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Comparison of two formulations of buprenorphine in cats administered by the oral transmucosal route

Elisa Bortolami, Louisa Slingsby and Emma J Love

Abstract

This randomised, blinded, cross-over study investigated the ease of oral transmucosal administration of two formulations of buprenorphine using glucose as a control in 12 cats. The cats received three treatments: buprenorphine multi-dose, buprenorphine and the equivalent volume of glucose 5%. Ease of treatment administration, observation of swallowing, changes in pupil size, sedation, salivation, vomiting, behaviour and food intake were assessed. The data were analysed using MLwiN and multi-level modelling. Ease of administration of buprenorphine multi-dose was statistically different from glucose (P <0.001), and the administration of all treatments became easier over the study periods. Swallowing was not statistically different between groups (P >0.05). Mydriasis was evident after the administration of both formulations of buprenorphine. Sedation, salivation, vomiting, behavioural changes or in-appetence were not observed after any treatment. Cats tolerated oral transmucosal administration of glucose better than buprenorphine multi-dose, while buprenorphine administration was tolerated as well as glucose.

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Introduction

Several surveys have revealed that feline pain has been largely undertreated in clinical practice.[1–4] The lack of analgesic treatment stems from different reasons, including difficulty in recognising pain, lack of licensed analgesic drugs, fear of side effects and lack of information specific to cats.[5–7] In addition, administering drugs to cats can be challenging. However, these studies were performed quite a few years ago and pain management in cats has progressed considerably in the last few years. There is much more awareness of what the normal feline behaviour is[8] and how to recognise, assess and treat pain in cats.[6,9]

Buprenorphine is one of the most commonly used analgesics in cats in the UK,[2] continental Europe and in other continents.[3–4] It is a highly lipophilic semi-synthetic partial mu opioid agonist.[10] It has UK marketing authorisation for administration to cats and can be administered by intramuscular (IM) injection pre-operatively at a dose of 10–20 µg/kg and repeated if, necessary, once after 2 h.[11] IM and intravenous (IV) injections can be difficult in fractious cats,[12] thus the oral transmucosal (OTM) route of drug administration is an attractive alternative. It is a simple, non-invasive and pain-free technique which only requires minimal restraint of the cat.[13] It also reduces the risk of needle-stick injury to the animal and the person restraining the cat.[14] OTM administration of buprenorphine could also be considered particularly useful when multiple injections or home therapy are necessary,[13] although it does not have marketing authorisation for administration by this route.

Different routes of drug administration influence bioavailability, efficacy and side effects.[14] Buprenorphine has significant antinociceptive effects in a feline thermal threshold model when administered by the IM and IV routes;[7,15] however subcutaneous (SC) and transdermal administration resulted in limited or no antinociception.[16,17] OTM administration of buprenorphine has been demonstrated experimentally to be as effective as IV treatment,[15] most likely because the alkaline pH (8–9) of cat's mouth favours the unionised form of buprenorphine, which is a weak base with a high pKa (8.24), allowing its absorption. The pharmacokinetics and thermal antinociceptive effects of buprenorphine after a dose of 20 µg/kg given by the intravenous or OTM route were

University of Bristol, School of Veterinary Sciences, Bristol UK

Corresponding author:
Elisa Bortolami DVM, MRCVS, University of Bristol, School of Veterinary Sciences, Langford House, Langford, Bristol BS40 5DU, UK
Email: Elisa.Bortolami@bristol.ac.uk

studied by Robertson et al.[15] Both routes of administration resulted in an onset of action within 30 min, a peak effect at 90 min and a 6 h duration of action. The median bioavailability after OTM dosing was 116.3%.[15] Other clinical studies[13,18,19] evaluating sedative and analgesic effects of OTM administration of buprenorphine reported that it provided less sedation and analgesia than other routes of administration or less analgesia than a non-steroidal, anti-inflammatory drug. These conflicting results may have been caused by the fact that other factors, such as concomitant use of α_2-adrenoreceptor agonists, timing of drug administration, and inadequate volume and dilution of buprenorphine, might have interfered with absorption and disposition of buprenorphine following OTM dosing.

In all the studies where buprenorphine was administered by the OTM route, cats did not resent drug administration and adverse events, such as salivation and vomiting, were not observed. Different brands of buprenorphine were used in these studies but in all cases a single-use, preservative-free formulation was used.[5,13,15,18,19]

Buprenorphine without a preservative (Vetergesic Injection; Alstoe) (BUP) has been available in the UK for a number of years as a 1 ml single-use vial. More recently a buprenorphine multi-dose bottle containing a preservative (Vetergesic Multidose Injection; Alstoe) (MD) has been introduced to the UK market. Both buprenorphine formulations consist of buprenorphine hydrochloride in a 5% glucose solution (pH 3.5–6.5) but the MD preparation also contains 0.135% chlorocresol as a preservative.[11] After MD became available anecdotal reports were received suggesting that the multi-dose formulation was more difficult to administer to cats compared with the preservative-free formulation, and profuse salivation and vomiting were also observed. These adverse events were reported to us by colleagues working at our institution and by local practitioners. These adverse effects would impact negatively on cats' hospitalisation experience, and, as OTM dosing is performed, in part, to reduce the stress of drugs administration, this would be counterproductive.

The aim of this study was to assess the ease of administration of the two different formulations of buprenorphine in cats by the OTM route in comparison to 5% glucose as a control.

Materials and methods

Animals and housing

This study was performed under Home Office Licence. Twelve purpose-bred, healthy, neutered, adult (4 years old), domestic shorthair cats (eight female, four males), with a mean body mass of 4.78 kg (range 2.9–6.7 kg) were enrolled in this study. The cats were housed in groups of two to six, in accordance with UK Home Office regulations.

Food, but not water, was withheld for at least 12 h before each study. Cats were allowed unlimited access to water throughout the assessment period.

Table 1 Scoring system for ease of treatment administration

Scores	Classification	Descriptors
1	Very easy	No resistance to administration
2	Easy	Some resistance, eg head turning
3	Difficult	A lot of resistance but successful at first attempt
4	Very difficult	Multiple attempts to successfully administer

Treatments

The study was performed in the cats' home environment and the investigators had been familiarised with them before starting the study.

Prior to treatment administration, salivary pH was measured by placing a 5 cm strip of pH paper (pH indicator paper, Fisher Scientific) in the side of the cat's mouth until it was moist; the colour was compared with the standard pH chart and recorded, as previously reported in other studies.[5,15]

All twelve cats received each of the following three treatments by the OTM route: MD (10 µg/kg) (Vetergesic Multidose Injection 0.3 mg/ml; Alstoe), BUP single-use vials (10 µg/kg) (Vetergesic Injection 0.3 mg/ml; Alstoe) and the equivalent volume of glucose (GLU) 5% (Vetivex 6; Dechra Veterinary Products). Treatments were administered in a randomly-allocated, balanced cross-over design with a 3-week interval between test cycles. The investigators were blinded to treatment allocation. Treatment administration and all of the assessments were performed by one investigator (EB).

OTM dosing was achieved by inserting the nozzle of a 1 ml syringe into the side of the cat's mouth, into the cheek and gently squirting the syringe contents into the buccal cavity, as previously described in other studies.[5,13–15,18,19] Food was offered from 45 min to 4 h after drug administration because cats were fed collectively at scheduled times.

Assessments

All the assessments were performed by one observer only (EB), who was blinded to treatment allocation, and data were recorded contemporaneously. The ease of treatment administration was ranked from 1 (very easy) to 4 (very difficult), as shown in Table 1.

Cats were monitored before, and for 60 min after, drug administration to answer the following yes/no

Table 2 Scores for ease of administration by the oral transmucosal route of buprenorphine multi-dose (MD), preservative-free buprenorphine (BUP) and glucose 5% (GLU) in 12 healthy cats in the three test cycles

Test cycle	Treatment	Ease of administration score				Median (range) scores
		1	2	3	4	
All cycles	MD	1	5	4	2	2.5 (1–4)
	BUP	2	8	1	1	2 (1–4)
	GLU	5	6	0	1	2 (2–4)
Cycle 1	MD	-	1	3	-	
	BUP	-	2	1	1	
	GLU	1	2	-	1	
Cycle 2	MD	-	3	-	1	
	BUP	2	2	-	-	
	GLU	2	2	-	-	
Cycle 3	MD	1	1	1	1	
	BUP	-	4	-	-	
	GLU	2	2	-	-	

dichotomous questions: were swallowing, mydriasis, sedation, salivation/vomiting, behavioural changes (ie, euphoria: purring, rolling, rubbing, kneading with forepaws) or food intake changes observed?

Any adverse events were noted throughout the course of the study.

Statistics

Data regarding the ease of treatment administration, presence of swallowing, pupil size changes, behavioural changes, nausea, salivation, vomiting, sedation and change in food intake were analysed using multi-level modelling with MLwiN v 2.22.[20]

In addition to the effect of the treatment itself, the effect of treatment period on ease of administration of the three different drugs was also compared. The data were analysed using the statistics package MLwiN v2.22 to model the repeated measures within cats.[20] The effect of the treatment was entered into both analyses as a categorical predictor and prior experience of treatment was entered as a continuous variable, coded as 1, 2 or 3. Statistical significance was assumed at $P < 0.05$.

Results

All cats remained healthy throughout the study period. Cats' salivary pH ranged from 8.7 to 9. The volume of buprenorphine administered ranged from 0.1 ml to 0.22 ml.

Median (range) scores for ease of administration and scores for each test cycle are presented in Table 2. The administration of MD (median score 2.5) was more difficult than GLU (median score 2.0); this was found to be statistically significant ($P < 0.001$), while the ease of administration of BUP (median score 2.0) was not statistically different from GLU ($P = 0.169$). The statistical model demonstrated that for each additional period there was an accustomisation to administration of a treatment with a decrease in ease of administration score of 0.28 (standard error = 0.12, $P = 0.02$). That is, the OTM administration of all three treatments became easier over the course of the study, but the MD remained the most difficult to administer in comparison to GLU.

Swallowing was observed more frequently in the MD group (42%), followed by the BUP (25%) and GLU groups (17%), but this was not statistically significant ($P > 0.05$). In most cats mydriasis was noticed within minutes after buprenorphine, but this was not consistent, particularly in cats that swallowed after drug administration. In the MD group, six out of 12 cats swallowed and mydriasis was noticed in eight cats. In the BUP group, three out of 12 cats swallowed and mydriasis was noticed in 10 cats. In the GLU group, two out of 12 cats swallowed and mydriasis was noticed in one cat. Neither sedation, salivation nor vomiting were observed in any cats after any treatment. Behavioural changes and changes in food intake were not observed in any treatment group and no other adverse effects were observed over the course of the study.

Discussion

The importance of providing effective analgesia for cats is being increasingly recognised and the OTM administration of buprenorphine is an easy and effective way to treat pain. Buprenorphine is a weak base with a high pKa (8.24) and in an alkaline environment, such as cat's mouth, its absorption is enhanced as the unionised form of the drug predominates.[21,22] In this study, the cats' salivary pH ranged from 8.7 to 9; these results were consistent with previously reported results.[5,15,23]

In this study, OTM administration of GLU was better tolerated than the MD formulation, while there was no difference between the tolerance of BUP and GLU. The

OTM administration of treatment was fairly easy in all groups, as demonstrated by the median scores of 2.0 for BUP and GLU, and 2.5 for MD.

Over the course of the study it became easier to administer the treatments but the MD remained the most difficult to administer. It is difficult to determine whether treatment administration became easier because of an increased familiarity of handling the cat by the investigators or if the cats themselves became more tolerant to the procedure. This may have important implications regarding the potential value for long-term treatment; the OTM administration of buprenorphine could be a promising stress- and pain-free way to treat pain in cats.

The multi-dose formulation of buprenorphine contains chlorocresol as a preservative, which has a characteristic phenolic odour.[24] In high concentrations, chrorocresol is harmful in contact with skin and may cause damage to eyes and sensitisation by skin contact.[24] It is present in very minimal percentages (0.135%), but this might explain why MD is less tolerated by cats, as they have a very sensitive sense of smell and taste.[25,26] It is known that various medications and toxins may cause ptyalism as a result of their disagreeable taste[27,28] or by irritating the oral mucosa;[29] this has been described with agents such as cresol.[28,29] The intention was to include in the study a treatment containing chlorocresol (0.135%) in 5% glucose (without buprenorphine), but it was not possible to obtain a suitable formulation.

Swallowing following OTM administration of drugs may be influenced by several factors. Cats may be reluctant to swallow after OTM administration because of adverse drug flavouring, but, alternatively, an increase in the frequency of swallowing could be a response to salivation and may have prevented ptyalism being observed.

Although a pharmacokinetic study has already been perfomed,[15] further work would include another pharmacokinetic study in order to assess the effects of swallowing immediately after drug administration and also to assess if drug dilution with saliva interferes with drug absorption. Pharmacokinetic analysis was not performed as part of this study because it was designed to evaluate behaviour and the collection of blood samples would have biased other outcome measurements.

Mydriasis was noticed after administration of both formulations of buprenorphine and this may indicate that buprenorphine was absorbed following administration by the OTM route, confirming previous results.[5,15] Although mydriasis can indicate buprenorphine absorption, opioid-induced mydriasis does not specifically correlate with the duration of analgesia[17,30] or with a cat's behavioural changes.[17] According to our observations, mydriasis was observed in some cats who had swallowed the drug; however, it was not noticed in other cats who had not swallowed it. A change in pupil size was observed in a cat who had received glucose. These conflicting and uncorrelated findings are a result of the fact that swallowing is a very quick action that can happen in a few seconds' time and can be subtle and so difficult to observe. Additionally, cats were not restrained after the treatment administration and could roam freely in the room and it was possible that the mydriasis after GLU administration may have been caused by the particular position of the cat in the room at the time of the assessment.

This study was designed in order to assess the anedoctal low tolerability of MD; according to colleagues working at our institution and local practices its administration had been related to hypersalivation and vomiting in hospitalised cats. After the administration of MD these adverse effects were not observed, possibly because the cats were healthy and assessed in their home environment. In the clinical setting, pre-existing diseases (ie, pancreatitis), concomitant administration of other medications or the stress related to the hospitalisation may influence salivation and vomiting.[31]

It is important to emphasise that the study was performed in the cats' home environment. Moving a cat to an unfamiliar location can result in significant stress as cats develop a very important bond to their environment. Moving the cats to another place could have interfered with their normal behaviour,[32–36] with them becoming either more passive and unresponsive or more active.[31,37,38] In this study, no sedation was observed after buprenorphine administration, probably because the cats were already relaxed in their usual environment. Moreover, in behavioural-observational studies, the cat's temperament plays a very important role.[38] This population of cats is generally very friendly and used to handling. Purring, rolling, rubbing, kneading with forepaws and meowing are typical normal behaviour, therefore, the effects of buprenorphine on behaviour might have been masked.

This study, (performed in healthy, pain-free cats in their home environment) confirmed the anecdotal reports, as buprenorphine multi-dose was more difficult to administer. Our results may not be entirely applicable to the whole target population, when other factors such as diseases, stress and environment play an important role. A clinical prospective study assessing hospitalised cats would be the next stage of investigation into the relative ease of administration of buprenorphine multi-dose buprenorphine compared with the preservative-free formulation. Administration of buprenorphine multi-dose by the OTM route was not sufficiently aversive to suggest that it should never be used by this route but our data would indicate that preservative-free buprenorphine is preferable in terms of palatability.

Conclusions

This study demonstrated that while there was no difference between the tolerance of BUP and GLU, healthy cats tolerated OTM administration of GLU better than MD. This seems to confirm the anecdotal evidence of poor acceptance of OTM administration of MD when used clinically to provide analgesia. Therefore, these results suggest that BUP is less aversive when the OTM route of buprenorphine is being used to provide analgesia in cats.

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Conflict of interest The authors work at the University of Bristol, School of Veterinary Sciences. The University of Bristol Clinical Research Fund sponsored this study; there were no external sponsors.

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