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Short Communication

Pharmacokinetics of dexamethasone after intravenous and intramuscular administration in pigs

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ABSTRACT

The pharmacokinetics of dexamethasone (DEX) were investigated after an intravenous (IV) or intramuscular (IM) bolus injection of 0.3 mg/kg bodyweight DEX sodium phosphate in pigs. The plasma concentrations of DEX were determined using a validated high-performance liquid chromatography–tandem mass spectrometry (LC–MS/MS) method and the pharmacokinetics were determined by one-compartmental analysis.

The mean area under the plasma concentration–time curve and the mean elimination half-life were 133.07 ± 39.59 ng.h/mL and 0.77 h, and 173.24 ± 53.59 ng h/mL and 1.06 h following IV and IM administration, respectively. The volume of distribution and clearance recorded after IV administration were 2.78 ± 0.88 L/kg and 2.39 ± 0.57 L/h kg, respectively.

An IM bolus injection of DEX sodium phosphate in pigs resulted in a fast and complete absorption, with a mean maximal plasma concentration of 80.94 ± 21.29 ng/mL at 0.35 ± 0.21 h and a high absolute bioavailability of $131.06 \pm 26.05\%$.

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Dexamethasone (DEX) is a long-acting synthetic hydrocortisone analogue and is one of the most potent glucocorticoid drugs. It is extensively used in veterinary medicine to treat inflammatory, immunological and allergic disorders (Toutain et al., 1982; EMA, 2004; Ferguson et al., 2009). In livestock, the use of DEX is indicated in inflammatory processes such as mastitis, septic laminitis, arthritis and primary ketosis. DEX is also reported to be used as an illegal growth promoter (Courtheyn et al., 2002; Ferguson et al., 2009; Vincenti et al., 2009).

In order to improve water solubility, glucocorticoids are often formulated as a phosphate ester prodrug, which rapidly hydrolyses and releases free and active alcohols (Rohdewald et al., 1987; EMA, 2004). The pharmacokinetic (PK) properties of DEX have been previously described in humans and diverse animal species, but not in pigs although it has been approved for treatment of inflammatory and allergic disorders in this species (EMA, 2004).

The aim of this study was to determine the PK properties of DEX in pigs. The results will be applied in ongoing research studying the immunomodulatory properties of DEX, either alone or in combination with several antibiotics in a porcine lipopolysaccharide (LPS) inflammation model (Wyns et al., 2013).

The experiment was approved by the Ethical Committee of the Faculty of Veterinary Medicine of Ghent University (EC 2011/156).

Six clinically healthy male pigs (Landrace) with a mean bodyweight (BW) of 28.3 ± 3.01 kg were randomly divided in two groups. The animals had free access to feed and drinking water. The experiment was performed as a two-way cross-over design with a wash-out period of 5 days. A bolus of 0.3 mg/kg BW DEX sodium phosphate (DEXA 0.2%, Kela Laboratoria) was injected intravenously (IV) in the ear vein or intramuscularly (IM) in the *gluteus* muscle via a sterile winged infusion needle (25 G; Micro-flo, Novolab). Blood was collected by venepuncture of the jugular vein into EDTA-coated tubes (Vacutest Kima) before administration (time 0 h) and at 0.08, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12 and 24 h post-administration (p.a.). Blood samples were centrifuged at 2800 g for 10 min at 4 °C and plasma was stored at ≤ -15 °C until analysis within 2 months.

Quantification of DEX in porcine plasma was performed using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method, which was previously described in detail by our department (Watteyn et al., 2013). The PK properties were determined by means of WinNonlin, version 6.2.0 software program (Pharsight Corporation) using a one-compartmental model. Values below the limit of quantification of 2 ng/mL were not included in the analysis.

The mean area under the plasma concentration–time curve ($AUC_{0 \rightarrow \infty}$) was calculated using the linear trapezoidal method with extrapolation to infinity. The absolute bioavailability (F) was calculated from the following equation:

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$$F(\%) = \frac{AUC_{0 \rightarrow \infty IM}}{AUC_{0 \rightarrow \infty IV}} \times 100$$

Data are presented as means $\pm$ standard deviation (SD) and were statistically analysed by single-factor analysis of variance (ANOVA), using SPSS Version 20.0 software for Windows. The level of significance was $\alpha = 0.05$.

No adverse effects following IV or IM administration were observed during the course of the study. Semi-logarithmic plots of the mean plasma concentration–time curves following IV and IM administration are presented in Fig. 1. Quantifiable concentrations of DEX were measured in plasma until 4 h after both IV and IM administration. The PK properties of DEX (mean $\pm$ SD) are summarised in Table 1.

Following an IV bolus injection of 0.3 mg/kg BW DEX sodium phosphate, the $AUC_{0 \rightarrow \infty}$ was 133.07 ± 39.59 ng h/mL. The elimination half-life ($t_{1/2el}$) was 0.77 h and the volume of distribution (V_d) and clearance (Cl) were 2.78 ± 0.88 L/kg and 2.39 ± 0.57 L/h kg, respectively. Following an IM bolus injection of 0.3 mg/kg BW DEX sodium phosphate, the $AUC_{0 \rightarrow \infty}$ was 173.24 ± 53.59 ng h/mL. A maximal plasma concentration (C_{max}) of 80.94 ± 21.29 ng/mL was reached at 0.35 ± 0.21 h (t_{max}). The $t_{1/2el}$ was 1.06 h and the absolute bioavailability of DEX after IM injection was $131.06 \pm 26.05\%$. None of the PK properties significantly differed between both administration routes.

The present study is the first to describe the pharmacokinetics and bioavailability of DEX after IV and IM administration in pigs. DEX was supplied as a water-soluble and stable sodium phosphate ester to pigs and, as previously established by Rohdewald et al. (1987), DEX sodium phosphate is rapidly converted to the free and active alcohol form of DEX. Therefore, DEX alcohol, and not the esterified prodrug, was currently measured in plasma using the previously validated LC–MS/MS method.

An IM bolus injection of 0.3 mg/kg BW DEX sodium phosphate in pigs resulted in a relatively fast absorption and a C_{max} of DEX at 0.35 h (t_{max}). However, in horses a faster t_{max} of 0.16 h was recently observed (Soma et al., 2013). After an IM injection, DEX sodium phosphate is fully bioavailable in pigs ($F = 131\%$), horses ($F = 100\%$; Soma et al., 2013) and broiler chickens ($F = 123\%$; Watteyn et al., 2013). In dogs, an IM administration of DEX alcohol resulted in a relatively early C_{max} at 0.63 h and a complete absorption, while in cattle a delayed C_{max} at 4.27 h and an absolute bioavailability of only 67% was observed. Likewise, after an IM bolus injection of DEX 21-isonicotinate, an early C_{max} at 0.50 h and a de-

Table 1

Pharmacokinetic parameters (mean $\pm$ SD) of dexamethasone (DEX) in pigs after intravenous (IV) and intramuscular (IM) bolus injection of 0.3 mg/kg BW DEX sodium phosphate ($n = 6$).

Parameter	Units	IV	IM
$AUC_{0 \rightarrow \infty}$	h ng/mL	133.07 ± 39.59	173.24 ± 53.59
k_{abs}	/h	–	12.90 ± 10.57
k_{el}	/h	0.90 ± 0.28	0.65 ± 0.30
$t_{1/2abs}$	h	–	0.05^a
$t_{1/2el}$	h	0.77^a	1.06^a
V_d	L/kg	2.78 ± 0.88	–
Cl	L/h kg	2.39 ± 0.57	–
t_{max}	h	–	0.35 ± 0.21
C_0	ng/mL	114.89 ± 26.56	–
C_{max}	ng/mL	–	80.94 ± 21.29
F	%	–	131.06 ± 26.05

AUC, area under the curve; k_{abs} , absorption rate constant; k_{el} , elimination rate constant; $t_{1/2abs}$, half-life of absorption; $t_{1/2el}$, half-life of elimination; V_d , volume of distribution; Cl, clearance; t_{max} , time to maximum plasma concentration; C_0 , maximum plasma concentration at 0 h; C_{max} , maximum plasma concentration; F , absolute bioavailability.

^a Harmonic mean.

layed C_{max} at 3.57 h was observed in dogs and cattle, respectively. However, the absolute bioavailability was barely 40% in dogs compared to 72% in cattle (Toutain et al., 1982, 1983).

In comparison with other mammalian species, a remarkably high clearance of DEX was observed in pigs (2.39 L/h kg). Conversely, in dogs, cattle, horses and humans, a clearance of <0.6 L/h kg was reported (Toutain et al., 1982, 1983; Rohdewald et al., 1987; Greco et al., 1993; Hochhaus et al., 2001; Soma et al., 2013). In most species, the V_d of DEX is <2 L/kg (Toutain et al., 1982, 1983; Hochhaus et al., 2001; Soma et al., 2013). Interestingly, the V_d of DEX in pigs was 2.78 L/kg, which suggests good tissue penetration. However, a relatively short $t_{1/2el}$ (0.77 h) was observed in pigs. In other species, DEX is considered to be a long-acting (>48 h) glucocorticoid in comparison to hydrocortisone and prednisolone. Notwithstanding the PK results observed in this study, DEX could have a longer action in pigs from the pharmacodynamic perspective.

In conclusion, an IM bolus injection of DEX sodium phosphate in pigs resulted in fast and complete absorption, followed by a fast elimination of the active DEX alcohol. The V_d and particularly the clearance of DEX are much higher in pigs compared with other mammalian species.

Fig. 1. Mean ($\pm$ SD) plasma concentration–time profiles of dexamethasone (DEX) after IV and IM bolus injection of 0.3 mg/kg BW DEX sodium phosphate in pigs ($n = 6$). Quantifiable concentrations of DEX were measured in plasma for 4 h after IV and IM administration (LOQ = 2 ng/mL).

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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