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Short Communication

# Pharmacokinetics of oral gabapentin in greyhound dogs

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ABSTRACT

The purpose of this study was to assess the pharmacokinetics of gabapentin in healthy greyhound dogs after single oral doses targeted at 10 and 20 mg/kg PO. Six healthy greyhounds were enrolled (3 males, 3 females). Blood was obtained at predetermined times for the measurement of gabapentin plasma concentrations by liquid chromatography/mass spectrometry. Pharmacokinetic parameters were determined with computer software.

The actual mean (and range) doses administered were 10.2 (9.1–12.0) mg/kg and 20.5 (18.2–24) mg/kg for the 10 mg/kg and 20 mg/kg targeted dose groups. The mean $C_{MAX}$ for the 10 and 20 mg/kg groups were 8.54 and 13.22 μg/mL at 1.3 and 1.5 h, and the terminal half-lives were 3.3 and 3.4 h, respectively. The relative bioavailability of the 10 mg/kg group was 1.13 compared to the 20 mg/kg group. Gabapentin was rapidly absorbed and eliminated in dogs, indicating that frequent dosing is needed to maintain minimum targeted plasma concentrations.



Gabapentin is an anticonvulsant and analgesic drug producing its pharmacological effects through incompletely understood mechanisms. It has minimal direct effects on gamma-aminobutyric acid (GABA) receptors (Cheng and Chiou, 2006). Gabapentin binds to the α2δ subunit of voltage gated calcium channels acting pre-synaptically to decrease the release of excitatory neurotransmitters and it may increase brain concentrations of GABA or antagonize AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors.

Gabapentin has been recommended or used in dogs, but few data are available on its pharmacokinetics, safety or efficacy in the species (Govendir et al., 2005; Platt et al., 2006; Lamont, 2008; Cashmore et al., 2009). Previous studies have examined the pharmacokinetics of gabapentin in Beagles at supra-therapeutic doses (Vollmer et al., 1986; Radulovic et al., 1995; Rhee et al., 2008). The purpose of this study was to assess the pharmacokinetics of gabapentin in dogs at clinically relevant doses. The study included healthy greyhounds (3 males, 3 females) aged 1.5–3 years and weighing 25–42 kg. The Institutional Animal Care and Use Committee at Kansas State University approved the study.

Gabapentin was administered PO at a targeted dose of 10 mg/kg, to the nearest whole capsule (300 and 400 mg capsules, Apotex Inc.) on day 1 and at a targeted dose of 20 mg/kg, to the nearest whole capsule on day 2. Animals were fasted for 12 h prior to dosing. Immediately after dosing all animals were offered a treat (Milk-Bone, Del Monte Foods); animals not eating the treat were administered 5 mL water PO to ensure swallowing of the capsule(s). Dogs were offered food 4 h after dosing and food was removed 12 h prior to the second dose.

Blood samples (9 mL) were collected into heparin tubes prior to drug administration and 15, 30 and 45 min and 1, 1.5, 2, 4, 6, 8, 12 and 24 h after administration, from a jugular catheter (Venocath-16, Abbott Ireland). Plasma was separated by centrifugation (2000 *g* for 15 min) and stored at −70 °C.

Plasma concentrations of gabapentin, *m*/*z* 172.1 → 154.1 (Spectrum Chemical), and the internal standard (IS) pregabalin, *m*/*z* 160.0.1 → 142.0 (Lyrica, Pfizer) were determined by liquid chomatography (Shimadzu Prominence, Shimadzu Scientific Instruments) with mass spectrometry (API 2000, Applied Biosystems) (Table 1). The standard curve was linear from 0.1 to 25 μg/mL. The accuracy and coefficient of variation of the analytical method for gabapentin were 102 ± 9% and 8%, respectively, at 0.1, 1, and 25 μg/mL in replicates of five each. Plasma, 0.1 mL, 0.1 mL IS (5 μg/mL), and 0.4 mL methanol with 0.1% formic acid were combined then vortexed for 5 s. The samples were centrifuged for 10 min (10 000 *g*) and 20 μL of the supernatant injected.

Separation was achieved at 40 °C using a C18 column (Supelco Discovery, 50 mm × 2.1 mm × 5 μm, Sigma–Aldrich). The mobile phase consisted of A: methanol with 0.1% formic acid and B: 0.1% formic acid, with a flow rate of 0.3 mL/min (Table 1). Pharmacokinetic analysis was performed with computer software (WinNonlin 5.2, Pharsight Corporation) and the calculated pharmacokinetic parameters are included in Table 2.

The actual doses of gabapentin administered on day 1 were 9.1–12.0 mg/kg and 18.2–24.0 mg/kg on day 2 (Table 3). Gabapentin

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was rapidly absorbed and eliminated (Table 3, Figs. 1–3). The terminal half-lives for the 10 and 20 mg/kg doses were 3.3 and 3.4 h, respectively.

The relative fraction of the dose absorbed for each oral dose rate (*F*) of the 10 mg/kg dose, compared to the 20 mg/kg dose was 1.13.

**Table 1**
Mass spectrometer settings and the mobile phase gradient for the determination of gabapentin and the internal standard (IS) pregabalin.

| Mass spectrometer settings | |
|---|---|
| Source temperature (°C) | 300 |
| Dwell time (ms) | 200 |
| Ion source gas 1 (psi) | 20 |
| Ion source gas 2 (psi) | 20 |
| Curtain gas (psi) | 10 |
| Collision gas 1 (psi) | 6 |
| Ion Spray voltage (V) | 4500 |
| Entrance potential (V) | 10 |
| Declustering potential (V) | 50 |
| Collision energy (V) | 20 (gabapentin), 17 (IS) |
| Collision cell exit potential (V) | 10 |
| Mode of analysis | Positive ionisation |
| *Mobile phase gradient (min)* | |
| 0–0.5 | 100% B |
| 0.5–2.5 | Linear gradient to 70% B: 30% A |
| 2.5–3 | Hold at 70% B: 30% A |
| 3–3.5 | Linear gradient to 100% B |
| 3.5–5 | Hold at 100% B |
| | A = Methanol with 0.1% formic acid<br>B = 0.1% formic acid in water |

**Table 2**
Abbreviations for the pharmacokinetic parameters.

| | |
|---|---|
| AUC extrapolated | Percent of the AUC extrapolated to infinity |
| $AUC_{inf}$/dose | The area under the curve from 0 to infinity per dose administered |
| $AUC_{inf}$ | Area under the curve from time 0 to infinity |
| $AUMC_{inf}$ | Area under the first moment curve from time 0 to infinity |
| Cl/*F* | Plasma clearance per fraction of the dose absorbed |
| $C_{MAX}$ | Maximum plasma concentration |
| $C_{MAX}$/dose | Maximum plasma concentration per dose administered |
| $T_{½λz}$ | Terminal half-life |
| λz | First-order rate constant |
| $MRT_{inf}$ | Mean residence time extrapolated to infinity |
| $T_{MAX}$ | Time to maximum plasma concentration |
| Vz/*F* | Apparent volume of distribution of the area fraction of the dose absorbed |
| Relative *F* | Relative fraction of the dose absorbed for each oral dose rate |

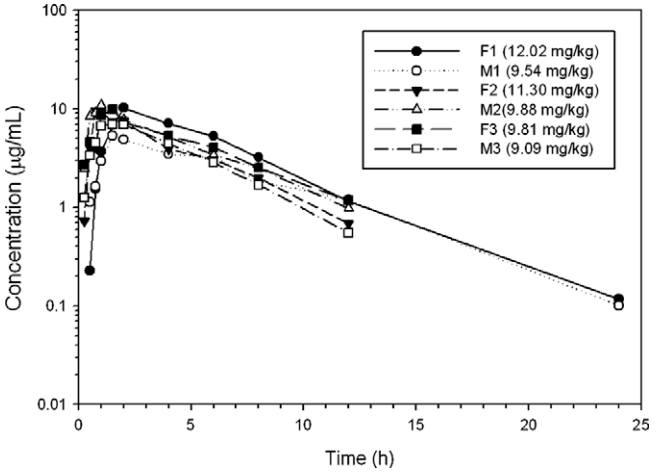


**Fig. 1.** Plasma concentrations of gabapentin in six healthy greyhounds after oral administration of a target dose of 10 mg/kg to the nearest whole capsule (actual dose administered in parenthesis).

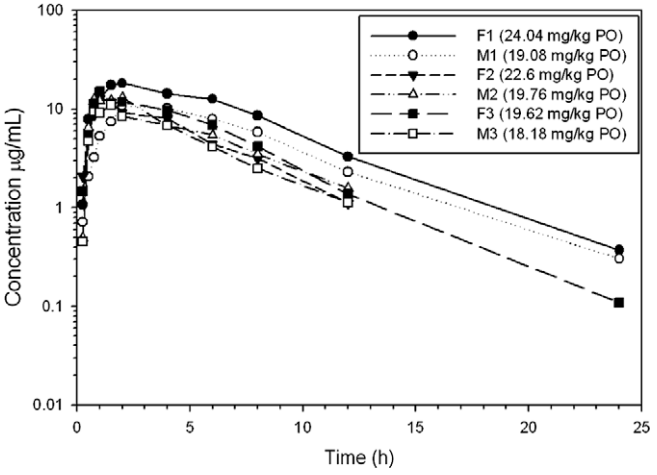


**Fig. 2.** Plasma concentrations of gabapentin in six healthy greyhounds after oral administration of a target dose of 20 mg/kg to the nearest whole capsule (actual dose administered in parenthesis).

**Table 3**
Pharmacokinetic parameters of oral gabapentin in healthy greyhound dogs.

| | | 10 mg/kg targeted dose | | | | 20 mg/kg targeted dose | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Geometric | | | | Geometric | | | |
| | | Mean | Min | Median | Max | Mean | Min | Median | Max |
| Dose | mg/kg | 10.2 | 9.1 | 9.9 | 12.0 | 20.5 | 18.2 | 19.7 | 24.0 |
| Non-compartmental pharmacokinetic parameters | | | | | | | | | |
| AUC extrapolated | % | 4.00 | 0.92 | 5.98 | 11.17 | 3.08 | 0.56 | 4.52 | 10.32 |
| $AUC_{inf}$/dose | h µg/mL | 4.77 | 3.92 | 4.81 | 5.61 | 4.21 | 3.00 | 4.22 | 6.29 |
| $AUC_{inf}$ | h µg/mL | 48.77 | 39.77 | 49.50 | 63.02 | 86.02 | 60.00 | 83.01 | 151.24 |
| $AUMC_{inf}$ | h µg/mL | 264.76 | 182.92 | 274.78 | 374.51 | 489.41 | 315.59 | 447.60 | 964.42 |
| Cl/*F* | mL/min/kg | 3.49 | 2.97 | 3.49 | 4.26 | 3.96 | 2.65 | 3.97 | 5.56 |
| $C_{MAX}$ | µg/mL | 8.54 | 5.32 | 9.68 | 10.90 | 13.22 | 10.70 | 12.95 | 18.20 |
| $C_{MAX}$/dose | µg/mL | 0.84 | 0.56 | 0.84 | 1.10 | 0.65 | 0.56 | 0.63 | 0.77 |
| $T_{½λz}$ | h | 3.25 | 2.63 | 3.35 | 3.68 | 3.41 | 3.07 | 3.39 | 3.91 |
| λz | 1/h | 0.213 | 0.189 | 0.207 | 0.263 | 0.203 | 0.177 | 0.205 | 0.226 |
| $MRT_{inf}$ | h | 5.43 | 4.60 | 5.40 | 6.78 | 5.69 | 5.01 | 5.40 | 6.94 |
| $T_{MAX}$ | h | 1.31 | 0.75 | 1.50 | 2.00 | 1.51 | 1.00 | 1.75 | 2.00 |
| Vz/*F* | L/kg | 0.983 | 0.850 | 0.942 | 1.256 | 1.170 | 0.835 | 1.207 | 1.476 |
| Relative *F* | | 1.13 | 0.83 | 1.28 | 1.41 | N/A | N/A | N/A | N/A |

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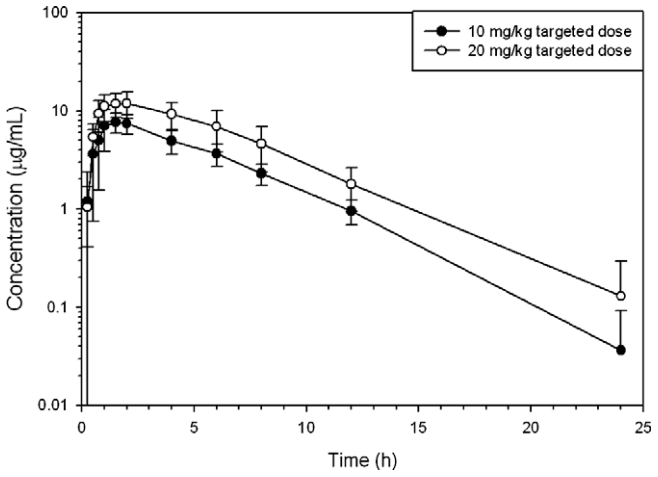


**Fig. 3.** Mean ± SD plasma concentrations of gabapentin in six healthy greyhounds after oral administration of targeted doses of 10 and 20 mg/kg to the nearest whole capsule.

The mean peak plasma concentrations in the 10 and 20 mg/kg dose groups were 8.54 and 13.22 μg/mL, respectively. The $C_{MAX}$ in humans is not proportional to the dose as decreases in bioavailability occur with increased doses resulting in less than proportional increases in plasma concentrations.[1] Sample size analysis indicates that eight dogs are needed to statistically compare the $C_{MAX}$ dose proportionality with an alpha of 0.05 and a power of 0.8.

The efficacy of gabapentin in greyhounds was not evaluated. Efficacy in humans is associated with 2 μg/mL plasma concentrations, but the effective concentrations are unknown in the dog. Gabapentin exceeded 2 μg/mL in the 10 mg/kg dose group in 6/6 dogs at 6 h, 4/6 dogs at 8 h and 0/6 dogs at 12 h after dosing. Gabapentin exceeded 2 μg/mL in the 20 mg/kg dose group in 6/6 dogs at 8 h, and 2/6 dogs at 12 h after dosing. These data suggest 10–20 mg/kg every 8 h would maintain 2 μg/mL plasma concentrations in dogs.

The study was a non-randomized block design with doses administered on consecutive days, therefore day to day variability, carryover, or treatment order could have affected the pharmacokinetics. Comparisons of the two doses must be made cautiously, but the study does provide preliminary data. Another limitation of the study was the lack of IV drug administration. A commercially available injectable solution was not available at the time of the study. Additionally, budgetary constraints limited the number of crossovers that could be conducted. The bioavailability, mean absorption time, clearance and volume of distribution can only be determined with IV studies. Further studies including IV administration are needed to completely understand the pharmacokinetics of gabapentin in dogs.

The current study was not designed to assess the safety of gabapentin. Loose stools occurred in three dogs on the second day of the study but it is not clear whether this was related to the drug administration or another cause. The dogs were offered a treat which is not a routine component of their diet. The dogs were also transported from their runs to the study location 24 h prior to the beginning of the study. Loose stools have been observed in these dogs in other studies, after transport from their runs to the study location, but before the study started (unpublished observations). Further studies are needed assessing the effects of multiple doses of gabapentin in dogs. In conclusion, gabapentin was rapidly absorbed and eliminated in dogs indicating multiple doses are needed per day in order to maintain targeted plasma concentrations.

## Conflict of interest statement

Dr. KuKanich has been a consultant for Bayer Animal Health, Pfizer Animal Health, and Farnam Animal Health.

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## References

Cashmore, R.G., Harcourt-Brown, T.R., Freeman, P.M., Jeffery, N.D., Granger, N., 2009. Clinical diagnosis and treatment of suspected neuropathic pain in three dogs. Australian Veterinary Journal 87, 45–50.

Cheng, J.K., Chiou, L.C., 2006. Mechanisms of the antinociceptive action of gabapentin. Journal of Pharmacological Sciences 100, 471–486.

Govendir, M., Perkins, M., Malik, R., 2005. Improving seizure control in dogs with refractory epilepsy using gabapentin as an adjunctive agent. Australian Veterinary Journal 83, 602–608.

Lamont, L.A., 2008. Adjunctive analgesic therapy in veterinary medicine. Veterinary Clinics of North America Small Animal Practice 38, 1187–1203.

Platt, S.R., Adams, V., Garosi, L.S., Abramson, C.J., Penderis, J., De Stefani, A., Matiasek, L., 2006. Treatment with gabapentin of 11 dogs with refractory idiopathic epilepsy. Veterinary Record 159, 881–884.

Radulovic, L.L., Türck, D., von Hodenberg, A., Vollmer, K.O., McNally, W.P., DeHart, P.D., Hanson, B.J., Bockbrader, H.N., Chang, T., 1995. Disposition of gabapentin (neurontin) in mice, rats, dogs, and monkeys. Drug Metabolism and Disposition 23, 441–448.

Rhee, Y.S., Park, S., Lee, T.W., Park, C.W., Nam, T.Y., Oh, T.O., Jeon, J.W., Han, S.B., Lee, D.S., Park, E.S., 2008. In vitro/in vivo relationship of gabapentin from a sustained-release tablet formulation: a pharmacokinetic study in the beagle dog. Archives of Pharmacological Research 31, 911–917.

Vollmer, K.O., von Hodenberg, A., Kölle, E.U., 1986. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. Arzneimittel-Forschung 36, 830–839.

[1] See Neurontin, package insert: www.pfizer.com/files/products/uspi_neurontin.pdf.

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