Review
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A Review of the Studies Using Buprenorphine in Cats

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Pain management is a crucial component of feline medicine and surgery. This review critically evaluates studies using buprenorphine in cats and highlights the clinical application of the opioid in this species. The pharmacokinetic-pharmacodynamic (PK-PD) modeling of IV buprenorphine has been best described by a combined effect compartmental/receptor association-dissociation model with negative hysteresis. Therefore, plasma concentrations of the drug are not correlated with analgesia, and clinicians should not expect to observe pain relief immediately after drug administration. In addition, a ceiling effect has not been demonstrated after administration of clinical doses of buprenorphine in cats; dosages of up to 0.04 mg/kg have been reported. The route of administration influences the onset, duration, and magnitude of antinociception and analgesia when using this drug in cats. At clinical dosages, the SC route of administration does not appear to provide adequate antinociception and analgesia whereas the buccal route has produced inconsistent results. Intravenous or IM administration at a dosage of 0.02–0.04 mg/kg is the preferred for treatment of pain in the acute setting. A literature search found 14 clinical trials evaluating buprenorphine sedation, analgesia, or both in cats. There were 22 original research studies reporting the antinociceptive effects of buprenorphine by means of thermal threshold, mechanical threshold, or both, minimal alveolar concentration, or PK-PD. Individual variability in response to buprenorphine administration has been reported, indicating that buprenorphine may not provide sufficient analgesia in some cats. Pain assessment is important when evaluating the efficacy of buprenorphine and determining whether additional analgesic treatment is needed.

Key words: Analgesia; Antinociception; Feline; Pain.

Pain relief is an important component of veterinary medicine. Pain itself produces undesirable effects including stress and sympathetic nervous system activity, altered food intake and metabolism, as well as behavioral abnormalities.[1] Increased attention has been given to pain management in cats, and it is now generally regarded as a mandatory component of clinical veterinary care in this species.[2] Recently, the need for analgesia has become better acknowledged, and many clinical and research studies have been undertaken to understand the pharmacology of analgesics and the unique features of particular behaviors, recognition, assessment, and treatment of pain in cats.[1,3–5] Among the opioid analgesics, buprenorphine is extensively used for the management of pain in cats. The drug has market authorization in the United Kingdom and much of continental Europe, Canada, South Africa, and other countries and has become one of the most popular opioids in small animal practice.[6] This review investigates and critically evaluates reported data on the antinociceptive and analgesic effects of buprenorphine in cats. Guidance on the clinical application of this opioid in cats is provided.

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Abbreviations:

EPI	epidural
MAC	minimum alveolar concentration
MT	mechanical threshold
OTM	buccal
PD	pharmacodynamic
PK	pharmacokinetic
SCSR	subcutaneous sustained release formulation
TD	transdermal
TT	thermal threshold

General Pharmacology of Buprenorphine

Buprenorphine is a potent semisynthetic, highly lipophilic opioid derivative of thebaine that originally was developed in the 1970s. The drug provides analgesia with minimal respiratory depression.[7,8] Buprenorphine is considered to be a "partial agonist" at μ (mu) opioid receptors,[7] although some other classifications considered it to be a κ (kappa) antagonist, or a μ receptor antagonist at high doses, or even as a "full agonist" depending on the species studied.[8,9] For this reason, some authors consider buprenorphine a unique drug with a complex pharmacologic profile. The drug binds avidly to, and dissociates slowly from, opioid receptors, but does not elicit a maximal clinical response, because it is not a classic "full agonist" like morphine.[7,9,10] This terminology is confusing, however, because it depends on the criteria used to define a "full" or "partial agonist" in research studies and should not be used solely for predicting efficacy of the drug.[11] Because of its pharmacodynamic (PD) profile, which exhibits a slow biophase equilibration and receptor binding,[5] buprenorphine is considered to have a delayed onset of action and long-acting analgesic properties that exert moderate analgesia with few adverse effects.[10,12]

The dosage of buprenorphine commonly has been restricted as a result of early antinociceptive studies using animal models demonstrating a notorious bell-shaped dose-response curve, where higher dosages led to a decreased effect or produced no analgesia.[7,13–15] However, there is good evidence, at least in cats, that dosages that might decrease the analgesic effect are much higher than those used under clinical conditions (0.01–0.04 mg/kg), and dosages higher than 0.01 mg/kg provide more analgesia, not less.[16] Moreover, dosages of 0.04 mg/kg administered by IM route have been beneficial in cats requiring rescue analgesia after ovariohysterectomy.[4]

Literature Search

A literature search was performed to identify and evaluate studies using buprenorphine in cats. Original, prospective or retrospective studies, and case series published in peer-reviewed journals in English between 1970 and 2013, and reporting data on the effects of buprenorphine in cats were searched using MEDLINE, Google Scholar, and CAB abstracts. Search words included "analgesia", "anesthesia", "antinociception", "buprenorphine", "cat", "feline", "pain", and "opioid". The appropriateness of the aim, hypothesis, interpretation, and reporting of results, as well as the methodology to answer the research question were evaluated by 2 observers (P.V.M.S. and B.P.M.S.). Internal validity and the procedures used to minimize or avoid bias were assessed. Original research studies involved a population of experimental cats whereas clinical studies involved client-owned animals. Therefore, a randomized controlled intervention trial could be identified in both research and clinical settings.

Original Research Studies

Twenty-two original research studies reported the effects of buprenorphine on thermal or mechanical antinociception or both, minimum alveolar concentration (MAC), or plasma concentration and pharmacokinetics (PK). Most of these studies were designed as randomized controlled intervention trials (n = 18),[5,12,16–31] whereas others (n = 4)[32–35] were prospective observational longitudinal studies.

Most investigations of the antinociceptive effects of buprenorphine in cats used analgesiometric devices as a means of assessing pain. Such systems usually allow for objective recording of the onset, magnitude, and duration of action and can be conducted under controlled conditions with the inclusion of a cutoff to avoid tissue damage. Thermal and mechanical threshold (TT and MT, respectively) testing systems have been developed and validated in cats and used in numerous studies of analgesic drugs. Table 1 summarizes the TT and MT studies. The thermal stimulus was applied on the thoracic wall, and the mechanical stimulus was performed using blunt pins driven pneumatically against the skin of the antebrachium. Threshold is considered to be the point at which the cat clearly responds by turning toward or biting at the site, meowing, or jumping away from the stimulus.[36] When compared with baseline thresholds, significant increases in TT, MT, or both after treatment indicate antinociception. Some studies used the TT device and plasma concentrations to model the buprenorphine PK–PD relationship in cats. A more in-depth discussion of these data and the impact of routes of administration on antinociception are provided below.

Clinical Studies

Buprenorphine has been investigated in 14 clinical studies in cats, evaluating its sedative or analgesic effects, or both in comparison or in combination with other drugs (n = 11), or examining different routes of administration (n = 3). These reports are summarized in Table 2. Twelve clinical studies were designed as randomized controlled intervention trials, but 5 of them were unclear as to whether or not they adequately considered inclusion and exclusion criteria, bias, and data collection and analysis.[4,38,40,46,47] In 2 studies,[4,38] cats were not excluded from statistical analysis after rescue analgesia, which could underestimate the degree of pain the cat would have experienced if it had not been given intervention analgesia. This might have introduced analysis bias. In another study,[40] no significant differences were observed between buccal (or oral transmucosal; OTM) and SC administration of a sustained release formulation (SCSR) of buprenorphine, perhaps because meloxicam had been administered to both treated groups, an important confounding factor. The hypothesis could not be truly tested with such a study design because meloxicam already provides adequate analgesia after ovariohysterectomy in some cats.[50] In a 4th study,[47] cumulative and analog pain scores did not involve a thorough interactive approach with the cat. Scoring was based mostly on behaviors that are not affected by abdominal pain in cats, which were not known at that time.[3,49,51] For example, the report does not indicate whether or not surgical wounds were palpated after onychectomy. This might have affected the ability to differentiate analgesic effects of treated versus placebo groups, and jeopardized further interpretation of the data. Therefore, the conclusion of the study could be misleading. Lastly, 1 study[46] did not include a protocol for rescue analgesia. Despite the impact on individual well-being, the incidence of rescue analgesia and the number of animals requiring such intervention might be critical in identifying significant differences among treated groups.

Retrospective Studies and Case Series

One retrospective study concluded that buprenorphine does not induce hyperthermia in cats.[52] Two case series reported the use of buprenorphine as part of the analgesic management of severely wounded cats. In these 2 studies, the analgesic effects of buprenorphine could not be evaluated because several other analgesic treatments also were administered concurrently.[53,54]

Table 1. Studies using thermal and mechanical threshold testing devices for evaluation of the effects of buprenorphine (bupre) in cats.

Reference	*N*	Treatments	Testing Device	Other Assessments
[31]	6	(1) Bupre 0.02 mg/kg + Dex 0.04 mg/kg IM (2) Bupre 0.02 mg/kg + Dex 0.04 mg/kg OTM	MT	DIVAS Sedation score: NRS
[5]	6	(1) Bupre 0.02 mg/kg IV (2) Bupre 0.02 mg/kg IM (3) Bupre 0.02 mg/kg SC	TT	Plasma concentration and PK-PD
[18]	12	(1) Bupre 0.01 mg/kg IM (2) Naloxone 0.67 μg/kg IM (3) Bupre 0.01 mg/kg + Naloxone 0.67 μg/kg IM	TT and MT	Sedation score: VAS Pupil dilatation
[20]	12 (6/gr)	(1) Bupre 0.01 mg/kg IM (2) Bupre 0.02 mg/kg IM (3) Dex 0.02 mg/kg IM (4) Dex 0.04 mg/kg IM (5) Bupre 0.01 mg/kg + Dex 0.02 mg/kg IM	TT	Sedation score: VAS
[4]	8	(1) Bupre 0.01 mg/kg IV (2) Bupre 0.02 mg/kg IV (3) Bupre 0.04 mg/kg IV	TT and MT	N/A
[21]	8	(1) Bupre 0.02 mg/kg EPI (2) Medetomidine 0.01 mg/kg EPI (3) Bupre 0.01 mg/kg + Medetomidine 5 μg/kg EPI	TT and MT	N/A
[22]	6	(1) Bupre 0.012 mg/kg EPI (2) Morphine 0.1 mg/kg EPI (3) Saline 0.3 mL/kg EPI	TT	N/A
[23]	12 (10 or 12/gr)	(1) Bupre 0.02 mg/kg IM (2) Dex 2 μg/kg IM (3) Dex 5 μg/kg IM (4) Dex 10 μg/kg IM (5) Dex 20 μg/kg IM (6) Dex 40 μg/kg IM (7) Saline 0.06 mL/kg IM	TT	Sedation score: VAS
[24]	6	(1) Bupre 0.02 mg/kg + Saline 0.1 mL/kg IM (2) Butorphanol 0.2 mg/kg + Saline 0.1 mL/kg IM (3) Bupre 0.02 mg/Kg + Butorphanol 0.2 mg/kg IM (4) Saline 0.1 mL/kg + Saline 0.1 mL/Kg IM	TT	N/A
[34]	6	(1) Bupre 0.035 mg/h PATCH	TT	Plasma concentration and PK-PD
[25]	8	(1) Bupre 0.01 mg/kg SC (2) Carprofen 4 mg/kg SC (3) Saline 0.3 mL/kg SC	TT and MT	N/A
[26]	8	(1) Bupre 0.01 mg/kg SC (2) Carprofen 4 mg/kg SC (3) Saline 0.3 mL SC	MT	N/A
[27]	8	(1) Bupre 0.02 mg/kg SC (2) Morphine 0.2 mg/kg SC (3) Methadone 0.2 mg/kg SC (4) Saline 0.3 mL SC	TT and MT	N/A
[12]	6	(1) Bupre 0.02 mg/kg IV (2) Bupre 0.02 mg/kg OTM	TT	Plasma concentration, PK-PD and oral pH
[28]	8 (6/gr)	(1) Bupre 0.01 mg/kg IM (2) Morphine 0.2 mg/kg IM (3) Butorphanol 0.2 mg/kg IM (4) Saline 0.3 mL IM	TT	N/A

N, total number of cats studied; gr, group; Bupre, buprenorphine; Dex, dexmedetomidine; OTM, oral transmucosal route; IM, intramuscular route; IV, intravenous route; SC, subcutaneous route; EPI, epidural route; PATCH, transdermal patch; TT, thermal threshold; MT, mechanical threshold; NRS, numerical rating scale; DIVAS, dynamic and interactive visual analog scale; PK, pharmacokinetics; PD, pharmacodynamics; VAS, visual analog scale; N/A, not applicable.

Table 2. Clinical studies that evaluate the administration of buprenorphine in cats.

Reference	Procedure	*N*	Treatment Groups	Evaluation of Pain/Sedation
[37]	OHE, castration, and other surgical procedures	48	(1) Bupre 0.02 mg/kg + Acepromazine 0.03 mg/kg IM (2) Bupre 0.02 mg/kg + Dexmedetomidine 0.25 mg/m^2 IM	SDS, GCPS, and wound sensitivity by MT
[38]	OHE	30	(1) Bupre 0.02 mg/kg SC (2) Robenacoxib 2 mg/kg SC (3) Bupre 0.02 mg/kg + Robenacoxib 2 mg/kg SC	SDS
[39]	OHE	100	(1) Bupre 0.18 mg/m^2 IM + Carprofen 4 mg/kg SC (2) Bupre 0.18 mg/m^2 IM + Meloxicam 0.3 mg/kg SC (3) Burorphanol 6 mg/m^2 IM + Carprofen 4 mg/kg SC (4) Burorphanol 6 mg/m^2 IM + Meloxicam 0.3 mg/kg SC	SDS, DIVAS, and wound sensitivity by MT
[40]	OHE	21	(1) Bupre 0.02 mg/kg OTM (2) Bupre 0.12 mg/kg SCSR	VAS, CSUPCS, and wound sensitivity by von Frey
[41]	OHE	100	(1) Bupre 0.01 mg/kg IV (2) Bupre 0.01 mg/kg IM (3) Bupre 0.01 mg/kg SC (4) Bupre 0.01 mg/kg OTM	SDS and DIVAS
[42]	Placement of IV catheter	87	(1) Bupre 0.02 mg/kg + Dexmedetomidine 0.02 mg/kg OTM (2) Bupre 0.02 mg/kg + Dexmedetomidine 0.02 mg/kg IM	Sedation scores
[43]	OHE, castration, or other surgical procedures	153	(1) Bupre 0.01–0.02 mg/kg IM (2) Butorphanol 0.4 mg/kg IM	SDS
[4]	OHE	84	(1) Bupre 0.01 mg/kg IM (2) Carprofen 4 mg/kg SC (3) Bupre 0.01 mg/kg IM + Carprofen 4 mg/kg SC	SDS and DIVAS
[44]	Onychectomy	20	(1) Bupre 0.01 mg/kg IM (2) Bupre 0.01 mg/kg IM + bupivacaine (local block)	Discomfort score
[45]	OHE	51	(1) Bupre 0.01 mg/kg PO (2) Bupre 0.01 mg/kg SC (3) Meloxicam 0.3 mg/kg PO (4) Meloxicam 0.3 mg/kg SC (5) Saline SC	VAS and IVAS
[46]	Fracture repair	60	(1) Bupre 0.01 mg/kg SC (2) Carprofen 4 mg/kg SC (3) Levomethadone 0.3 mg/kg SC (4) Saline SC	NRS, wound sensitivity by MT and VAS
[47]	Onychectomy ± OHE or castration	68	(1) Bupre 0.01 mg/kg IM (2) Oxymorphone 0.05 mg/kg IM (3) Ketoprofen 2 mg/kg IM (4) Saline IM	Cumulative pain scores, visual analog pain score, and serum cortisol concentration
[48]	Surgical procedures	32	(1) Bupre 0.01 mg/kg + Acepromazine 0.05 mg/kg IM (2) Morphine 0.1 mg/kg + Acepromazine 0.05 mg/kg IM	VAS
[49]	OHE	60	(1) Bupre 0.006 mg/kg IM (2) Pethidine 5 mg/kg IM (3) Ketoprofen 2 mg/kg SC (4) No analgesic	VAS

OHE, ovariohysterectomy; IV, intravenous; *N*, total number of cats studied; Bupre, buprenorphine; IM, intramuscular; SC, subcutaneous; OTM, oral transmucosal; SR, sustained release; PO, *per os*; SDS, simple descriptive scale; GCPS, Glasgow composite pain scale; MT, mechanical threshold; DIVAS, dynamic and interactive visual analog scale; VAS, visual analog scale; CSUPCS, Colorado State University pain and comfort scale; IVAS, interactive VAS; NRS, numerical scoring system.

Studies on the PK and PD of Buprenorphine in the Cat: The Impact of Route of Administration on Antinociception and Potential Clinical Implications

Several studies have reported that the route of administration influences the onset, duration, and magnitude of antinociception and analgesia when buprenorphine is administered to cats.[5,12,21,32,34,41] For example, different routes of administration have produced variable thermal antinociception. The highest mean TT recorded was approximately 54°C after intravenous (IV), 51°C after OTM and IM,[12,28] and approximately 45°C after SC administration.[25] PK and PD studies have provided a better understanding of the impact of route of administration on the antinociception of buprenorphine in cats.

PK values or plasma concentrations of buprenorphine after OTM, epidural (EPI), IV, IM, SC, and transdermal (TD) administration have been reported elsewhere.[5,12,32,34,35] Differences in PK data observed in these studies probably are because of both variability among individuals, number of cats, PK modeling, and the different analytical techniques used to measure plasma buprenorphine.[5,12,32,34,35] Additional data interpretation should take these differences into consideration. PD parameters have been published elsewhere[5,12] and are summarized here.

Some of the combined studies on PK and PD have demonstrated negative hysteresis after buprenorphine administration when plasma concentration and effect data were plotted.[5,12,34] Such PK-PD modeling in the cat thus has shown poor correlation between antinociception and the plasma concentration of buprenorphine after IV and IM administration.[5,12,34] This negative hysteresis occurs as a result of the time taken for diffusion of buprenorphine into the effect compartment as well as slow association with the receptor.[5] On the other hand, persistence of antinociception with this opioid is explained by slow receptor dissociation in cats.[5] The PK-PD relationship was examined after dosing by the IV route and was best described by a combined effect compartment/receptor association-dissociation model.[5] In feline practice, clinicians should not expect to observe analgesia immediately after buprenorphine administration because the drug exhibits a longer onset of action in comparison with other opioids.[28]

In a recent study, PK modeling was not possible after SC administration because of erratic absorption, and thermal antinociception was not demonstrated.[5] In cats, the IV, IM, EPI, and OTM routes of administration provided much clearer antinociception than the SC route.[5,12,16,27,28,33] Similar observations were reported after SC administration of hydromorphone which resulted in a short duration of antinociception and least effect when compared with IV and IM routes.[55–57] These findings have been further corroborated by clinical studies in which cats receiving SC buprenorphine (0.02 mg/kg) had significantly higher pain scores after ovariohysterectomy than those receiving the drug by the IV or IM routes,[41] and also higher scores than those treated with robenacoxib by the SC route.[38] There was a significantly higher prevalence of treatment failure in the SC buprenorphine groups (52%[41] and 90%[38]) when compared with the IV (24%) and IM (16%) buprenorphine,[41] or robenacoxib (20%) groups.[38] The number of cats that required more than 1 dose of rescue analgesia also was significantly higher after SC buprenorphine than robenacoxib.[38] At clinical dosages (0.02 mg/kg), the SC route does not provide adequate analgesia after buprenorphine administration.

The OTM route has been investigated in cats because it allows pain- and stress-free administration.[12,33,41,45] Currently, there is some controversy on the analgesic and antinociceptive effects of buprenorphine after OTM administration. This route was shown to have high bioavailability (approximately 116%) when blood samples were collected from the jugular vein, and to provide antinociception similar to the IV route, which could be explained partially by the buccal pH of cats (8–9).[12,33] Because buprenorphine is a weak base with pKa of 8.24, a high percentage of the drug exists in the nonionized form in the feline oral cavity, thereby enhancing absorption.[33] However, when blood samples were collected from the carotid artery, OTM buprenorphine had significantly lower bioavailability (20–52%) when compared with samples collected from the jugular vein (34–67%).[58] Thus, the sampling site affects the drug concentration-time profile.[58] Maximum drug concentrations, area under the curve, and bioavailability may have been erroneously increased in the previous study,[12] and the OTM route might not be as efficacious as first considered. Differences in the buccal pH, method of drug analysis, and swallowing of the drug by some cats might explain variable bioavailability among studies.[12,58] Clinically, the OTM route (0.01 mg/kg) failed to provide adequate analgesia in cats undergoing ovariohysterectomy with a high prevalence of treatment failure.[41,45] Seventeen of 25 cats[41] and 3 of 10 cats[45] required rescue analgesia after OTM administration. Pain scores were significantly higher in the OTM group than with IV and IM administration at various time points[41] and were significantly higher than in meloxicam-treated cats.[45]

Higher peak plasma concentrations of buprenorphine were detected after application of a transdermal matrix patch (5.4–13.7 ng/mL) than after SC administration.[5,34] However, there were no significant changes in TT over time, nor was there a strong relationship between buprenorphine plasma concentration and changes in TT in either study. The authors hypothesized that a loading dose of IV or IM buprenorphine might be required to drive the drug into the effect compartment to produce analgesia and antinociception.[34] Currently, these data suggest that the TD route of administration provides limited pain relief in the clinical setting. Randomized, controlled, prospective studies evaluating TD buprenorphine with and without a loading dose are needed before any definitive recommendation can be made.

Buprenorphine was rapidly absorbed into plasma after injection of 0.02 mg/kg into the lumbosacral epidural space, followed by elimination similar to that after the OTM or IM routes, and clearance after IV administration.[32,35] Epidural buprenorphine (0.0125 mg/kg) produced thermal antinociception after 1–10 h in 1 study,[22] and after 15 min to 24 h in another study using a 0.02 mg/kg dosage.[21] The differences between the 2 studies may be explained by the use of different statistical analysis, testing time points, technique of EPI administration, location of testing device, and dose-related effects.

A SCSR formulation of buprenorphine recently has been used in a clinical trial.[40] However, there are no published PK or PD studies of this formulation and additional recommendations will only follow after the efficacy and safety of this compound have been reported in a larger number of cats.

Studies on PK, PD, and routes of administration also have provided useful insight into the behavioral effects of buprenorphine administration in cats. These effects include euphoria, purring, rolling, rubbing, and kneading with the forepaws.[4,5,12,21,34] Adverse effects such as vomiting, nausea, dysphoria, or hyperthermia rarely occur. Mild increases in body temperature have been documented after buprenorphine in cats, but this does not appear to be clinically relevant.[52] Mydriasis usually occurs.[5] Opioid-induced mydriasis and behavioral changes do not correlate with antinociception or analgesia. For example, SC or TD administration of buprenorphine produced euphoric behavior without changes in thermal antinociception.[5,34]

Antinociception of Buprenorphine with Other Opioids

There has been interest in the effects of co-administration of buprenorphine with other opioid drugs. Studies were designed to observe either an increase or decrease in antinociception with the combination when compared with buprenorphine alone. For example, naloxone (an opioid antagonist) was administered with buprenorphine (0.01 mg/kg) and did not increase thermal and mechanical thresholds, demonstrating that the overriding effect is for naloxone to antagonize the effects of buprenorphine.[18]

Although the combination of buprenorphine and butorphanol (κ receptor agonist and μ receptor antagonist) has been anecdotally used in clinical practice, it did not provide better thermal antinociception than either drug administered alone under laboratory conditions.[24] Anecdotally, the rationale for co-administration of buprenorphine and butorphanol is that buprenorphine has a slow onset of action and butorphanol provides analgesia in the interim, and the long duration of buprenorphine takes over after the short duration of butorphanol's effect. This assumption may not be correct because the interactions at the receptor level are unknown. In the authors' experience, clinical effects are normally unpredictable and pain management may be less than optimal.

Guidelines for Clinical Use of Buprenorphine in Cats

Buprenorphine is widely employed as an analgesic in cats. Therefore, it is important to provide general recommendations on its use in feline practice. As discussed above, buprenorphine is considered to have a delayed onset of action and long-acting analgesic properties that exert moderate analgesia with few adverse effects.[28,41] Onset of analgesia may only be observed 30–45 minutes after IV or IM injection. In addition, the duration of action might be shorter than recommended in textbooks.[59] A recent clinical trial demonstrated that several cats undergoing ovariohysterectomy may require a 2nd dose of buprenorphine 4 hours after surgery, especially if an NSAID had not also been administered.[4] Cats should routinely be reassessed for rescue analgesia requirements after buprenorphine administration.

The authors do not recommend the SC route for buprenorphine in cats at clinical dosages (0.02 mg/kg). Moreover, IV injection has been associated with a much greater magnitude of antinociception, speed of onset, and duration of action when compared with other routes of administration.[5,16] Based on these results, buprenorphine should be given IV to cats whenever an IV catheter is in place. A dosage of 0.02 mg/kg has been reported,[5,16] and it is commonly used by the authors for acute pain in cats.[5]

In the clinical setting, when OTM buprenorphine is to be used, the cat is routinely given a dose of a "full agonist" opioid (eg, morphine, methadone, meperidine, hydromorphone, fentanyl infusion) or even buprenorphine beforehand (ie, premedication). In the perioperative period, buprenorphine is used commonly for premedication in combination with dexmedetomidine or acepromazine for procedures involving mild to moderate pain.[20,37,60] Optimal pain relief usually is obtained when buprenorphine is combined with an NSAID, loco-regional anesthesia, or both.[4,44] Multimodal analgesia appears to be the best approach to pain management in cats.[4]

Overall, critical evaluation of clinical trials in this review showed that the analgesic effects of buprenorphine were inconsistent as a result of different methods of pain evaluation, different surgical procedures or technique, the experience of the evaluator (students versus board-certified veterinarians), dose-related effects, routes of administration, or failure of buprenorphine to provide analgesia. Clearly, pain assessment is important to confirm efficacy of buprenorphine or to indicate the need for further analgesic treatment.

No studies evaluating the analgesic and adverse effects of buprenorphine after prolonged administration were found, nor were any clinical studies evaluating its inhalant anesthetic-sparing effect identified. Clinicians should not expect a reduction in anesthetic requirements during general anesthesia because it has been shown experimentally that neither epidural nor systemic administration of buprenorphine significantly decreases the MAC of isoflurane in cats.[29,30] The role

of buprenorphine on maladaptive (chronic) pain in cats is yet to be elucidated.

Individual Variability

Individual variation in response to analgesic treatment has been described in a number of different species,[61] and genetic variability has been hypothesized as the underlying cause of inconsistent sensitivity to analgesics in cats.[24,55,56,62] Cats may have great individual variability with respect to number, morphology, and distribution of opioid receptors as observed in other species.[63] Such differences seem to be genetically determined and could affect both PK and PD by variation in uptake, biotransformation, transport (blood-brain barrier), and elimination.[64,65] The fact remains that buprenorphine may not provide sufficient analgesia in some cats.[41] Again, it highlights the importance of assessing each patient for evidence of pain and tailoring analgesic treatment accordingly.

Conclusion

Buprenorphine PK and PD reported in the literature by plotting plasma concentration against thermal threshold demonstrate negative hysteresis. The analgesic and antinociceptive effects of buprenorphine are affected by the route of administration, and the IV and IM routes are preferable in the clinical setting. Individual variability has been reported after buprenorphine administration in cats and must be taken into account in the clinical setting; buprenorphine administration should be tailored to individual requirements.

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