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Pharmacokinetic profile and behavioral effects of gabapentin in the horse

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Gabapentin is being used in horses although its pharmacokinetic (PK) profile, pharmacodynamic (PD) effects and safety in the equine are not fully investigated. Therefore, we characterized PKs and cardiovascular and behavioral effects of gabapentin in horses. Gabapentin (20 mg/kg) was administered i.v. or p.o. to six horses using a randomized crossover design. Plasma gabapentin concentrations were measured in samples collected 0–48 h postadministration employing liquid chromatography-tandem mass spectrometry. Blood pressures, ECG, and sedation scores were recorded before and for 12 h after gabapentin dosage. Nineteen quantitative measures of behaviors were evaluated. After i.v. gabapentin, the decline in plasma drug concentration over time was best described by a 3-compartment mammillary model. Terminal elimination half-life ($t_{1/2\gamma}$) was 8.5 (7.1–13.3) h. After p.o. gabapentin terminal elimination half-life ($t_{1/2e}$) was 7.7 (6.7–11.9) h. The mean oral bioavailability of gabapentin (±SD) was 16.2 ± 2.8% indicating relatively poor absorption of gabapentin following oral administration in horses. Gabapentin caused a significant increase in sedation scores for 1 h after i.v. dose only ($P < 0.05$). Among behaviors, drinking frequency was greater and standing rest duration was lower with i.v. gabapentin ($P < 0.05$). Horses tolerated both i.v. and p.o. gabapentin doses well. There were no significant differences in $t_{1/2\gamma}$ and $t_{1/2e}$. Oral administration yielded much lower plasma concentrations because of low bioavailability.

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INTRODUCTION

Gabapentin, [1-(aminomethyl)cyclohexaneacetic acid, $C_9H_{17}NO_2$, M.W. 171.24], is an anti-epileptic drug licensed in human medicine since 1993 and is used as an adjunctive therapy for refractory partial seizures (Kong & Irwin, 2007). More recently the drug has also been used in humans to treat a variety of neuropathic pain states and early postsurgical pain (Maneuf *et al.*, 2006; Gilron, 2007). In performance horses, gabapentin is listed as a class 3 performance-enhancing substance by the Association of Racing Commissioners International (Lehner *et al.*, 2007).

Despite being a structural analog of gamma-aminobutyric acid (GABA), gabapentin does not appear to bind to GABA-A or GABA-B receptors or to high affinity GABA transporters (Taylor *et al.*, 1998; Jensen *et al.*, 2002). While still incompletely understood, gabapentin's anticonvulsive and analgesic mechanisms of action are thought to involve the inhibition of neurotransmitter release within the peripheral and central nervous system (CNS) through interaction with the α_2-δ accessory subunit of voltage-gated calcium channels (Gee *et al.*, 1996; Baillie & Power, 2006; Maneuf *et al.*, 2006). The expression of the α_2-δ subunit has been shown to increase in chronic pain states, as well as in both afferent sensory neurons and the spinal dorsal horn in experimental neuropathic pain models (Luo *et al.*, 2001; Newton *et al.*, 2001). This correlates well with the observation that gabapentin primarily demonstrates analgesic properties in sensitized or hyperalgesic states (Pan *et al.*, 1999; Maneuf *et al.*, 2006). Gabapentin has also been shown to inhibit the processes of temporal summation and spinal cord 'wind-up' in healthy human volunteers (Harding *et al.*, 2005; Arendt-Nielsen *et al.*, 2007), thus prompting its use as a perioperative analgesic (Gilron, 2007). Markers of neuronal injury are up-regulated in the digital nerves and dorsal root ganglia of horses with laminitis (Jones *et al.*, 2007). Gabapentin therefore may provide or be adjunctive in providing analgesia in horses with laminitis, neuropathic or chronic pain states.

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The pharmacokinetic profile of gabapentin has been extensively studied in humans (Vollmer *et al.*, 1989; Boyd *et al.*, 1999; Gidal *et al.*, 2000), monkeys, dogs and rodents (Vollmer *et al.*, 1986; Radulovic *et al.*, 1995). Being currently commercially available only in tablet, syrup, and capsule formulations, reports of gabapentin use in the horse refer only to oral (p.o.) administration of doses extrapolated from use in other species (2.5 mg/kg at intervals of 8, 12 or 24 h; Davis *et al.*, 2007, 2.0–3.3 mg/kg at intervals of 8 or 12 h; Dutton *et al.*, 2009). A recent study (Dirikolu *et al.*, 2008) described the pharmacokinetic properties of a single p.o. dose (5 mg/kg) of gabapentin in four horses; however the oral bioavailability, behavioral effects and safety in the horse have not been documented. In humans, gabapentin is considered to be relatively safe and well tolerated with the most common side effects comprising somnolence, dizziness, sedation, and ataxia (Gilron, 2007).

The aims of this study were to (i) determine gabapentin's pharmacokinetic profile following i.v. and p.o. administration in healthy horses at a dose that produced an identifiable CNS effect, (ii) estimate the bioavailability of gabapentin at this dose, and (iii) assess cardiovascular and behavioral changes following gabapentin dosage to describe the pharmacodynamic effects, side effect and safety profiles in the horse.

MATERIALS AND METHODS

Animals

The study protocol was approved by the University of Pennsylvania's Institutional Animal Care and Use Committee. Six clinically healthy Thoroughbred geldings, 12.7 ± 5.0 (mean ± SD) years old and weighing 530 ± 49 kg, were used in the study. Two days before the experiment, horses were brought from pasture into stalls. They were fed grass hay and water *ad libitum* and received grain at 6:00 hours and 16:00 hours. The horses remained housed for the duration of the study but were turned out for 2 h daily into small paddocks except on days of testing. All experiments started at 7:00 hours.

Drug administration and sample collection

Gabapentin (20 mg/kg) was administered i.v. or p.o. to horses in a crossover, randomized design. Intravenous gabapentin, in a range of 30 to 90 mg/kg, significantly attenuates allodynia in nerve-injured rats (Pan *et al.*, 1999). While data regarding gabapentin's anticonvulsive and anti-neuropathic efficacy in horses are currently not available, pharmacokinetic parameters were previously determined in various species including dog and monkey following a 50 mg/kg i.v. and p.o. dose (Radulovic *et al.*, 1995). To avoid overdosing yet ensuring a pharmacodynamically effective dose being used, a pilot study was initially conducted in which the drug was administered to two horses by constant rate infusion (CRI; 1 mg/kg/min) until a clear central nervous effect (i.e. sedation) was noted. In the crossover study, there was a 2-week wash-out period between the i.v and p.o. dosage of gabapentin. Blood samples were collected by the use of a 14 gauge catheter (Angiocath, Becton Dickinson, Sandy, UT, USA) placed in the left jugular vein using an aseptic technique after previous intradermal mepivacaine 2% (Carbocaine HCl USP, Hospira, Inc., Lake Forest, IL, USA) infiltration. Intravenous administration was via a second catheter placed in the right jugular vein.

The gabapentin solution (100 mg/mL aqueous solution with benzyl alcohol (3% w/w) as preservative) to be administered i.v. was provided by a compounding pharmacy (Wedgewood Pharmacy, Swedesboro, NJ, USA) and subject to internal quality control using the analytical technique detailed below. The 20 mg/kg dose was diluted in 500 mL sterile saline (0.9% NaCl) and infused over 30 min at ~ 0.67 mg/kg/min in an attempt to avoid severe or unpredicted responses to drug administration (Vollmer *et al.*, 1989). Blood samples were collected at time 0 and 2, 4, 6, 10, 15 and 30 min during the CRI and 2, 4, 6, 10, 15, 30, 45 min and 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36 and 48 h postinfusion. Samples were transferred into vials containing potassium oxalate with sodium fluoride as the anticoagulant (Tyco Healthcare Group, Mansfield, MA, USA).

The orally administered solution was prepared by suspending crushed gabapentin tablets (Actavis Elizabeth Llc, Elizabeth, NJ, USA) in 10 mL of water and 5 mL of molasses within a 60 mL dose syringe. This suspension was delivered directly into the mouth of the animals followed by flushing with water. Blood samples were collected at time 0 and 2, 4, 10, 15, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36 and 48 h after p.o. dose. The horses received their morning grain 2 h before drug dosing and were allowed hay up to half an hour before dosing. Hay was then reintroduced 1 h after the oral dose was administered. Blood samples were centrifuged (2,500 ***g*** for 15 min) to obtain plasma. Aliquots of 2 mL plasma were immediately frozen at −20 °C and later stored at −70 °C until analyzed after 4 months. Each aliquot of plasma was used once to eliminate any effect of freeze-thaw cycles on the concentration of gabapentin in the sample.

Each horse also received an i.v. saline infusion as a control treatment during which all monitoring and sampling procedures were the same as those for the i.v. gabapentin treatment. The timing of the control treatment was randomly assigned to 2 days either before or after the i.v. gabapentin dose.

Plasma gabapentin detection and quantification by LC-MS/MS

Plasma gabapentin concentrations were measured using LC-MS/MS in positive electrospray ionization mode, following previously described techniques (Carlsson & Reubsaet, 2004; Lehner *et al.*, 2007). The concentrations of gabapentin in plasma samples were determined by incorporating internal standard (IS (S)-(+)-α-amino-cyclohexane-propionic acid hydrate (ACP), and using product ion chromatographic peak area ratios and linear regression analysis with 1/x weighting factor.

Preparation of primary reference and calibrator solutions.
A stock solution of gabapentin (Sigma-Aldrich, St. Louis, MO, USA; 1 mg/mL) was prepared in HPLC grade methanol and

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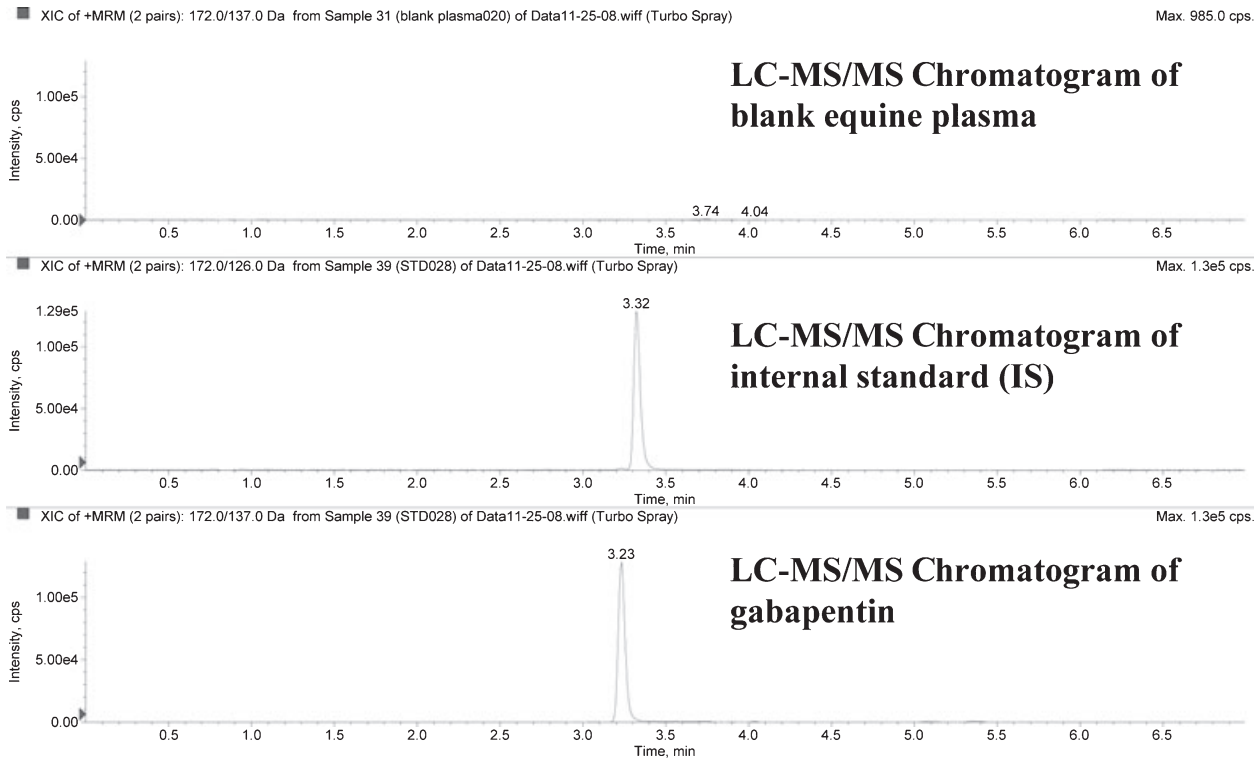

Fig. 1. Mass-spectrums of blank equine plasma, plasma spiked with (S)-(+)-α-amino-cyclohexane-propionic acid hydrate (ACP) serving as internal standard (IS), and plasma containing gabapentin.

subsequently diluted with water/methanol (50:50, v/v) to yield calibrator working solutions of 200, 400, 800, 1600, 4000, 8000, 16 000, 40 000 and 50 000 μg/mL. Likewise a 1 mg/mL IS stock solution (ACP; Sigma-Aldrich, St. Louis, MO, USA) was prepared and then diluted with water/-methanol (50:50) to 500 ng/mL. Finally, a plasma calibration solution was prepared by adding 50 μL of each calibrator working solution of gabapentin to 950 μL of blank plasma (from a pooled sample) in labeled 1.5 mL microcentrifuge tubes (Thermo Fisher Scientific Pierce, Fair Lawn, NJ, USA).

Extraction of gabapentin from equine plasma. Samples were prepared by protein precipitation with acetonitrile (LC/MS grade, Burdick & Jackson, Muskegon, MI, USA). For this purpose, 100 μL plasma aliquots (controls, calibrators, samples) were transferred into labeled 1.5 mL microcentrifuge tubes, then 100 μL of ACP was added to all tubes except the negative control samples followed by 500 μL acetonitrile. The solutions were thoroughly Vortex mixed and then centrifuged at 6800 ***g*** for 3 min to achieve a separation of the phases. The resulting supernatant (100 μL) was transferred to autosampler vials fitted with 200 μL limited volume inserts (Restek, Bellefonte, PA, USA) for analysis by LC-MS/MS.

Instrumentation and operating parameters. The LC-MS/MS system consisted of an Applied Biosystems (ABI) 4000 Q Trap hybrid triple-quadrupole linear ion trap mass spectrometer with Analyst Version 1.4.2 for system control and data acquisition and processing (Life Technologies Corporation, Carlsbad, CA, USA) and a Shimadzu 20AD LC with SIL-HTc autosampler (Shimadzu Scientific Instruments, Columbia, MD, USA). Liquid chromatographic separations were achieved using reverse-phase ACE C_{18} column (7.5 cm × 2.1 mm ID, 5 μm particle size; MAC-MOD Analytical, Inc., Chadds Ford, PA, USA) with guard column (1 cm × 2.1 mm ID, 5 μm particle; MAC-MOD Analytical, Inc.) at 30 °C and 0.2 μm column filter (MAC-MOD Analytical, Inc.). The mobile phase comprised 5 mM ammonium formate (pH = 3.51; solvent A) and acetonitrile (solvent B). Gabapentin was eluted with a mobile phase gradient using a flow rate was 300 μL/min, i.e. for analysis, a mobile phase gradient program was employed: 99% solvent A and 1% solvent B for the first 0.1 min, solvent B was increased to 80% from 0.1 to 3 min, and held for 1 min prior to returning to initial condition for 3 min (oven temperature 30 °C). Total analysis time was 7 min. Turbo source temperature was 350 °C; ion source gas 1 and gas 2 each was at 40 psi; curtain gas was 25 psi, collision gas was 5 psi and ion spray voltage was 5500 V. Declustering potential (DP) for gabapentin and IS was 50 V, collision energy (CE) was 25 for gabapentin and 20 V for IS, entrance potential (EP) was 10 V for both gabapentin and IS whereas collision cell exit potential (CXP) for gabapentin was 8 and that for IS was 10 V.

Both gabapentin and IS were detected in the MS/MS mode by monitoring m/z 172 → m/z 137 transition for gabapentin and m/z 172 → m/z 126 transition for IS (Fig. 1) in the quantification on gabapentin. Dwell time per transition was

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200 msec. No metabolite of gabapentin in plasma was detected.

Validation procedure. The intra- and inter-day accuracy and precision were assessed by analyzing six replicate samples at three different concentrations. The best linear fit with least-squares residuals for the calibration curves was determined by 1/x weighting factor with the line of best fit through the origin ($r^2 > 0.995$ for the analyte; Analyst v. 1.4.2). The ratio of peak area of the analyte to that of IS was proportional to analyte concentration. Intra-day and inter-day accuracy and precision for quantification of gabapentin in equine plasma were assessed by analyzing plasma samples spiked with gabapentin at three concentrations (40, 400 and 2000 ng/mL) in six replicates. Intra-day and inter-day precisions (coefficient of variation in %) were 0.96% and 3.75%, respectively. Intra-day and inter-day accuracies (bias %) were 99.1% and 102.7%, respectively. The limit of detection (LOD) was 1 ng/mL, the limit of quantification (LOQ), being defined as the lowest concentration in a calibration curve yielding precision with a coefficient of variation of <20% and accuracy of 80–120%, was 10 ng/mL. The limit of confirmation (LOC) was the lowest concentration at which the product ions were sufficient to produce stable product ion intensity ratio for confirmation of the presence of gabapentin in a test sample; the LOC was 20 ng/mL.

Pharmacokinetic analysis

Plasma concentration versus time curves of gabapentin following i.v. and p.o. dosage were analyzed using a nonlinear regression program (WinNonlin Version 5.2.1, Pharsight Corp., Cary, NC, USA). Two and 3-compartment models were fitted to the i.v. plasma concentration versus time curve from each horse. The model best describing the plasma concentration versus time curve for the i.v. and p.o. doses were based on the appearance of the observed and predicted concentrations, the reduction in the sums of squares, and the Akaike's information criterion (Akaike, 1976; Yamaoka *et al.*, 1978).

The 3-compartment that best described the i.v. infusion data is described by the following equation:

$$C_p^t = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t},$$

where A, B, and C were the coefficients (ng/mL) and α, β, and γ were exponents (h^{-1}) and C_p^t was the plasma concentration (ng/mL) of gabapentin at time t.

A 1-compartment model with absorption into and elimination from the central compartment was fitted to the p.o. plasma concentration versus time curve from each horse and is described by the following equation:

$$C_p^t = D * k_{01}/V/(k01 - k10) * (\exp(-k10 * t) - \exp(-k01 * t),$$

where D is the dose (mg), V is the volume of distribution (mL), $k_{01,}$ and k_{10} are the first order absorption from the gut and elimination rate constants from plasma, respectively. The equation assumes 100% bioavailability and absorption of the drug.

The A, B, and C coefficients (ng/mL) for the i.v. dose were calculated from the dose, volume of central compartment (V_C), and the relevant compartmental rate constants. Half-lives were calculated as the Ln2 divided by the exponents. Plasma concentration at 0 time (C_p^0) was the sum of the coefficients A, B, and C. The total area under the plasma concentration curve (AUC_0^∞) was determined by direct integration from 0 to infinity. The fractional quantity of gabapentin absorbed from the gastrointestinal tract into plasma was calculated as:

$$AUC\text{po}/AUC\text{iv}$$

The volume of the central compartment (V_C) was calculated as:

$$V_C = D\text{iv}/C_p^0,$$

where $D_{\text{i.v.}}$ is the dose administered i.v. and C_p^0 is the plasma concentration at zero time. Ratios of the inter-departmental rate constants $k12/k21$ and $k13/k31$ times V_c were used to calculate the volumes of compartments V_2 and V_3, and the volume of distribution at steady-state (V_{SS}) following i.v. dosage was calculated as the sum of all compartments (Gabrielsson & Weiner, 2000).

Total body clearance (Cl) was calculated as:

$$Cl = D\text{iv}/AUC_0^\infty$$

Clearance following p.o. dose was corrected to fraction of drug absorbed following p.o. dosage.

Pharmacodynamic monitoring

Changes in heart rate (HR) and rhythm were monitored using a telemetric ECG system (Telemetric ECG system, Model #: DI-205-C; DataQ Instruments Inc., Akron, OH, USA) and systolic, diastolic and mean arterial blood pressures were noninvasively recorded at the time of blood sampling using an oscillometric blood pressure monitor and a cuff placed around the root of the tail (Cardell® 9401 BP, Minrad Inc., Orchard Park, NY, USA). Blood pressure recordings were corrected by the distance (in cm) between the point of the shoulder (position of the heart) and the root of the tail. Sedation was assessed during the first 12 h postadministration employing the following sedation scoring system adopted from Hubbell and Muir (2006):

0. No sedation - Normal movement, normal ear and neck position, normal posture.
1. Mild sedation - Slightly decreased frequency and rapidity of movement, lowered ear and neck, lip drooping, slightly relaxed postural tone.
2. Moderate sedation - Moderately decreased frequency and rapidity of movement, ear tip separation, neck position below the horizontal plane.
3. Deep sedation - Prolonged periods of immobility, pronounced ear tip separation, loss of postural tone, base wide stance.

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To eliminate inter-observer variability, the same observer (R.T) scored each animal during the study. The barn routine and experimental protocol were standardized for all experiments and video recording was used to record the horse's behavior for 12 h postdrug administration.

Behavioral analysis

For each i.v. gabapentin and saline (control) treatment, a continuous 11 h VHS video recording of the horse in its stall was determined, beginning 1 h and continuing to 12 h after gabapentin or saline infusion. Video recordings were evaluated by a technician who was trained in the viewing and analysis of behavior of stalled horses. The first hour following gabapentin or saline infusion was not evaluated because of frequent interruption of ongoing behavior of the horse as a result of blood sampling, cardiovascular parameter monitoring and other measures. The video viewing and data summarizing technician was blind both to the purpose of the study and to the treatment status of the animals.

Video recordings were scanned at 22× real time, with review at 1× as needed, to record on a timeline each occurrence of eating, drinking, standing alert, standing rest (graded as light or deep), recumbent rest, urination, defecation, and any atypical or abnormal behaviors. Additionally, immediately after viewing each 11 h sample, the technician assessed the horse's overall demeanor using custom-designed 10-point rating scales for calmness (1 = calm to 10 = not calm), alertness (1 = normally alert to 10 = not alert) and reactivity (normally reactive to 10 = hyper reactive).

Statistical analysis

Pharmacokinetic parameter estimates of gabapentin were expressed as median and range and plasma concentrations of gabapentin were expressed as mean ± standard deviation (SD). All parametric pharmacodynamic data are presented as mean ± SD. For cardiovascular parameters and sedation scores a categorical regression blocked on horse or *t*-test analysis was performed. Within-animals comparisons of behavior measures after gabapentin and saline (in controls) infusion were evaluated using dependent *t*-tests or Wilcoxin signed ranks tests with $\alpha = 0.05$. Differences were considered to be significant when $P < 0.05$ (Statistical software program Statistix 8, Analytical Software, Tallahassee, FL, USA).

RESULTS

Pharmacokinetic analysis

Pharmacokinetic parameter estimates after i.v. and p.o. gabapentin dosage are summarized in Table 1, and plasma concentrations measured at all time points after i.v. and p.o. gabapentin are shown in Fig. 2. The i.v. plasma-concentration–time curve of gabapentin was best fitted to a 3-compartment mammillary model. The C_{max} at the end of the CRI (i.e. at 0.5 h) was 73.0 μg/mL and progressively decreased to 0.27 ± 0.16 μg/mL at 48 h. The $t_{1/2\alpha}$ and $t_{1/2\beta}$ half-lives of gabapentin were 0.09 and 1.8 h, respectively and were followed by a slower $t_{1/2\gamma}$ elimination phase of 8.5 h.

Table 1. Pharmacokinetic parameter estimates following continuous intravenous infusion of gabapentin (20 mg/kg) over a period of 30 min and oral administration of gabapentin (20 mg/kg) in six horses

Parameter	Median	Range
Intravenous administration		
A (μg/mL)	174.7	145.0–190.6
α (⁻h)	7.55	6.48–9.46
$t_{1/2\alpha}$ (h)	0.09	0.07–0.11
B (μg/mL)	16.3	15.0–25.6
β (⁻h)	0.40	0.16–0.62
$t_{1/2\beta}$ (h)	1.81	1.11–4.43
C (μg/mL)	12.8	0.82–15.8
γ (⁻h)	0.08	0.03–0.10
$t_{1/2\gamma}$ (h)	8.53	7.06–13.3
AUC_0^∞ (μg·h/mL)	216.6	195.1–267.5
C_{max} (μg/mL)	73.0	66.2–76.3
Cl (mL·h/kg)	96.7	77.0–100.8
V_C (mL/kg)	96.5	86.3–114.2
V_2 (mL/kg)	350.4	309.4–483.8
V_3 (mL/kg)	386.8	75.9–463.2
V_{ss} (mL/kg)	809.7	663.6–898.7
Oral administration		
k_a (h^{-1})	1.63	0.80–2.07
ta (h)	0.42	0.33–0.86
k_e (h^{-1})	0.09	0.06–0.10
te (h)	7.73	6.70–11.93
Cl/F (mL·h/kg)	87.2	72.6–95.8
T_{max} (h)	1.00	0.75–2.00
C_{max} (μg/mL)	3.75	1.89–5.76
AUC_0^∞ (μg·h/mL)	38.8	22.9–61.6

A, *B*, *C*, coefficients; α, β, γ, exponents; $t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$ = elimination half-lives; V_C, volume of central compartment; V_2, V_3, estimated volume of compartments 2 and 3. AUC_0^∞ = area under the plasma concentration–time curve 0 to infinity; *Cl*, total body clearance; V_{ss}, steady-state volume of distribution; k_a, absorption rate constant; $t_{1/2a}$ = absorption half-life; k_e, elimination rate constant; $t_{1/2e}$ = elimination half-life; *Cl/F*, fractional oral plasma clearance; T_{max}, time of maximum concentration; C_{max}, maximum plasma concentration.

The p.o. plasma-concentration–time curve of gabapentin was best fitted to a 1-compartment model with absorption into and elimination from a central compartment. After oral gabapentin C_{max} and T_{max} were 3.75 μg/mL and 1.0 h, respectively and the plasma concentration declined to 0.06 ± 0.04 μg/mL at 48 h. The terminal elimination half-life $t_{1/2e}$ was 7.7 h (Table 1) and oral bioavailabilty was 16.2 ± 2.8%. There was no significant difference between the terminal half-lives of i.v. and p.o. doses (Fig. 2).

Cardiovascular and behavioral effects

Cardiovascular parameters were not significantly affected by either i.v. or p.o. gabapentin. Average heart rate recordings

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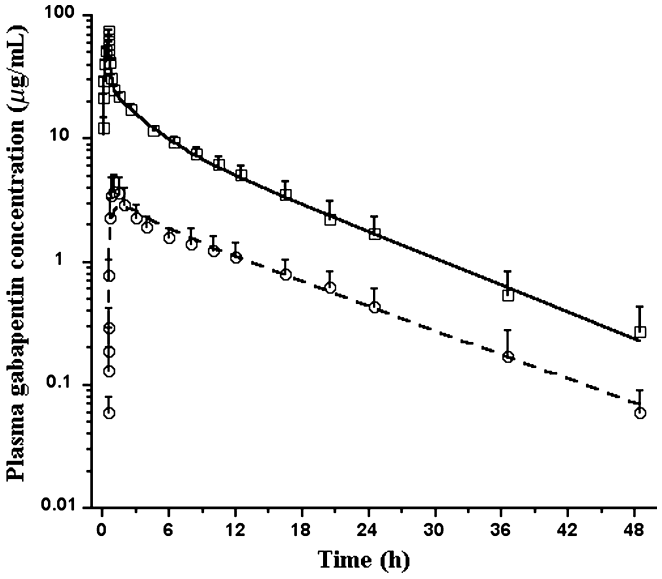

Fig. 2. Plasma gabapentin concentration (mean ± SD) following either i.v. drug infusion (20 mg/kg) over 30 min (–□–) or oral administration (—○—). Solid and dashed lines represent the curves of best fit (n = 6).

ranged from 34 to 39 and 34 to 38 beats/min while average mean arterial blood pressure recordings ranged from 94 to 119 and 98 to 116 mmHg following i.v. and p.o. drug administration, respectively. Intravenous gabapentin caused a significant increase in sedation scores for 1 h after drug infusion when compared with baseline measurements at 10 min ($P < 0.05$). All the horses reached and maintained a sedation score of at least 1 (Table 2). However, horses appeared more dormant than deeply sedated and were easily arousable throughout the period of the elevated sedation scores, with the exception of one animal (horse # 2; Table 2) that exhibited sedation of greater depth and duration than the other five, almost reaching sedation score 3 between 60 and 90 min after drug infusion started. All horses had returned to sedation score 0 by 150 min after the beginning of CRI. Gabapentin p.o. did not produce any noticeable effects or changes in the sedation score.

When compared with the control treatment, i.v. gabapentin dose significantly increased drinking frequency and decreased the duration of standing rest ($P < 0.05$). No significant differences were observed in the other 17 behavioral measures analyzed (Table 3). Subjectively no obvious behavioral effects were observed following p.o. dosage of gabapentin, however full analysis against a p.o. control treatment was not conducted.

Table 2. Sedation scores recorded after continuous intravenous infusion of gabapentin (20 mg/kg) over a period of 30 min and oral administration of gabapentin (20 mg/kg) in six horses

Time after the beginning of gabapentin infusion (min)	Horse						Median	Range
	1	2	3	4	5	6		
−10	0	0	0	0	0	0	0	0–0
2	0	0	0	0	0	0	0	0–0
4	0	0	0	0	0	0	0	0–0
6	0	0	0	0	0	0	0	0–0
10	0	0	0	0	1	0	0	0–1
15	0	1	1	0	0	0	0	0–1
30	1	1	2	1	1	1	1*	1–2
32	1	1	1	1	1	0	1*	0–1
34	1	1	1	1	1	0	1*	0–1
36	1	2	1	1	1	0	1*	0–2
40	1	2	2	1	0	1	1*	0–2
45	1	2	1	1	1	1	1*	1–2
60	1	2	2	2	2	1	2*	1–2
75	0	2	1	2	1	1	1*	0–2
90	0	1	1	2	1	0	1*	0–2
150	0	0	0	0	0	0	0	0–0
270	0	0	1	1	0	0	0	0–1
390	0	0	0	0	1	0	0	0–1
510	0	1	0	0	1	0	0	0–1
630	0	0	0	0	0	0	0	0–0
750	0	0	0	0	0	0	0	0–0

*$P < 0.05$ (based on categorical regression analysis).

DISCUSSION

Pharmacokinetics

The i.v. dosage of gabapentin in the horse was best described by a 3-compartment model (Fig. 2, Table 3), a pharmacokinetic profile similar to that reported for humans and other species (Vollmer *et al.*, 1986, 1989; Beydoun *et al.*, 1995), but different from the dog in which plasma concentration–time data were best fitted to a 2-compartment model (Radulovic *et al.*, 1995). The V_C (96.5 mL/kg) was similar to the circulating blood volume in horses (Kohn *et al.*, 1978; Naylor *et al.*, 1993). In the canine administered i.v. radioactive gabapentin, equilibrium was attained between erythrocytes and plasma after 10 min followed by an elimination from plasma and erythrocytes that were similar (Vollmer *et al.*, 1986). This may explain V_C being limited to the equine blood volume. The initial distribution of most drugs following an i.v. dosage attains an equilibration between plasma and the interstitial/tissue spaces with an estimated volume of V_C usually larger than the blood volume. Therefore we may speculate that the initial very rapid α disposition phase reflects the continuous uptake of gabapentin into erythrocytes following i.v. infusion. This would be especially relevant in the horse with the large splenic reserve of erythrocytes. The time course of gabapentin in distribution spaces V_2 and V_3 relative to V_C following the i.v. infusion is shown in Fig. 3. This distribution pattern into V_2 and V_3 was similar to that described in the rat (Vollmer *et al.*, 1986). Distribution into V_2 suggests an initial uptake by a group of tissues followed by equilibration in all tissues as there was no significant difference in the final volume of the two distribution spaces. Results of studies conducted in other species suggest that the β-phase represents the distribution of the drug into the pancreas, skin, and kidney, as these three tissues had higher concentrations than blood. All other tissues were in the range of

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Table 3. Summary of behavioral observations following continuous 30 min intravenous (i.v.) infusion of gabapentin (20 mg/kg) or saline in six horses. Period of observation was 1–12 h after gabapentin or saline infusion

Behavior measure 11-h videotaped sample	i.v. Gabapentin	i.v. Saline (control)	Dependent *t*-test (5 df)
Major activity shifts	26.2 (8.1)	30.3 (9.3)	n.s.
Eating hay			
Total duration (min)	403.1 (93.3)	376.3 (81.0)	n.s.
Bout frequency	38.8 (20.8)	31.0 (9.0)	n.s.
Bout mean duration (min)	14.0 (10.0)	12.7 (3.2)	n.s.
Drink frequency	25.8 (9.8)	19.6 (7.6)	$P < 0.05$
Standing rest			
Total duration (min)	111.4 (64.7)	151.9 (51.4)	$P < 0.05$
Bout frequency	13.6 (7.8)	13.5 (6.9)	n.s.
Bout mean duration (min)	9.0 (5.4)	16.3 (16.7)	n.s.
Standing alert			
Total duration (min)	61.3 (53.4)	57.9 (38.7)	n.s.
Bout frequency	16.6 (11.5)	18.6 (9.1)	n.s.
Bout mean duration (min)	3.5 (2.9)	3.0 (1.2)	n.s.
Urination frequency	3.0 (0.4)	2.7 (1.2)	n.s.
Defecation frequency	6.0 (2.9)	6.3 (2.2)	n.s.
Interruptions (staff enter stall)	8.3 (3.2)	8.4 (1.7)	n.s.
		Wilcoxin signed ranks	
Overall rating scale scores			
Calm (0) to not calm (10)	2.5 (1.7)	1.8 (2.4)	n.s.
Normally alert (0) to sedate (10)	1.3 (1.5)	2.3 (2.2)	n.s.
Normally reactive (0) to hyper-reactive (10)	1.0 (1.5)	0.8 (1.5)	n.s.

In video recordings determined for each horse; 19 quantitative measures were recorded for each. In addition, for each 11-h video sample, subject was scored by the viewing technician on 10-point rating scales for (a) normally calm versus agitated, ill-at-ease, or restless, (b) normally alert versus sedate, and (c) normally reactive versus hyper-reactive. All data are presented as means (SD). Within-subjects comparisons of behavior measures were evaluated using dependent *t*-tests or Wilcoxin signed ranks tests with 5 degrees of freedom (df).

the concentrations measured in blood, including the brain. The exception was adipose tissue, in which the concentration was much lower (Vollmer *et al.*, 1986; Radulovic *et al.*, 1995).

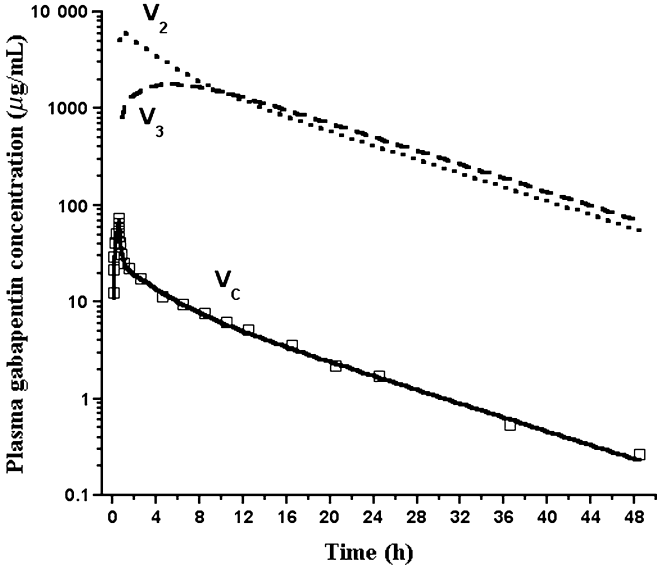

Fig. 3. Gabapentin concentration–time course in the central compartment (V_C) and the distribution spaces (V_2) and (V_3) following the i.v. infusion of 20 mg/kg over 30 min in six horses.

The estimated median $t_{1/2\gamma}$ of 8.5 h after i.v. gabapentin corresponded well with elimination half-lives reported after i.v. dosage in humans (5–9 h; Vollmer *et al.*, 1989). However, $t_{1/2\gamma}$ was longer in the horse than in other animal species (rats, dogs, monkeys) in which half-lives between 2 and 3 h had been determined (Vollmer *et al.*, 1986, 1989; Radulovic *et al.*, 1995; Berry *et al.*, 2003). No metabolites of gabapentin were identified in plasma, similar to findings in humans, rats, and monkeys in which the drug did not undergo liver metabolism and was almost entirely cleared by the kidneys (Vollmer *et al.*, 1986; Radulovic *et al.*, 1995).

The mean oral bioavailability of gabapentin was 16% in horses included in this study. While this value is lower than data reported in the literature for humans (29–83%), rat (79–83%), dog (80%), and monkey (24–40%) after p.o. or intragastric drug administration of 6–23, 50, 50, and 3–4 mg/kg, respectively (Vollmer *et al.*, 1986, 1989; Beydoun *et al.*, 1995; Radulovic *et al.*, 1995; Gidal *et al.*, 1998, 2000), a direct comparison may not be appropriate because not all studies employed *AUC* for calculation of oral bioavailability or used a sufficient number of subjects. The time to maximum drug concentrations in plasma [T_{max} 1.0 (0.8–2.0) h] was well within the range reported by the same authors in humans (2–3 h), rats (1.7–1.9 h), dogs (1.1 h), and monkeys (1.8–2.3 h) and by Dirikolu *et al.* (2008) in horses (1.4 h). The reason for

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the low bioavailability in our horse population is unclear; it may be as a result of lower stability of gabapentin in the oral drug solution, low solubility in the dosing form, saturation of intestinal transporters as speculated upon in other species (Berry *et al.*, 2003; Del Amoa *et al.*, 2008), or the larger dose in horses (compared with smaller animals) quickly by-passing the absorption window in the small intestine where the transporters are located. Food was not withheld except for half an hour before and an hour after dosing in our experiments to approximate a clinically relevant dosing procedure, this may have affected bioavailability.

After p.o. gabapentin dosage of 20 mg/kg in this study the median C_{max} (3.75 μg/mL) compared with the maximum concentration of 0.27 μg/mL reported by Dirikolu *et al.* (2008) after p.o. dosage of 5 mg/kg was much higher. These authors did not determine bioavailability at this lower dose. Based on proportional dose administration the C_{max} and *AUC* of the 5 mg/kg dose were also low suggesting that even at this lower dose the drug was poorly absorbed. This argues against the idea of a higher bioavailability with lower doses of gabapentin as proposed in other species (Stewart *et al.*, 1993; Del Amoa *et al.*, 2008).

For both i.v. and p.o. gabapentin dose we were able to detect gabapentin plasma concentrations above 70 ng/mL even at 48 h postdrug administration and those were clearly above the LOQ of 10 ng/mL. Although Dirikolu *et al.* (2008) applied a GC-MS/MS technique with similar LOQ (17 ng/mL; Lehner *et al.*, 2007), the authors could not include any time point beyond 20 h in their pharmacokinetic analysis because in all study animals the plasma concentrations of gabapentin at 24 h had decreased below the lowest standard concentration (50 ng/mL). The inability to fully define the complete excretion curve may explain why these investigators determined a plasma elimination half-life of gabapentin in horses (3.4 h) that is approximately half as long as the half-life we determined in our study after oral drug administration (7.7 h). In other species the pharmacokinetics were commonly shown to be linear over a wide dose range (Vollmer *et al.*, 1986) therefore the 4-fold difference in the horse dosage in our study is unlikely to explain the difference in half-life.

Cardiovascular and behavioral effects

The administration of 20 mg/kg gabapentin by i.v. infusion over 30 min or p.o. was well tolerated by all 6 horses. After i.v. dosage plasma gabapentin concentrations remained for approximately 15 h above the 3–4 μg/mL range which has been associated with significant analgesic effects in adult human volunteers (Eckhardt *et al.*, 2000) and anticonvulsive activity in pediatric and adult patients (Gatti *et al.*, 2003). In contrast, with oral administration plasma gabapentin concentrations decreased much more rapidly, i.e. within 2–3 h below this threshold. Neither route of gabapentin dosage was associated with effects on heart rate, rhythm or blood pressure, nor severe central nervous effects, which concurs with experiences in human patients in which the drug was found to be safe and well tolerated (Beydoun *et al.*, 1995, Gilron, 2007).

Some variation was observed in the depth and duration of sedation following i.v. gabapentin dosage in our study but overall the calming effect was mild as observed in rats after an i.v. dose of 90 mg/kg (Pan *et al.*, 1999). In rodent studies an equilibration was established between blood and various brain tissues at 60 min (Vollmer *et al.*, 1986) but not at 30 min, when all horses in our study were at least slightly sedate with a median score of 1. Four of the six horses were still slightly sedate at 90 min postadministration (Table 2). The plasma concentration during this period was 22.5–73.9 μg/mL. If we assume an equilibration between blood and brain tissue after 30 min, this 3-fold difference in plasma concentrations with minimal variability in the sedation score suggests a limitation on the degree of sedation that can be produced by gabapentin. These are concentrations that would be difficult to attain by p.o. dosage. A large inter-subject variability in side effects is also recognized in human patients receiving p.o. gabapentin, though side effects such as dizziness and somnolence generally appear to be dose-dependent and usually resolve after dose reduction (Gilron, 2007). No obvious reason was noted for the prolonged, deeper sedation in one horse and the plasma concentration was not markedly different from those measured in the remaining horses in the study.

During the 11 h period of behavioral analysis the only changes that were significantly affected by the i.v. dose of gabapentin were drinking frequency and standing rest time, which were increased and decreased, respectively. Gabapentin and the related drug pregabalin have not been reported to increase thirst in other species and hence it remains unknown why the animals drank more frequently. Environmental conditions were not controlled, however large fluctuations in ambient temperature were not present.

The sedation scoring system chosen had previously been used to assess the effect of α_2-agonists (Hubbell & Muir, 2006) but may not be sensitive enough to fully detect the mild calming effects gabapentin causes in horses after i.v. dosage. Indeed, the results of a recent study in humans by Foldvary-Schaefer *et al.* (2002) suggested that gabapentin primarily changes sleep patterns (increase in slow wave sleep) with only minor reductions in arousal and awakening, unlike other centrally acting tranquilizers. As all our experiments were conducted in normal pain-free horses, it has not been determined if higher sedation scores would be attained in horses with existing pain, following multiple doses or part of other therapy. This is the challenge in determining the efficacy of this drug clinically.

CONCLUSION

Administration of 20 mg/kg gabapentin in the horse was not associated with any cardiovascular or behavioral effects that would warrant its preclusion as a future therapy. Its pharmacokinetic profile in the equine is broadly consistent with that in other species; however its oral bioavailability is relatively low in the horse. Further work is required to assess the analgesic

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efficacy of this drug in horses and appropriate dosing based on its bioavailability.

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