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Antinociceptive effects of tramadol and acepromazine in cats

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Effects of tramadol and acepromazine on pressure and thermal thresholds were examined in eight cats. After baseline measurements, subcutaneous (SC) tramadol 1 mg/kg, acepromazine 0.1 mg/kg, tramadol 1 mg/kg with acepromazine 0.1 mg/kg, or saline 0.3 ml were given. Serial measurements were made for 24 h. Mean thermal thresholds did not change significantly [analysis of variance (ANOVA)] from baseline. The maximum thermal threshold increase above baseline was 2.8 ± 2.8°C at 6 h ($P > 0.05$) after tramadol; it was above the 95% confidence interval (CI) at 0.75, 3 and 6 h. Pressure thresholds increased above baseline from 0.25 to 2 h after acepromazine ($P < 0.05$) and from 0.5 to 3 h after the combination ($P < 0.05$), with a maximum increase of 132 ± 156 mmHg 0.25 h after acepromazine and 197 ± 129 mmHg 0.5 h after the combination. Pressure thresholds were above the 95% CI from 0.25 to 2 h after acepromazine and from 0.5 to 3 h after the combination. SC tramadol at 1 mg/kg in cats had limited effect on thermal and pressure nociception, but this was enhanced by acepromazine. Acepromazine alone had pressure antinociceptive effects.

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Although arguably the best analgesics, opioids are not always chosen for pain control in cats (Williams et al 2005). A number of opioids are subject to controlled drugs regulations and many veterinarians are unwilling to use them. A further disincentive in cats is the feline reputation for opioid-induced excitement, although when appropriate dosing schedules are used, especially with severe pain, excitement is rare (Lascelles and Waterman-Pearson 1997, Robertson and Taylor 2004). Equally, there is concern about non-steroidal anti-inflammatory drugs (NSAIDs) in cats, as their glucuronidation pathways are deficient and NSAID-induced gastrointestinal ulceration and renal failure have been reported (Lascelles and Waterman-Pearson 1997, Briggs et al 1998, Robertson and Taylor 2004).

Tramadol hydrochloride is a phenylpiperidine analogue of codeine, with weak binding affinity to all types of opioid receptors, especially OP3 (μ) opioid receptors (Desmeules et al 1996, Taylor 1999, Teppema et al 2003). Tramadol is reported also to activate descending inhibitory spinal monoaminergic pathways (Desmeules et al 1996), providing an additional non-opioid analgesic mechanism. There are few reports of tramadol use in veterinary medicine, particularly in cats (Desmeules et al 1996, Taylor 1999, Mastrocinque and Fantoni 2003, Teppema et al 2003, Robertson 2005).

Combination of an opioid with acepromazine, a form of neuroleptanalgesia, is widely used for premedication in cats (Brearley 1994). Compared to individual use of each drug, the combination is apparently synergistic, increasing the intensity of sedation and analgesia, allowing lower doses of each drug to be used (Sawyer et al 1993). Acepromazine is the most widely used phenothiazine sedative in veterinary medicine, and is generally considered not to have any analgesic action although it decreases reaction to external stimuli through its sedative effect (Barnhart et al 2000).

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There are few reports evaluating either tramadol or neuroleptoanalgesia in cats. This study aimed to evaluate tramadol's antinociceptive effect and to explore the hypothesis that its combination with acepromazine would enhance the antinociception. Analgesia was assessed using thermal and pressure thresholds.

Materials and methods

Cats

The study was approved by the Ethical Committee for Animal Experimentation at the Faculty of Medicine, University of São Paulo State, Botucatu, Brazil (protocol 260/05). Two male and six female neutered adult domestic cats (3.0–4.9 kg) were studied. They were treated with anthelmintics and vaccinated against *Chlamydia psittacii*, panleucopenia, calicivirus and feline rhinotracheitis before the study. Biochemical analysis and haematology were also performed. Polymerase chain reaction assays against feline leukaemia and feline immunodeficiency viruses were negative. Health checks were made at regular intervals between testing sessions.

The cats were group housed and fed dry laboratory cat food. For testing they were moved to the research laboratory, where feed was supplemented with tinned food. Water was always supplied ad libitum. During testing days, cats were housed individually in cages of 120 (height) × 80 (width) × 60 (depth) cm. Cages were equipped with wall mirrors, toys, a bed and a litter tray, and positioned in a quiet and clean environment. All cats had previously been well handled and familiarised with the procedures.

Measurements

Thermal and pressure thresholds were measured by applying a mild, transient heat or mechanical stimulus as developed by Dixon et al (2002, 2006). For each test the observer (PVMS) attracted the cats' attention so they were not sleeping, eating or playing. Behaviour was assessed at the same time points and sedation or any abnormal behaviour was recorded.

Thermal threshold

Thermal threshold was measured on unrestrained cats as described by Dixon et al (2002). A small probe containing a heater element and a temperature sensor provided thermal stimulation at increments of 0.6°C/s. The probe was attached to an elasticated band around the shaved thorax. A bladder modified from a neonatal blood pressure cuff was inflated manually to 100 mmHg to ensure consistent contact between probe and skin. A minimum of 15 min was allowed for the probe to reach skin temperature. The temperature was read from a digital voltmeter with a hold facility. The probe heater was activated and stopped immediately the cat reacted, generally with a skin flick, a jump forward or turning to bite the cable. The temperature at which the cat reacted was recorded as the thermal threshold for that test. The circuit included a safety cut-off at 55°C when heating was stopped if the cat had not already reacted. Four measurements were made at 15 min intervals before any drugs were administered, and their mean value was taken as control thermal threshold.

Pressure threshold

Pressure threshold was measured on unrestrained cats as described by Dixon et al (2007). The stimulus was applied using a 5 g plastic bracelet taped around the forearm. Three 2.4 mm diameter ball-bearings within the bracelet were advanced against the craniolateral surface of the forearm by manual inflation of a modified blood pressure bladder connected to a pressure transducer and a 30 ml syringe. The pressure was read from a handheld digital voltmeter with a hold facility. The syringe was inflated by the investigator until the cat reacted. At this point, the digital voltmeter reading was held and the pressure released. Reaction was shown by a leg shake, a head turn, biting at the probe, and rarely with vocalisation. The bladder pressure at the point of reaction was recorded as pressure threshold. If the cat had not reacted, an automatic safety cut-out occurred at approximately 650 mmHg when the syringe was empty. Before any drugs were administered, four measurements were made at 15 min intervals and their mean value was taken as control pressure threshold.

Drug treatment

After baseline threshold recordings, each cat received subcutaneous (SC) tramadol hydrochloride (Anangor; Biosintetica, Sao Paulo, Brazil) 1 mg/kg, or acepromazine (Acepran 0.2%; Lab Univet, Sao Paulo, Brazil) 0.1 mg/kg, or tramadol 1 mg/kg with acepromazine 0.1 mg/kg, or saline 0.3 ml, as part of a randomised six period cross-over study, with a week interval. The other

two treatments were carprofen (4 mg/kg SC) and buprenorphine (0.01 mg/kg SC); data from the additional treatments have been reported elsewhere (Steagall et al in press). Measurements were made at 15, 30, 45 min and at 1, 2, 3, 4, 6, 8 and 24 h after drug administration. The observer did not know which treatment had been given.

Statistics

Data were analysed using GraphPad Prism. Within-group changes with time were analysed using analysis of variance (ANOVA) for repeated measures followed by Dunnett's test if appropriate. Thresholds from different treatment groups were compared using two-way ANOVA (factors: treatment and time) with a Bonferroni post-test.

Drug effect within each group was further examined by comparison of post-treatment thresholds with a placebo reference range generated from the means of the thresholds for each cat recorded during the 24 h testing period after saline administration. These means were used to generate 95% confidence intervals (95% CIs) for all the cats when not given an analgesic. Thresholds after each treatment lying outside the 95% CI were considered to indicate hyper- or hypoalgesia (Dixon et al 2002).

Results

Mechanical and thermal thresholds

Thermal threshold did not change significantly from baseline after any treatment (repeated measures ANOVA) (Fig 1). The maximum increase above baseline was 2.8 ± 2.8°C 6 h after tramadol injections ($P > 0.05$). There were no differences in thermal thresholds when groups were compared (two-way ANOVA).

Thermal threshold increased just above the upper 95% CI at 45 min, 3 h and 6 h after tramadol only. There was considerable individual variation after tramadol, as thermal threshold was high in some cats, but did not increase at all in others. Thermal threshold decreased below the lower 95% CI at 24 h after acepromazine alone.

Pressure threshold increased above baseline after acepromazine and after the tramadol–acepromazine combination, but not after tramadol or saline (repeated measures ANOVA) (Fig 2). Pressure threshold increased from 15 min until 2 h after acepromazine ($P < 0.05$, repeated measures ANOVA) and the maximum increase in threshold above baseline was 132 ± 156 mmHg at 15 min. Pressure threshold increased from 30 min until 3 h after the acepromazine–tramadol combination ($P < 0.05$, repeated measures ANOVA) and the maximum increase

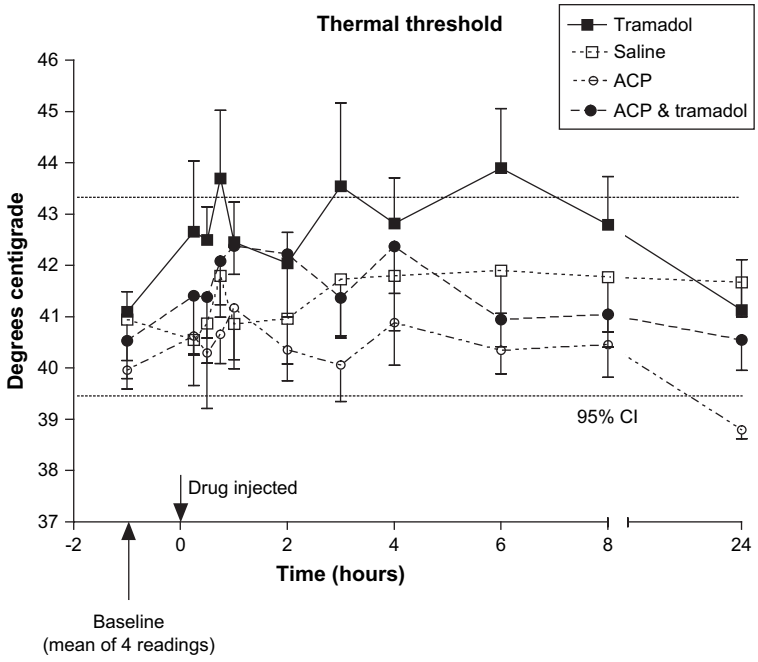

Fig 1. Mean ± standard deviation (SD) thermal thresholds after SC administration of tramadol 1 mg/kg, acepromazine 0.1 mg/kg, tramadol 1 mg/kg and acepromazine 0.1 mg/kg, or saline, at time 0. Horizontal lines represent upper and lower 95% CIs of mean thermal thresholds from all cats after saline treatment.

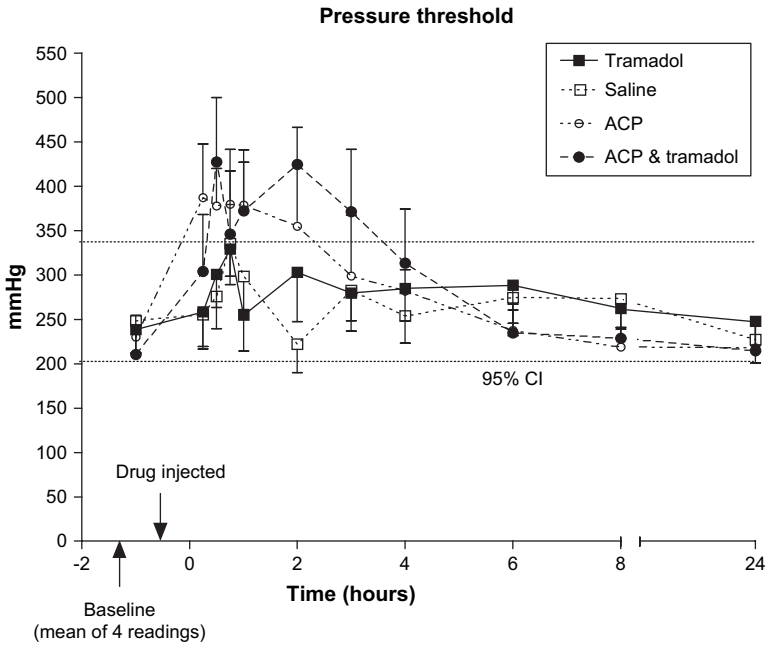

Fig 2. Mean ± SD pressure thresholds after SC administration of tramadol 1 mg/kg, acepromazine 0.1 mg/kg, tramadol 1 mg/kg and acepromazine 0.1 mg/kg, or saline, at time 0. Horizontal lines represent upper and lower 95% CIs of mean thermal thresholds from all cats after saline treatment.

above baseline was 197 ± 129 mmHg at 30 min. When groups were compared, pressure thresholds were higher with the combination than after saline at 2 h ($P < 0.05$, two-way ANOVA).

Pressure thresholds were above the 95% CI after acepromazine from 15 min to 2 h and after the acepromazine–tramadol combination from 30 min to 3 h.

No skin damage was caused at the testing site by either thermal or pressure stimulus in any cat.

Behavioural changes

There was no sedation or abnormal behaviour in the saline group. All cats in the acepromazine group became sedated, and most of them fell asleep during the first hour. In the tramadol group, behaviour differed between animals. Most appeared euphoric and comfortable, rolling, playing with toys, kneading with the forepaws, were alert and interacted willingly with people. However, two of the cats became dysphoric, appearing uncomfortable and distressed, staring into space and wary of people. All tramadol effects were seen until 4–6 h after treatment. After the combination, most cats were sedated and calm for 2–3 h. Thereafter, they started to roll, knead with their forepaws and play with toys. However, one of the cats that became dysphoric with tramadol alone did not become tranquillised with the combination. None of the cats vomited after any treatment.

Discussion

Objective comparison of analgesics can be accomplished using pressure, electric current or heat as noxious stimuli. They should not injure the animal and should produce quantifiable, repeatable stimuli that are easy to administer and well tolerated (Raffe 1992). The thermal and pressure systems have been developed specifically for evaluation of analgesics in unrestrained cats (Dixon et al 2002, 2007).

Pain assessment depends on the ability to produce pain in controlled trials and to measure grades of response in order to compare analgesics (Nolan et al 1988, Raffe 1992, Dixon et al 2002). The thermal system has proved effective for such studies in cats (Robertson et al 2003, Lascelles and Robertson 2004a,b, Wegner et al 2004, Robertson et al 2005a,b, Steagall et al 2006, Wegner and Robertson 2007) and a close relation between analgesic effect under laboratory conditions and clinical efficacy has been demonstrated (Dixon et al 2002, Robertson et al 2003, Lascelles and Robertson 2004a,b, Steagall et al 2006), leading to the development of better clinical treatment protocols (Robertson and Taylor

2004). The pressure system has been developed more recently and information about its value in feline pain research is still limited (Steagall et al 2006, in press, Taylor et al in press). However, use of more than one stimulus should provide information more relevant to clinical pain than a single modality.

It might be argued that behavioural changes produced by tramadol and acepromazine would affect interpretation of the cats' response to noxious stimuli. Behavioural change reduces the quality of blinding; however, inclusion of a combination and variable behavioural responses to tramadol rendered this of little importance. Acepromazine's sedative effect might be expected to mimic 'analgesia' as the cat's response to any stimulation would be suppressed. However, studies in cats with dexmedetomidine using the same thermal threshold device demonstrate that, despite deep sedation, the cat still responds to the thermal stimulus (Slingsby et al 2006). Hence, the data presented here can be considered a true representation of responses to a noxious stimulus.

Tramadol acts as an analgesic at least in part via opioid mechanims (Duthie 1998). Tramadol is a racemic mixture and is metabolised to both (+) and (−) enantiomer metabolites. The (+) enantiometer, *O*-desmethyltramadol, has the greater affinity for the μ-opioid receptor and some serotonergic effects. The (−) enantiometer inhibits noradrenalin reuptake (Lintz et al 1981, Taylor 1999). Species differences in production of the (−) isomer (Lintz et al 1981, Wu et al 2001), may decrease the analgesic effect in cats, as metabolism is based on the cytochrome P450 enzyme via demethylation, with subsequent sulphation or glucuronidation (Duthie 1998). Cats have a low capacity for hepatic glucuronidation, due to reduced hepatic uridine diphosphate-glucuroninosyltransferase (UGT) isoforms (Court and Greenblatt 2000). This is likely to result in reduced tramadol metabolism in cats as is seen with morphine, and potentially less analgesic effect (Taylor et al 2001). α_2 receptor activation plays a significant role in spinal monoaminergic modulation of pain and this probably contributes to tramadol's effects; Desmeules et al (1996) demonstrated that tramadol's antinociceptive effects were reversed by yohimbine, an α_2 adrenoceptor antagonist.

In man, tramadol is recommended for postoperative analgesia but not for treatment of severe pain (Duthie 1998). Its potency and efficacy are similar to pethidine (Calvey and Williams 2001) with less respiratory depression than morphine (Teppema et al 2003). Investigations in dogs have shown 2 mg/kg tramadol to have a similar effect to 0.2 mg/kg morphine (Mastrocinque and Fantoni 2003). However, in the present study, tramadol did not increase the pressure threshold and had only a limited effect on thermal threshold in cats, suggesting that it was not an efficient analgesic in this species when given subcutaneously at 1 mg/kg. Opioids used as clinical analgesics in cats have all increased thermal and pressure thresholds in this analgesiometric model (Dixon et al 2002, Robertson et al 2003, Lascelles and Robertson 2004a,b, Wegner et al 2004, Robertson et al 2005a,b, Steagall et al 2006, Dixon et al 2007, Wegner and Robertson 2007). In the randomised cross-over study described in this report, SC buprenorphine (0.01 mg/kg) also increased thermal and pressure thresholds (Steagall et al in press). All these investigations indicate that the model and the individuals tested were suitable to detect an increase in thermal and pressure nociceptive thresholds, further adding weight to the view that 1 mg/kg tramadol given subcutaneously was not an effective analgesic in cats. There was considerable variation between individuals, suggesting that some cats may respond to tramadol better than others. Opioid 'non-reactors' have been previously noted in cats and a similar effect may occur with tramadol (Taylor et al 2007).

Tramadol's lack of analgesic effect may be a result of dose; we used 1 mg/kg, which is at the low end of the reported doses in dogs. A cautious low dose was chosen for this preliminary investigation in cats, as violent behaviour was a potential hazard. Furthermore, as neuroleptoanalgesia was to be evaluated, lower doses were appropriate in order to evaluate any enhanced effect. However, 2 mg/kg tramadol given subcutaneously in cats undergoing ovarohysterectomy required little intervention analgesia and was superior to vedaprofen (Brondani et al 2006).

Acepromazine appeared to increase the analgesic effect and duration over tramadol alone. The tramadol−acepromazine combination was the only treatment to increase the pressure threshold significantly above those after saline, although acepromazine alone had a limited effect. Similar effects were reported with acepromazine and oxymorphone in dogs, where the combination increased thermal and pressure thresholds, with a longer duration of analgesia than oxymorphone alone; however, acepromazine alone did not

increase the thresholds (Barnhart et al 2000). Acepromazine is often used to complement postoperative analgesia in animals with pain that is difficult to control although it is not generally regarded to be an analgesic (Brearley 1994). Nevertheless, it is useful to reduce anxiety in animals under treatment for severe pain, as pain is intensified by the anxiety (Carroll 1999). In our study, acepromazine alone increased the pressure threshold where tramadol did not. This suggests that acepromazine had some analgesic effect, although it did not increase the thermal threshold. The pressure stimulus has not been widely tested in cats, but pressure thresholds were significantly raised by buprenorphine, butorphanol, methadone and morphine (Steagall et al 2006, Dixon et al 2007, Steagall et al in press). Buprenorphine was given to the same cats in the same cross-over study as in the current report, making their data directly comparable (Steagall et al in press). These results suggest that increased pressure thresholds are associated with analgesia, and that, therefore, acepromazine produced analgesia. This is a surprising effect that warrants further investigation. Acepromazine alone also resulted in a decrease in thermal threshold below the lower 95% CI at 24 h. This may reflect some rebound effect, which also requires further investigation.

In a visceral pain model in cats, acepromazine did not produce analgesia, nor did it increase ketamine's analgesic effect (Sawyer et al 1993). However, the combination enhanced sedation and prolonged the effect of ketamine alone. In another study, acepromazine did not produce visceral analgesia during colorectal distension, but, when combined with oxymorphone and butorphanol, threshold responses were transiently increased (Briggs et al 1998). Our study suggests that acepromazine alone may have analgesic effects, but also clearly showed acepromazine enhancement of both the duration and the analgesic effect of tramadol. There is recognised controversy as to whether the phenothiazines produce analgesia (McGee and Alexander 1979, Patt et al 1994). Even recent surveys generally conclude that the phenothiazines, with the possible exception of methotrimeprazine, have little intrinsic analgesic effect (Fishbain et al 2004). However, they undoubtedly enhance opioid-induced postoperative analgesia (Chiang et al 2005), and acepromazine–tramadol combinations appear to have potential value for clinical use in cats in the same way as acepromazine-opioid combinations.

The general lack of effect on thermal threshold when pressure thresholds were increased may be due to the complexity of pain neurophysiology, involving different nociceptor types. Tramadol, acepromazine and the combination had somewhat different effects on thermal and pressure thresholds, in contrast with the effects of buprenorphine, methadone and morphine, where the response patterns were similar, although they tended to have a smaller effect on the pressure theshold (Steagall et al 2006, in press). Nolan et al (1988) and Barnhart et al (2000) reported similar differences between thermal and pressure thresholds measured in sheep and dogs treated with pethidine hydrochloride and acepromazine–oxymorphone, respectively. They concluded that the two stimuli cause different degrees of pain, making it impossible to judge whether linear increments in each test represent similar increases in pain severity. Robertson et al (2005c) reported differences between mechanical and thermal threshold response in horses receiving a lidocaine infusion, possibly a result of methodology and dose rate. Such considerations, as well as the route of injection (Steagall et al 2006), may apply to our data.

In conclusion, tramadol alone had a minimal effect on nociceptive thresholds, suggesting that, at 1 mg/kg subcutanesously, it has a limited analgesic effect in cats. Acepromazine itself appeared to have some antinociceptive effect, and also increased tramadol's effect, suggesting that the acepromazine–tramadol combination enhances analgesia above that of either drug alone. This study supports the concept that neuroleptanalgesia may be valuable for treatment of feline pain; particularly when high doses of opioids are not sufficient, or in cats that have become excited with opioids.

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