confirm these results, comparing flunixin (2.4 mg/kg im 30 or 0 min before surgery) or meloxicam (0.8 mg/kg 0 min before surgery) to sham castrated piglets and piglets castrated without analgesia, in regard to pain, stress and discomfort during and after castration. Serum cortisol values of both NSAID-treated piglet groups were significantly higher compared to the sham castrated group. Within 24 hours, piglets showed longer lying periods, impaired walking activity, shorter teat stimulation activity, but increased tail wagging (meloxicam group), compared to the untreated castration group. These results were partly abolished after 96 hours, with better results in the flunixin group compared to the meloxicam group. Moreover, scrotal temperature was significantly decreased by NSAIDs, but the time point of administration made no difference. NSAIDs led to retarded wound healing in treated animals, probably due to relative ischaemia. Reiner *et al*[74] concluded that NSAIDs might decrease nociception after piglet castration, though the overall results indicate distress and lowering of piglets' welfare compared to sham castrated animals.

Periparturient period

In 2003, Hirsch *et al*[33] (see Meloxicam section) demonstrated that 2 mg/kg of flunixin improved the clinical condition of sows with PDS. However, twice the number of piglets of affected sows treated with flunixin died, when the piglets themselves got sick (diarrhoea, weakness, lameness, etc), compared with diseased piglets of affected sows treated with meloxicam (31.7% and 14.0%, respectively). Tummaruk *et al*[75] investigated the effect of NSAIDs used post-partum on the incidence of post-parturient disorders in sows in the field. They compared flunixin treatment (0.5 mg/kg im once after farrowing and if needed 24 hours later) and metamizole treatment (see Metamizole section). Farrowing duration and parity number were also taken into account. The number of sows with fever was significantly decreased from 61.3% on day 1 to 22.6% on day 3 post-partum after flunixin treatment. The number of sows with vaginal discharge was also lower, although the percentage of sows with vaginal discharge was even higher at day 1 in the flunixin-treated sows compared with the metamizole-treated sows. These findings indicate that flunixin represents a good candidate in the alleviation of PDS in sows with a high risk of post-partum disorders (eg, dystocia). Nevertheless, the long withdrawal period of flunixin in pigs (±22 days) may limit its use in commercial pig farms.

Locomotion disorders

The use of flunixin for the treatment of locomotion problems is very poorly documented, probably because flunixin is primarily prescribed for infectious respiratory diseases. However, in 2015, Pairis-Garcia *et al*[34] explored the effect of flunixin (2.2 mg/kg) (and meloxicam) in experimentally induced lameness in sows (amphotericin B). The time point of maximal concentration was reached after 1 hour and the $T_{1/2el}$ of flunixin was 8 hours. Flunixin improved lameness and mitigated pain sensitivity very rapidly (1 hour after administration).

Systemic infectious diseases

Most research has been done in analysing the impact of flunixin in pigs with respiratory disease. Olson *et al*[76] used the pig as a model to study human respiratory disease. They injected a bolus of flunixin (2 mg/kg) 30 min before endotoxin challenge (*E. coli* LPS) in 10- to 12-week-old piglets, followed by 1 mg/kg/hour. Leukopenia, neutropenia and lymphopenia persisted until 4.5 hours but thrombocytopenia was blocked. In addition, mean pulmonary arterial pressure and pulmonary vascular resistance were significantly lower (absolute levels) compared to the endotoxin-only challenged group. Moreover, lung lesions were less severe. Swinkels *et al*[60] inoculated *Actinobacillus pleuropneumoniae* endobronchially and injected 2 mg/kg flunixin 8 hours and 32 hours after challenge. Compared to ketoprofen (see Ketoprofen section), flunixin showed no antipyretic effect and no improvement in food and water consumption. However, food and water consumption was numerically higher (but not statistically significant) compared to the non-treated control group. The pigs also showed typical fibrinous pleuropneumonic lesions. Another porcine respiratory disease study demonstrated that flunixin or meloxicam (see Meloxicam section) did not show any antipyretic effect and improvement of respiratory signs in PRRSV and LPS (*E. coli*) challenged 5-week-old pigs.[37] A comparable study with challenge of LPS (*E. coli*) and *Pasteurella multocida* showed no advantage for the group treated with antibiotic and flunixin (2 mg/kg over 3 days) compared to the group only treated with antibiotic (ceftiofur 3 mg/kg for 5 days).[77]

Wallgren *et al*[78] investigated a challenge with *Salmonella typhimurium* in boars preceded by flunixin treatment (2.2 mg/kg 10 min before challenge). Signs of acute endotoxaemia appeared later and were milder, with a delay in raised rectal temperature and cortisol concentrations of 1 hour compared to the control group, which confirms a strong anti-endotoxin effect of flunixin. Besides the anti-endotoxin capacities of flunixin, the authors also investigated possible andrological alterations through flunixin treatment. An initial decrease in testosterone and prostaglandin concentrations was noticed over the first 2 hours after challenge, followed by an increase. Flunixin did not have a major impact on sexual behaviour in boars.[79]

Metamizole and tolfenamic acid

Metamizole: characteristics and indications

Only limited literature reports are available on metamizole, also known as dipyrone, in animals and it does not seem to be a drug of interest for pig practitioners. Metamizole is mainly used in combination with hyoscine butylbromide in animals because of its spasmolytic effects.[80] From a pharmacological point of view, metamizole does not belong to the group of NSAIDs, as it has no anti-inflammatory effects, but to the group of non-opioid analgesic drugs. Metamizole acts via the opioidergic system,[81] the cannabinoid system[82] and by inhibiting COX-1b. This triple system makes metamizole a very effective analgesic drug with central analgesic activity.[83] Moreover, metamizole also seems to potentiate the anti-nociceptive effect of opioids, when administered together.[81] Apart from the analgesic effect of metamizole, little is known about its exact mode of action as an antipyretic drug. There might be prostaglandin-dependent and prostaglandin-independent mechanisms, as it is only a weak COX-1 inhibitor and not an effective COX-2 inhibitor.[84]

In pigs, Tummaruk *et al*[75] analysed the effect of metamizole compared with flunixin in post-parturient disorders in sows—that is, rectal temperature, vaginal discharge, degree of appetite and inflammation of the udder. Metamizole (50 mg/kg im) did not decrease fever significantly and post-partum discharge was only reduced at day 3 after farrowing. As a non-treated control group was not included, no firm conclusions could be drawn on the effect of metamizole in PDS sows. Thus the use of metamizole to treat post-parturient problems in sows is questionable.

In 1987, Bowden *et al*[85] demonstrated an increased feed intake of healthy pigs after administration of metamizole (90 mg/kg im). The underlying mechanism still remains unclear. Stirnimann *et al*[86] investigated metamizole in a case report of sows with urinary tract infection. They reported that 29/34 sows treated with metamizole (10 g Novaminsulfon) in addition to 3 g ampicillin were healed clinically compared with 22/34 sows after ampicillin treatment only. From the sows that were healed clinically, only 50% were also urologically healed, that is, there were no more detectable bacteria; the others remained chronically sick. It was suggested that metamizole may stimulate urination and thus urine infections could be eliminated more rapidly.

Tolfenamic acid: characteristics and indications

Tolfenamic acid is an NSAID with analgesic, anti-inflammatory and antipyretic effects in humans, dogs[87 88] and cats.[89 90] It is registered for use in sows with PDS (1×2 mg/kg, which may be repeated if needed 12–24 hours later).

Two studies have investigated the analgesic effect of tolfenamic acid in piglet castration. Wavreille *et al*[91] reported that tolfenamic acid treated piglets (2 mg/kg, 1 hour before castration) cried less, stayed less isolated and tended to scratch less compared with untreated controls. They suggested that tolfenamic acid may be more effective than meloxicam (see Meloxicam section) during and after castration, although this is based on clinical interpretation. In contrast, Gottardo *et al*[16] showed that treatment with tolfenamic acid (10 min before castration) resulted in higher cortisol

concentrations after castration, compared with meloxicam or ketoprofen, but lower concentrations when compared with the control group. Thus, time of administration of tolfenamic acid seems to be a crucial factor in pain alleviation after surgery.

To sum up, the use of metamizole or tolfenamic acid has not yet been sufficiently investigated to clarify their efficacy and address the clear indications for their use in pigs.

Orally administered NSAIDs

NSAIDs that are orally administered in pigs include paracetamol and sodium salicylate. They are mostly used in fattening farms, where a large number of animals need to be treated. Ketoprofen, which can be administered orally as well, was described already in the section on parenterally used NSAIDs.

Paracetamol

Main characteristics

Most research has focused on the use of paracetamol for its analgesic and antipyretic potential. Its antiphlogistic potential is minimal as paracetamol only inhibits prostaglandins within the central nerve system. Therefore, strictly speaking, it does not belong to the group of NSAIDs. It is normally administered at 15–30 mg/kg/day over 3–5 days. Binding of paracetamol to plasma proteins is minimal (around 15%).[92 93] Bailie *et al*[94] reported a mean $T_{1/2el}$ of 1 hour in Handford miniature swine. Neirinckx *et al*[93] reported a comparable $T_{1/2el}$ of 1.17 hours and 1.41 hours for iv and po administration (10 mg/kg), respectively, in landrace pigs.

Indications

Surgical intervention and systemic infectious diseases

To evaluate the analgesic effect of paracetamol, piglets between 8 and 20 days of age were subjected to 100 mg/kg paracetamol (rectal suppository) after implantation of a central arterial catheter. In this study, $T_{1/2el}$ of paracetamol was 2.5 hours (compared with meloxicam 3.4 hours, see Meloxicam section). Paracetamol was significantly less effective than meloxicam in terms of behavioural parameters (lameness, restlessness, vocalisation, appearance, agitation), but there were no differences in the physiological parameters (blood pressure, temperature, heart rate, respiratory rate).[17] A higher concentration of paracetamol is possibly needed for COX inhibition.

A few studies have focused on the antipyretic functions of paracetamol. In two herds with porcine respiratory disease, paracetamol (15 mg/kg twice a day with a 12 hour interval) increased the efficacy of antibiotic treatment with doxycycline, probably through its antipyretic effects. Nevertheless, no increased feed intake could be detected.[95] Another study showed that paracetamol (30 mg/kg) reduced fever to baseline levels within 2 hours after oral administration in an LPS-challenged pig model and that bolus administration was more effective than administration via the drinking water.[62] In another LPS-challenged pig model, N-acetylcysteine (60 mg/kg/day over 5 days), a cellular antioxidant, reinforced the effects of paracetamol (30 mg/kg/day over 5 days) in vitro and in vivo by a significant reduction of inflammatory cytokines.[96]

Salicylates: sodium salicylate and acetylsalicylic acid

Main characteristics

Most studies have investigated the pig as a model for use of these drugs in human medicine.

Even though sodium salicylate, an active metabolite of acetyl salicylate, is registered for use in pigs, there are almost no studies publicly available about its efficacy specifically in pigs. Patterson *et al*[97] investigated the plasma concentrations in healthy nursery pigs after oral treatment (continuously over 72 hours via water) of different concentrations of sodium salicylate (2268, 4913, 9827 and 19 654 mg/L in water). Within 24 hours, 0.41, 1.28, 1.41 and 7.22 mg/mL mean plasma concentrations were detected. Those then decreased until the last measurement at 72 hours.

Acetylsalicylic acid, also known as 'aspirin' and a precursor of sodium salicylate, has a strong anticoagulant effect as it inhibits platelet aggregation by irreversible inhibition of thromboxane A_2 in thrombocytes.[98] Additionally, acetylsalicylic acid provokes vessel lesions due to its antiproliferative effect in cells.[99] This underlines the higher bleeding risk after administration of acetylsalicylic acid. However, Xu *et al*[100] could find no effect on haemoglobin concentrations or blood clotting times, when acetylsalicylic acid (125, 250, 500 or 1000 mg/kg) was given via feed over 5–6 weeks to nursery piglets. Moreover, they detected a better feed intake and average daily weight gain in piglets after oral administration of 125 or 250 mg/kg compared to piglets fed with the basal diet. No negative impact on organs could be seen macroscopically at the slaughterhouse (eg, gastrointestinal tract, liver, pancreas, heart).

Indications

Castration and systemic infectious diseases

In 1993, McGlone *et al*[101] could not demonstrate an analgesic effect of acetylsalicylic acid (22 mg/kg, 30 min before castration) in castrated 8-week-old piglets. There was a tendency for lower feed and drinking water intake, and fewer piglets were standing and more were lying. This could be due to a described T_{max} of 6.6 hours following administration of acetylsalicylic acid granules, whereas the castration was performed 30 min after drug administration.[102]

Acetylsalicylic acid inhibited tumour necrosis factor α (TNFα) in porcine pulmonary intravascular macrophages after LPS stimulation, but did not reduce

COX-2 expression.[103] In 2014, Duan *et al*[104] analysed in more detail the inhibition of this inflammatory signalling pathway. Acetylsalicylic acid inhibited COX-2 expression and PGE_2 production in a protein kinase C and protein tyrosine phosphatase dependent manner. In the study of Salichs *et al*,[62] 100 mg/kg acetylsalicylic acid (recommended dose 30 mg/kg twice daily) reduced temperature to baseline in an LPS-challenged inflammatory model. Pigs treated at a dosage of 35 mg/kg showed an elevated temperature over the whole follow-up period. Acetylsalicylic acid treatment also alleviated the side effects of foot-and-mouth-disease vaccination in pigs, namely a lower increase in rectal temperature and a higher average daily weight gain, but had no influence on food intake or feed conversion ratio.[105]

Conclusion and future perspectives

Pain, fever and/or inflammation frequently occur in pigs. Therefore, there are many indications where NSAIDs could be considered to alleviate these conditions and to safeguard animal welfare, health and production. Nevertheless, studies that have investigated the efficacy of NSAIDs for different conditions, using different treatment regimens, are scarce. Additionally, very little information is available on the side effects and the consequences of possible long-term administration of NSAIDs in pigs.

Most studies have focused on pain treatment during castration of piglets. Meloxicam and ketoprofen have been demonstrated to be the most effective NSAIDs in the treatment of pain in piglets during and after castration. It should be kept in mind, however, that NSAIDs alone are insufficient to control intraoperative pain and thus have to be used together with appropriate anaesthetics. A recent study revealed that other analgesic drugs—opioids—are suitable for pain relief during castration.[106] However, their use is currently not licensed in commercial pigs or other food-producing animals and thus are not practicable for on-farm use.

A few studies assessed the use of NSAIDs for treatment of sows in the periparturient period. Meloxicam, ketoprofen and flunixin are promising drugs for antiphlogistic and antipyretic treatment in sows with PDS.

The effects of NSAID treatment on locomotion problems in pigs have only been poorly analysed. Anti-inflammatory treatment seems to be difficult, not least because locomotion problems may have different causes and have often been present for some time, meaning that treatment is applied in the chronic phase of the condition.

Ketoprofen and flunixin are the two most commonly examined NSAIDs for the treatment of infectious diseases. However, most of the studies have been conducted under experimental conditions using single infections with one pathogen, which may differ from the treatment required for PRDC in pig herds.

Many studies have been conducted in species other than the pig, or the pig has served only as a model for humans. If we exclude studies describing the analgesic efficacy of various NSAIDs for piglet castration, there are almost no published field studies. It would be of interest to analyse the use of specific NSAIDs in the field and to analyse their effectiveness as well as their adverse effects in pigs. This information is required in order to practice evidence based veterinary medicine. NSAIDs will play an important role in the future in order to support the reduction in the use of antimicrobials. For this reason, further research is also needed to investigate combined therapies of NSAIDs and antimicrobials in defined cases.

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