

ORIGINAL ARTICLE

Pharmacokinetics of single and repeated oral doses of pregabalin oral solution formulation in cats

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Abstract

The study was designed to determine the pharmacokinetic profile and bioavailability of a novel pregabalin 50 mg/ml oral solution formulation (Bonqat[®], Orion Corporation Orion Pharma) in 6 healthy laboratory cats. The cats received pregabalin as single oral doses of 2.5, 5, and 7.5 mg/kg, dose 5 mg/kg on two consecutive days, and a single intravenous dose of 2.5 mg/kg. The washout period between each administration was four weeks. The cats were monitored for clinical signs and level of sedation, and blood samples were taken before pregabalin dosing and at pre-defined time points up to 168 h after dosing. Plasma concentrations of pregabalin were determined using a validated liquid chromatography–tandem mass spectrometry method. The mean maximum plasma concentration of 10.1 µg/ml was reached between 0.5 and 1 h after oral administration of the clinical dose 5 mg/kg. The mean half-life after oral administration of dose 5 mg/kg was 14.7 h and the mean systemic bioavailability was 94%. Pregabalin showed linear pharmacokinetics from 2.5 to 7.5 mg/kg. Exposures after a single dose and re-dosing of 5 mg/kg at 24 h were comparable. Pregabalin was well tolerated with mild sedation and mildly uncoordinated movements observed in few cats at dose 7.5 mg/kg. As a conclusion, study results show rapid absorption, linear pharmacokinetics, and high oral bioavailability of pregabalin without safety concerns after administration of oral solution in cats.

KEYWORDS

cat, pharmacokinetics, pregabalin, repeated oral dose, single oral dose

1 | INTRODUCTION

Anxiety and fear in cats associated with transportation and veterinary visits is a well-known welfare challenge among cat owners (Mariti et al., 2017; Niblett et al., 2015; Quimby et al., 2011; Volk et al., 2011). To help the cat, owners and veterinarians are advised to employ actions such as training, using treats, applying gentle handling, and providing a cat-friendly environment (Hammerle et al., 2015; Moody et al., 2020; Pratsch et al., 2018; Riemer et al., 2021; Rodan et al., 2011). In addition to behavioural and

environmental modification, anxiolytic medication can be used to reduce anxiety during transportation and to enable patient-friendly, low-stress and physical examination (Hammerle et al., 2015). The feline specific oral solution formulation of pregabalin with the strength of 50 mg/ml was developed to alleviate cats' anxiety and fear during transportation and veterinary visits. The anxiolytic efficacy of the novel pregabalin formulation with the dose 5 mg/kg has been demonstrated to significantly and clinically relevantly alleviate anxiety in cats (Lamminen, Korpivaara, Aspegrén, Palestrini, Overall, unpublished data).

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Pregabalin is a structural analogue of the gamma-aminobutyric acid (GABA) neurotransmitter and binds to the alpha-2-delta subunit of the voltage-dependent calcium channel in the central nervous system (Li et al., 2011). It decreases the release of glutamate and monoamine neurotransmitters, which have been implicated to play a role in the pathophysiology of anxiety (Frampton, 2014; Mico & Prieto, 2012). In rodent models, pregabalin has shown dose-dependent anxiolytic-like effects (Field et al., 2001; Lotarski et al., 2011; Wang et al., 2012). Pregabalin is approved in the EU for treatment of generalized anxiety in humans (EMA, 2021a) and for alleviation of acute anxiety and fear related to transportation and veterinary visit in cats (EMA, 2021b).

Pharmacokinetics of pregabalin have been earlier described in several species including humans (Bockbrader, Radulovic et al., 2010), dogs (Salazar et al., 2009) and cats (Esteban et al., 2018). In their study in cats, Esteban et al. (2018) used a capsule formulation with a dose 4 mg/kg, which produced plasma concentrations reported to be similar to those considered efficacious for the control of seizures in human patients with epilepsy. Pharmacokinetics of the oral solution formulation developed for cats have not been reported earlier.

The objective of this study was to determine the pharmacokinetics and bioavailability of the novel formulation of pregabalin 50mg/ml oral solution after single doses of 2.5, 5 and 7.5 mg/kg and dose 5 mg/kg on two consecutive days in 6 healthy adult cats.

2 | MATERIALS AND METHODS

All procedures were conducted in accordance with the Dutch Act on Animal Experimentation (December 2014), approved by the Central Authority for Scientific Procedures on Animals and the Animal Welfare Body of Charles River Laboratories Den Bosch B.V. and conducted under the authority of the Project License AVD2360020172866.

2.1 | Animals and housing

Six laboratory cats, three neutered males and three intact females, were included in the study. The domestic shorthair cats were 1–4.5-year-old at the initiation of the study. Males weighed between 4.8 and 5.4 kg and females between 4.4 and 4.6 kg. The animals were deemed healthy based on a physical examination and clinical chemistry and were trained for restraining and food regime prior to the start of the study. Veterinary care was available throughout the study.

Cats were socially housed (same sex) except at times when they were separated for study procedures on the days of dosing the study treatment. At those occasions, animals were housed individually until approximately 4 h after dosing.

The cats were housed in two connected stainless steel cages with litter box. For environmental enrichment, cats were provided with items such as balls in the cages. Environment temperatures of

21–22°C with a relative humidity of 40%–82% and a 12-h light/12-h dark cycle were maintained. The cats were provided commercially available pelleted complete cat feed (IAMS cat adult chicken, IAMS Company) in the morning ad libitum for approximately up to 4 h. Water was available ad libitum all the time. On the day of dosing, the cats were fasted until 4 h after dosing, after which the feed was available for a period of approximately up to 4 h.

2.2 | Study design

The study was conducted according to Good Laboratory Practice and included 5 dosing periods separated by a 4-week washout period between each dosing. The cats received single doses of 2.5, 5 and 7.5 mg/kg of pregabalin (Bonqat 50mg/ml oral solution, Orion Corporation Orion Pharma) into the mouth in fasted state. The clinical dose 5 mg/kg was also studied after oral dosing on two consecutive days to evaluate pharmacokinetics of the second dose if given 24 h after the first one, as the product was planned to be used in practice as a single dose that is given at the maximum on two consecutive days, not for longer treatment periods. In addition, an intravenous (IV) bolus injection of dose 2.5 mg/kg of pregabalin was given via cephalic vein using a butterfly needle to the same cats as a reference to estimate the bioavailability of pregabalin oral solution. Injectable solution was prepared by dissolving pregabalin into sterile 0.9% sodium chloride (Dechra Veterinary Products, the Netherlands) on the day of dosing at the study laboratory. A validated analytical procedure was used to verify that the target concentration, 5 mg/ml, was achieved.

2.3 | Blood collection

Blood samples (0.75 ml) were collected from the jugular or cephalic vein by puncture into K₂-EDTA tubes (Greiner Bio-One GmbH). In oral administration periods, the samples were collected on the following time points: predose, 30 min, 1, 2, 3, 4, 8, 12, 24, 36, 96 and 168 h after dosing. In the period of dosing on two consecutive days, the samples post administration were collected after the second dosing. In the IV administration period, the samples were collected at predose, 5, 15, 30 min, 1, 2, 3, 4, 8, 12, 24, 36, 96 and 168 h after the IV injection. The cephalic vein that was used for IV dosing was not used for blood sampling.

Samples were centrifuged at approximately 2000 g for 10 min at 2–8°C. Plasma was transferred into polypropylene tubes (Micronic) on ice and frozen at ≤–75°C in an upright position, protected from light at all times.

2.4 | Bioanalytical method

Plasma samples were analysed in a laboratory (Ardena Bioanalysis BV Assen) for the concentrations of pregabalin using a validated

liquid chromatography–tandem mass spectrometry method. Quality control (QC) and calibration standard data were acceptable according to the requirements of the Food and Drug Administration Guidance for Industry, and the European Medicines Agency guidance on bioanalytical method validation.

Pregabalin (TRC) was used as the reference standard and $^2\text{H}_6$ -labelled pregabalin (Cerilliant Corporation) as the internal standard (IS). The analyte and IS were extracted from cat K_2 -EDTA plasma using solid phase extraction cartridges (Oasis HLB 30 mg 1 cc; Waters). The purified samples were analysed by a Prominence HPLC or Nexera UPLC system (Shimadzu) using an XBridge C18 column (4.6 × 100 mm, 3.5 μm; Waters) coupled with an API4000 mass spectrometer (AB Sciex).

The lower limit of quantification (LLOQ) was 5.00 ng/ml. The upper limit of quantification was 5000 ng/ml or 20,000 ng/ml, depending on the linearity of the range.

The calibration standard mean precision (CV) varied between 1.4% and 6.7% and the mean accuracy was between 93.2% and 104.0%. The mean precision (CV) and accuracy of the QC samples were 4.7% and 105.6% at 0.015 μg/ml, 3.2% and 104.8% at 0.40 μg/ml, 7.6% and 100.1% at 4.0 μg/ml and 3.1% and 106.9% at 16.0 μg/ml respectively.

2.5 | Pharmacokinetic analysis

Pharmacokinetic parameters were estimated using pharmacokinetic software (Phoenix WinNonlin 6.4, Certara). A non-compartmental approach consistent with the oral or IV route of administration was used for parameter estimation. All values below the LLOQ were assigned a value zero for pharmacokinetic purposes. Nominal sampling times were used in pharmacokinetic calculations, except where the deviation was >5%; in this case, actual times were used. Minimal spillage of the formulation during dosing and salivation after dosing could affect dosing accuracy. Therefore, all cats that showed either spillage or salivation after dosing were excluded from the descriptive statistics of the pharmacokinetic parameters. Descriptive statistics (*N*, mean, standard deviation and variation) for males, females and males and females combined were generated using Phoenix WinNonlin 6.4.

2.6 | Clinical observations

The cats were observed for general health twice daily throughout the study and during the dosing days for any clinical signs predose, 2,

4 and 12 h after dosing. Any observed signs were graded for severity as slight, moderate, severe or very severe. In addition, possible level of sedation was recorded at predose, 2, 4 and 8 h on the dosing days and graded according to Table 1. The scores were modified from the sedation scale published by Lamont et al. (2012). The differences between the sedation levels were discussed in a pre-study meeting with the involved technicians conducting the evaluation to allow for reproducible scoring.

3 | RESULTS

The pharmacokinetic parameters of pregabalin in cats after administration of a single oral dose of 5 mg/kg, and the parameters of the same dose on two consecutive days, are listed in Table 2. Figure 1 illustrates the mean plasma concentrations of doses 2.5, 5 and 7.5 mg/kg after a single oral administration of pregabalin in fasted cats, and Figure 2 correspondingly after a single and two consecutive doses of 5 mg/kg. The figures include data until 24 h to enlighten the plasma concentrations related to the effect of the treatment based on level of sedation. Table 3 presents the pharmacokinetic parameters in cats after IV administration of a single dose of 2.5 mg/kg. Variation of maximum plasma concentration (C_{max}) and area under plasma concentration curve (AUC) evaluated by coefficient of variation percentage ranged between 2% and 20%. As no sex differences were detected in pharmacokinetic parameters, the results are reported as combined. To accurately determine the pharmacokinetic properties of the formulation, only animals with the complete dosing, without any spillage or salivation after it, were included in the descriptive statistics of the pharmacokinetic parameters and the Figures 1 and 2.

No clinical signs or sedation were noted after single oral dosing at 2.5 and 5 mg/kg. Following single dosing at 7.5 mg/kg, mild signs of sedation and mildly uncoordinated movements were reported in two cats, and salivation directly after dosing in one cat. Following the first dosing of repeated oral dose 5 mg/kg, mydriasis of both eyes in all six cats was observed, and salivation was noted in two cats.

4 | DISCUSSION

In this study, we investigated the pharmacokinetics of a novel pregabalin oral solution formulation in cats. Pregabalin was quickly absorbed after a single dose of 5 mg/kg with time to maximum

TABLE 1 Scoring of the level of sedation

Category	Description
No sedation	No signs of depression, drowsiness or ataxia
Slight sedation	Mild signs of depression, drowsiness or ataxia. Decreased reaction to stimuli
Moderate sedation	Severe ataxia, reluctant to move, may attain sternal recumbency
Deep sedation	Depressed, drowsy and sleepy, no resistance to positioning on lateral recumbency

TABLE 2 Pharmacokinetic parameters of pregabalin after single doses of 2.5, 5 and 7.5 mg/kg and 5 mg/kg on two consecutive days of pregabalin 50 mg/ml oral solution formulation in fasted cats

Parameter ^a	Pregabalin 5 mg/kg (N = 4) ^b	Pregabalin 5 mg/kg twice (N = 5) ^b	Pregabalin 2.5 mg/kg (N = 6)	Pregabalin 7.5 mg/kg (N = 5) ^b
C _{max} (µg/ml)	10.1 ± 0.8	12.9 ± 2.6	5.7 ± 0.7	19.1 ± 3.1
T _{max} (h)	0.5–1	0.5–4	0.5–3	0.5–1
AUC _{0–24h} (h*µg/ml)	129 ± 3.0	157 ± 21.7	65 ± 7.9	200 ± 17.0
t _{1/2} (h)	14.7 ± 2.7	15.6 ± 3.6	12.0 ± 3.2	12.1 ± 2.6
F (%)	94.3 (87.3–102)	NA	95.6 (75.4–130)	89.4 (81.0–95.3)

Abbreviations: AUC_{0–24h}, area under plasma concentration time curve within 24 h after dosing; C_{max}, peak plasma concentration; F, oral bioavailability; NA, not available; SD, standard deviation; t_{1/2}, elimination half-life; T_{max}, time to maximum concentration.

^aMean ± SD values, except range for T_{max} and mean (range) for F.

^bAnimals with incomplete dosing, due to spillage or salivation after dosing, excluded.

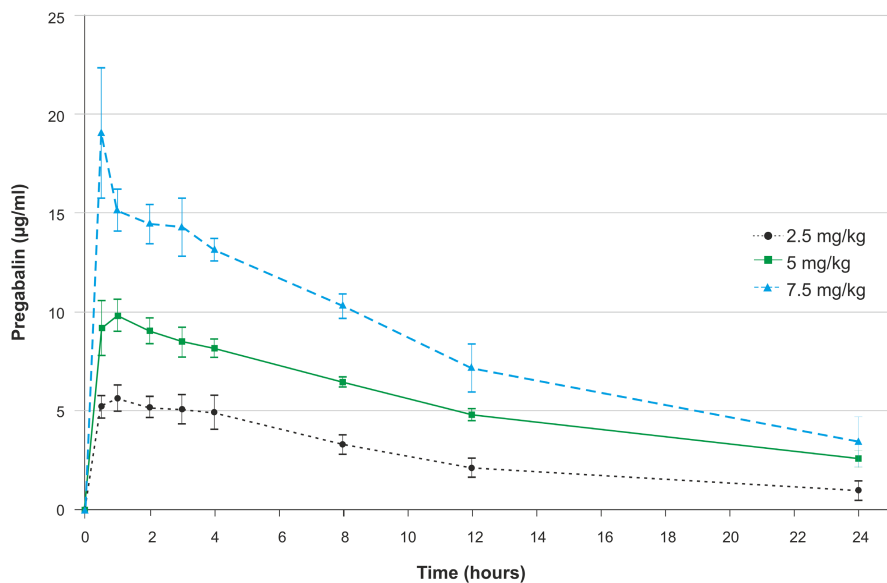


FIGURE 1 Pregabalin mean (± standard deviation) concentrations achieved in plasma after an accurate single dose of 2.5 (N = 6), 5 (N = 4) and 7.5 (N = 5) mg/kg of pregabalin 50 mg/ml oral solution formulation in fasted cats

concentration (T_{max}) ranging between 0.5 and 1 h after the administration of the oral solution in a fasted state. The absolute oral bioavailability was excellent, average 94% at the clinical dose 5 mg/kg. The systemic exposure to pregabalin, in terms of AUC and C_{max}, showed linear pharmacokinetics at the studied dose range of 2.5–7.5 mg/kg and the interindividual variability was low. This allows reliable dose-dependent effect in clinical use. After re-dosing of 5 mg/kg at 24 h, the exposure, in terms of AUC, C_{max} and elimination half-life (t_{1/2}), was comparable with the exposure following single dosing suggesting no clear signs for accumulation. Albeit dosing on two consecutive days is sufficient for pregabalin indication of reducing anxiety in cats for a specified event, it is only limited data to determine the pharmacokinetic properties after chronic dosing. Pregabalin has a relatively large volume of distribution in cat, as the value is higher than the extracellular fluid volume (Davies and Morris, 1993). This means that pregabalin is highly distributed into tissues, as is also described for humans (Bockbrader, Radulovic et al., 2010).

The total exposure in terms of AUC and C_{max} are in line between our study and earlier published data in cats (Esteban et al., 2018). On

the contrary, T_{max} is shorter with the cat-specific novel oral solution used in our study than with the capsule formulation administered in the study by Esteban et al. (2018). This could result in a quicker clinical effect after dosing of the cat-specific formulation.

Pregabalin is quite slowly eliminated from the body of cats. Based on the results of our study, pregabalin t_{1/2} in cats is approximately twice as long as the ones reported in humans (Bockbrader, Radulovic et al., 2010) and dogs (Salazar et al., 2009). This finding is supported by Esteban et al. (2018). The t_{1/2} of pregabalin in cats seems to be clearly longer than the t_{1/2} of gabapentin in the same species (Adrian et al., 2018; Siao et al., 2010). In practice, this can influence the dosing interval and probably also the duration of effect after administration.

Gabapentin is currently used off-label as an anxiolytic medication in cats (Van Haafen et al., 2017). However, pregabalin is a newer and more potent gabapentinoid compared with gabapentin and has been recently approved for alleviation of acute anxiety and fear associated with travel and veterinary visits in cats (EMA, 2021b). Even though not studied in cats, in mice, rats and monkeys pregabalin has been shown to cross the blood–brain barrier (EMA, 2021a), which

FIGURE 2 Pregabalin mean (\pm standard deviation) concentrations achieved in plasma after an accurate single dose of 5 mg/kg ($N = 4$) or after a dose of 5 mg/kg ($N = 5$) given on two consecutive days as pregabalin 50mg/ml oral solution formulation in fasted cats

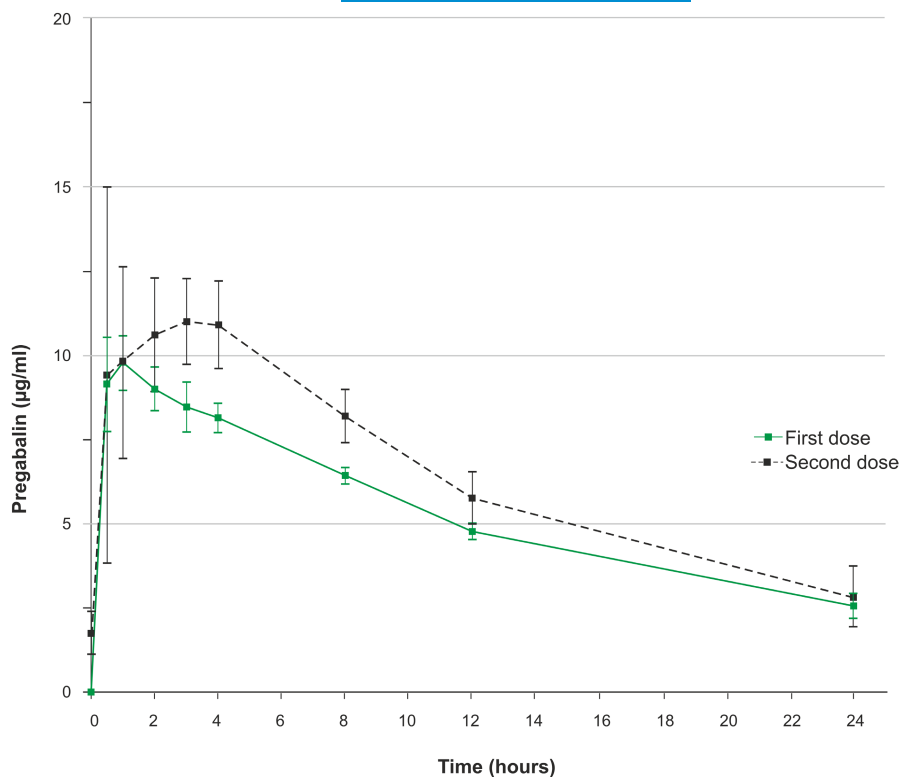


TABLE 3 Pharmacokinetic parameters of pregabalin after single intravenous (IV) dose of 2.5 mg/kg of pregabalin in fasted cats

Parameter ^a	Pregabalin 2.5 mg/kg IV ($N = 6$)
V_{ss} (L/kg)	0.4 ± 0.02
Cl (ml/h/kg)	30 ± 7.5
$t_{1/2}$ (h)	12.3 ± 3.1
AUC_{0-24h} ($h \cdot \mu\text{g/ml}$)	69 ± 7.9

Abbreviations: AUC_{0-24h} , area under plasma concentration time curve within 24 h after dosing; Cl, plasma clearance; SD, standard deviation; $t_{1/2}$, elimination half-life; V_{ss} , volume of distribution at a steady state.

^aMean \pm SD values.

allows the anxiolytic effect by decreasing of release of excitatory neurotransmitters. Pregabalin has been also reported to have more favourable pharmacokinetic properties than gabapentin in humans with nonsaturable absorption, linear pharmacokinetics and clear dose–response relationship (Bockbrader, Wesche et al., 2010). The same seems to apply also to cats based on the results of our studies (data on file, Orion Pharma) and earlier published data in this species (Adrian et al., 2018; Esteban et al., 2018; Siao et al., 2010).

The anxiolytic plasma concentrations of pregabalin have not been determined in humans or in cats. Based on the clinical study in anxious cats (unpublished data), pregabalin given with the clinical dose 5 mg/kg seems to have a duration of effect of approximately 7 h. In that study, plasma concentrations were not measured. In this pharmacokinetic study, conducted with the same oral solution formulation as the clinical trial, the mean plasma concentrations up to 24 h were comparable with previously published plasma concentrations up to at least 12 h in cats (Esteban et al., 2018). These plasma

concentrations were considered to be efficacious for seizure control in humans (Arroyo et al., 2004; Berry and Millington, 2005) and dogs (Dewey et al., 2009; Salazar et al., 2009). However, these data do not give reliable information on the duration of the actual anxiolytic effect or anxiolytic plasma concentrations in cats.

There were no safety concerns detected in this study in laboratory cats with pregabalin. With the highest dose 7.5 mg/kg, some mild signs of sedation were seen in few cats. Similar signs of tiredness and incoordination have been reported as adverse events in clinical use in cats (Lamminen, Korpivaara, Aspegren, Palestini, Overall, unpublished data), dogs (Sanchis-Mora et al., 2019; Thoenner et al., 2020) and humans (Zaccara et al., 2011). A corresponding adverse event profile has been reported also with gabapentin in cats (Van Haafen et al., 2017).

5 | CONCLUSIONS

Our study describes the pharmacokinetic profile of the novel pregabalin 50mg/ml oral solution formulation in cats. The results show fast absorption, linear pharmacokinetic profile and high oral bioavailability of the formulation. No safety concerns were observed with pregabalin in healthy laboratory cats.

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ANIMAL WELFARE AND ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received.

Ethical approval has been collected from the Animal Welfare Body of Charles River Laboratories Den Bosch B.V. within the framework of project license AVD2360020172866 approved by the Central Authority for Scientific Procedures on Animals in the Netherlands. [Correction added on 6 September 2022, after first online publication: The Animal Welfare and Ethics Statement was included in this current version.]

CONFLICT OF INTEREST

TL, JK and MH-H are employees of Orion Corporation.

AUTHOR CONTRIBUTIONS

TL, JK and MH-H have contributed to conception of the study. JK and MH-H have designed the study and contributed to interpretation of the data. AD has contributed to the design of the study and to the acquisition, analysis and interpretation of the data. TL made the first draft and all authors have contributed to the writing of the manuscript. All authors have read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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