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ABSTRACT

Biopharmaceutical profile of tramadol in the dog

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Abbreviations

AUC	area under the curve
CYP	cytochrome P450
LOQ	limit of quantitation
MEC	minimum effective concentration
M1	*O*-demethylatedtramadol
M2	*N*-demethylatedtramadol
M5	*O,N*-didemethylatedtramadol
T	tramadol

Introduction

Tramadol (T) is an analgesic opioid drug clinically used since the 1990's in the relief of mild to moderate pain in humans. The lack of side effects, characteristic of opioid derivatives, shown by this drug, and the absence of typical side effects due to non-steroidal anti-inflammatory drugs, suggest T as a potential molecule for long term therapy of chronic pain in animals. Its analgesic effect is due to a dual mechanism of action: 1) the re-uptake inhibition of norepinephrine and serotonin; 2) agonism of the μ-opioid receptor (the most important mechanism). Such agonism is owed both to the parental drug, then mainly to its

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metabolite *O*-demethylated M1 reported as having a 200 fold greater affinity at the μ-receptor. Recently, T has been demonstrated to be metabolized quickly to inactive metabolites, in goats (de Sousa et al. 2008), horses (Giorgi et al. 2007; Shilo et al. 2008) and dogs (Kukanich and Papich 2004; Giorgi et al. 2009) in contrast with cats (Pypendop and Ilkiw 2008) and camels (Elghazali et al. 2008); in these two latter species the M1 metabolite has been detected at high plasma concentrations. Consequently, in veterinary medicine, the effectiveness of this drug seems aleatory and strictly related to the animal species. The aim of the present study reporting the biopharmaceutical profile of T and its main metabolites in the dog, is to suggest the best pharmaceutical formulation to administrate in this species.

Materials and methods

Six healthy male beagle dogs weighing from 18 to 23 kg, 3–6 years old, were administered with a single dose of T 100 mg (Contramal® Formenti, Milan, Italy) in different pharmaceutical formulations (intravenous and intramuscular injections, immediate and sustained release tablets, rectal suppository). The washout periods among the different administrations were of 7 days. A catheter was placed into the right cephalic vein to facilitate blood withdrawal. Blood samples were collected at 0, 5, 15, 30, and 45 min and 1, 1.5, 2, 4, 6, 8, 10 and 24 h. The blood was then placed into collection tubes containing lithium heparin. The samples were centrifuged within 30 min of collection and the harvested plasma was frozen at −20°C until substance detection. The measurement of the plasma concentration of T and its main metabolites (M1, M2 and M5) was achieved through a previously validated HPLC-FL method (Giorgi et al. 2007). A liquid chromatography LC ProStar Workstation (Varian, Walnut Creek, CA, USA), consisting of a high pressure pump (ProStar, 230), fluorimetric detector (ProStar, 363) and manual injector (Rheodyne®, 7725i) coupled with a 20 μl loop, was used. All the samples were analysed twice under the following conditions: the mobile phase consisted of acetonitrile 40 % (phase A) and 60 % phase B (20 mM sodium dihydrogenphosphate, 30 mM SDS and 15 mM TEA maintained at pH 3.9 with 20 % phosphoric acid), flow of 0.8 ml/min and Luna C18 analytical column (150 mm × 2.1 mm i.d., 3 μm; Phenomenex, Bologna, Italy) kept at 23±2°C. The wave lengths of emission and excitation were of 275 and 300 nm, respectively. The pharmacokinetic analysis was carried out using the WinNonLin v. 5.1 program (Pharsight Corp., Cary, NC, USA).

Results

Following intravenous and intramuscular injections animals showed some side effects such as excitation and tremors, but these effects were transient and resolved within one hour. The T pharmacokinetic is best described by a bi- and mono-compartmental model following intravenous or intramuscular injection and other administration routes, respectively. Metabolites were analysed using a non-compartmental model. After intravenous and intramuscular injection the AUC values were higher than after other administration routes. Consequently, the absolute bioavailability of the intramuscular route was 100 %, while after oral immediate release administration bioavailability was 30 % and was 10 % following oral sustained release and rectal administration. T showed a rapid absorption, good distribution and fast biotransformation to M5 and M2 metabolites after oral and rectal

administration. In these two latter administration routes, the amounts of the metabolites (M2 and M5) in plasma were always higher than the plasma parental drug level. Contrarily, the M1 concentrations were quite low, very close to the LOQ of the method and extremely variable; for these reasons it was not possible to calculate the pharmacokinetic parameters for this metabolite for some dogs.

Discussion

T shows both faster pharmacokinetics and a more extensive metabolism in the dog than in humans (Grond and Sablotzki 2004). Both rectal and sustained release oral administrations may be ineffective due to both their poor bioavailability and the low plasma amount of the M1 active metabolite. Taking into account as drug efficacy parameter the minimum effective concentration (MEC) reported in humans, the injective administrations in the dog, could appear to be effective up to 3–4 hours after administration. However, the analgesic effect seems only due to the parental drug T, since M1 plasma concentrations are always below the MEC. The extensive biotransformation to inactive metabolites (M2 and M5), shows in the dog and also reported for other species (Giorgi et al. 2007; de Sousa et al. 2008; Shilo et al. 2008), seem to be ascribable to a flip/flop mechanism wherein the rate conversion of T to M1 is slower than the elimination/biotransformation rate of M1.

This speculation is supported by the higher metabolisation rate of CYP 2B and 3A, accounting for biotransformation of T to M2 and M1 to M5 rather than CYP 2D, accounting for biotransformation of T to M1 and M2 to M5 (Hojo et al. 2002). In conclusion, in the dog, T seems to be effective after injective administrations (formulations indicated for attack therapies), whereas it may be ineffective following oral and rectal administrations (formulations suggested for long-term therapies).

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References

de Sousa A.B., Santos A.C., Schramm S.G., Porta V., Górniak S.L., Florio J.C., de Souza Spinosa H., 2008. Pharmacokinetics of tramadol and o-desmethyltramadol in goats after intravenous and oral administration. *Journal of Veterinary Pharmacology and Therapeutics*, **31**, 45–41.

Elghazali M., Barezaik I.M., Abdel Hadi A.A., Eltayeb F.M., Al Masri J., Wasfi I.A., 2008. The pharmacokinetics, metabolism and urinary detection time of tramadol in camels. *Veterinary Journal*, **178**, 272–277.

Giorgi M., Soldani G., Manera C., Ferrarini P.L., Sgorbini M., Saccomanni G., 2007. Pharmacokinetics of tramadol and its metabolites M1, M2 and M5 in horses following intravenous, immediate release (fasted/fed) and sustained release single dose administration. *Journal of Equine Veterinary Science*, **27**, 481–488.

Giorgi M., Saccomanni G., Lebkowska-Wieruszewska B., Kowalski C., 2009. Pharmacokinetic evaluation of tramadol and its major metabolites after single oral sustained tablet administration in the dog: a pilot study. *Veterinary Journal*, **180**, 253–255.

Grond S. and Sablotzki A., 2004. Clinical pharmacology of tramadol. *Clinical Pharmacokinetic*, **43**, 879–923.

Hojo T., Ohno R., Shimoda M., Kokue E., 2002. Enzyme and plasma protein induction by multiple oral administrations of phenobarbital at a therapeutic dosage regimen in dogs. *Journal of Veterinary Pharmacology and Therapeutics,* **25**, 121–127.

Kukanich B. and Papich M.G., 2004. Pharmacokinetics of tramadol and the metabolite O-desmethyltramadol in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **27**, 239–246.

Pypendop B.H. and Ilkiw J.E., 2008. Pharmacokinetics of tramadol, and its metabolite O-desmethyltramadol, in cats. *Journal of Veterinary Pharmacology and Therapeutics*, **31**, 52–59.

Shilo Y., Britzi M., Eytan B., Lifschitz T., Soback S., Steinman A., 2008. Pharmacokinetics of tramadol in horses after intravenous, intramuscular and oral administration. *Journal of Veterinary Pharmacology and Therapeutics*, **31**, 60–65.