J. vet. Pharmacol. Therap. **31**, 175–177, doi: 10.1111/j.1365-2885.2008.00943.x. SHORT COMMUNICATION

Pharmacokinetics of gabapentin in horses

L. DIRIKOLU*
A. DAFALLA†
K. J. ELY†
A. L. CONNERLY†
C. N. JONES†
H. ELKHOLY†
A. F. LEHNER‡
K. THOMPSON§ &
T. TOBIN¶

Department of Veterinary Biosciences, University of Illinois, College of Veterinary Medicine, Urbana, IL; †Department of Biomedical Sciences, College of Veterinary Medicine, Nursing and Allied Health, Tuskegee University, Tuskegee, AL; ‡Livestock Disease and Diagnostic Center, College of Agriculture, University of Kentucky, Lexington, KY; §Department of Large Animal Clinics, College of Veterinary Medicine, Nursing and Allied Health, Tuskegee University, Tuskegee, AL; ¶128C Maxwell Gluck Equine Research Center, Department of Veterinary Science, University of Kentucky, Lexington, KY, USA

(Paper received 7 June 2007; accepted for publication 20 December 2007)

Dr Levent Dirikolu, Department of Veterinary Biosciences, 3830 VMBSB, MC-002, 2001 South Lincoln Avenue, Urbana, IL 61802, USA. E-mail: dirikolu@uiuc.edu

Gabapentin, [1-(aminomethyl)cyclohexaneacetic acid with molecular formula of $C_9H_{17}NO_2$, m.w. 171.24; Neurontin®; Pfizer Inc., New York, NY, USA], is an anticonvulsant drug used as adjunctive therapy in humans for the treatment of partial seizures not adequately controlled with standard antiseizure drugs (Wolf *et al.*, 1996; Gambelunghe *et al.*, 2005). Gabapentin is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and therefore, like benzodiazepines and barbiturates, it is very likely that gabapentin has the potential to produce anxiolytic, analgesic, sedative, and/or tranquilizing, skeletal muscle relaxant, and anticonvulsant activities in racing horses.

Gabapentin is generally used as an add-on therapy for control of partial seizures in patients who have not achieved satisfactory control with, or who are intolerant to standard anticonvulsants. Although its structure resembles GABA, the actual mode of action of gabapentin is still unknown (Goa & Sorkin, 1993; Berry *et al.*, 2003). It has been shown that gabapentin does not possess affinity for $GABA_A$ or $GABA_B$ receptors, it is not metabolized to a GABA or GABA agonist, and it does not inhibit GABA uptake or degradation (Gambelunghe *et al.*, 2005). It has been proposed that gabapentin may alter the metabolism of amino acids in the brain and may bind to specific neuronal proteins in the brain (Chadwick, 1994; Taylor, 1994). Several other possible modes of action of gabapentin were recently summarized by Stefan and Feuerstein (2007) including augmentation of nonspecific cation channels like the hyperpolarization-activated cation channel, acting as an agonist of ATP-dependent potassium channels, and binding with high affinity to the ∞_2 δ type 1 and 2 subunits of voltage-gated calcium channels.

The pharmacokinetics of gabapentin have been studied in humans. The plasma elimination half-life of gabapentin in humans was reported to be between 5 and 9 h (Mclean, 1995; Berry *et al.*, 2003). Limited information is available in the literature about the usage (Govendir *et al.*, 2005; Platt *et al.*, 2006) or pharmacokinetics of gabapentin in the veterinary field (Vollmer *et al.*, 1986; Radulovic *et al.*, 1995; Stevenson *et al.*, 1997a,b; Matar *et al.*, 2000).

Medications capable of improving the racing performance of horses are classified by the Association of Racing Commissioners International (ARCI) based on their performance-enhancing potential. Gabapentin is currently classified as an ARCI class 3 agent [available from the ARCI (2004); http://www.arci.com/druglisting.pdf]. As such, gabapentin is considered to have significant potential to influence the outcome of a race, and its administration to a horse shortly before a race would clearly contravene the rules of racing in most jurisdictions. It is essential for the welfare and integrity of the racing industry that accurate and specific analytical tests exist for quantitation of this drug in the serum/plasma of racing horses to control either its inadvertent or intentional misuse.

In the present study, four mature Thoroughbred mares (8 to 9 years old) weighing 465–505 kg were used. A routine clinical examination was performed before each experiment to assure that the animals were healthy and sound. Animals used in these experiments were managed according to the rules and regulations of the Tuskegee University Institutional Animal Care Use Committee, which also approved the experimental protocol.

The skin over the left jugular vein was washed with povidone–iodine scrub (Poviderm, Burns Veterinary Supplies, Westbury, NY, USA) and rinsed with ethanol. An i.v. catheter (Abbocath-T, 14-gauge × 5.5 inch; Abbott Animal Health, North Chicago, IL, USA) was inserted into the left jugular vein and sutured in place. Horses were given single oral doses of gabapentin (5 mg/kg mixed with maple syrup). Blood samples were collected from the left jugular vein for analyses at 0, 15, 30, and 45 min and 1, 2, 4, 6, 8, 24, 48, and 72 h into heparinized Vacutainer plasma tubes (Becton Dickinson, Franklin Lakes, NJ, USA) and then centrifuged at 4 °C at 2000 ***g*** for 15 min; the plasma was stored and refrigerated in 5-mL aliquots until assayed. Gabapentin was analyzed by using Perkin-Elmer AutoSystem XL Gas Chromatography and TurboMass Mass Spectrometer (Perkin-Elmer, Norwalk, CT, USA) set in positive ion mode as described previously (Lehner *et al.*, 2007). The quantitative method of gabapentin was validated by examining the measurement of consistency of results (within-run and between-run), correlation (coefficient of determination of the standard curve), and extraction efficiency of the assay as previously reported (Lehner *et al.*, 2007).

Pharmacokinetic analyses were performed, using a nonlinear regression program (WINNONLIN, version 5.1; Pharsight Corporation, Cary, NC, USA). The goodness-of-fit was evaluated by the Akaike Information Criterion (Yamaoka *et al.*, 1978), residual plots and visual inspection. The data were weighted as $1/(y_{pred})^2$, where y_{pred} was the model-predicted concentration at the actual time.

Analysis of the plasma samples showed rapid absorption of gabapentin following oral administration in horses included in our study (Fig. 1). The mean plasma concentration of gabapentin at 15 min following oral dose was 82.5 (±33) ng/mL (Fig. 1). Observed maximum plasma concentrations (C_{max}) of 320 (±37.5 SD) ng/mL of gabapentin were determined within 1 h (T_{max}) after administration, and the observed C_{max} values were in reasonably close agreement. Thereafter, observed plasma concentration declined to values below our lowest calibrator, interpolated as 16 (±2 SD) ng/mL, at 24 h after oral administration of gabapentin. Since the plasma concentration of gabapentin at 24 h was less than our lowest standard (50 ng/mL) in all horses included in our study, this time point was not included in pharmacokinetic analyses. The mean plasma concentration of gabapentin at 8 h postadministration time was 92.5 (±31) ng/mL with an apparent plasma elimination half-life of 3.4 h. Gabapentin was not detectable in plasma samples of horses at 48 h following 5 mg/kg oral administration of gabapentin. The apparent pharmacokinetic parameters of gabapentin following oral administration are shown in Table 1.

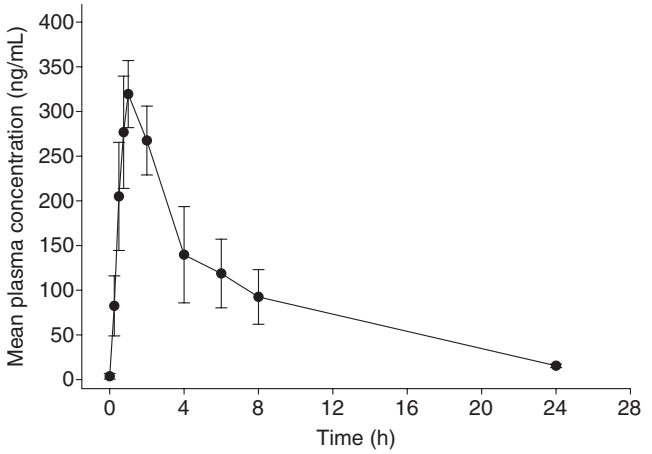

Fig. 1. Mean (±SD) plasma concentration of gabapentin from four horses following single 5 mg/kg oral administration.

In the present study, it was shown that gabapentin is rapidly absorbed following a single 5 mg/kg oral administration in horses. The pharmacokinetics of gabapentin has been studied in humans and also in various animal species. In one of these studies, it was shown that C_{max} value of gabapentin in 24 human volunteers following single oral dose of 400 mg of gabapentin was 3.2 μg/mL (Bahrami & Mohammadi, 2006), which is significantly higher than that in horses reported in the present study following single 5 mg/kg oral administration of gabapentin or roughly the same dose. In similar studies, it was shown that C_{max} values of gabapentin were 3.2 and 4 μg/mL following single 400 and 200 mg oral administration of gabapentin to a human male volunteer, respectively (Hengy & Kölle, 1985; Zhu & Neirinck, 2002). Additionally, gabapentin was shown to attain C_{max} values ranging from 3.74 to 4.52 μg/mL following single 10 mg/kg oral administration of gabapentin in 48 human pediatric patients (ages from 1 month to 12 years; Haig *et al.*, 2001). Gabapentin has been reported to attain C_{max} values of 16.4, 56.3, and 8.90 μg/mL in rats, dogs, and monkeys, respectively, following single oral dose of 50 mg/kg of gabapentin (Radulovic *et al.*, 1995). Even though the dose of gabapentin in this study (Radulovic *et al.*, 1995) was only 10-fold higher than that used in our equine study, the C_{max} values in rats, dogs, and monkeys were approximately 51-, 176-, and 28-fold higher than that in horses, respectively. These studies clearly indicate that gabapentin is relatively poorly absorbed or more rapidly metabolized in horses in comparison to humans and various other animal species following its oral administration. The plasma elimination half-life of gabapentin in

Table 1. Pharmacokinetic parameters of gabapentin after a single oral administration (5 mg/kg)*

Parameter	Horse 1	Horse 2	Horse 3	Horse 4	Mean (± SD)
$t_{1/2}$ K_{01} (h)	0.40	0.53	0.31	0.42	0.415 (±0.045)
$t_{1/2}$ K_{10} (h)	2.74	2.68	3.46	4.73	3.40 (±0.477)
$AUC_{0-inf.}$ (ng/mL/h)	1593	1276	1787	2497	1788.3 (±258.66)
Oral clearance (L/h/kg)	3.14	3.92	2.80	2	2.97 (±0.398)
T_{max} (h)	1.31	1.55	1.18	1.60	1.41 (±0.099)
C_{max} (ng/mL)	289	221	283	290	270.75 (±16.66)
R^2	0.94	0.91	0.95	0.97	0.94 (±0.013)

*Using a nonlinear regression program (WINNONLIN, version 5.1; Pharsight Corporation, Cary, NC, USA).

horses (3.4 h) is very similar to that reported in dogs (3–4 h) (Vollmer *et al.*, 1986). Further studies are required to determine the clinical pharmacologic effects of gabapentin in horses following single or multiple doses administration of this drug.

ACKNOWLEDGMENTS

This research was supported by grants from the Birmingham Racing Commission Breeding and Development Fund, Birmingham, AL, and Tuskegee University Research and Graduate Studies Development Fund, Tuskegee, AL. The authors thank Pharsight Corporation (Cary, NC) for providing WINNONLIN, version 5.1, for pharmacokinetics analysis.

REFERENCES

ARCI (2004) *Uniform Classification Guidelines for Foreign Substances and Recommended Penalties and Model Rule*. Association of Racing Commissioners International, Lexington, KY. Available at: http://www.arci.com/druglisting.pdf; accessed on April 2007.

Bahrami, G. & Mohammadi, B. (2006) Sensitive microanalysis of gabapentin by high-performance liquid chromatography in human serum using pre-column derivatization with 4-chloro-7-nitrobenzofurazan: application to a bioequivalence study. *Journal of Chromatography. Part B, Analytical Technologies in the Biomedical and Life Sciences*, **837,** 24–28.

Berry, D.J., Beran, R.G., Plunkeft, M.J., Clarke, L.A. & Hung, W.T. (2003) The absorption of gabapentin following high dose calculation. *Seizure*, **12,** 28–36.

Chadwick, D. (1994) Drug profile: gabapentin. *The Lancet*, **343,** 89–91.

Gambelunghe, C., Mariucci, G., Tantucci, M. & Ambrosini, V. (2005) Chromatography-tandem mass spectrometry analysis of gabapentin in serum. *Journal of Chromatography*, **19,** 63–67.

Goa, K.L. & Sorkin, E.M. (1993) Gabapentin, a review of its pharmacological properties and clinical potential in epilepsy. *Drugs*, **46,** 409–427.

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.

Haig, G.M., Bockbrader, H.N., Wesche, D.L., Boellner, S.W., Ouellet, D., Brown, R.R., Randinitis, E.J. & Posvar, E.L. (2001) Single-dose gabapentin pharmacokinetics and safety in infants and children. *Journal of Clinical Pharmacology*, **41,** 507–514.

Hengy, H. & Kölle, E.U. (1985) Determination of gabapentin in plasma and urine by high-performance liquid chromatography and pre-column labelling for ultraviolet detection. *Journal of Chromatography*, **341,** 473–478.

Lehner, A.F., Stewart, B., Dafalla, A., Ely, K.J., Connerly, A.L., Jones, C.N., ElkHoly, H., Lehner, A.F., Thompson, K., Tobin, T. & Dirikolu, L. (2007) Gabapentin in horses: validation of an analytical method for quantitation. *Journal of Analytical Toxicology*, **31,** 555–565.

Matar, K.M., Nicholls, P.J., Bawazir, S.A., Al-Hassan, M.I. & Tekle, A. (2000) Effect of vigabatrin and gabapentin on phenytoin pharmacokinetics in the dog. *Pharmacological Research*, **42,** 517–521.

Mclean, M.J. (1995) Gabapentin. *Epilepsia*, **36** (Suppl. 2), S72–S86.

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., Turck, 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.

Stefan, H. & Feuerstein, T.J. (2007) Novel anticonvulsant drugs. *Pharmacology & Therapeutics*, **113,** 165–183.

Stevenson, C.M., Kim, J. & Fleisher, D. (1997a) Colonic absorption of antiepileptic agents. *Epilepsia*, **38,** 63–67.

Stevenson, C.M., Radulovic, L.L., Bockbrader, H.N. & Fleisher, D. (1997b) Contrasting nutrient effects on the plasma levels of an amino acid-like antiepileptic agent from jejunal administration in dogs. *Journal of Pharmaceutical Sciences*, **86,** 953–957.

Taylor, C. (1994) Emerging perspectives on the mechanism of action of gabapentin. *Neurology*, **44,** S10–S16.

Vollmer, K.O., Von Hodenberg, A. & Kolle, E.U. (1986) Pharmacokinetics and metabolism of gabapentin in rat, dog and man. *Arzneimittel-Forschung*, **36,** 830–839.

Wolf, C.E., Saady, J.J. & Poklis, A. (1996) Determination of gabapentin in serum using solid-phase extraction and gas-liquid chromatography. *Journal of Analytical Toxicology*, **20,** 498–501.

Yamaoka, K., Nakaqawa, T. & Uno, T. (1978) Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. *Journal of Pharmacokinetics and Biopharmaceutics*, **6,** 165–175.

Zhu, Z. & Neirinck, L. (2002) High-performance liquid chromatographic method for the determination of gabapentin in human plasma. *Journal of Chromatography. Part B, Analytical Technologies in the Biomedical and Life Sciences*, **779,** 307–312.