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Practical use of opioids in cats: a state-of-the-art, evidence-based review

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Abstract

Rationale Recent recognition of the need to improve pain management in cats has led to the investigation of the pharmacokinetics and efficacy of opioid analgesic drugs in this species. The results of these studies may be difficult to interpret because the effect of these drugs varies with dose, route of administration and the method used to assess them. As equipotency of different opioids is not known, it is hard to compare their effects. Animals do not verbalise the pain they feel and, in cats, it may be more difficult to recognise signs of pain in comparison with other species such as dogs.

Aim This article reviews the use of opioid analgesics in cats. It must be remembered that not all drugs are licensed for use in cats, and that marketing authorisations vary between different countries.

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Introduction

In recent years research into pain assessment and management in cats has increased. This interest and focus may have been in response to reports that cats have been undertreated for pain in comparison with other species.[1–4] Advances in knowledge have led to internationally recognised veterinary bodies issuing guidelines on pain management in cats, including those very recently from the American Animal Hospital Association and the American Association of Feline Practitioners.[5] In 2014, the World Small Animal Veterinary Association also published guidelines on the recognition, assessment and treatment of pain.[6]

Pain assessment in cats

Pain assessment and quantification in animals is challenging because pain is a subjective sensory and emotional experience and animals are unable to verbalise their suffering. The most reliable way to assess pain in cats is thought to be through a combination of behavioural observations and interaction with the animal.[7] Various scales have been created to try to quantify pain in cats. For example, the Colorado State University Veterinary Medical Center has designed a feline acute pain scale,[8] whereby psychological and behavioural components are evaluated in conjunction with the cat's response to palpation of the site of surgery and its body tension. In many studies the visual analogue scale (VAS) is used: an assessor marks a point on a 100 mm line that best correlates with the cat's pain intensity; VAS is based on visual observation and '0' is considered no pain, while '100' is considered the worst pain imaginable. The so-called dynamic interactive visual analogue scale (DIVAS) also includes interaction with the cat, such as palpation of the wound. Recently, a multidimensional composite scale for assessing postoperative pain in cats has been validated.[9] This tool combines evaluations of postoperative psychomotor changes, reaction to palpation of the wound area and vocal expression of pain, together with appetite and arterial blood pressure. It is important to remember that increased arterial blood pressure can be a sign of stress, fear and anxiety, and not necessarily pain. Another method with the potential to assess pain in cats is the evaluation of facial expressions.[10]

Limitations of pain assessment using the aforementioned methods include the subjective nature of the evaluation and the difficulties in recognising behavioural clues that may be indicative of pain, particularly in a hospital environment. However, use of a pain scale has the advantages that it focuses the attention of members of staff on pain and also means that an individual cat's response to analgesic administration can be assessed and monitored.

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Nociceptive threshold testing has been used to assess the antinociceptive effects of analgesic drugs in a more objective way. In cats, mechanical, thermal and electrical threshold testing has been employed in experimental settings to evaluate the effects of opioids.[11,12] For each of these techniques a baseline nociceptive threshold is measured, an analgesic is then administered and the thresholds are measured again at specific time points. An increase in the threshold is usually accepted as evidence of a drug's anti-nociceptive effect. Nociceptive threshold testing does have a number of limitations,[13] including the lack of evaluation of the emotional components of pain. Despite these limitations it is a useful tool for identifying drugs and dosages for further evaluation in clinical cases. In a clinical setting, mechanical nociceptive testing has also been used, in conjunction with subjective assessments of pain, in cats undergoing surgery.[14]

There are numerous publications investigating the effects of drugs on the minimum alveolar concentration (MAC) of inhalant anaesthetics in cats. However, this is not an effective way to evaluate the analgesic effects of opioids[15] since it only indicates the immobilising potency of the inhalation anaesthetic at the spinal cord level, while pain also involves supraspinal pathways. Several opioids, including morphine, buprenorphine, methadone, butorphanol, hydromorphone, fentanil, alfentanil, remifentanil and tramadol, have been proven to decrease, to different degrees, the MAC of inhalant anaesthetics, but the effects were not always clinically relevant and were not as profound as have been reported in other species, including dogs.[16–23] Thus, a significant reduction in volatile anaesthetic concentration after opioid administration should not be expected in the clinical setting.

When discussing opioids, opioid receptors and comparisons between different opioid drugs, some concepts should be made clear. Affinity refers to how avidly a drug binds to a receptor, efficacy indicates the magnitude of the effect produced by the drug–receptor interaction, and potency indicates the quantity of drug needed to produce a maximal effect.[24]

Opioids and cats

Opioids play an important role in the clinical management of pain in cats. Ideally, analgesics should be administered before noxious stimulation (preventive analgesia) with the aim of preventing sensitisation of the central nervous system, which could lead to the development of hyperalgesia. A multimodal approach is also recommended; this involves the concurrent administration of different classes of analgesics, such as opioids, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics and α_2-adrenoreceptor agonists, with the aim of decreasing the doses and thus the side effects of individual agents, while improving the control of pain in the animal.[6]

In cases of acute pain, opioids are effective and versatile analgesics, with wide therapeutic margins and relatively minor side effects in cats.[6] Their effects can also be antagonised if required. Historically there was a reluctance to administer opioids to cats due to concerns over the potential excitatory effects reported by Wikler in 1944.[25] However, 'morphine mania' was elicited at doses 100-fold higher (15 mg/kg) than those used in the clinical setting.[26] Sufentanil and alfentanil administration in cats is associated with an increase in sympathetic outflow and central stimulatory effects,[27,28] but a study investigating morphine administered to cats at clinical (0.3 mg/kg) and supraclinical (0.6–2.4 mg/kg) doses reported no excitement.[29] At clinically used doses the behavioural effects of opioids include euphoria, manifesting as purring, rubbing, rolling and kneading with the forepaws.[30–35]

Opioids cause mydriasis in cats,[36] which outlasts their analgesic effects and may affect vision. In dogs, the incidence of vomiting and salivation following morphine, hydromorphone and oxymorphone administration was reduced by prior administration of acepromazine.[37] This has not been studied in cats but it is possible that a similar effect may be seen. Decreased intestinal motility is a potential adverse effect of opioids but the clinical relevance of this in healthy cats is questionable, and in a study where buprenorphine was administered with acetylpromazine the orocaecal transit time, assessed by the breath hydrogen method, was not affected.[38]

Postanaesthetic hyperthermia, defined as a rectal temperature higher than 39.2°C, has been associated with opioid administration in cats. Moreover, it was shown in a prospective clinical study of 40 healthy adult cats that body temperature at extubation was inversely related to the degree of postanaesthetic hyperthermia; that is, the colder the cat was at the end of anaesthesia, the higher the temperature was reported to be during recovery.[39] In a prospective randomised crossover study, buprenorphine (0.02 mg/kg IM), butorphanol (0.2 mg/kg IM), morphine (0.5 mg/kg IM) and hydromorphone (0.05–0.2 mg/kg IM) caused mild/moderate and self-limiting increases in body temperature (<40.1°C).[40] Alfentanil infusion increased body temperature in isoflurane-anaesthetised cats,[20] but not in propofol-anaesthetised cats.[41] An increase in body temperature has been detected with transdermal fentanyl patches in cats undergoing onychectomy, with mean rectal temperatures ranging from 38.8–39.4°C in the postoperative period.[30] Morphine and pethidine may cause hyperthermia at doses much higher than those recommended.[42,43] In the light of these findings, it is recommended that a cat's body temperature is closely monitored during anaesthesia and in the perioperative period.

Other side effects of opioid therapy in people are opioid-induced hyperalgesia and tolerance,[44] but these

have not been reported in cats to date. This may be due to the relatively short duration of opioid administration in animals compared with people (where they may be used for long periods, particularly in the palliative care setting), meaning that opportunities for detecting these phenomena are limited. Challenges associated with determining whether changes in response to opioids are due to hyperalgesia/tolerance or disease progression, or due to different metabolisation of drugs in cats compared with people, might also be a factor.[15]

As in people, great variability in the response of individual cats to opioids has been observed;[7,45,46] a phenomenon known as 'pharmacogenomics'.[47] Hence it is important to tailor the analgesic protocol to fit the individual patient's needs in order to maximise pain relief while minimising side effects. Although adverse events may occur, opioids are effective analgesic drugs to be used in cases of moderate/severe pain and the risk of severe side effects is low in comparison with other classes of analgesics, such as NSAIDs.[48]

In this review of the use of opioids in cats, opioids licensed for use in cats are discussed before those that are not licensed. Licensing of drugs is country-specific and readers need to be aware of the prescribing laws pertaining to their own country.

Pethidine (meperidine)

Pethidine is a synthetic full μ receptor agonist[49] that has a marketing authorisation at a dose of 3.3 mg/kg by intramuscular (IM) injection in cats in some European countries, including the UK. It should not be administered intravenously (IV) because it causes histamine release.[50] Vomiting is a rare side effect.[43]

Clinical and experimental studies have evaluated various doses of pethidine, ranging from 2–10 mg/kg, alone and in combination with other drugs (Table 1). The onset of analgesic effect is rapid (30 mins) and the duration of action is dose-dependent, ranging from 1–2 h.[11,14,55] These characteristics mean that pethidine may be a good option in cats that require short-term pain relief and/or frequent re-evaluation of the neurological system. However, other opioids may be more suitable where a longer duration of analgesia is required, such as after surgery.

Table 1 Studies evaluating pethidine in cats

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	P 2.5mg/kg + DEXM 10 μg/kg IM	Subjective evaluation of nociceptive response to digital pad clamp and tail clamp	Decrease in pain score (multifactorial scale) 30 mins after P administration; the protocol allowed completion of several clinical manipulations	51
Experimental	P 5 mg/kg IM	TNT MNT ENT	TNT increased at 15 and 60 mins after treatment. MNT increased at 30 and 45 mins after treatment. No change in ENT detected	12
Experimental	P 5 mg/kg IM	TNT	TNT increased at 30, 45 and 60 mins after treatment	11
Experimental	P 5 mg/kg IM	PK	$T_{½\,el}$ = 216 mins Cl_p = 20.8 ml/kg/min	52
Clinical: castration	P 5 mg/kg IM	MNT VAS	Lower VAS pain scores at 0.5 and 1 h postsurgery in cats being administered P in comparison with cats not receiving P. In control cats significant hyperalgesia was recorded at all postoperative time points	14
Clinical: OHE	B 6 μg/kg IM, P 5 mg/kg IM, KETO 2 mg/kg SC	VAS	Cats in KETO group had lower pain scores than cats in other groups from 1 h postoperatively	53
Clinical: neutering	P 3.3 mg/kg IM, CAR 4 mg/kg SC	VAS	P provided less analgesia than CAR from 4 h after OHE and at 18–24 h after castration	54
Clinical: OHE	P 5 mg/kg IM, P 10 mg/kg IM, CAR 1–2–4 mg/kg SC	VAS DIVAS	P 10 mg/kg provided better analgesia than CAR up to 2 h post-extubation. From 2–20 h post-extubation CAR 4 mg/kg provided better analgesia than P	55

*'+' identifies where drugs were given in combination; where individual drugs were compared in different groups of animals, these are separated by commas

B = buprenorphine; CAR = carprofen; Cl_p = plasma clearance; DEXM = dexmedetomidine; DIVAS = dynamic interactive visual analogue scale; ENT = electrical nociceptive threshold; KETO = ketoprofen; MNT = mechanical nociceptive threshold; OHE = ovariohysterectomy; P = pethidine; PK = pharmacokinetics; $T_{½\,el}$ = elimination half-life; TNT = thermal nociceptive threshold; VAS = visual analogue scale

Methadone

Methadone has recently received marketing authorisation for use in cats at a dose of 0.3–0.6 mg/kg in the United Kingdom, Italy and some other European countries. The results of various studies on methadone in cats are summarised in Table 2. Methadone is a synthetic μ opioid receptor agonist drug, consisting of a racemic mixture of D and L enantiomers. In addition to its interaction with the μ opioid receptor, the D isomer exerts an antagonistic action at the N-methyl-D-aspartate (NMDA) receptor.[60] Moreover, methadone plays a role in the descending pain pathways by inhibiting the reuptake of serotonin and noradrenaline, and by blocking the nicotinic cholinergic receptors.[61,62] These receptor interactions could explain the good analgesic and possible anti-hyperalgesic effects that have been demonstrated using mechanical nociceptive testing in cats receiving methadone as part of pre-anaesthetic medication before ovariohysterectomy.[31]

In the experimental setting, methadone administration (0.2–0.6 mg/kg) resulted in antinociception to thermal and mechanical stimuli.[32,33] The duration of antinociception to the thermal stimulus was longer than that to the mechanical stimulus, and also depended on the dose and route of administration; the duration of antinociception to the mechanical stimulus after 0.2 mg/kg SC was only 45–60 mins, whereas it was up to 4 h after 0.3 mg/kg IV. This suggests that the IV route is preferable where a longer duration of action is required.

Table 2 Studies evaluating methadone in cats

Type of study	Dose and route*	Assessment	Results	Reference
Clinical: neutering	MET 0.5 mg/kg IM, B 0.02 mg/kg IM, BUT 0.4 mg/kg IM	IVAS MNT	IVAS pain scores were not different between groups at any time point up to 6 h after premedication. Postoperatively in female cats there was no significant variation in MNT over time in the MET group; in the B and BUT groups MNT decreased over time, becoming lower than baseline	31
Experimental	MET 0.3 mg/kg IV, MET 0.6 mg/kg OTM	MNT	IV group: increased MNT values from 10 mins to 4 h postadministration. OTM group: increased MNT values from 10 mins to 6 h postadministration. MNT values higher in the IV group in comparison with the OTM group at 10 mins and 1 h postadministration	33
Experimental	MET 0.3 mg/kg IV	Tail clamp technique	Sevoflurane MAC after MET administration decreased by 25%, 15% and 7% at 26, 76 and 122 mins, respectively	17
Experimental	MET 0.2 mg/kg SC	TNT MNT	TNT increased at 1–3 h and MNT increased at 45–60 mins after MET administration	32
Clinical: orthopaedic surgery	Levomethadone 0.3 mg/kg SC q8h for 5 days	NRT VAS MNT	Analgesic effect of levomethadone was similar to B 0.01 mg/kg administered SC q8h. Higher MNT values were observed in both groups from 30 mins post-extubation until the end of day 4	56
Clinical: OHE	MET 0.6 mg/kg IM	Wound palpation	Analgesia up to 4 h postoperatively, except in one cat	57
Clinical: OHE	MET 0.5 mg/kg IM	Behavioural observation Wound palpation	Analgesia for 1.5–6.5 h	58
Experimental	MET 0.3 mg/kg OTM, MOR 0.2 mg/kg OTM, HYDRO 0.1 mg/kg OTM, OXY 0.25 mg/kg OTM	Bioavailability/ pharmacokinetic study	Mean ± SE bioavailability was 44.2 ± 7.9%, 36.6 ± 5.2%, 22.4 ± 6.9% and 18.8 ± 2.0% for buccal administration of MET, MOR, HYDRO and OXY, respectively	59

*See footnote to Table 1

B = buprenorphine; BUT = butorphanol; HYDRO = hydromorphone; IVAS = interactive visual analogue scale; MAC = minimum alveolar concentration; MET = methadone; MNT = mechanical nociceptive threshold; MOR = morphine; NRT = numerical rating scale; OHE = ovariohysterectomy; OTM = oral transmucosal; OXY = oxymorphone; TNT = thermal nociceptive threshold; VAS = visual analogue scale

In clinical studies, methadone, at doses of 0.3–0.5 mg/kg IM or SC, provided a dose-dependent period of analgesia lasting from 1.5–6.5 h.[31,56–58]

In some countries the levorotatory enantiomer is available; when levomethadone (0.3 mg/kg IM) was compared with racemic methadone (0.6 mg/kg IM) it produced satisfactory postoperative analgesia after ovariohysterectomy.[57] Mechanical nociceptive threshold testing has been used to compare oral transmucosal (OTM) (0.6 mg/kg) with IV (0.3 mg/kg) administration of methadone.[33] A similar duration of antinociception to a mechanical stimulus was reported, although a less profound response for up to 1 h after administration was evident, suggesting a slower onset of full effect after OTM administration. It is worth noting that the OTM dose was double that administered IV, but these data suggest that methadone is absorbed by this route and recently a mean bioavailability of 44.2% was reported after buccal administration of methadone in cats.[59]

The OTM route does look promising for administering methadone to difficult-to-inject cats, but further studies are required to determine the efficacy in clinical cases. Assessing the depth of anaesthesia and titrating the amount of anaesthetic agent to obtain a suitable depth of anaesthesia is important in all anaesthetised animals. Methadone (0.3 mg/kg IV) has been reported to decrease the MAC of sevoflurane in cats by 7–25%, so the vaporiser setting may need to be reduced.[17] As already mentioned, MAC reduction cannot be considered as a surrogate for analgesia.

Buprenorphine

Buprenorphine is a highly lipophilic semi-synthetic partial μ agonist opioid,[63] with a marketing authorisation for use in cats in the USA and several European countries. A wide variation in the duration of analgesic and antinociceptive effects has been reported for buprenorphine (Table 3). This variation may be attributed to different doses, routes of administration and methods of assessment, and individual variation between cats.

In experimental studies buprenorphine 0.01–0.02 mg/kg given IV or IM had a thermal antinociceptive effect lasting from 30 mins to 12 h.[34,46,73] The dose-related antinociceptive effects of intravenous buprenorphine have been investigated; buprenorphine 0.02 mg/kg and 0.04 mg/kg produced a greater degree of mechanical antinociception than the 0.01 mg/kg dose, but no dose-related response was found with a thermal threshold model.[70]

Clinical studies have indicated that buprenorphine appears to be an effective analgesic in cats undergoing various procedures including ovariohysterectomy, onychectomy and orthopaedic surgery.[53,65,69,77,78]

The pharmacokinetics of buprenorphine administered by the IV, IM, SC, transdermal and OTM routes have been described.[46,52,64,72] Buprenorphine has good bioavailability when administered by the OTM route and experimental studies suggested that it was both effective and well tolerated by cats.[46,76,81] Clinical studies have reported conflicting results regarding the analgesic efficacy of OTM buprenorphine.[67,68,75] This is possibly due to the timing of drug administration, the concomitant use of α_2-adrenoreceptor agonists (which could cause vasoconstriction and potentially reduce the uptake of buprenorphine across the oral mucous membranes), and the volume and dilution of buprenorphine. Experimental data suggested that SC and transdermal administration of buprenorphine resulted in erratic absorption and disposition, and a limited intensity of antinociception.[32,64,72]

Two studies evaluated the thermal antinociceptive effects of epidurally administered buprenorphine, which lasted from 1–10 h and from 15 mins to 24 h, at doses of 0.0125 mg/kg and 0.02 mg/kg, respectively.[71,79] In another study, epidural administration of buprenorphine did not reduce the MAC of isoflurane.[74]

Vomiting and dysphoria are rarely associated with buprenorphine administration and its efficacy and long duration of action make it a good analgesic for cats in the perioperative period. The reported variability in intensity and duration of analgesia reflects the different doses and routes of administration used in different studies. These factors, coupled with the differences in response between cats, emphasise why it is important to monitor the response to treatment and titrate analgesic therapy to suit the individual's needs.

A sustained-release preparation of buprenorphine that may produce analgesia for up to 72 h after SC injection has been produced; this shows promise for providing analgesia in cats following ovariohysterectomy, as it was as effective as the standard formulation of buprenorphine administered by the OTM route q12h.[66] Very recently, the safety of long-acting buprenorphine administered SC has been tested in young cats.[80] Cats were administered buprenorphine for 9 consecutive days at a dose of 0.24, 0.72 or 1.20 mg/kg/day. These doses represent 1 x, 3 x and 5 x the licensed dose and they were reported to be well tolerated by cats.

A review of studies describing the clinical application of buprenorphine in cats is now available.[82]

Butorphanol

Butorphanol is a synthetic opioid analgesic with agonist/antagonist activity.[83] Its pharmacology is complex and it has species-specific affinity for the μ-, δ- and κ-opioid receptor subtypes.[84] Butorphanol has a marketing authorisation for use in cats in several European countries and in North America, where it is widely used. In general, butorphanol is administered at doses from 0.1–0.4 mg/kg via the IV, IM or SC route. The OTM route has been investigated but it was not efficacious due to

Table 3 Studies evaluating buprenorphine in cats

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	B 0.02 mg/kg IV, B 0.02 mg/kg IM, B 0.02 mg/kg SC	TNT	B 0.02 mg/kg IV: increased TNT values from 15–480 mins. B 0.02 mg/kg IM: increased TNT values at 30 and 60 mins. TNT values were higher in IV than IM or SC groups at 15, 60, 120 and 180 mins. SC group showed erratic absorption and disposition	64
Clinical: neutering	B 0.02 mg/kg IM, MET 0.5 mg/kg IM, BUT 0.4 mg/kg IM	VAS MNT test	B provided as effective analgesia as M during the 6 h test period	31
Clinical: OHE	B + CAR, B + MEL, BUT + CAR, BUT + MEL; B 180 µg/m^2 IM, BUT 6 µg/m^2 IM, CAR 4 mg/kg SC, MEL 0.3 mg/kg SC	VAS DIVAS TNT	All protocols tested provided low pain scores with no differences between groups	65
Clinical: OHE	SRB 0.11 mg/kg SC, B 0.02 mg/kg OTM	VAS CSUCPS VFF	SRB provided analgesia for up to 72 h postsurgery. No rescue analgesia required. SRB as efficacious as OTM B administered every 12 h	66
Clinical: OHE	B 0.01 mg/kg IV, B 0.01 mg/kg IM, B 0.01 mg/kg OTM	DIVAS SDS	No differences between groups detected with SDS. DIVAS pain scores higher in the OTM than IV or IM group at 1, 3, 4, 8 and 12 h. DIVAS pain scores after SC administration significantly higher than IV and IM administration at 2, 3, 4, 8, 12 and 24 h. OTM and SC groups required more rescue analgesia than IV and IM groups	67
Clinical	B 0.02 mg/kg + DEXM 0.02 mg/kg IM, B 0.02 mg/kg + DEXM 0.02 mg/kg OTM	NRS to evaluate sedation	OTM treatment produced less sedation than IM treatment for IV catheterisation	68
Clinical: various surgeries	B 0.01–0.02 mg/kg IM, BUT 0.4 mg/kg IM	SDS	Overall cats in B group had lower pain scores than BUT group. At 2 and 24 h time points B pain scores were lower. B provided better and longer lasting postoperative analgesia than BUT	69
Experimental	B 0.01 mg/kg IV (B1), B 0.02 mg/kg IV (B2), B 0.04 mg/kg IV (B4)	TNT MNT	Increased TNT values for 4, 2 and 8 h for B1, B2 and B4 groups, respectively. Increased MNT values at 15 and 45 mins for B2, and 30 and 45 mins, and 1 and 2 h for B4. B2 and B4 produced more mechanical antinociception and a longer duration of action than B1, respectively. No dose response effect to thermal stimulation detected	70
Experimental	B 12.5 µg/kg EPI, MOR 100 µg/kg EPI, SAL EPI	TNT	TNT increased from 1–10 h in B group and from 1–16 h in MOR group in comparison with SAL. The maximum cut-off temperature of 55°C was reached 0, 74 and 11 times in SAL, MOR and B groups, respectively	71
Experimental	B 35 µg/kg TD	TNT	No significant changes in TNT during the 16 h test period	72
Experimental	B 0.02 mg/kg IM, BUT 0.2 mg/kg IM, SAL IM	TNT	Compared with baseline, B increased TNT from 35 mins to 5 h post-treatment. Similar antinociception between B and BUT. Large inter-cat variation in magnitude and duration of response	73
Experimental	B 12.5 µg/kg EPI, MOR 100 µg/kg EPI	MAC determination by tail clamp technique	No significant MAC-sparing effect in either B or MOR group	74

(Continued)

Table 3 (Continued)

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	B 0.02 mg/kg SC, MET 0.2 mg/kg SC, MOR 0.2 mg/kg SC	TNT MNT	TNT significantly increased at 45 mins after B administration; MNT increased at 30–45 mins after B administration	32
Clinical: OHE	B 0.01 mg/kg PO, B 0.01 mg/kg SC, MEL 0.3 mg/kg SC, MEL 0.3 mg/kg PO	IVAS	IVAS scores were higher for B groups than MEL groups	75
Experimental	B 0.02 mg/kg IV, B 0.02 mg/kg OTM	PK TNT	TNT increased between 30 and 360 mins in both IV and OTM groups. OTM treatment was as effective as IV treatment	46
Experimental	B 0.01 mg/kg IV, B 0.01 mg/kg OTM	PK	PK by the OTM and IV routes were similar	76
Experimental	B 0.01 mg/kg IM	TNT	TNT increased between 4 and 12 h post-B administration. Euphoria was recorded for up to 24 h in some cats. Mild sedation noted	34
Experimental	B 0.005 mg/kg IV, B 0.05 mg/kg IV	MAC determination by tail clamp technique	Maximal MAC reductions were 17 ± 7% and 11 ± 6% with the lowest and highest doses of B, respectively, and were considered not clinically relevant	16
Clinical: various surgeries or invasive diagnostic investigations	B 0.01 mg/kg IM, MOR 0.1 mg/kg IM	VAS	B provided better postoperative analgesia than MOR at 60, 120 and 180 mins postanaesthesia. Rescue analgesia was necessary in 5/14 and 3/18 cats in MOR and B groups, respectively	77
Clinical: onychectomy± neutering	B 0.01 mg/kg IV, OXY 0.05 mg/kg IM, KETO 2 mg/kg IM	Cumulative pain scores VAS	B cumulative pain scores were lower than OXY and KETO at 12 h post-extubation and lower than OXY at 4 h	78
Experimental	B 0.01 mg/kg IV and IM	PK	IV: mean ± SD $T_{½\ el}$ = 416 ± 176.8 mins Cl_p = 16.7 ± 6.2 ml/kg/min V_{dss} = 7.1 ± 3.2 l/kg IM: mean ± SD $T_{½\ el}$ = 380.2 ± 131 mins Cl_p = 23.7 ± 12.6 ml/kg/min V_{dss} = 8.9 ± 5.9 l/kg	52
Clinical: OHE	B 6 µg/kg IM, P 5 mg/kg IM, KETO 2 mg/kg SC	VAS	Cats in KETO group had lower pain scores than cats in other groups from 1 h postoperatively	53
Experimental	B 20 µg/kg EPI, MEDET 10 µg/kg EPI, B 10 µg/kg + MEDET 5 µg/kg EPI	TNT MNT	TNT increased from 30 mins to 1 h after B and at 45 mins after MEDET. MNT increased from 45 mins to 2 h after B, from 15 mins to 1 h after MEDET and at 30, 45 mins and 2 h after B + MEDET. TNTs were above the upper 95% CI from 15 mins to 24 h after B, from 15 mins to 4 h after MEDET and from 15 mins to 8 h after B + MEDET. MNTs were above the upper 95% CI from 15 mins to 5 h, and at 8, 12 and 24 h after B, from 15 mins to 6 h after MEDET and from 15 mins to 6 h and at 12 and 24 h after B + MEDET	79
Experimental	B 0.24 mg/kg/day SC for 9 days, B 0.72 mg/kg/day SC for 9 days, B 1.20 mg/kg/day SC for 9 days, SAL	Safety study	Young cats tolerated the different doses well. Adverse events related to B administration were noted in two cats being administered the 0.24 and 0.72 mg/kg/day dose, and consisted of mydriasis and behavioural changes such as hyperactivity, difficult handling, agitation and disorientation	80

*See footnote to Table 1

B = buprenorphine; BUT = butorphanol; CAR = carprofen; CI = confidence interval; Cl_p = plasma clearance; CSUCPS = Colorado State University Cat Pain Scale; DIVAS = dynamic interactive visual analogue scale; DEXM = dexmedetomidine; EPI = epidural; IVAS = interactive visual analogue scale; KETO = ketoprofen; MAC = minimum alveolar concentration; MEDET = medetomidine; MEL = meloxicam; MET = methadone; MNT = mechanical nociceptive threshold; MOR = morphine; NRS = numerical rating scale; OHE = ovariohysterectomy; OTM = oral transmucosal; OXY = oxymorphone; P = pethidine; PK = pharmacokinetics; SAL = saline; SDS = simple descriptive scale; SRB = sustained release buprenorphine; $T_{½\ el}$ = elimination half-life; TD = transdermal; TNT = thermal nociceptive threshold; VAS = visual analogue scale; V_{dss} = volume of distribution at steady state; VFF = von Frey filaments

Table 4 Studies evaluating butorphanol in cats

Type of study	Dose and route*	Assessment	Results	Reference
Clinical: neutering	B 0.02 mg/kg IM, MET 0.5 mg/kg IM, BUT 0.4 mg/kg IM	VAS MNT test	BUT and B produced similar sedation during the 6 h test period	31
Experimental	MID 0.4 mg/kg + BUT 0.4 mg/kg IM, MID 0.4 mg/kg + BUT 0.4 mg/kg + KETA 3 mg/kg IM, MID 0.4 mg/kg + BUT 0.4 mg/kg + DEXM 5 µg/kg IM, KETA 3 mg/kg + DEXM 5 µg/kg IM	Sedation score in response to tactile and auditory stimulation. NRS to assess recovery	MID + BUT was associated with the lowest sedation score and the poorest quality of recovery. KETA + DEXM was associated with the highest sedation score and best quality recovery. Stroke volume decreased by 24%, 21%, 24% and 36%, and cardiac output by 23%, 34%, 54% and 53% in MID + BUT, MID + BUT + KETA, MID + BUT + DEXM and KETA + DEXM treatment, respectively	86
Experimental	ACE 0.1 mg/kg + BUT 0.25 mg/kg IM, ACE 0.1 mg/kg + BUT 0.25 mg/kg IM + KETA 1.5 mg/kg IV	Echocardiography	In ACE + BUT + KETA group heart rate increased significantly; in ACE + BUT group systolic blood pressure decreased significantly. The two sedation protocols did not alter echocardiography variables significantly, with the exception of a mild decrease in left ventricular end-diastolic dimensions and a mild increase in left ventricular end-diastolic wall thickness	87
Experimental	DEXM 20 µg/kg IM, DEXM 10 µg/kg + PETH 2.5 mg/kg IM, DEXM 10 µg/kg + BUT 0.4 mg/kg IM	Multifactorial sedation scale. Subjective pain score to digital pad clamp and tail clamp. Subjective assessment of muscle tone	No statistically significant differences between groups regarding sedation, analgesia and muscle relaxation	51
Clinical: OHE	B + CAR, B + MEL, BUT + CAR, BUT + MEL; B 180 µg/m^2 IM, BUT 6 µg/m^2 IM, CAR 4 mg/kg SC, MEL 0.3 mg/kg SC	VAS DIVAS TNT	All protocols tested provided low pain scores, with no differences between groups	65
Clinical	KETA 5 mg/kg + MID 0.2 mg/kg + BUT 0.3 mg/kg, SEVO	Monitoring of physiological parameters	Both groups achieved adequate restraint for blood collection. SEVO was associated with a faster recovery. Hypotension (SAP <70 mmHg) requiring intervention was reported in 42% and 84% of cats in the KETA + MID + BUT and SEVO groups, respectively	88
Clinical: various surgeries	BUT 0.4 mg/kg IM, B 0.01–0.02 mg/kg IM	SDS	Overall, cats in the B group had lower pain scores than those in the BUT group. At 2 and 24 h time points, B pain scores were lower. B provided better and longer lasting postoperative analgesia than BUT	69
Experimental	BUT 0.2 mg/kg IM	MNT	At 30 mins after BUT administration MNT was higher than baseline	89

(Continued)

Table 4 (Continued)

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	BUT 0.4 mg/kg IM, BUT 0.4 mg/kg OTM	PK	IM: mean ± SD $T_{½ el}$ = 6.28 ± 2.77 h Cl/F = 775.01 ± 302.17 ml/h/kg V_d/F = 7603.2 ± 6276.89 ml/kg C_{max} = 0.35 h OTM: mean ± SD $T_{½ el}$ = 5.23 ± 1.72 h Cl/F = 2120.27 ± 392.87 ml/h/kg V_d/F = 15,633.54 ± 4697.48 ml/kg C_{max} = 1.1 h OTM BUT absorption was 37.16%	85
Experimental	SAL, T + BUT, T + HYDRO; T 8.6 mg/kg PO, T 11.6 mg/kg PO, BUT 0.4 mg/kg IV, HYDRO 0.1 mg/kg IV	Tail clamp	Mean ± SEM MAC for sevoflurane after SAL was 2.45 ± 0.22%. MAC decreased to 1.48 ± 0.20%, 1.20 ± 0.16%, 1.76 ± 0.15%, 1.48 ± 0.20% and 1.85 ± 0.20% with T, BUT, HYDRO, T + BUT and T + HYDRO, respectively. Naloxone reversed the reductions in MAC	18
Experimental	BUT 0.4 mg/kg SC	MNT	MNT values increased from baseline for 45 mins after BUT administration. Maximum increase was recorded at 10 mins	90
Experimental	BUT 0.2 mg/kg IM, B 0.02 mg/kg IM, SAL IM	TNT	Compared with baseline, BUT increased TNT from 50 mins to 8 h post-treatment. Similar antinociception between B and BUT. TNT of BUT was different from SAL at 50 mins. Large inter-cat variation in magnitude and duration of response reported	73
Clinical: OHE	BUT 0.44 mg/kg IM before surgery, CAR 2.2 mg/kg PO before surgery, KETO 2.2 mg/kg SC before surgery, BUPI 1.1 mg/kg local infiltration	VAS IVAS	VAS and IVAS pain scores were not different in BUT, CAR or KETO groups at any time point. In BUPI group, VAS and IVAS pain scores were higher than BUT group at 1 and 2 h after surgery	91
Clinical: onychectomy ± neutering	BUT 0.4 mg/kg SC prior to GA, MEL 0.3 mg/kg SC prior to GA	VAS Composite pain score Gait lameness score	In comparison with BUT, MEL group showed a lower VAS pain score, composite pain score and gait lameness score from 1–24 h following surgery. Rescue analgesia was required more often in BUT than MEL group	92
Clinical: OHE	CAR 4 mg/kg SC at induction, BUT 0.4 mg/kg SC at the end of surgery, SAL SC	Composite pain scale until 24 h postoperatively	There were no differences between CAR and BUT in pain scores at any time points. Pain scores were increased from baseline in BUT and CAR groups for 12 h postsurgery	93
Experimental	HYDRO 0.1 mg/kg IM, BUT 0.4 mg/kg IM, SAL IM	TNT	TNT values were higher compared with SAL in BUT group from 15–165 mins, and in HYDRO group from 15–345 mins	94
Experimental	BUT 0.1 mg/kg IV	TNT	Mean TNT values increased from baseline from 15–450 mins after BUT administration. Nausea was reported in 4/6 cats	95

(Continued)

Table 4 (Continued)

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	BUT 0.2 mg/kg IM	TNT	Significant increase in TNT values only 5 mins after BUT administration. Hyperalgesia was present 2 h after BUT administration. Euphoria was recorded for less than 30 mins after drug administration. Mild sedation reported	34
Clinical: onychectomy	TFP 25 µg/h, BUT 0.2 mg/kg administered at the time of sedation, at extubation, and every 4 h thereafter for 12 h.	Plasma cortisol concentrations Subjective pain scores	Lower pain scores in the TFP group than BUT group only at 8 h after surgery. Plasma cortisol concentrations not different between groups	30
Clinical: OHE	BUT 0.1 mg/kg IM, MEDET 15 µg/kg IM, SAL IM	Subjective sedation and pain score	BUT provided better analgesia than MEDET and SAL during the 120 mins test period	96
Experimental	BUT 0.08 mg/kg IV, B 0.8 mg/kg IV	MAC determination by tail clamp technique	Maximal MAC reductions were 19 ± 3% and 18 ± 4% with the lowest and highest doses of B, respectively, and were considered clinically relevant	16
Clinical: onychectomy, onychectomy + OHE, onychectomy + castration	TFP 25 µg/h, BUT 0.5 mg/kg IM and repeated at extubation at 0.2 mg/kg IM	Subjective pain score Lameness assessed with pressure-sensitive mat	Pain scores for TFP group were significantly lower than scores for BUT group at all time points from 30 mins after extubation to the end of the study. Lameness score was significantly lower for TFP group than BUT group the day after surgery and 2 days after surgery. Mean ratios of digital pad-to-metacarpal pad force were not significantly different between groups at any time point	97

*See footnote to Table 1
ACE = acepromazine; B = buprenorphine; BUPI = bupivacaine; BUT = butorphanol; CAR = carprofen; Cl = apparent clearance; C_{max} = maximum plasma concentration; DEXM = dexmedetomidine; DIVAS = dynamic interactive visual analogue scale; F = relative bioavailability; GA = general anaesthesia; HYDRO = hydromorphone; KETA = ketamine; IVAS = interactive visual analogue scale; MAC = minimum alveolar concentration; MEL = meloxicam; MET = methadone; MID = midazolam; MEDET = medetomidine; MNT = mechanical nociceptive threshold; NRS = numerical rating scale; OHE = ovariohysterectomy; OTM = oral transmucosal; PETH = pethidine; PK = pharmacokinetics; SAL = saline; SAP = systolic arterial pressure; SDS = simple descriptive scale; SEVO = sevoflurane; $T_{1/2\ el}$ = elimination half-life; T = tramadol; TFP = transdermal fentanyl patch; TNT = thermal nociceptive threshold; VAS = visual analogue scale; V_d = apparent volume of distribution

the limited systemic absorption in comparison with IM administration.[85]

Many experimental studies have evaluated the analgesic effects of butorphanol. Some of the results are summarised in Table 4. The effects and duration of action vary according to the dose administered, the route of administration, the type of pain studied (visceral, somatic) and the type of pain model (electrical, mechanical, thermal threshold, colonic balloon, surgery).[34,45,73,89,90,94,95,98,99] Experimental studies suggest that butorphanol provides short-lasting antinociception lasting from 5–165 mins,[34,45,89,90,94,95] with the exception of one study where thermal nociceptive threshold values were increased for up to 8 h after 0.2 mg/kg butorphanol IM.[73] Early clinical studies showed that butorphanol decreased the stress response to surgery,[100,101] and provided more analgesia than saline in cats undergoing onychectomy.[102] Subsequent studies reported that butorphanol administered to cats undergoing onychectomy or onychectomy plus neutering provided short-lasting analgesia for up to 2 h.[30,96,97]

In a multicentre study, butorphanol (0.4 mg/kg) provided poorer analgesia, and for a shorter time duration, than buprenorphine (0.01–0.02 mg/kg) after a variety of surgeries.[69] In contrast to these findings, another study, of cats undergoing ovariohysterectomy,[65] reported no differences in analgesia between cats receiving butorphanol vs buprenorphine; these results may reflect the fact that an NSAID was administered in combination with the opioid prior to surgery.[65] NSAIDs have been reported to be more efficacious analgesics in the postoperative period than butorphanol in cats undergoing ovariohysterectomy and onychectomy,[92,93] but another study showed similar pain-associated behaviour after ovariohysterectomy.[91]

Butorphanol has isoflurane and sevoflurane MAC-sparing effects;[16,18] moreover, butorphanol is a versatile agent that can be used in combination with other drugs to

provide the sedation required to perform clinical and diagnostic procedures when only mild pain is anticipated.[51,86,87] Most clinical studies report a few hours' analgesic effect for butorphanol;[93,100,101] those reporting a longer duration of action included repeat dosing.[30,97,102] Frequent re-dosing in order to provide analgesia would be impractical when pain is expected to last for a long period postoperatively.[7]

Morphine

Morphine is a full agonist at the μ, δ and ƙ opioid receptors.[103] Although morphine is not licensed for use in veterinary species, it is generally considered the 'gold standard' opioid.[104] Several of the experimental and clinical studies that have evaluated the use of morphine in cats are summarised in Table 5.

Pharmacokinetic data for morphine (0.2 mg/kg IV and IM) have been reported.[52] In comparison with other species, the production of the metabolite morphine-6-glucuronide is limited in cats. Morphine-6-glucuronide is responsible for some of morphine's analgesic effects in people,[109] and the lack of production of this metabolite in cats may be the reason why morphine (0.1 mg/kg) appears to be less effective than buprenorphine (0.01 mg/kg) in cats undergoing various surgeries or invasive diagnostic procedures.[77]

Thermal nociceptive threshold testing has been used to evaluate morphine (0.2 mg/kg IM); the thermal threshold was increased from 4–6 h after injection.[34] When the same dose was administered SC, an increase in thermal threshold was measured 45 mins and 1 h after injection and pressure thresholds were increased compared with baseline at 45–60 mins and 3–6 h after injection.[32]Adverse effects after IV injection are vomiting and histamine release.[49] Morphine's relative hydrophilicity means that its administration by the epidural or subarachnoid route provides long lasting analgesia.[49,71,103,107] Morphine can also be combined with bupivacaine and administered by the epidural route.[108] Hypotension is a side effect of epidural anaesthesia with local anaesthetic agents, while very rarely reported side effects of morphine also include urinary retention, pruritus, and chronic urinary and bowel dysfunction.[105,106,108]

Morphine can also exert a significant isoflurane MAC-sparing effect when administered at a dose of 1 mg/kg IV, but this dose is considerably higher than that usually used in clinical settings and physiological and behavioural effects were not reported.[16] Until the behavioural and physiological effects of such a high dose are established, it would be prudent to continue to use more conventional doses (0.1–0.2 mg/kg) when administering morphine by the IV route.

Hydromorphone

Hydromorphone is a semi-synthetic full μ-agonist analgesic that is widely used in the United States. It does not have a marketing authorisation for administration to animals in Europe. It has higher potency than morphine.[110] The analgesic effects of hydromorphone are similar to those of oxymorphone, but it is cheaper.[111,112]

Adverse effects in cats include hypersalivation, nausea, vomiting, respiratory depression and postanaesthetic hyperthermia.[111–113] In patients admitted to an intensive care unit for painful procedures, hydromorphone (0.05 mg/kg) appeared to provide adequate analgesia with a similar efficacy to oxymorphone.[112] IV administration of 0.1 mg/kg hydromorphone was more efficacious than a 0.025 or 0.05 mg/kg dose in a thermal antinociception model.[114] The epidural administration of 0.05 mg/kg hydromorphone caused thermal and some mechanical antinociception without hyperthermia.[115]

SC administration of hydromorphone provides a slower onset of peak effect, shorter duration of antinociception and more undesirable side effects (emesis and salivation) than IV or IM administration, so this route of administration is not recommended.[116] Hydromorphone increases skin temperature in cats; patients should be monitored closely for postanaesthetic hyperthermia.[39,113] It also has sevoflurane MAC-sparing effects.[18]

Studies evaluating hydromorphone are summarised in Table 6.

Oxymorphone

Oxymorphone is a semi-synthetic derivative of morphine, characterised by higher potency (lower dose required) and a faster onset of action than morphine.[118] Like hydromorphone, it is used in the USA but it does not have a marketing authorisation for administration to animals in Europe.

Pharmacokinetic data after IV administration of 0.1 mg/kg oxymorphone suggest a moderate volume of distribution and a short terminal half-life.[119] Oxymorphone administration does not seem to be associated with vomiting, hyperthermia or adverse behavioural changes and the clinical efficacy of oxymorphone is comparable with hydromorphone, the latter being cheaper.[111,112] When compared with buprenorphine in cats undergoing onychectomy or onychectomy and neutering, oxymorphone seemed to be a less effective analgesic; however, as commented by the authors of the study, the results might have been influenced by the methodology of measuring pain, and it would have been appropriate to include other more sensitive evaluations.[78]

Studies evaluating oxymorphone are summarised in Table 7.

Fentanyl

Fentanyl is a very potent short-acting, lipid soluble, synthetic μ agonist.[49] Studies evaluating fentanyl in cats are summarised in Table 8.

A pharmacokinetic study of IV administered fentanyl in cats reported rapid distribution and elimination.[128]

Table 5 Studies evaluating morphine in cats

Type of study	Dose and route*	Assessment	Results	Reference
Case report	MOR 0.06 mg/kg + BUPI 0.33 mg/kg in 0.13 ml/kg SAL intrathecal	Clinical	Within minutes of injection, a decrease in heart rate (from 150 to 110 bpm) and hypotension (MAP 60 mmHg) were recorded and resolved with the administration of 0.01 mg/kg glycopyrrolate and 10 ml/kg Ringer's solution	105
Case report	MOR 0.43 mg in 0.86 ml SAL EPI	Clinical	Cat showed chronic urinary retention, constipation and decreased perineal reflex	106
Experimental	MOR 0.5 mg/kg IM, HYDRO 0.05–0.1– 0.2 mg/kg IM, B 0.02 mg/kg IM, BUT 0.2 mg/kg IM	Body temperature measured with a thermistor	All treatments caused an increase in body temperature in comparison with baseline values	40
Experimental	MOR 0.1 mg/kg EPI, T 1 mg/kg EPI, SAL 0.22 ml/kg EPI	SDS VAS Tail clamp test	T group had a higher SDS and VAS score when compared with MOR at 8, 10 and 12 h postepidural. SAL group had a higher SDS and VAS score at all time points when compared with T and MOR groups. Euphoria was observed in five cats from MOR group and four from T group, and persisted up to 12 h postepidural	107
Experimental	MOR 100 µg/kg EPI, B 12.5 µg/kg EPI, SAL EPI	TNT	TNT increased from 1–16 h in MOR group and from 1–10 h in B group in comparison with SAL	71
Experimental	MOR 0.2 mg/kg SC	TNT MNT	TNT significantly increased from 45–60 mins, while MNT increased at 45–60 mins and 3–5 h after MOR administration	32
Experimental	MOR 0.2 mg/kg IM	TNT	TNT increased from 4 and 6 h, and euphoria was observed for 2–3 h after MOR administration. Mild sedation	34
Clinical	MOR EPI, MOR + BUPI EPI		Mean dose ± SEM of MOR and MOR + BUPI was 0.16 ± 0.02 mg/kg and 1.16 ± 0.14 mg/kg, respectively. Two cats had urine retention	108
Experimental	MOR 0.1 mg/kg IV, MOR 1 mg/kg IV	MAC determination by tail clamp technique	Maximal MAC reductions were 28 ± 9% and 12 ± 4% with the lowest and highest doses of MOR, respectively. MOR 1 mg/kg IV provided clinically relevant isoflurane MAC reduction	16
Clinical: various surgeries or invasive diagnostic investigations	B 0.01 mg/kg IM, MOR 0.1 mg/kg IM	VAS	B provided better postoperative analgesia than MOR at 60, 120 and 180 mins postanaesthesia. Rescue analgesia was necessary in 5/14 and 3/18 cats in MOR and B groups, respectively	77
Experimental	MOR 0.2 mg/kg IV and IM	PK	IV: mean ± SD $T_{½\,el}$ = 76.3 ± 17.6 mins Cl_p = 24.1 ± 10.3 ml/kg/min V_{dss} = 2.6 ± 1.3 l/kg IM: mean ± SD $T_{½\,el}$ = 93.6 ± 7.5 mins Cl_p = 13.9 ± 4 ml/kg/min V_{dss}= 1.7 ± 0.8 l/kg	52

*See footnote to Table 1

B = buprenorphine; bpm = beats per minute; BUPI = bupivacaine; BUT = butorphanol; Cl_p = plasma clearance; EPI = epidural; HYDRO = hydromorphone; MAC = minimum alveolar concentration; MAP = mean arterial pressure; MNT = mechanical nociceptive threshold; MOR = morphine; PK = pharmacokinetics; SAL = saline; SDS = simple descriptive scale; T = tramadol; $T_{½\,el}$ = elimination half-life; TNT = thermal nociceptive threshold; VAS = visual analogue scale; V_{dss} = volume of distribution at steady state

Table 6 Studies evaluating hydromorphone in cats

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	HYDRO 0.05 mg/kg EPI, SAL EPI	TNT MNT	In comparison with baseline, MNT and TNT values were significantly higher at 15, 120 and 180 mins in HYDRO group. In comparison with SAL, TNT and MNT values were higher in HYDRO group at 30 mins, 15 mins and from 200–300 mins. No hyperthermia detected	115
Experimental	HYDRO 0.1 mg/kg SC	TNT	Significant increase in TNT values at 15, 60 and 210 mins. Time to peak TNT values was 105 mins. 5/6 cats vomited; 2/6 showed marked dysphoria	116
Clinical: intensive care setting	OXY 0.05 mg/kg IV, HYDRO 0.05 mg/kg IV	Cumulative pain score scale	OXY and HYDRO showed similar potency and efficacy (total number of doses administered, time between first and second dosing, rescue analgesia). Four cats in the HYDRO group and one in the OXY group experienced nausea	112
Experimental	T + BUT, T + HYDRO, SAL; T 8.6 mg/kg PO, T 11.6 mg/kg PO, BUT 0.4 mg/kg IV, HYDRO 0.1 mg/kg IV	Tail clamp test	Mean ± SEM MAC for sevoflurane after SAL was 2.45 ± 0.22%. MAC decreased to 1.48 ± 0.20%, 1.20 ± 0.16%, 1.76 ± 0.15%, 1.48 ± 0.20% and 1.85 ± 0.20% with T, BUT, HYDRO, T + BUT and T + HYDRO, respectively. Naloxone reversed the reductions in MACs	18
Experimental	HYDRO 0.025 mg/kg IV, HYDRO 0.05 mg/kg IV, HYDRO 0.1 mg/kg IV	TNT	Dose-related antinociceptive effects of HYDRO. HYDRO 0.05 mg/kg IV increased TNT values from 5–80 mins and from 35–80 mins in comparison with baseline values and lower dose, respectively. HYDRO 0.1 mg/kg IV increased TNT values from 5–200 mins in comparison with baseline values and lower doses. A 1–2°C increase in skin temperature was reported	114
Clinical: OHE, castration, onychectomy	HDK, HP, MDK, MP; HDK = HYDRO 0.1 mg/kg SC + DIAZEPAM 0.1 mg/kg IV + KETA 5 mg/kg IV, HP = HYDRO 0.1 mg/kg SC + PROPOFOL 6 mg/kg IV, MDK = MEDETOMIDINE 7.5 µg/kg SC + DIAZEPAM 0.1 mg/kg IV + KETA 5 mg/kg IV, MP = MEDETOMIDINE 7.5 µg/kg SC + PROPOFOL 6 mg/kg IV	Postanaesthetic body temperature	Postanaesthetic body temperatures higher than basal temperatures were reported for 86%, 80%, 25% and 34% of observations in groups HDK, HP, MDK and MP, respectively	39

(Continued)

Table 6 (Continued)

Type of study	Dose and route*	Assessment	Results	Reference
Retrospective	HYDRO 0.05–0.2 mg/kg IM or SC, B 0.01–0.02 mg/kg IM, SC or OTM	Postanaesthetic body temperature Hyperthermia = >40°C	There is an association between HYDRO administration and postanaesthetic hyperthermia	113
Experimental	HYDRO 0.1 mg/kg IV	PK TNT	Median ± SEM $T_{1/2\beta}$ = 98.9 ± 10.87 mins V_c = 1272 ± 132.24 ml/kg V_{dss} = 2957 ± 293.4 ml/kg Cl = 24.6 ± 2.35 ml/min/kg. TNT increased from baseline from 15–450 mins	117
Experimental	HYDRO 0.1 mg/kg IM	TNT	TNT increased from baseline from 15–345 mins. A statistically significant increase in skin temperature was reported	90

*See footnote to Table 1
B = buprenorphine; BUT = butorphanol; Cl = clearance; EPI = epidural; HYDRO = hydromorphone; KETA = ketamine; MAC = minimum alveolar concentration; MNT = mechanical nociceptive threshold; OHE = ovariohysterectomy; OTM = oral transmucosal; OXY = oxymorphone; PK = pharmacokinetics; SAL = saline; T = tramadol; TNT = thermal nociceptive threshold; $T_{1/2\beta}$ = terminal half-life; V_c = apparent volume of distribution of the central compartment; V_{dss} = apparent volume of distribution at steady state

Table 7 Studies evaluating oxymorphone in cats

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	OXY 0.1 mg/kg IV	PK	Median ± SEM values for V_c and V_{ss} were 1.1 ± 0.2 and 2.5 ± 0.4 l/kg, respectively. Harmonic mean ± jackknife pseudo-SD values for Cl and $T_{1/2\beta}$ were 26 ± 7 ml/kg/min and 96 ± 49 min, respectively	119
Clinical: intensive care setting	OXY 0.05 mg/kg IV, HYDRO 0.05 mg/kg IV	Cumulative pain score scale	OXY and HYDRO showed similar potency and efficacy (total number of doses administered, time between first and second dosing, rescue analgesia). Four cats in the HYDRO group and one in the OXY group experienced nausea	112
Clinical: onychectomy ± neutering	B 0.01 mg/kg IM, OXY 0.05 mg/kg IM, KETO 2 mg/kg IM	Cumulative pain scores VAS	B cumulative pain scores were lower than OXY and KETO at 12 h post-extubation and lower than OXY at 4 h	78

*See footnote to Table 1
B = buprenorphine; Cl = clearance; HYDRO = hydromorphone; OXY = oxymorphone; PK = pharmacokinetics; KETO = ketoprofen; $T_{1/2\beta}$ = terminal half-life; VAS = visual analogue scale; V_c = apparent volume of distribution of the central compartment; V_{ss} = apparent volume of distribution at steady state

A more recent study showed that, following a single dose of fentanyl (10 µg/kg IV), the onset of action was rapid and thermal antinociception could be detected from 5–110 mins; antinociception was detected at plasma values higher than 1.07 ng/ml.[122] In conscious cats, the pharmacokinetics and pharmacodynamics of a 5 µg/kg/h fentanyl infusion, following a 5 µg/kg loading dose, and its effect on mechanical and thermal threshold have recently been studied.[120] Side effects consisted of mild sedation and salivation following the loading dose in 1/7 cats; antinociception could be detected at fentanyl plasma concentrations higher than 1.3 ng/ml. In an experimental setting an infusion of fentanyl at 6 µg/kg/h combined with a continuous rate infusion of propofol resulted in satisfactory anaesthesia in cats.[41] One clinical study in injured cats undergoing anaesthesia

Table 8 Studies evaluating fentanyl in cats

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	FEN LD 5 µg/kg IV, FEN 5 µg/kg/h IV for 2 h, SAL IV	TNT MNT	SAL administration did not significantly change MNT or TNT over time. In FEN group, TNT was higher than baseline from 0.25–0.75 h; MNT was higher than baseline from 0.25–1 h. Plasma FEN concentrations <1.33 ± 0.30 ng/ml were not associated with antinociception. Mild sedation recorded	120
Clinical: orthopaedic surgery in traumatised cats	FEN + ISO (end-tidal 1%), FEN + PPF; FEN 0.02 mg/kg/h IV, PPF 12 mg/kg/h IV	Monitoring of physiological parameters	Mean end-expiratory isoflurane concentration was 1.19 ± 0.19%, while PPF infusion rate was 11.4 ± 0.8 mg/kg/h. Heart rate was not different between groups. Arterial blood pressure was better maintained in FEN + PPF; MAP was significantly lower in FEN + ISO in comparison with FEN + PPF group during skin incision, during surgery without intense surgical stimulation and during surgery with intense surgical stimulation. 1/11 cats and 9/11 cats required IPPV in FEN + ISO and FEN + PPF groups, respectively. Oxygen saturation was not different between groups	121
Experimental	FEN 10 µg/kg IV, SAL IV	PK TNT	Median maximum plasma concentration was 6.6 ng/ml at 2 mins after FEN administration. Plasma FEN concentration was <0.2 ng/ml at 95 mins after administration. TNT increased above baseline from 5–110 mins; TNT was different from SAL from 5–110 mins and at 125 and 155 mins. Mild euphoria recorded	122
Clinical: unilateral onychectomy	TFP 25 µg/h, BUT IM, BUPI topical	Gait analysis	Limb function was better in TFP and BUT groups than BUPI group. Limb function still reduced 12 days after surgery	123
Experimental	TFP 25 µg/h, TFP 50 µg/h	MAC evaluation (tail clamp method and standard technique)	ISO MAC was reduced by 17.8 ± 7.4% and 18.1 ± 10.3 % in TFP 25 µg/h and TFP 50 µg/h groups, respectively. MAC reductions between groups were not statistically significant	19
Clinical: OHE	Full or partial (half) exposure to TFP 25 µg/h	Plasma FEN concentration Subjective pain scores	Steady-state plasma FEN concentrations significantly lower in half than in full TFP exposure groups (1.14 ± 0.86 vs 1.78 ± 0.92 ng/ml; mean ± SD). Pain scores were not different between groups	124
Experimental	PPF + SAL, PPF + FEN, PPF + SUF, PPF + ALF; PPF 7 mg/kg + 0.2 mg/kg/min IV, FEN 0.1 µg/kg/min IV, SUF 0.01 µg/kg/min IV, ALF 0.5 µg/kg/min IV	Interdigital skin clamp to detect MIR	In comparison with baseline values, PPF + FEN group showed a decrease in heart rate from 30–90 mins of infusion; the decrease in heart rate was significantly greater 30 mins after anaesthetic induction in the PPF + ALF group than in other groups. In the PPF + FEN group, systolic blood pressure was significantly lower than baseline values from 15–90 mins of infusion, while mean blood pressure and diastolic blood pressure were not different from baseline. Respiratory rate decreased and $ETCO_2$ increased from baseline from 15–90 mins of infusion	41

(Continued)

Table 8 (Continued)

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	TFP + 4 h GA + hypothermia TFP + 4 h GA, TFP 25 µg/h	FEN serum concentrations and temperature monitoring	In the hypothermia group, FEN serum concentrations were significantly lower than baseline from 1–4 h of GA. Independently from body temperature, serum FEN concentrations returned to baseline values within 1 h of the end of GA	125
Experimental, preclinical: OHE	TFP, TFP + GA, TFP + GA + OHE; TFP 25 µg/h	PK	Mean plasma FEN concentrations at different time points and other PK parameters were not different between groups. Halothane anaesthesia and GA + OHE did not significantly alter plasma FEN concentrations. High individual variability reported in parameters measured within and between groups	126
Clinical: onychectomy	TFP 25 µg/h, BUT 0.2 mg/kg administered at the time of sedation, at extubation, and every 4 h thereafter for 12 h	Plasma cortisol concentrations Subjective pain scores	Lower pain scores in the TFP group than BUT group only at 8 h after surgery. Plasma cortisol concentrations not different between groups	30
Preclinical: OHE	TFP 25 µg/h, No TFP	SDS for pain Cortisol and glucose plasma concentrations	In TFP cats cortisol concentration was lower than in No TFP cats during surgical procedure (3.3 vs 4.7 µg/dl) and early postsurgical period (14–25 h post-TFP application) (3.7 vs 5.5 µg/dl). Glucose concentration was lower in TFP cats than in No TFP cats during surgical and early postsurgical period (75 vs 93 mg/dl). Pain scores not significantly different between groups	127
Clinical: onychectomy, onychectomy + OHE, onychectomy + castration	TFP 25 µg/h, BUT 0.5 mg/kg IM, and repeated at extubation at 0.2 mg/kg	Subjective pain score Lameness assessed with pressure-sensitive mat	Pain scores for TFP group cats were significantly lower than for BUT group cats at all evaluation times from 30 mins post-extubation to the end of the study. Lameness score was significantly lower in TFP than BUT group cats the day after surgery and 2 days after surgery. Mean ratios of digital pad-to-metacarpal pad force were not significantly different between groups at any time point	97
Experimental	FEN 7.19 ± 1.17 µg /kg IV, FEN 25 µg/h TD	PK	IV group: mean ± SEM $T_{½\ el}$ = 2.35 ± 0.57 h Cl_p = 1.19 ± 0.16 l/kg/h $V_{d\beta}$ = 3.43 ± 0.58 l/kg TD group: mean ± SEM R_{ab} = 8.48 ± 1.7 µg/h C_{ss} = 1.88 ± 0.14 ng/ml	128
Experimental	FEN 4 µg/kg EPI + MED 10 µg/kg EPI	Electrical cutaneous stimulation	Compared with baseline values, MED and FEN increased electrical threshold values in the hindlimb from 20–245 mins and at 20 mins, respectively. Compared with baseline values, MED increased electrical threshold values in the forelimb from 15–120 mins, while FEN did not have any effect	129

(Continued)

Table 8 (Continued)

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	FEN 4 µg/kg EPI, MED 10 µg/kg EPI, SAL EPI	Monitoring of physiological parameters	In the MED group, MAP was significantly increased from 5–20 mins and decreased from 30–120 mins post-injection. In the FEN group, MAP was decreased from 5–120 mins post-injection compared with baseline. In the MED and FEN groups, heart rate and respiratory rate were lower from 5–120 mins compared with baseline	130

*See footnote to Table 1
ALF = alfentanil; BUPI = bupivacaine; BUT = butorphanol; C_{ss} = concentration at steady state; Cl_p = plasma clearance; EPI = epidural; FEN = fentanyl; GA = general anaesthesia; IPPV = intermittent positive pressure ventilation; ISO = isoflurane; LD = loading dose; MAC = minimum alveolar concentration; MAP = mean arterial pressure; MED = medetomidine; MIR = minimum infusion rate; MNT = mechanical nociceptive threshold; OHE = ovariohysterectomy; PK = pharmacokinetics; PPF = propofol; R_{ab} = rate of absorption; SAL = saline; SDS = simple descriptive scale; SUF = sufentanil; $T_{½\ el}$ = elimination half-life; TD = transdermal; TFP = transdermal fentanyl patch; TNT = thermal nociceptive threshold; $V_{d\beta}$ = apparent volume of distribution

reported that a fentanyl infusion (20 µg/kg/h) combined with a propofol infusion (12 mg/kg/h) maintained the haemodynamic variables better than fentanyl and isoflurane anaesthesia, although respiratory depression was more marked and intermittent positive pressure ventilation was required.[121]

The analgesic and cardiovascular effects of epidural fentanyl (4 µg/kg) have been evaluated in isoflurane-anaesthetised cats. Electrical threshold was increased 20 mins post-injection and no side effects were reported in one study.[129] In a separate study by the same investigators cardiopulmonary effects included a decrease in mean arterial pressure, heart rate and respiratory rate from 5–120 mins post-injection, and an increase in arterial partial pressure of carbon dioxide from 15–120 mins post-injection.[130]

The need for a 'hands off' approach to longer-term analgesia in cats led to an interest in transdermally administered fentanyl and many studies have been carried out over the past 15 years.[19,30,97,123–128] In a pharmacokinetic study, steady state plasma concentrations were reached 12–24 h after the application of a fentanyl patch (25 µg/kg). Sustained plasma fentanyl concentrations were detected throughout a 5 day period, with a mean concentration at steady state of 1.58 ng/ml. The mean calculated delivery rate of fentanyl was 8.48 µg/h, with high variability among cats.[128] A few clinical studies have suggested that fentanyl patches can be considered effective analgesics in cats undergoing onychectomy or ovariohysterectomy;[30,97,123,127] however, if a fentanyl patch is chosen to provide perioperative analgesia, the patch has to be applied 12–24 h before the surgical procedure.[7,19,124,128]

It is important to note that the presence of a fentanyl patch does not negate the need for pain assessment. In fact, this becomes imperative since there is considerable variability in the absorption of fentanyl, and thus analgesic efficacy. Also, a cat with a painful condition will require administration of additional analgesics, particularly in the time before the fentanyl patch becomes effective. The primary advantages of administering fentanyl by the transdermal route are the avoidance of repeated injections and a decrease (approximately 18%) in the MAC of isoflurane, which may promote more stable haemodynamics during anaesthesia.[19,30] Moreover this method of fentanyl delivery can be used in cats weighing less than 4 kg by decreasing the amount of patch-exposed surface area.[124]

However, there are also some disadvantages associated with the use of fentanyl patches. As mentioned, there is great individual variability in drug absorption by this method.[19,128] Although anaesthesia and/or surgery do not appear to alter plasma fentanyl concentrations, hypothermia during anaesthesia can cause a reduction in serum fentanyl concentration.[125,126] Skin permeability, altered skin perfusion and hypovolaemia are other factors that may affect plasma levels of fentanyl.[7] For all of these reasons, cats with transdermal fentanyl patches should be carefully monitored (mental status, behaviour, physiological variables) to assess efficacy and any potential adverse effects.[126,128]

There are also important safety considerations associated with the use of fentanyl patches, particularly if cats are discharged into their owners' care after application of the patch. Fentanyl is an addictive drug that can be abused by people, and the risk of ingestion by the treated animal, other animals or humans has to be considered. There are reports of fatalities caused by ingestion of fentanyl patches by children and drug addicts, among others, as well as by monkeys.[131–133] There may also be legal implications associated with dispensing fentanyl

patches; in the UK, fentanyl is a Schedule 2 controlled drug.

MAC reduction reported 24 h after placement of a 25 µg/h fentanyl patch (corresponding to a possible delivery dose of 5.8 µg/kg/h) and antinociception after fentanyl infusion of 5 µg/kg/h were achieved with different fentanyl plasma levels, of 0.54 ± 0.41 and >1.3 ng/ml, respectively.[19,120]

Fentanyl analogues

Alfentanil, remifentanil and sufentanil are potent µ agonists of the anilidopiperidine family and are characterised by a more rapid onset of action and shorter context-sensitive half-life after prolonged infusion in comparison with the structural analogue fentanyl.[134] They are used mainly in the intraoperative period.[49] These are Schedule 2 controlled drugs in the UK and do not have marketing authorisations for administration to animals. In the UK they can only be prescribed under the 'cascade' when their use can be justified in an individual animal and with informed owner consent. Further information on the use of the cascade and unlicensed drugs in the UK can be found on the Veterinary Medicines Directorate website (www.gov.uk/government/organisations/veterinary-medicines-directorate).

Alfentanil

Studies evaluating alfentanil in cats are summarised in Table 9. Alfentanil administered IV to conscious cats at a dose of 50 µg/kg produced analgesic effects for approximately 21 mins, as assessed by applying a clamp to the base of the tail, and the alfentanil was rapidly metabolised.[137] Recently the disposition of alfentanil in isoflurane-anaesthetised cats was studied.[135] The results were broadly similar to those published by Pascoe et al,[137] but the volume of the central compartment and volume of distribution at steady state were greater.[135] The same research group showed that plasma levels of alfentanil of 500 ng/ml had MAC-sparing effects on isoflurane, which, compared with isoflurane alone, increased heart rate, mean arterial pressure, stroke index, cardiac index, haemoglobin and oxygen delivery index, and blunted haemodynamic responses to a noxious stimulant.[28] Another study showed that a plasma alfentanil concentration of 500 ng/ml produced a maximal isoflurane MAC reduction of 35%; mild metabolic acidosis and decreased arterial partial pressure of oxygen were reported as adverse effects.[20]

A clinical study evaluated total IV anaesthesia with propofol (0.2 mg/kg/min) alone or in combination with fentanyl (0.1 µg/kg/min), alfentanil (0.5 µg/kg/min) or sufentanil (0.01 µg/kg/min) infusions. In cats treated with alfentanil, diastolic blood pressure and mean blood pressure were significantly decreased compared with baseline from 30–90 and from 15–90 mins after induction, respectively.[41] More recently, a clinical study evaluated the combination of alfentanyl and propofol in cats undergoing ovariohysterectomy: propofol was infused at 0.3 mg/kg/h while the overall infusion rate of alfentanil was 0.97 ± 0.22 µg/kg/min.[136] In this study intermittent assisted ventilation was provided during anaesthesia in order to maintain normocapnia.

Remifentanil

Remifentanil is metabolised by non-specific plasma and tissue esterases.[138] In people and dogs it is characterised by a short context-sensitive half-time (time required for the plasma concentration to decrease by 50% after termination of an infusion) that does not depend on the duration of the infusion; thus there are no cumulative effects after prolonged infusions.[139,140] Moreover, the extrahepatic metabolism of remifentanil is potentially advantageous in cats that lack some hepatic metabolic pathways,[52,141] and especially in cats with liver and kidney disease.

Studies evaluating remifentanil in cats are summarised in Table 10. Pharmacokinetics data have been published. In conscious and isoflurane-anaesthetised cats an IV infusion of remifentanil at 1 µg/kg/min over 5 mins resulted in a rapid distribution to peripheral compartments, and a high clearance and a relatively short terminal half-life (17.4 and 15.7 mins in awake and anaesthetised cats, respectively).[142] Anaesthesia decreased the volume of the central compartment.[142] However, another study in cats showed that the MAC of isoflurane decreased significantly after a 30 min remifentanil infusion;[21] according to the authors this might have been caused by a 'cumulative effect of repeated infusions of remifentanil or by a modified response to the repeated electrical stimulation' (electrical stimulation was the method used to determine MAC), or by the use of 'high doses which might have facilitated the cumulative effects'.[21] In the same study, three remifentanil constant rate infusions (CRIs) were examined, 0.25, 0.5 and 1 µg/kg/min, and the MAC reduction from baseline ranged from 23–30% with no statistical difference between groups. This may mean that there is a ceiling to the isoflurane-sparing effect. The study also reported that the remifentanil CRI was associated with an increase in heart rate of 26% and an increase in systolic arterial pressure of 23%.[21]

IV infusion of remifentanil was shown to result in a dose-dependent increase in thermal threshold in conscious cats.[15] Behaviours suggestive of euphoria were apparent in conscious cats when infusion rates were equal to or higher than 1 µg/kg/min. In the same study a relationship between the immobilising potency of remifentanil, assessed as a MAC-sparing effect, and analgesic potency was not detected; nor was hyperalgesia detected on termination of the infusion.[15] Another study evaluated remifentanil infusions in association with propofol anaesthesia (0.3 mg/kg/

Table 9 Studies evaluating alfentanil in cats

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	ALF 100 µg/kg	PK	Volume of the central compartment was 0.10 ± 0.01 (0.07–0.14) l/kg (mean ± SEM [range]); volume of distribution at steady state was 0.89 ± 0.16 (0.68–1.83) l/kg (mean ± SEM [range]); clearance was 11.6 ± 2.6 (9.2–15.8) ml/min/kg (harmonic mean ± pseudo-SD [range]); and terminal half-life was 144 (118–501) mins (median [range])	135
Clinical: OHE	PPF + ALF 10 µg/kg, 0.8 µg/kg/min IV, PPF + REMI 2.5 µg/kg, 0.2 µg/kg/min IV; PPF 0.3 mg/kg/h IV	Monitoring of cardiovascular parameters	In both groups, RT, RR, $ETCO_2$ and SpO_2 values were not significantly different when compared with baseline, with the exception that RT was lower at skin closure compared with baseline. In the ALF group, but not in the REMI group, HR was higher at some time points during the surgical procedure when compared with baseline. During ligation of the ovary, SAP was higher in the ALF group; from ligation of the ovary to skin closure, SAP was higher in both groups when compared with baseline. There were no significant differences between groups for RR, $ETCO_2$, HR and SpO_2. From coeliotomy until ligation of the ovaries, SAP was lower in ALF compared with the REMI group. Overall, the infusion rates of REMI and ALF were 0.24 ± 0.05 mg/kg/min and 0.97 ± 0.22 mg/kg/min, respectively	136
Experimental	PPF + SAL, PPF + SUF, PPF + FEN, PPF + ALF; PPF 7 mg/kg + 0.2 mg/kg/min IV, SUF 0.01 µg/kg/min IV, FEN 0.1 µg/kg/min IV, ALF 0.5 µg/kg/min IV	Interdigital skin clamp to detect MIR	In comparison with baseline values, the ALF group showed a decrease in HR from 30–90 mins of infusion; the decrease in HR was significantly greater 30 mins after anaesthetic induction in the ALF group than in other groups. In the ALF group diastolic blood pressure and mean blood pressure were significantly lower than baseline values from 30–90 and from 15–90 mins after induction, respectively. RR decreased from baseline from 30–90 mins of infusion; $ETCO_2$ increased from 15–90 mins of infusion	41
Experimental	ALF administered IV in order to achieve estimated plasma concentration of 500 ng/ml	MAC determination	ALF reduced isoflurane MAC and caused a significant increase in body temperature, heart rate, mean arterial pressure, mean pulmonary arterial pressure, stroke index, cardiac index, haemoglobin, oxygen delivery index, dopamine, epinephrine, norepinephrine and cortisol values, and a significant decrease in arterial and venous pH	28
Experimental	ALF administered IV in order to achieve plasma concentrations of 50, 100, 250, 500, 750 and 1000 ng/ml		Isoflurane MAC reduction was estimated to be maximal (35.0 ± 6.6%) at a plasma ALF concentration of 500 ng/ml	20
Experimental	ALF 50 µg/kg IV	Tail clamp test	Harmonic mean for the half-life of the rapid distribution was 4.12 mins; slow distribution was 18.8 mins; and elimination phase was 119.2 mins. Analgesia lasted for 21.7 ± 14 mins. ALF caused a transient increase in blood pressure, and respiratory and metabolic acidosis	137

*See footnote to Table 1

ALF = alfentanil; $ETCO_2$ = end-tidal carbon dioxide; FEN = fentanyl; HR = heart rate; MAC = minimum alveolar concentration; MIR = minimum infusion rate; OHE = ovariohysterectomy; PK = pharmacokinetics; PPF = propofol; REMI = remifentanil; RR = respiratory rate; RT = rectal temperature; SAP = systolic arterial pressure; SAL = saline; SpO_2 = oxygen saturation of haemoglobin; SUF = sufentanil

Table 10 Studies evaluating remifentanil in cats

Type of study	Dose and route*	Assessment	Results	Reference
Clinical: OHE	PPF + REMI LD 2.5 µg/kg + 0.2 µg/kg/min IV, PPF + ALF LD 10 µg/kg + 0.8 µg/kg/min IV; PPF 0.3 mg/kg/h IV	Monitoring of cardiovascular parameters	In both groups, RT, RR, $ETCO_2$ and SpO_2 values were not significantly different when compared with baseline, with the exception that RT was lower at skin closure compared with baseline. During ligation of the ovary, SAP was higher in the ALF group; from ligation of the ovary to skin closure, SAP was higher in both groups when compared with baseline. There were no significant differences between groups for RR, $ETCO_2$, HR and SpO_2. From coeliotomy until ligation of the ovaries, SAP was lower in the ALF group compared with the REMI group. Overall, the infusion rates of REMI and ALF were 0.24 ± 0.05 mg/kg/min and 0.97 ± 0.22 mg/kg/min, respectively. Mean (range) extubation time was 9.5 (6–10) and 12 (8–27) mins for REMI and ALF groups, respectively, and this was statistically significant	136
Experimental	REMI 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 µg/kg/min IV	Isoflurane MAC determination by tail clamp technique TNT in awake cats	REMI infusions did not significantly change isoflurane MAC. Mean ± SEM median effective concentration for REMI and its active metabolite, GR90291, for TNT test was 1 ± 0.35 ng/ml and 307 ± 28 ng/ml of blood, respectively. There was no relationship between REMI immobilising potency (MAC determination) and its analgesic potency (TNT). Euphoria was detected in awake cats during REMI infusions at 8 and 16 µg/kg/min	15
Experimental	REMI 0.25 µg/kg/min IV, REMI 0.5 µg/kg/min IV, REMI 1 µg/kg/min IV	Isoflurane MAC determination by electrical stimulation	Compared with MAC_{BASAL}, $MAC_{REMI\ 0.25}$, $MAC_{REMI\ 0.5}$ and $MAC_{REMI\ 1}$ were significantly decreased by 23.4 ± 7.9%, 29.8 ± 8.3% and 26 ± 9.4%, respectively. MAC did not significantly differ between groups. Heart rate and SBP increased by 26% and 23%, respectively, during REMI infusion	21
Experimental	REMI 1 µg/kg/min IV, REMI 1 µg/kg/min IV + ISO 1.63%	PK in conscious and anaesthetised cats	Median (range) $T_{1/2\beta}$ = 17.4 (5.6–920.3) and 15.7 (3.8–410.3) mins; V_c = 1.596 (1.164–2.111) and 567 (278–641) ml/kg; V_{ss} = 7.632 (2.284–76.039) and 1.651 (446–29,229) ml/kg; Cl = 766 (408–1473) and 371 (197–472) ml/min/kg in conscious and anaesthetised cats, respectively. Large variability in disposition of REMI was observed between cats	142
Experimental, Preclinical: OHE	REMI 0.2 + PPF, REMI 0.3 + PPF, REMI + PPF + OHE; REMI 0.2 µg/kg/min, REMI 0.3 µg/kg/min, PPF 0.3 mg/kg/min	Electrical stimulation Surgery	No significant differences in arterial blood pressure between the two infusions in PPF-anaesthetised cats. REMI 0.3 group did not respond to noxious stimulation from 30–90 mins of infusion. During OHE the highest REMI dosage (mean ± SEM) that prevented cardiovascular response was 0.23 ± 0.01 µg/kg/min. Recovery time from REMI + PPF anaesthesia ranged from 115–140 mins	143

*See footnote to Table 1

ALF = alfentanil; Cl = clearance; $ETCO_2$ = end-tidal carbon dioxide; HR = heart rate; ISO = isoflurane; LD = loading dose; $MAC_{REMI\ 0.25}$ = isoflurane minimum alveolar concentration determined during infusion of 0.25 µg remifentanil/kg/min; MAC = minimum alveolar concentration; MAC_{BASAL} = basal isoflurane minimum alveolar concentration; $MAC_{REMI\ 0.5}$ = isoflurane minimum alveolar concentration determined during infusion of 0.5 µg remifentanil/kg/min; $MAC_{REMI\ 1}$ = isoflurane minimum alveolar concentration determined during infusion of 1 µg remifentanil/kg/min; mmHg = millimetres of mercury; OHE = ovariohysterectomy; PK = pharmacokinetics; PPF = propofol; REMI = remifentanil; RR = respiratory rate; RT = rectal temperature; SAP = systolic arterial pressure; SBP = systolic blood pressure; SpO_2 = oxygen saturation of haemoglobin; TNT = thermal nociceptive threshold; $T_{1/2\beta}$ = terminal half-life; V_c = apparent volume of distribution of the central compartment; V_{ss} = apparent volume of distribution at steady state

Table 11 Studies evaluating sufentanil in cats

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	SUF 1 µg/kg	PK	Volume of the central compartment was 0.06 ± 0.01 (0.04–0.10) l/kg (mean ± SEM [range]); volume of distribution at steady state was 0.77 ± 0.07 (0.63–0.99) l/kg (mean ± SEM [range]); clearance was 17.6 ± 4.3 (13.9–24.3) ml/min/kg (harmonic mean ± pseudo-SD [range]); and terminal half-life was 54 (46–76) mins (median [range])	135
Experimental	PPF + SAL, PPF + SUF, PPF + FEN, PPF + ALF; PPF 7 mg/kg + 0.2 mg/kg/min IV, SUF 0.01 µg/kg/min IV, FEN 0.1 µg/kg/min IV, ALF 0.5 µg/kg/min IV	Interdigital skin clamp to detect MIR	In comparison with baseline values, SUF + PPF group showed a decrease in HR from 30–90 mins of infusion; RR decreased from baseline from 15–90 mins of infusion; $ETCO_2$ increased (from 34–56 mmHg) from 15–90 mins of infusion. From 70–90 mins, mean infusion rate of PPF was significantly lower when cats were treated with SUF than when they were treated with FEN	41

*See footnote to Table 1
ALF = alfentanil; $ETCO_2$ = end-tidal carbon dioxide; FEN = fentanyl; HR = heart rate; MIR = minimum infusion rate; PK = pharmacokinetics; PPF = propofol; RR = respiratory rate; SAL = saline; SUF = sufentanil

min).[143] Remifentanil infusion rates ranging from 0.2–0.27 µg/kg/min were necessary in cats undergoing ovariohysterectomy to prevent cardiovascular responses, while a remifentanil CRI of 0.3 µg/kg/min was necessary to prevent motor responses to electrical stimulation. Bradycardia (lowest heart rate recorded = 68 beat per minutes) and hypotension (lowest mean arterial pressure = 49 mmHg) were noted in some cats.[143] Similarly, in an investigation involving propofol-anaesthetised cats (0.3 mg/kg/min) undergoing ovariohysterectomy, the time to extubation of the trachea was faster in cats that received a remifentanil infusion at 0.24 ± 0.05 µg/kg/min than in those that received an alfentanil infusion at 0.97 ± 0.22 µg/kg/min.[136]

It must be emphasised that in the aforementioned clinical studies intermittent positive pressure ventilation was required as remifentanil produces a significant degree of respiratory depression.[140]

Sufentanil

Sufentanil has a more rapid onset and shorter duration of action than fentanyl in people.[144] Sufentanil administration can elicit centrally mediated sympathetic stimulation, resulting in effects such as an increase in blood pressure and heart rate.[27]

Studies evaluating the use of sufentanil in cats are summarised in Table 11. To the authors' knowledge, there are currently no published studies evaluating the analgesic or antihyperalgesic effects of sufentanil in cats. Very recently an experimental study evaluated the pharmacokinetics of sufentanil in isoflurane-anaesthetised cats and demonstrated that the drug has a rapid disposition due to a small volume of distribution and moderate clearance.[135] An experimental study evaluated the cardiorespiratory effects of propofol (induction dose of 7 mg/kg, followed by an infusion at 0.2 mg/kg/min IV) alone or in combination with sufentanil (loading dose of 0.1 µg/kg, followed by an infusion at 0.01 µg/kg/min IV).[41] The cats breathed spontaneously during the 90 min study period, although an increase in expired carbon dioxide level, up to 69 mmHg, was noted, as well as a decrease in respiratory rate and heart rate in comparison with baseline values. Mean blood pressure and oxygen saturation did not change from baseline.[41]

Tramadol

Tramadol is a centrally acting analgesic, consisting of two enantiomers, which exerts its analgesic effect by binding to the opioid receptors (mainly µ) and by interfering with the neuronal release and reuptake of serotonin and noradrenaline in the descending inhibitory pathways.[145] The (+) enantiomer and its metabolite O-desmethyltramadol (M1) bind the opioid receptors and appear to contribute significantly to the analgesic effect of tramadol. The opioid effect of tramadol is believed to be related, at least in part, to its metabolite O-desmethyltramadol. In cats O-desmethyltramadol rapidly appears in plasma following tramadol administration and has a moderate half-life.[146]

Tramadol does not have a marketing authorisation for use in cats, but is licensed for use in dogs in some European countries. There is a great deal of interest in using tramadol for analgesia in companion animals. It is available in tablet form, facilitating administration by

owners at home, and could be an alternative to NSAIDs in cats in which these drugs are poorly tolerated and/or contraindicated, or used in addition to NSAIDs in animals with more severe pain.

Tramadol has recently been classified as a Schedule 3 controlled drug in the UK, but exempted from the safe custody requirements, and is a Schedule IV drug under the Federal Controlled Substances Act in the United States. The potential for human abuse should be carefully considered, as well as the potential for toxicity in cats. Recently, symptoms related to serotonin syndrome secondary to tramadol overdose (80 mg/kg administered PO twice) have been reported for the first time in a cat.[147] The serotonin syndrome is induced by pharmacological treatment with serotonergic agents that increase serotonin activity, including selective serotonin reuptake inhibitors, tricyclic antidepressants (amitriptyline), monoamine oxidase inhibitors, lithium, carbamazepine, amphetamine and derivatives, dextromethorphan, tramadol and meperidine; and also by St John's wort (*Hypericum perforatum*). In people symptoms include cognitive behavioural changes, neuromuscular excitability and autonomic instability.[148]

Studies evaluating the use of tramadol in cats are summarised in Table 12. Experimental studies have investigated the antihyperalgesic and MAC-sparing effects of various doses of tramadol administered by the SC, epidural or PO route. Steagall and colleagues reported that tramadol (1 mg/kg) administered by the SC route had no effect on mechanical nociceptive thresholds and only a limited effect on thermal thresholds, which increased above the 95% confidence interval only at 45 mins, 3 and 6 h.[35] Moreover, large variability in the antinociceptive response to tramadol was detected between cats. In the same study tramadol combined with acepromazine increased the pressure threshold values from 30 mins to 3 h after administration. This finding was unexpected since no antinociceptive effects were detected when tramadol was administered alone, and acepromazine is generally considered not to be analgesic.[154] It is possible that the acepromazine enhanced the tramadol-induced analgesia.

In another study the thermal antinociceptive effects of 0.5–4 mg/kg tramadol administered PO were investigated.[150] A dose-dependent antinociceptive effect was detected and significant analgesic effects that lasted up to 6 h were reported with doses of 2 and 4 mg/kg. In the same study a pharmacokinetic simulation was performed and it was predicted that a dose of 4 mg/kg q6h would maintain adequate analgesia in cats.

Orally administered tramadol (8.6–11.6 mg/kg) produces a significant reduction in the MAC of sevoflurane from 2.45 ± 0.2% to 1.48 ± 0.2%, and so it could be used in a multimodal anaesthetic protocol.[18] Another experimental study compared the effect of 1 mg/kg tramadol or 0.1 mg/kg morphine administered by the epidural route in cats with the use of a tail clamp test.[107] Tramadol provided analgesia comparable to morphine for up to 6 h, while morphine provided superior analgesia from 6–12 h after administration. The use of preservative-containing preparations of tramadol for epidural injection should be avoided as the toxicity of the preservatives on neuronal tissue in cats has not been established. Preservative-free preparations of tramadol are available in some countries.

In a clinical study, cats undergoing elective ovariohysterectomy received tramadol (2 mg/kg SC q8h for 3 days) or vedaprofen (0.5 mg/kg PO q24h for 3 days) alone or in combination. Cats receiving the two drugs combined had lower pain scores than cats that received one or other of the drugs on its own.[151] Haemostatic, biochemical and gastrointestinal function was not affected by the perioperative use of vedaprofen and/or tramadol in cats.[152] More recently, tramadol (2 mg/kg IV) provided adequate analgesia after neutering for up to 6 h.[149] In the aforementioned studies respiratory depression was not noted; however, in an experimental study in cats, tramadol at 2 and 4 mg/kg administered IV in α-chloralose-urethane anaesthetised cats exerted a depressant effect on ventilation by reducing the sensitivity of peripheral and central chemoceptors to carbon dioxide and increasing the apnoeic threshold.[153]

Naloxone

Naloxone is a pure opioid antagonist, with no intrinsic effect, used to antagonise the effects of opioids. It antagonises the analgesic effects as well as the adverse effects such as excessive sedation, bradycardia and respiratory depression.[49,155] Naloxone has a rapid onset of action (1–2 mins) and a duration of effect of approximately 30–60 mins.[155] It should be administered slowly IV (0.002–0.04 mg/kg). Renarcotisation can occur when the duration of action of the opioid agonist is longer than the antagonist.[155] The appropriate dosage in cats has not been evaluated. The authors would suggest preparing a syringe with 0.002 mg/kg of naloxone diluted with saline and titrating administration to effect; ie, until the adverse effects of opioids have disappeared. Some clinicians have suggested that if naloxone is not available, butorphanol can be used for antagonism of respiratory depression, while maintaining a certain degree of analgesia, but there are no studies evaluating this in cats. Nevertheless, butorphanol was used to reverse the effects of fentanyl and sufentanil in rats and rabbits.[156–158] By contrast, in dogs, butorphanol was not proven to reverse oxymorphone-induced postoperative respiratory depression.[159]

The effects of a combination of buprenorphine and naloxone have recently been investigated. In people and

Table 12 Studies evaluating tramadol in cats

Type of study	Dose and route*	Assessment	Results	Reference
Clinical: neutering	T 2 mg/kg IV	Subjective pain scoring	Pain scores were low and no rescue analgesia was necessary during the 6 h study period	149
Experimental	T 0.5 mg/kg PO, T 1 mg/kg PO, T 2 mg/kg PO, T 3 mg/kg PO, T 4 mg/kg PO	TNT	Thermal threshold was significantly higher than the baseline value at 80 and 120 mins for the 0.5 mg/kg dose; at 80 and from 120–360 mins for the 2 mg/kg dose; from 40–360 mins for the 3 mg/kg dose; and from 60–360 mins for the 4 mg/kg dose	150
Clinical: OHE	T for 3 days, VEDA for 3 days, T + VEDA for 3 days; SAL for 3 days; T 2 mg/kg SC q8h, VEDA 0.5 mg/kg PO q24h	IVAS CPS VFF	Pain scores higher than pre-surgical values were seen in T + VEDA and T cats up to 4 h, in VEDA cats up to 32 h, and in SAL cats up to 32 and 56 h postoperatively by CPS and IVAS evaluation, respectively. Pain scores in SAL were higher than T 1 h postsurgery and than T + VEDA from 1–72 h postsurgery. Pain scores in VEDA were higher than T 1 h postsurgery, and higher than T + VEDA from 1–56 h postsurgery. MNT was significantly reduced 1 h postsurgery in SAL and 1, 4 and 32 h postsurgery in VEDA cats; thresholds were not reduced in T + VEDA and T cats. SAL presented a lower mechanical nociceptive threshold than T + VEDA and T up to 4 h postsurgery. VEDA presented a lower mechanical nociceptive threshold than T up to 4 h postsurgery, and than T + VEDA up to 32 h postsurgery. Rescue analgesia was administered to all SAL and VEDA cats, and 50% of T cats. No T + VEDA cats needed rescue analgesia	151
Clinical: OHE	T 2 mg/kg SC q8h, VEDA 0.5 mg/kg PO q24h		There were no differences for platelet aggregation, blood platelets and bleeding time either between the groups or over time within each group. Perioperative use of VEDA, T or their combination did not modify primary homeostasis and renal, liver or gastrointestinal function	152
Experimental	T 1 mg/kg EPI, MOR 0.1 mg/kg EPI, SAL 0.22 ml/kg EPI	SDS VAS Tail clamp test	T group had a higher SDS and VAS score when compared with the MOR group at 8, 10 and 12 h postepidural. SAL group had higher SDS and VAS score at all time points when compared with T and MOR groups. Euphoria, observed in five cats in MOR group and four in T group, persisted for up to 12 h postepidural	107
Experimental	SAL, T + BUT, T + HYDRO; T 8.6 mg/kg PO, T 11.6 mg/kg PO, BUT 0.4 mg/kg IV, HYDRO 0.1 mg/kg IV	Tail clamp	Mean ± SEM MAC for sevoflurane after SAL was 2.45 ± 0.22%; MAC decreased to 1.48 ± 0.20%, 1.20 ± 0.16%, 1.76 ± 0.15%, 1.48 ± 0.20% and 1.85 ± 0.20% with T, BUT, HYDRO, T + BUT and T + HYDRO, respectively. Naloxone reversed the reductions in MAC	18
Experimental	T 1 mg/kg SC, ACP 0.1 mg/kg SC, T + ACP SC, SAL 0.3 ml SC	TNT MNT	After T administration, thermal threshold was above the 95% confidence interval at 0.75, 3 and 6 h while pressure threshold did not vary from baseline. After T + ACP pressure threshold increased above baseline from 0.5–3 h. Pressure thresholds increased above baseline from 0.25–2 h after ACP	35

(Continued)

Table 12 (Continued)

Type of study	Dose and route*	Assessment	Results	Reference
Experimental	T 1 mg/kg IV, T 2 mg/kg IV, T 4 mg/kg IV	Assessment of ventilation outputs	T 2mg/kg and T 4mg/kg reduced sensitivity of peripheral and central chemoceptors to carbon dioxide and increased the apnoeic threshold. Total carbon dioxide sensitivity was reduced by 31%, 59% and 68% by 1, 2 and 4 mg/kg T, respectively	153
Experimental	T 2 mg/kg IV, T 5 mg/kg PO	PK	After IV administration, the apparent volume of distribution of the central compartment, apparent volume of distribution at steady state, clearance and terminal half-life (mean ± SEM) were 1553 ± 118 ml/kg, 3103 ± 132 ml/kg, 20.8 ± 3.2 ml/min/kg, and 134 ± 18 mins, respectively. Systemic availability and terminal half-life after oral administration were 93 ± 7% and 204 ± 8 mins, respectively. O-desmethyltramadol rapidly appeared in plasma following T administration and had a terminal half-life of 261 ± 28 and 289 ± 19 mins after IV and PO T administration, respectively	146
Case report	T overdose (80 mg/kg PO administered twice)	Clinical evaluation	Signs of T toxicity: agitation, altered mentation, hypersalivation, jerky head movement, hypertension and tachycardia. Stabilisation and therapy included fluid therapy, cyproheptadine and buprenorphine. The cat recovered	147

*See footnote to Table 1
ACP = acepromazine; BUT = butorphanol; CPS = composite pain score; EPI = epidural; HYDRO = hydromorphone; IVAS = interactive visual analogue scale; MAC = minimum alveolar concentration; MNT = mechanical nociceptive threshold; MOR = morphine; OHE = ovariohysterectomy; PK = pharmacokinetics; SAL = saline; SDS = simple descriptive scale; T = tramadol; TNT = thermal nociceptive threshold; VFF = von Frey filaments; VAS = visual analogue scale; VEDA = vedaprofen

Table 13 Studies evaluating naloxone in cats

Type of route	Dose and route*	Assessment	Results	Reference
Experimental	B 0.01 mg/kg IM, N 0.67 µg/kg IM, B + N (15:1) IM	MNT TNT	B and N combination did not enhance B antinociception	161

*See footnote to Table 1
B = buprenorphine; N = naloxone; MNT = mechanical nociceptive threshold; TNT = thermal nociceptive threshold

rats naloxone can enhance the analgesic/antihyperalgesic effects of buprenorphine.[160] However, this did not appear to be the case in cats and the study showed that naloxone antagonised the thermal antinociceptive effects of clinically analgesic doses of buprenorphine in cats (Table 13).[161]

Conclusions

In summary, opioids can be used in cats, especially in cases of moderate to severe pain. Their effects should be closely monitored so that pain treatment is tailored to best suit the individual animal's needs.

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