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Pharmacokinetics of the novel atypical opioid tapentadol after intravenous, intramuscular and subcutaneous administration in cats

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ABSTRACT

Drugs that provide effective analgesia in cats are limited. The aim of the present study was to investigate the pharmacokinetics of the novel atypical drug tapentadol (TAP) after intravenous (IV), intramuscular (IM) and subcutaneous (SC) injection in six healthy cats using a 3 × 3 Latin square crossover study design. The dose rate used was 5 mg/kg and the concentrations of TAP in plasma were evaluated using high-performance liquid chromatography.

Some adverse effects including salivation, agitation and panting, were noted, especially following IV administration. In all three administration groups, TAP concentrations were detectable in plasma for up to 8 h. Bioavailability for each route was almost complete, accounting for 94% and 90% after IM and SC administrations, respectively. Drug absorption was faster after IM than SC administration (0.25 h vs. 0.63 h). The half-life of the terminal portion of the plasma concentration curve was not significantly different between the three routes of administrations (2–3 h). TAP appears to have some variation in its pharmacokinetic features in cats compared to other animal species. Further studies are needed to evaluate whether TAP would be suitable for use in cats that are experiencing moderate to severe pain, but are sensitive to the adverse effects of commonly prescribed opioids.

Introduction

As drug options to provide analgesia in cats are limited compared to those available for dogs, cats often receive inadequate analgesia, mainly because of the perceived risk of side effects and limited information on suitable alternatives (Lascelles et al., 1999). The investigation of new active ingredients suitable for feline therapy is therefore critical. Opioids are considered prototypical analgesics (Fox, 2010) and are used in veterinary medicine not only for analgesia but for their other clinical actions (e.g. antitussive, antidiarrheal and emetic). The classical strong opioid receptor agonists can have significant adverse effects (Vadivelu et al., 2011) and are therefore generally licensed as controlled substances (Pascoe, 2000; Clutton, 2010), which limits their use to trained personnel. However, atypical opioid drugs (especially tramadol) have gained popularity in small animal clinical practice.

Tramadol is one of the most widely sold atypical opioids. In Italy it is marketed for pain relief in cats and dogs, although its real efficacy in dogs has been questioned (Giorgi, 2008; Giorgi et al., 2009). Since most of its effect is the result of the active metabolite O-desmethyltramadol (M1), tramadol may not be safe for use in cats with liver disease. Tramadol possesses a weak agonist affinity for the mu opioid receptor (MOR), reducing the typical opioid side effects, which are due to the activation of this receptor. However, its efficacy for pain relief, especially the relief of chronic pain, is enhanced by a second synergistic mechanism of action, namely norepinephrine (NA) and serotonin (5-HT) reuptake (Raffa et al., 1992). Its application is generally limited to the treatment of mild to moderate pain and its effect is inferior to the strong classical opioids (morphine).

A new drug, tapentadol (TAP), has recently been added to the atypical opioid class. It was launched on the European market for human use in 2011. In humans, TAP has a lower incidence of adverse effects compared to equianalgesic doses of morphine (Kleinert et al., 2008) and oxycodone (Etropolski et al., 2011). TAP has attracted the attention of the veterinary world because its MOR affinity is 50-fold less than morphine but 120-fold higher than tramadol (Giorgi, 2012). Additionally, its second synergistic mechanism of action is known to not involve 5-HT reuptake, reducing the possibility of the 'serotonin storm effect' reported following rapid IV tramadol injections. In brief: (1) TAP is recommended in cases of moderate to severe pain (as is morphine); (2) compared to morphine, TAP produced much less nausea and vomiting and

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when these adverse effects were present, their duration was shorter (Tzschentke et al., 2009); (3) TAP is not restricted/regulated in most European countries; and (4) TAP does not require metabolic activation to be effective, so individual variations in drug metabolism should have limited effects on efficacy.

Very few studies to investigate the clinical uses of TAP have been undertaken in the veterinary field. The pharmacokinetic features of TAP have been investigated in dogs after IV and oral administration, demonstrating very low oral bioavailability (4%; Giorgi et al., 2012a). In a study of rabbits undergoing castration, it was reported that TAP had excellent efficacy for the reduction of surgical and post-surgical pain (Giorgi et al., 2013).

The aim of this study was to assess the pharmacokinetics of TAP after IV, IM and SC injection in healthy cats.

Materials and methods

Materials

TAP hydrochloride was supplied as a pure powder (>99.8% purity; Bepharm). M1 was used as an internal standard and supplied as pure powder (>99.8% purity; LCG Promochem). Additionally, high-performance liquid chromatography (HPLC) grade acetonitrile (ACN), dichloromethane (CH_2Cl_2) and diethyl ether (Et_2O) were used in the assays (Scharlau), as was analytical grade acetic acid and sodium tetraborate decahydrate (BDH). HPLC grade water was obtained by distilling deionised water produced by a Milli-Q Millipore water system (EDM Millipore). All the other reagents and materials were of analytical grade and supplied from commercial sources.

Animals and experimental design

Four male and two female mixed-breed cats, aged 3–6 years, with a bodyweight of 3.4–4.8 kg, were enrolled in the study. The cats were determined to be clinically healthy on physical examination, serum chemistry and haematological analyses. Animal care and handling was performed according to the provision of the EC council Directive 86/609 EEC and also according to Institutional Animal Care and Use directives issued by the Animal Welfare Committee of the University of Lublin, which approved the study protocol.

Cats were randomly assigned to three treatment groups, using six slips of paper marked with the numbers 1–6, selected blindly from a box. An open, single-dose, three-treatment, three-period crossover design (3 × 3 Latin square) was used. All cats were fasted for 12 h overnight before each experiment. Each cat in group 1 ($n = 2$) received a single IV dose of TAP (5 mg/mL) at 5 mg/kg. This dose was selected based on previous information describing the effectiveness of TAP in laboratory species (Giorgi et al., 2013). Group 2 cats ($n = 2$) received a single IM injection of 5 mg/kg of TAP. Group 3 ($n = 2$) received a single SC injection of TAP at the same dose.

The injectable solutions were prepared by dissolving the pure TAP hydrochloride powder in saline to produce a 5 mg/mL solution, which was then passed through a 0.45 μm filter, maintaining sterile conditions. A 1-week wash out period was observed, to ensure complete metabolism and excretion of TAP. After this period, the groups were rotated and the experiment was repeated (second period). After a further interval of 1 week, the groups were rotated and the experiment was repeated (third period). By the end of the study, each cat had received TAP by all the three administration routes.

The right cephalic vein was catheterised to facilitate blood sampling. Blood samples (1 mL) were collected at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8 and 10 h after the administration of TAP and placed in collection tubes containing lithium heparin. Specimens were centrifuged at 1000 *g* within 30 min of collection, and the harvested plasma was stored at −70 °C and used within 15 days of collection.

High performance liquid chromatography (HPLC)

Based on a previously published HPLC technique (Giorgi et al., 2012b), the analytical method was re-validated in plasma samples. The HPLC system was coupled with a multi lambda fluorescence detector (Waters). Data were processed using Empower Pro software (Waters). The chromatographic separation assay was performed with a SunFire C18 analytical column (150 × 4.6 mm inner diameter, 5 μm particle size, Waters), maintained at 25 °C. The mobile phase consisted of ACN (A): 0.2% acetic acid (B) at a flow rate of 1 mL/min. Excitation and emission wavelengths were set at 273 and 298 nm, respectively. The linear gradient elution system was performed as follows: 5–95% B (0–20 min), 95–5% B (20–25 min) and 5% B isocratically (25–32 min).

Preparation of plasma samples

Briefly, 50 μL of IS solution (0.5 μg/mL) and 0.2 mL 0.2 M borate buffer, adjusted to pH 9.3, were added to a 1.5 mL polypropylene snap cap tube (Sarstedt) containing 0.5 mL of plasma. After vortex-mixing, 0.4 mL of extraction solvent (Et_2O:CH_2Cl_2 7:3 v/v) was added, the tube was then placed in a vortex for 30 s, shaken for 5 min, and then centrifuged for 10 min at 15,625 *g* (rotor radius 10 cm). The organic layer (0.3 mL) was then transferred into a clean 0.5 mL polypropylene snap cap conical tube, placed in a vortex and then shaken with 0.2 mL of back-extraction solvent (0.05 M HCl:ACN 1:1 v/v) for 5 min, before being centrifuged for 10 min at 15,625 *g* (rotor radius 10 cm). The aqueous phase (50 μL) was injected into the HPLC system.

Pharmacokinetic evaluation

The pharmacokinetic calculations were carried out using WinNonLin v 5.3 (Pharsight). Maximum concentration (C_{max}) of TAP in plasma and the time required to reach C_{max} (T_{max}) were predicted from the data. The concentration at time 0 (C_0) for IV administration was estimated by back-extrapolating from the first two concentration values. The terminal rate constant (λ) was determined from the slope of the terminal phase of the plasma concentration curve that included a minimum of three points. The half-life of the terminal phase ($T_{1/2}\lambda z$) was calculated using $T_{1/2} = 0.693/\lambda$. The area under the concentration vs. time curve ($AUC_{0-\infty}$) was calculated using the linear trapezoidal rule. The IM and SC bioavailabilities were calculated from the ratio of the areas under the plasma TAP concentration curve after IM or SC and IV administration, respectively, indexed to their respective dose:

$$F\ (\%) = (AUC_{IM/SC} \times Dose_{IV})/(AUC_{IV} \times Dose_{IM/SC}) \times 100$$

Changes in plasma concentration of TAP were evaluated using the standard non-compartmental analysis, and the relative pharmacokinetic parameters were determined using standard non-compartmental equations (Gabrielsson and Weiner, 2002.).

Statistical analysis

Pharmacokinetic data were evaluated using ANOVA tests to determine statistically significant differences. The pharmacokinetic parameters are presented as means ± standard deviation and the TAP plasma concentrations are presented as means. All analyses were conducted using GraphPad InStat (GraphPad Software). In all experiments, differences were considered significant if $P < 0.05$.

Results

The HPLC method used was re-validated in feline plasma. Briefly, TAP was linear ($r^2 > 0.98$) in the range 10–4000 ng/mL. The intra-day repeatability was measured using coefficients of variation and was <7.3%. Accuracy was measured by measuring proximity to the concentration added on the same replicates and was <5.3%.

After IV administration, some adverse effects including salivation, agitation and panting, were noted in all cats. However, they resolved rapidly (15–20 min) and spontaneously. These adverse effects were also detected after IM and SC administration, but were less intense and of a shorter duration, and did not occur in all cats (3/6 IM; 1/6 SC).

In all three administration groups, TAP concentrations were detectable in the plasma for up to 8 h. Some variability in plasma drug concentrations was detected among the cats and groups. Figs. 1 and 2 show individual (A–F) and average TAP plasma concentrations vs. time curves after each administration route, respectively. After IM injection, TAP showed variable but fast absorption (T_{max} = 0.25 h, range 0.08–0.75 h), while after SC administration, absorption was significantly slower (T_{max} = 0.63 h). The $T_{1/2}\lambda z$ was quite similar between the three administration routes in the range of about 2–3 h. Also VZF and CLF values were constant among the treatment groups. In the elimination phase of the curve, the decline of TAP was linear without any evidence of a secondary peak. The average pharmacokinetic parameters calculated for the three administrations are reported in Table 1. The bioavailabilities were almost complete, accounting for 94% and 90% after IM and SC administrations, respectively.