A Review of Opioid Use in Cats

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Introduction

There are an estimated 200 million cats (*Felis catus*) kept as pets worldwide and in many countries including the United States of America (USA), the United Kingdom (UK) and China, pet cats outnumber pet dogs [1].

The need for peri-operative pain management is great since the majority of pet cats are spayed or castrated and in the USA many continue to be declawed. The feline practitioner is faced with several challenges when managing pain in cats including the lack of validated pain assessment tools, the cat's unique metabolism of many drugs, and the lack of licensed analgesic drugs. In the past, our understanding and treatment of pain in cats has lagged behind what is available for dogs, but fortunately in the last decade many advances have been made in feline analgesia and many cat-specific studies, both laboratory-based and clinical, have been published.

There are many causes of acute pain in cats including surgery, trauma, procedural pain, and several medical conditions such as peritonitis and cystitis. Opioids are the mainstay of any analgesic protocol for the management of acute pain.

The incidence of chronic pain in cats is not well documented but is associated with many conditions including osteoarthritis, cancer, interstitial cystitis, dental and gum disease, long-standing dermatitis, and wounds. It is only recently that we have begun to appreciate what the true incidence of osteoarthritis or degenerative joint disease might be in cats and it appears to be much more common than previously thought and could be a major cause of discomfort, especially in ageing cats [2-4]. Although opioids are used for long-term alleviation of chronic pain in humans there are only anecdotal reports of their use for this purpose in cats.

The aim of this paper is to review current knowledge of opioid use in cats and their place in pain management.

Drug Metabolism

Cats have a low capacity to handle drugs that require hepatic glucuronidation, a fact elucidated by molecular genetic studies. Domestic cats have fewer hepatic UDP-glucuroninosyltransferase (UGT) isoforms which represent major phase II drug metabolizing enzymes, as a result of mutations of UGT and the presence of pseudogenes [5-7]. It is suggested that because cats are carnivores they had no evolutionary need to develop systems that metabolized the phytoalexins, a group of compounds found in cruciferous plants. The clinical consequence of this is two-fold: toxic side effects may occur if doses and dosing intervals are not adjusted, or alternatively, if the parent compound is metabolized to an active component via this pathway, for example morphine, the drug may be less effective. The cat's susceptibility to toxic side effects of phenolic drugs such as acetaminophen (paracetamol) and the long half-life of aspirin can be explained by the deficient glucuronidation pathway. Because of their unique metabolism, there are few non-steroidal anti-inflammatory drugs licensed for use in cats and none have market authorization for long-term use as is the case for dogs. For these reasons it makes sense to focus efforts on the study of other analgesic drug classes in cats, including the opioids.

Opioids - General Overview

Because of their efficacy, good safety margin and versatility, opioids comprise the backbone of acute pain management in most species including humans. The use of alfentanil, butorphanol, buprenorphine, fentanyl, meperidine (pethidine), methadone, morphine, nalbuphine, hydromorphone and oxymorphone have been reported in cats.

A comprehensive review of opioid pharmacology is outside the scope of this chapter and for this information, the reader is referred to classic textbooks [8]. Briefly, butorphanol is classified as an agonist-antagonist which has a ceiling effect, buprenorphine as a partial agonist and the others are classified as opioid agonists. The opioid agonists have a linear dose-response and can be titrated to effect. Buprenorphine behaves clinically like an opioid agonist and the so-called "bell shaped" curve is not seen at clinically useful doses [9].

The lethal dose of individual opioids is not well documented in the cat, but in the rat the median lethal dose of morphine is 64 mg/kg and for buprenorphine it is 234 mg [10] which is 32 and over 4000 times the recommended analgesic dose, respectively. The safety of opioids is also enhanced by their reversibility with opioids antagonist drugs such as naloxone or naltrexone.

Evaluation of Opioids in the Cat

Opioids have been studied in the clinical arena and in research settings. Although our aim is to confirm which opioids, doses and routes of administration are effective in cats with clinical pain, this is confounded by our ability, or perhaps inability to assess pain in cats. There is no validated pain scoring tool available for cats and as in all animals our evaluation of their pain is subjective and based on behavioral changes. Many scoring systems have been used [11] but because of inter-observer variability and use of different systems it is difficult to compare clinical studies.

In the laboratory setting, opioids have been studied in cats using various noxious stimulus models and measuring changes in the threshold to the stimulus before and after drug administration. Although this is a measure of antinociception and these stimuli are not the same as clinical pain, these studies have been useful for measuring onset time, intensity and duration of antinociception produced by opioids and has also been used to study the effects of various routes of drug administration. The models used include thermal [12], mechanical [13], electrical [14,15] and visceral [16] stimulation. Another method has been the measurement of the minimum alveolar concentration (MAC) of inhalant anesthetic agents. This is an indirect method the basis of which is the assumption that because the technique involves a noxious stimulus (electrical or mechanical) applied to the anesthetized animal, a reduction in MAC after administering a putative analgesic supports its efficacy. This method has been used to evaluate bolus doses of opioids [17], opioid infusions [18] and epidural administration of opioids [19] in cats. Compared to the dog, MAC is reduced less in cats by most opioids and it does not appear to be dose related; for example, the same dose of morphine administered to dogs and cats reduced the MAC of isoflurane approximately 50% and 28%, respectively [17].

Side-effects of Opioids

It is a misconception that all opioids cause excitement or so-called "morphine mania" in cats. Unfortunately, this fear of excitement has been one of the reasons practitioners have historically been reluctant to use opioids in cats. Such reports were based on early literature when excessive doses (e.g., 20 mg/kg of morphine) were administered [20,21]. Recent studies show that with appropriate dosing, the behavioral effects usually include euphoria, with purring, rolling, and kneading with the front paws [22]. One exception is butorphanolwhich has been associated with dysphoric behavior [23].

An elevated body temperature is a concern in a sick or injured cat as the cause may be infection, administration of certain drugs or overzealous warming and the cause must be identified so that the correct treatment can be started and the adverse effects of hyperthermia prevented. The practitioner should be aware of opioid related hyperthermia in cats. At doses of morphine > 1.0 mg/kg cats may become hyperthermic [24] and pethidine (meperidine) at 3 times clinically recommended doses resulted in temperatures as high as 41.7°C (107°F) [25]. Alfentanil infusions in anesthetized cats resulted in significantly elevated rectal temperatures [18].

This phenomenon appears to be dose related, but even at commonly used clinical doses some opioids may result in elevated body temperature. In a retrospective clinical study [26] there was a strong association between the use of hydromorphone (at 0.05 - 1.0 mg/kg, IM or IV on one or more occasions) and hyperthermia (defined as a rectal temperature > 40°C, 104°F). Rectal temperatures over 40°C (104°F) were recorded in 75% of the cats that received hydromorphone and a peak temperature of 42.5°C (108.5°F) occurred in one cat. In a research setting, hydromorphone at 0.1 mg/kg IV was associated with a significant increase in skin temperature [27] whereas 0.025 and 0.05 mg/kg were not. In a prospective clinical study [28] Posner and others also concluded that hydromorphone was implicated in peri-anesthetic hyperthermia in feline patients although it may occur with other drugs. Cats given hydromorphone should have their body temperature closely monitored [27,28]. In a clinical study of cats undergoing onychectomy, those treated with a transdermal fentanylpatch had higher rectal temperatures than those given butorphanol [29].

Opioids cause marked mydriasis in cats and this may cause them to bump into objects and they may not see a handler approaching (Figure 1). For these reasons approach slowly, while talking to the cat so it is not startled. Also keep them out of bright light while their pupils are dilated.

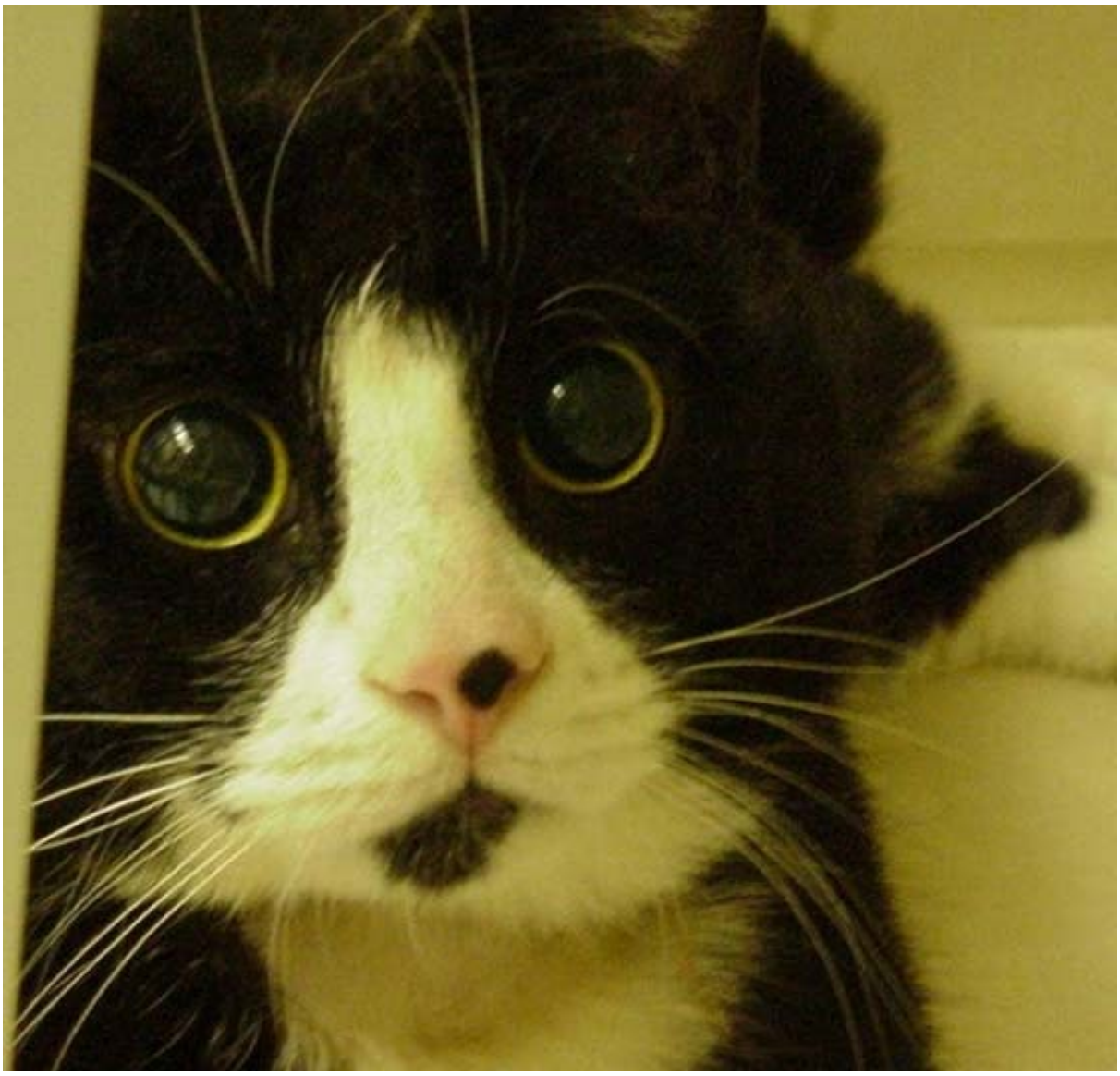

Figure 1. Unlike in many other species, opioids produce mydriasis rather than miosis in cats.

Vomiting and salivation (which suggests nausea) are seen after morphine and hydromorphone injection, but is uncommon after butorphanol, buprenorphine, meperidine or methadone [12,30,31]. The incidence of nausea and vomiting is also related to the route of administration; subcutaneous hydromorphone results in a higher incidence of vomiting than the intravenous or intramuscular route [31]. When administered to painful cats or in combination with acepromazine the incidence of opioid-induced vomiting is considerably less.

The effects on bowel function of pain itself and of analgesics and sedatives used clinically must be considered. Pain can cause bowel stasis, abdominal distension, discomfort and vomiting, all of which add to a patient's overall misery. Analgesic intervention often results in a dramatic improvement but opioids are known to decrease bowel motility especially with long-term use. Intramuscular acepromazine (0.1 mg/kg) combined with buprenorphine (0.01 mg/kg), or medetomidine (50 µg/kg) alone provided good restraint without altering orocaecal transit time in cats whereas ketamine (5 mg/kg) and midazolam (0.1 mg/kg) did decrease gastrointestinal motility [32]. The use of transdermal fentanyl patches has not sparked comments about constipation, and transdermal buprenorphine patches (discussed later) did not affect food intake or frequency of bowel movements in a group of research cats. However, systemic treatment (transmucosal, IV, IM or SQ) with buprenorphine at doses of 0.01 - 0.02 mg/kg can cause inappetence in some cats after 2-3 days, which often resolves when the dose is reduced or the drug withdrawn (author's own observations). The effects of opioids on bowel function may be both dose and duration related, but there is little scientific data available for cats.

Individual Variation

Individual variability in the antinociceptive effects of opioids has been demonstrated in many species and this variability appears to be multifactorial, with gender, genotype, and type of noxious stimulus affecting an individual's response. It is now apparent that individuals are unique with respect to number, morphology, and distribution of opioid receptors and that these differences are genetically determined [33]. It is likely that genetics affect both the pharmacokinetics and pharmacodynamics of opioids through alterations in uptake, biotransformation, transport, elimination, and receptor interaction [34,35]. Klepstad and others [36] discussed that even for one drug (morphine), genetic variability in patient response is multifactorial and involves genes that code for the enzymes that metabolize morphine, mu-opioid receptors and blood-brain barrier transporters. Pharmacogenetics is an increasingly important emerging area of research related to analgesia. Mice and humans with non-functional melanocortin-1 receptors encoded by the MC1R gene have an increased analgesic responsiveness to the OP3 opioid selective metabolite, morphine-6-glucuronide [37,38].

The morphology and sequencing of feline opioid receptors has not been extensively studied compared to other species [39], but in controlled research environments marked variation in analgesic response to opioids has been reported suggesting that cats also express genetic variability. In two independent studies of butorphanol in cats using a thermal stimulus to assess antinociception, investigators demonstrated significant inter-cat differences. In the first study, one cat had a pronounced and prolonged antinociceptive response while another had a response that was not significantly different from pretreatment when given 0.4 mg/kg butorphanol intravenously [23]. Similar findings were demonstrated with the administration of intramuscular butorphanol (0.2 mg/kg) in an unrelated group of cats; one cat had a significant elevation in thermal threshold lasting from 50 minutes until 8 hours, while another showed minimal response to the same treatment [40]. Individual variability in response to butorphanol was also noted in a visceral nociception model, where duration of effect varied from 0 to at least 360 minutes in individual cats [15]. Even in the same laboratory, using the same equipment and investigators, the duration of effect of intravenous hydromorphone was significantly different in two separate groups of cats [27,41].

This underscores the importance of carefully assessing pain in cats since one analgesic at a set dose is unlikely to be equally effective in all patients.

Dose Related Effects

In the literature, wide ranges of doses of opioids are often suggested with little foundation [42]. The effect of dose on onset, duration and intensity of effect is difficult to compare between studies, even laboratory-based studies because of the individual variation between cats as previously discussed. Two randomized cross over dose-response studies using a thermal threshold model have been published. In both, the intravenous route of administration was used to minimize any differences in absorption, uptake, distribution or metabolism between cats. The first study examined doses of 0.1, 0.2, 0.4 and 0.8 mg/kg of butorphanol [23]. Results indicated that the duration of the antinociceptive action of butorphanol was 90 minutes and there was no dose-response relationship in cats, supporting the assumption that butorphanol is an agonist-antagonist opioid and rapidly reaches a ceiling effect. Wegner and Robertson [27] concluded that doses of hydromorphone less than 0.1 mg/kg have a minimal effect and that perhaps a critical number of opioids receptors must be occupied before a response is measurable. It is not known if the response to doses over 0.1 mg/kg are dose-related or linear because the authors thought that higher doses are unlikely to be clinically useful because of the high incidence of hyperthermia related to this drug and therefore were not pursued. Whether or not the intensity or duration of effect of other opioids is dose-related is uncertain.

Routes of Administration

Intravenous, Intramuscular and Subcutaneous Administration

In a hospital setting the intravenous, intramuscular and subcutaneous routes of administration are most commonly used. In cats, studies comparing the administration of opioids given by the intravenous and intramuscular routes have been reported [43] and demonstrate that the route of administration does influence pharmacokinetic variables. However, what we are most interested in is the pharmacodynamic effect of opioids and with respect to the route of administration this has not been extensively studied in cats. The subcutaneous route is attractive in cats as it is simpler than an IV injection and less painful than an IM injection. The route of administration of hydromorphone affects the onset time, intensity of effect and duration of antinociceptive effects and also the incidence of nausea and vomiting [31]; see later under specific opioids / hydromorphone.

Oral Administration

Administering pills orally to cats is notoriously difficult and in most species oral administration of opioids results in greatly reduced plasma levels because of "first-pass" hepatic metabolism. For these reasons, the oral route of administration of opioids has not received much attention.

Transdermal Delivery Systems

There has been great interest in transdermal delivery of drugs because they may offer a "hands off" approach to pain management and could provide a constant delivery of drug thereby avoiding peaks and troughs seen with intermittent bolus administration. In addition, these systems are more attractive for cats that are difficult to handle. Both fentanyl and buprenorphine are available in a transdermal patch formulation and are discussed later. Despite their widespread use and promotion by compounding pharmacies, transdermal formulations of creams designed to be rubbed into the skin of cats cannot be scientifically supported [44].

Transmucosal Uptake of Opioids

Because of the limitations of the oral route, transmucosal administration of opioids has been investigated. Based on reports of the efficacy of transmucosal uptake of buprenorphine in humans, studies in cats were conducted and showed almost 100% bioavailability of the injectable formulation when placed on oral mucus membranes [45,46]. In addition, the transmucosal route was found to be well tolerated and as effective as the intravenous route when assessed using a thermal threshold model [46]. There was absorption of fentanyl from the oral cavity in cats but administration was associated with profuse salivation and resentment by the cats [44]. Transmucosal uptake of other opioids has not been reported in cats.

Epidural Administration

Morphine (0.1 mg/kg), buprenorphine (12.5 µg/kg), fentanyl (4 µg/kg), meperidine (pethidine) and methadone have been administered via the epidural route in cats [14,19,47-52]. Epidural buprenorphine did not decrease the minimum alveolar concentration (an indirect measure of analgesia or antinociception) of isoflurane [19]. In a clinical setting, morphine has been thought to be the most clinically useful epidural opioid in terms of analgesia achieved, duration of action and lack of side effects; although in one study 2 out of 23 cats that received epidural morphine had urinary retention [51]. In a laboratory based study, fentanyl only resulted in an increase in pain threshold at the 20 minute test point [14]. In a previous research-based study, epidural morphine was thought to be an effective analgesic [48] but more recently, Pypendop and others [19] have critically re-evaluated the effects of epidural morphine in cats and reported that it did not cause a decrease in the MAC of isoflurane. Interestingly, epidural morphine resulted in a significant decrease in the MAC of halothane in dogs when the noxious stimulus was applied to both the fore- and hindlimbs [53]. Whether this disparity is due to differences in experimental technique, a species specific effect or a reflection of individual variation in response to opioids as previously discussed is unknown and warrants further study.

Specific Opioids

Butorphanol

Butorphanol is a mu-antagonist, which produces analgesia through its kappa agonist activity. It is commonly used in cats in North America, and is generally given at doses from 0.1 to 0.4 mg/kg [54]. More recently its analgesic properties have been called into question in both dogs and cats [55]. Butorphanol exhibits a "ceiling" effect after which increasing the doses does not produce any further analgesia [23]; after IV administration there was no significant differences in thermal antinociception produced with 0.1, 0.2, 0.4 or 0.8 mg/kg. Butorphanol appears to be an effective visceral, but poor somatic analgesic [15]. In an experimental visceral pain model (rectal distension with a balloon) Sawyer and Rech reported that the most effective IV dose of butorphanol was 0.1 mg/kg which produced analgesia for 350 ± 10 minutes and the most effective SQ dose was 0.4 mg/kg which resulted in 298 ± 45 minutes of analgesia [15]. The same authors could only demonstrate somatic antinociception after high doses of intravenous butorphanol.

Both clinical impressions and experimental investigations indicate that butorphanol is short acting (< 90 minutes) [23,30,55] and requires frequent dosing to be effective. Recent data suggests that 0.2 mg/kg given by the intramuscular route may be more effective in cats [40], but there is no pharmacokinetic data comparing IV and IM dosing in cats to explain this difference; those authors concluded that it was difficult to compare studies and that individual variation in response may have accounted for the results they reported.

Butorphanol appears to be is a poor analgesic choice in the face of both somatic and visceral pain, but would be a reasonable choice for acute visceral pain such as that associated with acute cystitis, or enteritis.

Buprenorphine

Buprenorphine is the most popular opioid used in small animals practice in the UK [56] where it now has market authorization for use in cats and is also widely used in the rest of Europe, Australia and South Africa [57,58]. In research cats it has been studied after IM, IV and oral transmucosal (OTM) [30,40,45,46] administration. Intramuscular doses of 0.01 mg/kg resulted in a slow onset (2 hours) of analgesia with a variable duration ranging from 4 to 12 hours [30]. At a dose of 0.02 mg/kg IM the thermal threshold was significantly increased from 35 minutes to 5 hours after treatment [40]. Systemic uptake of buprenorphine after oral transmucosal dosing is almost 100% complete [45,46] in cats. The pH of the cat's mouth is between 8 and 9 which would enhance absorption and this may explain the effectiveness of this route in cats compared to other species with a neutral oral pH [45]. There was no difference in onset of analgesia (within 30 minutes), time to peak effect (90 minutes), or duration of action (6 hours) when 0.02 mg/kg was

administered by the IV or OTM route in research cats [46].

In clinical studies, buprenorphine produced better analgesia than morphine in cats undergoing a variety of soft tissue and orthopedic procedures [59], was superior to oxymorphone for sterilization (with or without onychectomy) [60], and provided longer pain relief than meperidine (pethidine) following ovariohysterectomy [61]. Buprenorphine rarely causes vomiting or dysphoria and has not been associated with hyperthermia [26].

A transdermal (matrix patch) delivery system for buprenorphine is now available for use in humans. In cats, there was systemic uptake after application of a 35µg/hour patch but plasma concentrations were quite variable, and over a 4 day period, no effective analgesia was demonstrated [62].

Fentanyl

Fentanyl is a potent, short acting pure mu agonist which is commonly used clinically as a constant rate infusion [CRI] [63] although there is no published data on the pharmacokinetic profile of fentanyl over time when administered in this fashion to cats. In a cat specific study 10 µg/kg (IV) provided rapid onset (peak action < 5 minutes) of significant analgesia that lasted 110 minutes, with no excitement, salivation or vomiting [44]. In that study, plasma fentanyl concentrations and analgesia were closely correlated and it was concluded that at a plasma value of > 1.07 ng/ml fentanyl provides analgesia, which is similar to that reported for dogs [64] and humans [65]. This data should be the basis of formulating more rational constant rate infusion and target controlled infusion protocols for cats.

Transdermal fentanyl (TDF) patches have been used for acute peri-operative pain in cats [29,66,67]. Plasma fentanyl concentrations are variable in cats after patch placement [29,66], and in one study [68], 2 out of 6 cats never achieved plasma fentanyl concentrations above 1 ng/ml. Factors affecting plasma levels include the size of the patch compared to the weight of the cat, skin permeability, and body temperature. In critical care patients, hypothermia, hypovolemia, and diminished skin perfusion will decrease absorption.

In normothermic (38°C) cats, mean serum levels were 1.83 ± 0.63 ng/ml compared to 0.59 ± 0.30 ng/ml in hypothermic (35°C) animals [69]. In cats weighing < 4kg, placement of a 25µg/h patch with full exposure of the adhesive layer resulted in a steady state plasma concentration of 1.78 ± 0.92 ng/ml compared to 1.14 ± 0.86 ng/ml when only one half of the adhesive was exposed [70]. In general, cats achieve steady state plasma concentration within 6-12 hours after patch placement [71] and this persists for up to 18-20 hours [68] after removal. During the uptake phase other opioids must be administered to provide analgesia and all except butorphanol, which may antagonize fentanyl, could be used. TDF patches have proved useful in a clinical setting [29,66,67].

The use of various drugs compounded in transdermal creams has become popular in veterinary medicine despite the lack of scientific studies [72]. Fentanyl compounded in pluronic lecithin organogel failed to be absorbed through the skin of the inner pinna or dorsum of the shaved neck of cats even after a dose of 30 µg/kg, therefore these formulations cannot be recommended [44].

Hydromorphone

Hydromorphone has become popular in veterinary medicine and has to a great extent replaced oxymorphone because it is less expensive [42]. Doses of 0.05-0.2 mg/kg of hydromorphone are generally recommended [42]. The relationship between dose and thermal antinociception (a measure of analgesia) following intravenous hydromorphone administration has been studied in cats. At doses of 0.025 and 0.05 mg/kg there was a small increase in thermal antinociception of short duration [27]. An intravenous dose of 0.1 mg/kg produced a substantial increase in thermal antinociception for up to 7 hours [27,73]. Route of administration has a significant effect on quality and duration of analgesia and side effects. When the analgesic and side-effects of 0.1 mg/kg given by the intravenous, intramuscular or subcutaneous route were compared, the intravenous route produced the greatest intensity and duration of antinociceptive effect with the least incidence of vomiting and salivation [31].

The incidence of hyperthermia associated with the use of hydromorphone in cats [26,28] as discussed previously in this chapter has limited its use by some veterinarians in clinical practice.

In contrast to the study by Briggs et al which studied the combination of oxymorphone and butorphanol [16], a combination of hydromorphone (0.1 mg/kg IM) and butorphanol (0.4 mg/kg IM) did not have additive effects on thermal antinociception, but rather produced a longer lasting (up to 9 hours) but less intense effect than hydromorphone alone [74].

Meperidine (Pethidine)

Meperidine is only given by the intramuscular or subcutaneous route due to reports of excitement after intravenous dosing. In clinical studies (3.3-10 mg/kg IM) it appears to be effective and has a fast onset but short duration of action [75,76]. Research studies suggest that at a dose of 5 mg/kg its duration of action is less than one hour [12].

Methadone

Methadone is a synthetic opioid agonist but also has considerable activity as an N-methyl-D-aspartate antagonist. It is widely used to manage cancer pain and "difficult" pain syndromes such as neuropathic-type pain with considerable success in humans [77,78]. In humans this drug is unusual in that it has good oral bioavailability and a long elimination half-life making it convenient for "at-home" use. In dogs, the pharmacokinetic profile of methadone was quite different from humans, with low oral bioavailability, rapid clearance and short elimination half-life [78]. The pharmacokinetics of this drug has not been reported in cats.

Methadone is used widely in the clinical setting, particularly in Europe. Racemic methadone has been evaluated in cats in a research setting [80], and both it and levo-methadone have been assessed peri-operatively in clinical cases [81,82]. In one study, 0.2 mg/kg of methadone given SQ increased the thermal threshold at 1 to 3 hours and the mechanical threshold from 45-60 minutes after administration [80]. Other doses and routes of administration have not been studied with this model.

Racemic methadone (0.6 mg/kg IM) and levo-methadone (0.3 mg/kg IM) given pre-operatively provided effective analgesia as judged by assessment of behavior and palpation of the wound in cats after ovariectomy and without behavioral, respiratory or cardiovascular side-effects [81]. Levo-methadone (0.3 mg/kg every 8 hours for 5 days, beginning at extubation) was not as effective as carprofen or buprenorphine in cats after major orthopedic surgery and was associated with excitement in some cats [82].

Morphine

Morphine has been widely used in cats and doses of 0.1-0.2 mg/kg are effective in clinical cases and do not cause excitement [83]. Both clinically [83] and in research models [30] onset of action is slow. Morphine appears less effective in cats compared to dogs and this may be related to their limited production of the active morphine metabolite morphine-6-glucuronide (M-6-G) [43] which may contribute significantly to morphine's overall analgesic effect in humans [84]. M-6-G could only be detected in 3 of 6 cats after IV administration and was not measurable after IM

dosing [43]. It may be that higher doses of morphine are required in cats because of the primary dependence on the parent compound to produce analgesia.

Nalbuphine

Nalbuphine is classified as an opioid agonist-antagonist and although it was popular in the past it is not widely used in cats today. Using an electrical stimulus to evaluate somatic antinociception, Sawyer and Rech [15] could not demonstrate any effects at doses ranging from 0.75 to 1.5 mg/kg IV. They were able to demonstrate a dose-related effect on visceral pain thresholds; 3.0 mg/kg IV had a duration effect of 180 ± 39 minutes, which was shorter than that produced by butorphanol, another agonist-antagonist used in their study.

Oxymorphone

Oxymorphone has been a popular analgesic for many years in the USA [60,86]. Using a visceral pain model, Briggs and others [16] reported that a combination of oxymorphone and butorphanol produced a greater degree of analgesia than either drug used alone and that this could be further enhanced by adding acepromazine. Clinically oxymorphone does not appear to be associated with hyperthermia, vomiting and nausea or adverse behavioral effects.

Tramadol

Although not classified as an opioid, tramadol has weak binding affinity at mu-receptors and is thought to activate monoaminergic spinal inhibition of pain. When used clinically in cats the effects of tramadol can be quite pronounced, including euphoria, dilated pupils and sedation (author's personal observations). The opioid actions of tramadol in cats may be more pronounced than in other species: in anesthetized cats, naloxone completely reversed the inhibiting effects of tramadol on ventilatory control and prevented more than 50% of the respiratory depression following 4 mg/kg IV [86]. There is no published pharmacokinetic data for tramadol in cats and species-specific data is required because metabolism in dogs was different compared to humans [87], therefore extrapolation from existing data is unwise. In dogs this drug shows promise for acute pain [88], but in a small group of research cats 1 mg/kg (SQ) did not produce thermal or mechanical antinociception [89]. A dose of 1-2 mg/kg IV has been suggested for clinical use in cats, but there are as yet no published reports of controlled clinical studies.

Drug	Dose (mg/kg)	Route	
Butorphanol	0.1-0.4	IV, IM, SQ	Often short acti more intense or
Buprenorphine	0.01-0.02 35 µg/hour patch	IV, IM, SQ transmucosal (oral) transdermal	Licensed for use (Vetergesic®) Uptake does oc clinical settings
Fentanyl	0.005- 0.01 25 µg/hour patch	IV continuous rate infusion (following bolus dose) transdermal	0.01 mg/kg IV p minutes May take up to concentration. Uptake affected
Hydromorphone	0.05-0.1	IV, IM, SQ	SQ route associ Doses of 0.1 mg
Meperidine (pethidine, Demerol)	5-10	IM or SQ only	Must not be giv
Methadone Levo-methadone	0.2-0.6 mg/kg 0.3 mg/kg	IV, IM, SQ IV, IM, SQ	Also has NMDA monoaminergic
Morphine	0.2-0.5 mg/kg	IV, IM, SQ	May be less effe to lack of active
Nalbuphine			
Oxymorphone	0.05-0.01	IV, IM, SQ	

Tramadol**	1-4 mg/kg 1-4 mg/kg	IV, IM PO (capsules, liquid, tablets available)	Has opioids acti drug. Monoamir 1 mg/kg SQ did model. Not a controlle IV formulation r
**The human product Ultracet ® contains acetaminophen and must not be used in cats			

Combinations of Opioids

The combination of oxymorphone and butorphanol [16], hydromorphone and butorphanol [75] and buprenorphine and butorphanol [40] have been reported in cats. The rationale behind these studies is to combine the attributes of each drug in the combination and minimize the side-effects of each. Multiple combinations are possible given the dose range of each drug. However, the results of the above combinations were quite different and may be a result of actual drug effects or the doses of each used. Low doses of oxymorphone and butorphanol in combination produced greater levels of antinociception than when used individually [16]. The addition of butorphanol (0.4 mg/kg IM) to hydromorphone (0.1 mg/kg IM) decreased the intensity of antinociception during the first 2 hours but extended the duration of observable antinociception from 5.75 to 9 hours [74]. A combination of 0.2 mg/kg IM of butorphanol and 0.02 mg/kg IM of buprenorphine had no demonstrable advantages over either drug used alone [40].

Constant Rate Infusion of Opioids

Fentanyl, alfentanil, sufentanil and remifentanil are used as infusions in humans and several domestic species. Constant rate infusions are used as part of a balanced anesthetic protocol, either with other injectable agents such as propofol, or with inhalant agents. They are also used post-operatively or in trauma patients to provide continuous analgesia and avoid the peaks and troughs and break-through pain associated with intermittent bolus administration. Fentanyl is the drug used most often in a clinical setting yet there is no data on the influence of inhalant anesthetics or propofol on its metabolism in cats. Used as a constant rate infusion over several hours accumulation may occur and clinically delayed recoveries are seen (author's own observation). Ideally, target controlled infusion rates based on pharmacokinetic data derived following bolus administration in cats [44] should be used, but as of yet this information is not available. In a prospective randomized study of injured cats, it was concluded that fentanyl (CRI of 0.02 mg/kg/hour) and propofol (12 mg/kg/hour) provided better cardiovascular stability than isoflurane and fentanyl but required intermittent positive pressure ventilation to maintain end-tidal CO2 values < 50 mmHg [90].

Target controlled infusions of alfentanil have been studied in isoflurane anesthetized research cats [18], but was not as effective at reducing MAC as in dogs, and was associated with an increase in rectal temperature, metabolic acidosis, decrease in PaO2 and excitement during recovery if the cats were handled. Combinations of propofol with fentanyl, alfentanil or sufentanil provided satisfactory anesthesia in a research setting using a noxious stimulus to evaluate depth of anesthesia [91]. Although it is not possible to compare infusion rates of alfentanil between the study by Ilkiw and others [18] and Mendes and Selmi [91] because of different methodologies, the latter authors reported hypothermia and not hyperthermia.

There are no published studies on the use of remifentanil infusions in cats, but based on its pharmacologic profile and studies in humans and other species it deserves exploration.

Long-term Use of Opioids

Because of the potential adverse side-effects of long-term non-steroidal anti-inflammatory administration in cats, it would be ideal if opioids could be used to manage chronic pain. Very little is known about long-term use of opioids in cats, including the issue of dependency.

In this author's experience, cats frequently become inappetent after 2-3 days of opioid treatment and this may be a result of decreased gastrointestinal motility. In addition the side-effects of euphoria and dilated pupils can be problematic. However, further work is warranted to look at the efficacy of drugs such as oral tramadol and methadone for long-term pain management or different dosing regimens, formulation or routes of administration of opioids that are effective for acute pain. The use of opioid antagonists that work only at peripheral sites to antagonize undesirable systemic effects but not centrally mediated analgesia show great promise in humans [92] but have not been widely explored in veterinary medicine.

Summary

The days of avoiding opioids in cats for the treatment of clinical pain because of unsubstantiated reports of excitatory effects are behind us. Although some effects of opioids seem unique to cats, there has been considerable work conducted specifically on opioids in cats in the past decade and the drugs, routes of administration and doses used today have a scientific basis. There is still much to be learned about the chronic use of opioids in cats and the development of target controlled infusions hold promise as part of balanced general anesthetic protocols.