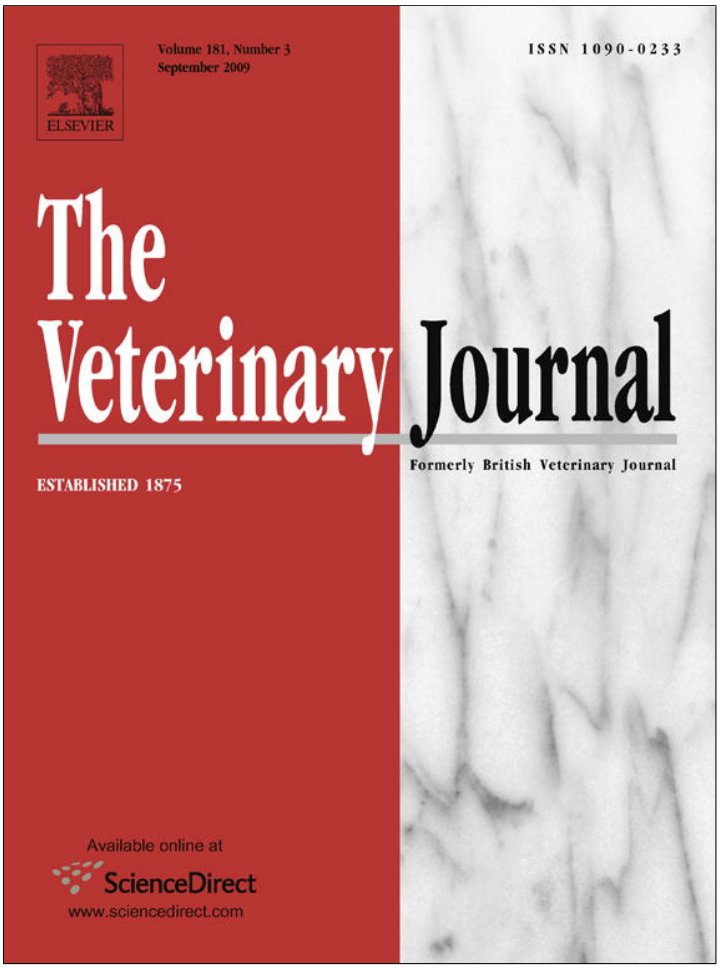

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The Veterinary Journal 181 (2009) 299–304
The Veterinary Journal
www.elsevier.com/locate/tvjl

Pharmacokinetics of buprenorphine after intravenous administration of clinical doses to dogs

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Accepted 4 March 2008

Abstract

The purpose of this study was to evaluate plasma concentrations and pharmacokinetic parameters of buprenorphine in dogs following intravenous (IV) administration of clinical doses of the opioid. An IV bolus of 0.02 mg/kg buprenorphine was administered to six healthy Beagles and blood samples were collected through a jugular catheter before and at 1, 5, 10, 15, 20, 30 and 45 min, and 1, 2, 4, 6, 8 and 12 h after administration. Plasma buprenorphine concentrations, measured using a commercial radioimmunoassay (RIA), decreased following a three-exponential curve. The two distribution and the elimination half-lives were 2.9 ± 1.8 min, 16.5 ± 3.7 min, and 266.6 ± 82.0 min, respectively; the clearance was 329.6 ± 62.2 mL/min, and the steady state volume of distribution was 83.7 ± 26.5 L.

The results demonstrated the feasibility of the RIA assay to analyse buprenorphine in dog plasma samples. Following IV administration buprenorphine showed a three-compartment kinetic profile, as has been described previously in humans, rabbits and cats. The relationship between plasma concentrations and dynamic effects in dogs remains to be established.

Keywords: Buprenorphine; Dogs; Pharmacokinetics; Intravenous; Radioimmunoassay

Introduction

Over the last decade, the effective management of pain in animals has undergone remarkable advances in veterinary medicine and this trend is likely to continue. Currently, there are many commercially available analgesic drugs with different mechanisms of action. Opiates have been widely used to control both acute and chronic pain, and particularly to relieve moderate or severe pain in animals. Buprenorphine is one of the opioid drugs most commonly used in the UK (Lascelles et al., 1999) and in Australia (Watson et al., 1996). It has high analgesic potency as compared with morphine and is an effective analgesic for moderate to severe pain management.

Buprenorphine is a potent, semisynthetic opioid with mixed agonist/antagonist properties – it is a partial agonist at μ-opioid receptors and an antagonist at the κ-receptor. It is highly lipophilic and is derived from thebaine (Budd, 2002). In dogs and cats, the clinical dose of buprenorphine usually varies from 0.01–0.02 mg/kg (Thurmon et al., 1999). When administered intramuscularly (IM) or intravenously (IV) it provides postoperative analgesia for 6–8 h (Brodbelt et al., 1997; Taylor and Houlton, 1984). Its long action and unusual receptor kinetics, gives it a special place in veterinary analgesia.

The analysis of buprenorphine in biological samples has been extensively described. Liquid chromatography (LC),

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1090-0233/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tvjl.2008.03.001

gas chromatography (GC) and mass spectrometry (MS) detection have all been used to analyse buprenorphine in plasma or serum, faeces, urine and hair (Garrett and Chandran, 1990; Ho et al., 1991; Ohtani et al., 1995; Taylor et al., 2001; Gopal et al., 2002; Ceccato et al., 2003; Robertson et al., 2005; Yassen et al., 2005; Yu et al., 2006). Because the clinical dose of buprenorphine in animals is quite low, plasma concentrations of buprenorphine and its active, dealkylated metabolite, norbuprenorphine, are at the sub-ng/mL level and the development of analytical methods for use with biological fluids is challenging (Ceccato et al., 2003).

Some studies have described the pharmacokinetics of buprenorphine in dogs after IV bolus using LC and subtherapeutic doses (0.7–2.6 mg/kg) (Garrett and Chandran, 1990). To our knowledge, there have been no reports on the pharmacokinetics of buprenorphine in dogs using therapeutic doses. Plasma concentrations have been measured in cats after clinical IM and IV doses (Taylor et al., 2001; Robertson et al., 2003; 2005) using radioimmunoassay (RIA), and with adequate sensitivity and reproducibility. The object of the present study was to characterise the pharmacokinetics of buprenorphine after single IV clinical doses in dogs.

Materials and methods

Animals

All procedures were performed under the Authorisation of the Ethical Commission of Animal and Human Experimentation (Spanish Government, Authorisation Number DARP 2981) and the Ethical Commission of the Autonomous University of Barcelona.

Six Beagle male dogs, 3–4 years of age and weighing 12–15 kg, were used. Health status was established based on clinical examination, haematological and biochemical analyses.

Drugs

The drugs administered during the anaesthetic procedure were propofol 4 mg/kg (Propofol-Lipuro, B. Braun), isofluorane (Forane, Abbott), heparin (Heparina Rovi 5%, Rovi) and 0.9% physiological saline (Fisiologico Braun, B. Braun). Buprenorphine hydrochloride (Buprex, Schering-Plough) was used for the animal treatment and pure standard buprenorphine chlorhydrate (99% purity) was supplied by Laboratories Esteve.

Study design

On the day before each experiment, the dogs were anaesthetised with a single bolus of propofol (4 mg/kg) administered through a catheter (Vasocan, B. Braun) placed in the cephalic vein. The animals were intubated and anaesthesia was maintained with isofluorane (vaporizer setting 2%) in oxygen (150 mL/kg/min) in a Bain coaxial breathing system. A 20 G polyurethane central venous catheter (Certofix Mono, B. Braun) was placed percutaneously into the left jugular vein and secured with suture material and an elastic bandage. When the dogs had regained their reflexes, they were returned to their kennel for a minimum of 24 h. During this period, the venous catheters were flushed with heparinised saline (0.9% saline with 5U heparin/mL) to avoid occlusion.

On the day of the study, an IV dose of 0.02 mg/kg buprenorphine was administered to each dog through the cephalic vein. Blood samples were taken through the jugular catheter before and at 1, 5, 10, 15, 20, 30 and 45 min, and 1, 2, 4, 6, 8 and 12 h after drug administration. The volume of blood collected was 2 mL per sample, so that <10% of the dog's total blood volume was drawn overall. An equal volume of normal saline was injected after each sample had been taken. The blood samples were transferred to lithium heparin tubes (Tapval, Aquisel) and centrifuged at 2600 *g* for 10 min. Plasma was separated and stored at −22 °C until analysis. Food but not water was withheld during all the study period.

Plasma concentrations of buprenorphine

Plasma buprenorphine concentrations were measured using a ^{125}I-labelled RIA (Buprenorphine double antibody RIA kit; Diagnostic Products Corporation) that had been commercially developed for human urine samples. Calibration samples (0, 0.5, 1, 2 and 5 ng/mL buprenorphine) and controls (1 ng/mL buprenorphine) were prepared using blank dog plasma loaded with a methanol solution of buprenorphine to obtain the desired concentrations. The analysis protocol recommended by the manufacturer for urine samples was applied to the plasma. To ensure linearity, samples with buprenorphine concentrations >5 ng/mL were diluted with blank dog plasma and reanalysed.

The mathematical model and transformations suggested by the manufacturers were used to fit the signal with the concentration of analyte. Regression analysis was applied to the logit transformation of the signal (B/Bo%, percentage of corrected counts/min) vs. logarithmic buprenorphine concentration. As a measure of the goodness of fit, the error (%) in the back-calculated concentration of the calibration samples was monitored. Samples with buprenorphine concentrations >5 ng/mL were diluted 1:10 using blank dog plasma and reanalysed.

Up to five replicates of one control sample were analysed for the determination of intra-assay precision and accuracy, while the inter-assay precision and accuracy were determined using the concentration values of the control sample obtained in three independent experimental assays. Precision was expressed as the relative standard deviation (RSD%) of the measurements performed, and accuracy was expressed as the relative error (%) of the value obtained with respect to the assigned value for the control sample.

To calculate the limit of quantification, a blank calibration sample (absence of analyte) was analysed five times in the same run. The standard deviation of the values obtained was taken as the measure of the noise. Limit of quantification was defined as the mean value obtained for the blank sample less 10 times the estimated value of the noise (due to the decrement sign of the slope of the calibration curve).

Pharmacokinetic analysis

Compartmental pharmacokinetic analysis of the concentration–time data was carried out using WinNonlin Software Package (version 4.1). Ordinary least square criteria were selected for fitting procedures to minimise the differences between the observed and predicted concentrations. The goodness of fit was checked by diagnostic plots and analysis of residuals. *F*-test, Akaike information criteria and Schwartz criteria were used for discrimination between models.

The pharmacokinetic parameters describing the equation were calculated for each dog. Buprenorphine plasma concentrations were fitted to a three-compartment open model. The following parameters were calculated: the area under the concentration–time curve ($AUC_{0-\infty}$), the systemic clearance, the distribution and elimination half-lives, the distribution volumes for every compartment, intercompartmental clearances, macro- and micro-constants.

Results

No side-effects were observed in any of the dogs following IV administration of buprenorphine, in agreement with previous published data (Thurmon et al., 1999; Martinez et al., 1997).

The results of the RIA assay validation for dog plasma samples are shown in Table 1. The differences between observed and predicted values were always <10%, showing a good fit of the calibration curve. As can be seen from Table 1, the intra- and inter-assay precisions and accuracies were <15%. The limit of quantification was estimated to be 0.04 ng/mL.

The concentration–time plot for buprenorphine in plasma after an IV bolus is shown in Fig. 1. Buprenorphine was detected in plasma for 12 h after administration in four dogs, for 6 h in one animal, and for 4 h in the last dog. The plasma concentrations were fitted to a three-compartment model. A weighing function of the reciprocal of concentration was used. There was a first phase where the buprenorphine plasma concentration fell rapidly, followed by two additional slower phases. The equation describing the plasma concentration behaviour was $C_p = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$, where A, B and C are the intercepts, and α, β and γ are the first-order rate constants for three compartments. The mean values for the coefficients are listed in Table 2. The calculated pharmacokinetic parameters for buprenorphine are also shown in Table 2.

Discussion

Buprenorphine is a partial opioid agonist that is often considered superior to other opioids available for use in animals. Relevant advantages of buprenorphine are its long lasting effect, its low tendency to induce vomiting, and negligible cardiovascular adverse effects in healthy animals (Thurmon et al., 1999; Martinez et al., 1997; Budd, 2002; Elkader and Sproule, 2005). For these reasons buprenorphine is one of the opioid drugs most commonly used in the UK and Australia.

Different studies have shown the suitability of buprenorphine for postoperative analgesia in dogs and cats (Brodbelt et al., 1997; Smith and Kwang-An, 2000; Smith and Kwang-An, 2001; Dobbins et al., 2002; Tusell et al., 2005). Brodbelt et al. (1997), in comparing the preoperative administration of buprenorphine and morphine, concluded that both opioids were equally suitable analgesics for postoperative analgesia for elective arthrotomy in dogs. Smith and Kwang-An (2001) considered that buprenorphine may offer certain advantages over morphine for epidural use. Although its use and effectiveness have been described

Table 1
Intra- and inter-assay precision and accuracy for RIA assay of buprenorphine in dog plasma

Intra-assay						Inter-assay				
Assay	*n*	Mean (ng/mL)	SD (ng/mL)	Precision[a] RSD (%)	Accuracy[b] Error (%)	*n*	Mean (ng/mL)	SD (ng/mL)	Precision RSD (%)	Accuracy[b] Error (%)
1	5	0.98	0.06	6.0	4.6	15	0.98	0.09	8.8	6.8
2	5	0.99	0.05	5.5	4.3					
3	5	0.97	0.14	14.3	11.4					

[a] Measured as relative standard deviation (RSD).
[b] Measured as the relative error respect the assigned control sample value.

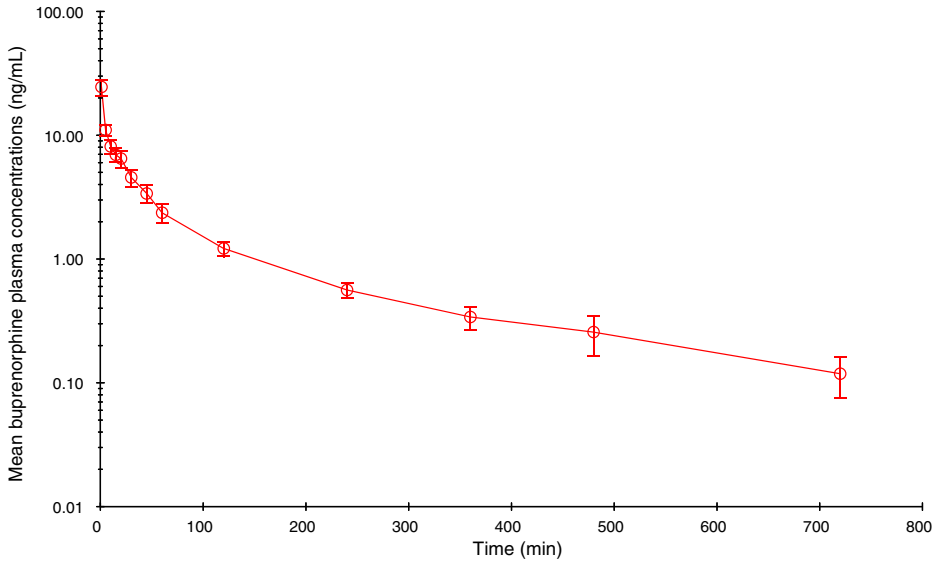

Fig. 1. Plasma concentration–time profile for buprenorphine (mean ± SD) in six dogs following an IV bolus of buprenorphine.

Table 2
Pharmacokinetic parameters for buprenorphine after an IV bolus to six dogs

Parameter	Units	Mean	SD
A	(ng/mL)	25.9	18.3
B	(ng/mL)	9.1	2.6
C	(ng/mL)	1.8	1.2
α	(L/min)	0.5	0.3
β	(L/min)	0.04	0.02
γ	(L/min)	0.004	0.003
K_{21}	(min^{-1})	0.131	0.035
K_{31}	(min^{-1})	0.009	0.003
K_{10}	(min^{-1})	0.037	0.007
K_{12}	(min^{-1})	0.213	0.076
K_{13}	(min^{-1})	0.047	0.016
$t_{1/2\alpha}$	(min)	2.9	1.8
$t_{1/2\beta}$	(min)	16.5	3.7
$t_{1/2\gamma}$	(min)	266.6	82.0
AUC	(ng min/mL)	633.0	114.4
C_{max}	(ng/mL)	26.1	5.3
CL	(mL/min)	329.6	62.2
CLD2	(mL/min)	1659.3	688.5
CLD3	(mL/min)	391.3	118.3
V_{ss}	(L)	83.7	26.52
V_1	(L)	8.54	2.32
V_2	(L)	9.32	3.43
V_3	(L)	65.94	23.40

A, B, C, intercepts with y axis of the equation; α, β, γ: macroconstants of the equation; K_{21}, K_{31}, K_{10}, K_{12}, K_{13}, microconstant from compartments 2 to 1, 3 to 1, 1 to output, 1 to 2, and 1 to 3, respectively; $t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$, half-life for first, second and third slopes, respectively; AUC, area under the curve; C_{max}, maximum concentration; CL, clearance; CLD2 and CLD3, clearance from compartment 1 to 2 and 1 to 3, respectively; Vss, steady state distribution volume; V_1, V_2 and V_3, distribution volume in compartment 1–3, respectively.
SD, standard deviation of the mean.

in both small and large animals, few data are available on the pharmacokinetic profile of buprenorphine after the administration of a therapeutic dose.

Several studies have been performed to determine plasma buprenorphine concentrations in both humans (Hand et al., 1990; Elkader and Sproule, 2005) and animals (Yu et al., 2006). In dogs, Garrett and Chandran (1990) determined the pharmacokinetics after an IV bolus but the dose used was higher than the clinical dose described for dogs by Thurmon et al. (1999), namely 0.7–2.6 mg/kg vs. 0.01–0.02 mg/kg. In our study, a dose was used that was within the accepted clinical range for dogs. Garrett and Chandran (1990) analysed plasma buprenorphine concentrations using LC but determination of some important pharmacokinetic parameters was not feasible due to the poor detection limit of the technique. In the present study, RIA was used to determine plasma buprenorphine concentrations and the validation results demonstrated the feasibility of the assay to measure buprenorphine in dog plasma samples; intra and inter-assay accuracy and precision were adequate, and the limit of quantification assay allowed the detection of very low concentrations of buprenorphine.

Following IV administration, buprenorphine plasma concentrations decreased with a three-phase kinetic profile, in accordance with its physicochemical characteristics, and as described previously for cats (Taylor et al., 2001; Robertson et al., 2003), rabbits (Ho et al., 1991), humans (Ho et al., 1991), rats (Gopal et al., 2002; Ohtani et al., 1995; Yassen et al., 2005) and mice (Yu et al., 2006). The pharmacokinetic data obtained in dogs were similar to those in humans, rabbits and cats. During the initial phase, buprenorphine concentrations showed a fast decrease, as indicated by the low $t_{1/2\alpha}$ (2.9 min). The value of $t_{1/2\alpha}$ obtained in dogs was similar to human and rabbit studies (Ho et al., 1991) but was not specified in the studies performed by Robertson et al. (2003, 2005) in cats. Nevertheless in those latter studies buprenorphine plasma concentrations declined in a curvilinear manner with a fast decrease during the first hour as we saw in our study. After the fast initial decrease, concentrations remained low with a long $t_{1/2\gamma}$, showing a slow elimination rate from the peripheral tissues. The elimination half-lives in the slow elimination phase were similar to those obtained in rabbits and humans (Ho et al., 1991). The results agree with those described by Robertson et al. (2005) following the administration of the same buprenorphine dose in cats.

In a multi-compartmental model, as described in this study, it is important to note that the drug may be retarded or slowly concentrated in the deep tissue compartment. Whereas central V_1 and V_2 compartments (8.54 ± 2.32 L; 9.328 ± 3.43 L), respectively, are similar to the total body water in the dog (0.5 L/kg), V_3 (65.94 ± 23.4 L) is around seven times greater than the central volume. After distribution to the first and second compartments, the elimination phase predominates and the drug is eliminated from the central compartment with a slow rate of elimination. These observations are in agreement with the intercompartmental clearances obtained: intercompartmental clearance from compartment 1–2 (CLD2) was four times faster than the clearance between the deeper and the central compartment (CLD3). Similar values for CL and CLD3 indicated that the clearance from the deeper compartment dictates the elimination phase of the drug.

In our study, buprenorphine concentrations remained low from 1 h after IV administration, and a similar pharmacokinetic profile has been described previously in humans and other animals (Ho et al., 1991; Gopal et al., 2002; Ohtani et al., 1995; Taylor et al., 2001; Robertson et al., 2003; 2005). The low plasma concentration range does not however seem to be in agreement with published clinical findings. The peak effect of buprenorphine does not occur until about 45–50 min following IV administration. In dogs, Taylor and Houlton (1984) considered the clinical effect to last 4 h, but other authors have described a longer duration of action (McKelvey and Hollingshead, 2000; Wagner, 2002).

Pharmacokinetics do not, however, always predict the length of a clinical effect. For many opioids, there is a significant time lag between peak concentration in the plasma and peak drug effect. This time lag, or hysteresis, is a function of drug movement into and action within the effect

site. Moreover, the pharmacokinetic parameters of opioids cannot be interpreted in isolation. In the case of buprenorphine, the duration of action is longer than might be predicted from its plasma concentration. The prolonged duration of action of (6–8 h) is caused by a high affinity for μ-receptors and a slow dissociation (Papich, 2000). This was observed in cats by Robertson et al. (2005), who demonstrated a considerable delay between peak drug concentration and dynamic effect after the administration of an IV dose. In that study, the maximum anti-nociceptive effect did not occur for 90 min, whereas maximum concentrations after IV dosing were recorded within the first 5 min. A similar phenomenon has been described for buprenorphine in sheep (Nolan et al., 1987) and in humans (Bullingham et al., 1980).

In our study, we did not evaluate the length of the clinical effect of buprenorphine. However, as the dose used was within the generally accepted clinical range for use in dogs (0.01–0.02 mg/kg), we expected that the clinical effects would last for at least the same time as has been described in the literature for cats. The results suggest a concentration of buprenorphine in the deeper compartment and strong receptor binding probably reflects the drug's high affinity for μ-receptors and slow dissociation constant.

Conclusions

After IV administration of clinical doses in dogs, buprenorphine showed three-compartmental model plasma kinetics, with two distribution phases and one elimination phase. We have shown that the pharmacokinetics of buprenorphine after an IV dose in dog were comparable to those described for the cat. Nevertheless the relationship between plasma concentrations and dynamic effects in dogs remains to be established.

Conflict of interest statement

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

References

Brodbelt, D.C., Taylor, P.M., Benson, G.J., 1997. A comparison of preoperative morphine and buprenorphine for postoperative analgesia for arthrotomy in dogs. Journal of Veterinary Pharmacology and Therapeutics 20, 284–289.

Budd, K., 2002. Buprenorphine: a review. In: Evidence based medicine in practice. Hayward Medical Communications; June 2002. <http://www.grunenthal.de>. (accessed 12.01.06.).

Bullingham, R.E.S., McQuay, H.J., Moore, A., Bennett, M.R.D., 1980. Buprenorphine kinetics. Clinical Pharmacokinetics and Therapeutics 28, 667–672.

Ceccato, A., Klinkenberg, R., Hubert, P., Strel, B., 2003. Sensitive determination of buprenorphine and its *N*-dealkylated metabolite norbuprenorphine in human plasma by liquid chromatography coupled to tandem mass spectrometry. Journal of Pharmaceutical and Biomedical Analysis 32, 619–631.

Dobbins, S., Brown, N.O., Shofer, F.S., 2002. Comparison of the effects of buprenorphine, oxymorphone hydrochloride, and ketoprofen for postoperative analgesia after onychectomy or onychectomy and sterilization in cats. Journal of American Animal Hospital Association 38, 507–514.

Elkader, A., Sproule, B., 2005. Buprenorphine. Clinical pharmacokinetics in the treatment of opioid dependence. Clinical Pharmacokinetics 44, 61–680.

Garrett, E.R., Chandran, V.R., 1990. Pharmacokinetics of morphine and its surrogates. X: analyses and pharmacokinetics of buprenorphine in dogs. Biopharmaceutics and Drug Disposition 11, 311–350.

Gopal, S., Tzeng, T.B., Cowan, A., 2002. Characterization of the pharmacokinetics of buprenorphine and norbuprenorphine in rats after intravenous bolus administration of buprenorphine. European Journal of Pharmaceutical Sciences 5, 287–293.

Hand, C.W., Sear, J.W., Uppington, J., Ball, M.J., McQuay, H.J., Moore, R.A., 1990. Buprenorphine disposition in patients with renal impairment. Single and continuous dosing with especial reference to metabolites. British Journal of Anaesthesia 64, 276–282.

Ho, S.T., Wang, J., Ho, W., Hu, O.Y., 1991. Determination of buprenorphine by high-performance liquid chromatography with fluorescence detection: application to human and rabbit pharmacokinetic studies. Journal of Chromatography 570, 339–350.

Lascelles, B.D., Capner, C.A., Waterman-Pearson, A.E., 1999. Current British veterinary attitudes to perioperative analgesia for cats and small mammals. Veterinary Record 145, 601–604.

Martinez, E.A., Hartsfield, S.M., Melendez, L.D., Matthews, N.S., Slater, M.R., 1997. Cardiovascular effects of buprenorphine in anaesthetized dogs. American Journal of Veterinary Research 58, 1280–1284.

McKelvey, D., Hollingshead, K.W., 2000. Analgesia. In: Veterinary Anaesthesia and Analgesia, 3rd ed. Mosby. St Louis, Missouri, pp. 315–350.

Nolan, A., Livingston, A., Waterman, A.E., 1987. Investigation of the antinociceptive activity of buprenorphine in sheep. British Journal of Pharmacology 92, 527–533.

Ohtani, M., Kotaki, H., Sawada, Y., Iga, T., 1995. Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic–pharmacodynamic modelling. The Journal of Pharmacology and Experimental Therapeutics 272, 505–510.

Papich, M.G., 2000. Pharmacologic considerations for opiate analgesia and nonsteroidal antiinflammatory drugs. Veterinary Clinics of North America: Small Animal Practice 30, 815–837.

Robertson, S.A., Lascelles, B.D., Taylor, P.M., Sear, J.W., 2005. PK–PD modelling of buprenorphine in cats: intravenous and oral transmucosal administration. Journal of Veterinary Pharmacology and Therapeutics 28, 453–460.

Robertson, S.A., Taylor, P.M., Sear, J.W., 2003. Systemic uptake f buprenorphine by cats after oral mucosal administration. Veterinary Record 31, 578–675.

Smith, L.J., Kwang-An, Yu J., 2000. Comparison of epidural buprenorphine with epidural morphine for postoperative analgesia in dogs. Veterinary Anesthesia and Analgesia 27, 97–111.

Smith, L.J., Kwang-An, Yu J., 2001. A comparison of epidural buprenorphine with epidural morphine for postoperative analgesia following stifle surgery in dogs. Veterinary Anesthesia and Analgesia 28, 87–96.

Taylor, P.M., Houlton, J.E.F., 1984. Postoperative analgesia in the dog: a comparison of morphine, buprenorphine and pentazocine. Journal of Small Animal Practice 25, 437–451.

Taylor, P.M., Robertson, S.A., Dixon, M.J., Ruprah, M., Sear, J.W., Lascelles, B.D., Waters, C., Bloomfield, M., 2001. Morphine, pethidine and buprenorphine disposition in the cat. Journal of Veterinary Pharmacology and Therapeutics 24, 391–398.

Thurmon, J.C., Tranquili, W.J., Benson, G.J., 1999. Preanesthetic and anesthetic adjuncts. In: Essentials of Small Animal Anesthesia and Analgesia, 3rd ed. Williams and Wilkins, Baltimore, pp. 187–194.

Tusell, J.M., Andaluz, A., Prandi, D., Costa, C., Garcia, F., 2005. Effects of epidural anaesthesia- analgesia on intravenous anaesthesia with propofol. The Veterinary Journal 169, 108–112.

Wagner, A.E., 2002. Opioids. In: Gayner, J.S., Muir, W. (Eds.), Handbook of Veterinary Pain Management. Mosby. St Louis, Missouri, pp. 164–184.

Watson, A.P., Nicholson, A., Church, D.B., Pearson, M.R., 1996. Use of anti-inflammatory and analgesic drugs in dogs and cats. Australian Veterinary Journal 74, 201–210.

Yassen, A., Olofsen, E., Dahan, A., Danhof, M., 2005. Pharmacokinetic-pharmacodynamic modelling of the antinociceptive effect of buprenorphine and fentanyl in rats: role of receptor equilibration kinetics. Journal of Pharmacology and Experimental Therapeutics 313, 1136–1149.

Yu, S., Zhang, X., Sun, Yichun, Peng, Y., Johnson, J., Mandrell, T., Shukla, A., Laizure, S., 2006. Pharmacokinetics of buprenorphine after intravenous administration in the mouse. Journal of the American Association for Laboratory Animal Science 45, 12–16.