The Veterinary Journal 259 (2020) 105459

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Short communication

Comparative pharmacokinetics of imepitoin after oral and rectal administration in healthy dogs

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ARTICLE INFO

Article history:
Accepted 29 April 2020

Keywords:
Dog
Epilepsy
Imepitoin
Pharmacokinetics
Rectal administration

ABSTRACT

The purpose of the present study was to investigate if rectal administration of imepitoin in healthy dogs leads to plasma concentrations comparable to those after oral administration. Significantly lower systemic exposure and maximal plasma concentration (C_{max}) of imepitoin was achieved after rectal compared to oral administration ($P \leq 0.001$). Therefore, this study does not support the rectal administration of imepitoin in dogs.

Cluster seizures (CS) and status epilepticus (SE) occur in 40–60% of dogs with idiopathic epilepsy (Saito et al., 2001; Monteiro et al., 2012; Berendt et al., 2015) and require emergency medical treatment to stop epileptic seizure activity. Imepitoin, an anti-epileptic drug (AED) approved for the treatment of canine idiopathic epilepsy since 2013,[2] is a low-affinity partial agonist at the benzodiazepine-binding site of the $GABA_A$-receptor (Sigel et al., 1998). Compared to the traditional benzodiazepines, such as diazepam, which act as full agonists at the benzodiazepine site of the $GABA_A$-receptor, partial agonists such as imepitoin show less sedative effects and are not associated with tolerance and dependence during long-term administration (Löscher et al., 2004; Rundfeldt et al., 2014). Dogs in SE might be too sedated to receive the AEDs orally so that other routes of administration should be considered. Since imepitoin is not available as a parenteral formulation, rectal administration could be a valuable alternative. The aim of this study was therefore to compare the pharmacokinetic behaviour of imepitoin after oral and rectal (suppository vs. rectiole) administration.

This study was approved by the Ethics Committee of the Faculties of Veterinary Medicine and Bioscience Engineering of Ghent University (Approval number, EC 2015/31; 6 May, 2015). Nine adult healthy Beagle dogs (five neutered male and four spayed female dogs), aged between 1.5 and 6.5 years, weighing between 7 and 17 kg were included in this study. To simplify preparation of the different formulations, a fixed dose (360 mg) of imepitoin per capsule, suppository or rectiole was used, which corresponds to a dose of 30 mg/kg BW. Mean bodyweight was 12 kg.

Imepitoin was suspended in a fatty base (Witepsol H15) to prepare suppositories containing 360 mg imepitoin per suppository. Rectioles were prepared by suspending 360 mg imepitoin in an aqueous hydroxypropyl methocellulose (HPMC) dispersion. For the oral administration commercial tablets (Pexion) were used to prepare capsules containing 360 mg imepitoin per capsule, using mannitol as filler.

A randomized three-way cross-over design was applied so that each dog received three single doses of imepitoin (360 mg) via three different formulations (orally, suppository, rectiole) with a wash out period of two weeks between each treatment. Sealed envelopes were used to randomly assign each dog to a group and Microsoft Excel (RAND) was used to further randomize treatment type and period per group. All dogs were fasted for at least 12 h before administration of the medication and 4 h after administration a small meal was provided. Dogs receiving rectal administration of imepitoin received a limited digital rectal exam for extraction of faecal material, if necessary, just before rectal

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[2] See: Pexion EPAR, 2013. European Medicine Agency: Veterinary Medicines – Pexion – EMA. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/veterinary/002543/WC500140840.pdf (Accessed 21 April 2020).

http://dx.doi.org/10.1016/j.tvjl.2020.105459
1090-0233/

imepitoin administration. The oral imepitoin dose was administered with a minimum amount of canned food. Venous blood samples were taken from the jugular vein immediately before (T0) and at 0.25, 0.5, 1, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 8, 10 and 24 h after imepitoin administration. All blood samples were collected in EDTA blood tubes and plasma was separated within 20 min by centrifugation (3500*g*, 10 min) at 4 °C and then immediately frozen at −20 °C until analysis. Dogs were closely monitored for adverse effects such as ataxia, sedation, gastrointestinal signs and behavioural abnormalities during 24 h after administration.

Imepitoin was quantified in dog plasma by a liquid chromatography–mass spectrometry (LC–MS/MS) method (unpublished). Non-compartmental toxicokinetic analysis of imepitoin was performed with WinNonlin 6.3 (Pharsight). The following pharmacokinetic parameters were calculated for oral administration: maximal plasma concentration (C_{max}), time to maximal plasma concentration (T_{max}), area under the plasma concentration–time curve from time 0 to 24 h (AUC_{0-t}), area under the plasma concentration–time curve from time 0 to infinite (AUC_{0-inf}), elimination rate constant (k_{el}), elimination half-life ($T_{1/2el}$), total body clearance divided by the absolute oral bioavailability (Cl/*F*) and volume of distribution divided by the absolute oral bioavailability (V_d/F). For rectal administration of imepitoin (suppository and rectiole) the C_{max}, T_{max} and AUC_{0-t} were calculated.

The values of the pharmacokinetic parameters were corrected for body weight and compared between administration routes using one-way analysis of variance (ANOVA; SPSS 21, IBM). Statistical significance was set at $P < 0.05$.

The administration of the three formulations was well tolerated in all dogs. The mean plasma concentration–time profiles are shown in Fig. 1, and the pharmacokinetic data are represented in Table 1. Analysis of the pharmacokinetic data of all dogs after oral administration revealed a mean (±SD) maximum plasma drug concentration (C_{max}) of 20.7 ± 7.4 μg/mL with a mean time to maximal concentration (T_{max}) of 2.3 ± 0.6 h. Rectal administration resulted in lower C_{max} compared to oral administration; 6.3 ± 6.3 μg/mL ($P < 0.001$) after suppository administration and 2.4 ± 3.4 μg/mL ($P = 0.001$) after rectiole administration. Furthermore, T_{max} after rectal administration of imepitoin was 5.5 ± 2.8 and 3.9 ± 2.7 h for suppository and rectiole, respectively. However, T_{max} was not significantly different ($P = 0.191$) after rectal vs. oral administration.

In this study, a single oral dose of imepitoin resulted in a comparable mean C_{max} and T_{max} as in a previous study using a similar dose (Rundfeldt et al., 2014). After rectal administration of a single dose of imepitoin the mean plasma concentrations were significantly lower compared to oral administration and the time to reach maximum plasma concentrations was much longer. Whether this was caused by insufficient release of imepitoin from the suppositories, by insufficient dissolution of imepitoin in the rectal fluids or by insufficient rectal absorption of imepitoin remains unclear for the moment.

Although it was not a goal of this pharmacokinetic study in normal dogs, it could have been interesting to compare the plasma concentrations after rectal administration with an antiepileptic therapeutic target range of imepitoin. Unfortunately, a therapeutic plasma concentration range of imepitoin could not be established in dogs with epilepsy due to the large variation of plasma concentrations and the lack of correlation with the seizure frequency (Rieck et al., 2006). Therefore, only studies in dogs with epilepsy can assess whether the low plasma concentrations of imepitoin after rectal administration could still have an antiepileptic effect.

This study does not support the use of rectally administered imepitoin in dogs. However, future studies could investigate the antiepileptic effect of rectal imepitoin using higher doses or different types of rectal formulations or other administration routes of imepitoin.

Table 1
Main pharmacokinetic parameters of imepitoin after oral (capsules) and rectal (rectiole and suppository) administration to beagle dogs ($n = 9$). Values are presented as mean ± standard deviation.

	Oral capsules	Rectiole	Suppository
C_{max} (μg/mL)	20.65 ± 7.65[a]	2.42 ± 3.37[b]	6.31 ± 6.28[b]
T_{max} (h)	2.25 ± 0.56[a]	3.92 ± 2.74[a]	5.53 ± 2.75[a]
AUC_{0-t} (h. μg/mL)	89.78 ± 27.83[a]	8.13 ± 11.72[b]	32.37 ± 31.10[b]
AUC_{0-inf} (h. μg/mL)	96.64 ± 33.87	ND	ND
Cl/*F* (L/h/kg)	0.97 ± 0.22	ND	ND
V_d/F (L/kg)	0.41 ± 0.21	ND	ND
$T_{1/2el}$ (h)	2.15 ± 0.93	ND	ND
k_{el} (h^{-1})	0.42 ± 0.15	ND	ND

C_{max}, maximal plasma concentration; T_{max}, time to maximal plasma concentration; AUC_{0-t}, area under the plasma concentration–time curve from time 0 to 24 h; AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinite; Cl/*F*, total body clearance uncorrected for the absolute oral bioavailability; V_d/F, volume of distribution uncorrected for the absolute oral bioavailability; k_{el}, elimination rate constant; $T_{1/2el}$, elimination half-life; ND, not determined.
[a,b] Statistically significant difference between formulations for each parameter ($P < 0.05$).

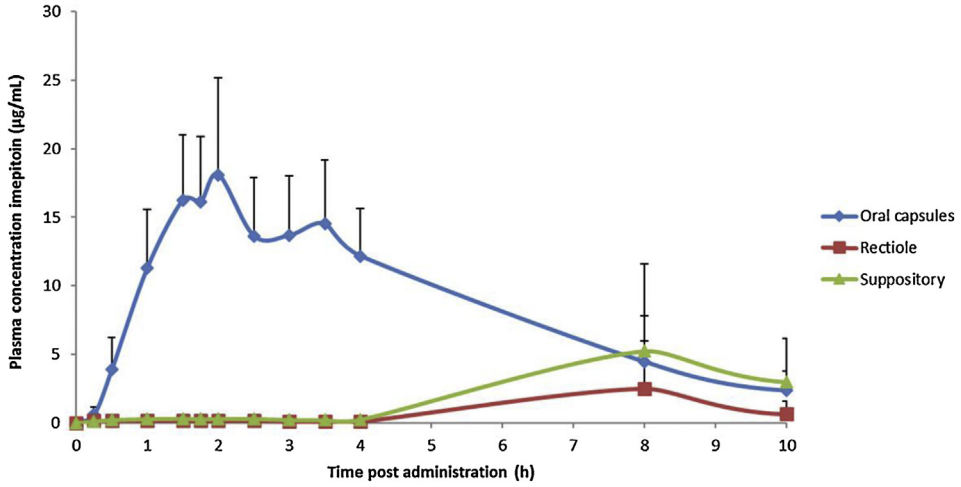

Fig. 1. Plasma concentration–time profile of imepitoin after a single oral dose (A), after rectal rectiole administration (B) and after rectal suppository administration (C) in healthy dogs. Values are presented as means ± standard deviation (SD, $n = 9$).

Conflict of interest

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

Acknowledgements

The authors would like to thank Bieke Weyn for her technical support in this study.

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