Original Article

The Antinociceptive Effects of Tramadol on the Thermal Threshold Response in Cats

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Abstract

The study is of the antinociceptive effects of tramadol on the thermal threshold response in eight cats using a thermal threshold-testing device which contained a heater element and a temperature sensor placed on the shaved lateral thoracic area. Each cat randomly received an intramuscular administration of tramadol 2 mg/kg, morphine 0.2 mg/kg and saline 0.04 ml/kg (placebo) at a weekly interval from an observer unaware of the treatment. The thermal thresholds were measured and recorded by activation of the heater until the cat showed a positive response (e.g. skin flicks, turning and looking at the probe and jumping forwards). Three baseline measurements were made at 15 min intervals before the treatment. The thermal thresholds were measured at 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 480 and 720 min after the drug administration. All cats tolerated well with repeated thermal stimuli and continued normal activities (e.g. eating, drinking, defecation, urination, playing, grooming, and responded to human contact) throughout the testing period. The mean thermal thresholds±SD over 12 hours were 42.0±0.5°C (placebo), 43.2±0.9°C (morphine) and 44.2±1.6°C (tramadol). There were significant differences (ρ<0.05) of the mean thermal thresholds over 12 hours between the experimental and control groups. When compared with the pre-injection baseline, thermal threshold was significantly increased (ρ<0.05) between 15-270 min and 330-360 min after morphine and between 45-90 min, 180-210 min and 270-300 min after tramadol. In conclusion, tramadol had an analgesic efficacy on thermal stimuli in cats by increasing the thresholds significantly above the pre-injection basal thermal thresholds.

Keywords: antinociception, cat, thermal threshold, tramadol

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บทคัดย่อ

ผลการระงับปวดของทรามาดอลต่อระดับความร้อนที่ทำให้แมวเริ่มมีการตอบสนอง

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การศึกษาผลการระงับปวดของทรามาดอลต่อระดับความร้อนที่ทำให้แมวเริ่มมีการตอบสนองในแมว 8 ตัว โดยใช้อุปกรณ์วัดระดับความร้อน ซึ่งประกอบด้วย แถบซิลิโคนให้ความร้อนและตัววัดอุณหภูมิติดแนบผิวหนังบริเวณช่องอก แมวทั้ง 8 ตัว ได้รับยาที่ใช้ศึกษาฉีดเข้ากล้ามเนื้อ แบบสุ่ม คือ ทรามาดอล ขนาด 2 มก.ต่อ กก. มอร์ฟีนขนาด 0.2 มก.ต่อ กก. และ normal saline ปริมาณ 0.04 มล.ต่อ กก. (กลุ่มควบคุม) โดยมีระยะพักระหว่างยาแต่ละชนิดอย่างน้อย 1 สัปดาห์ และผู้ทำการทดลองจะไม่ทราบชนิดของยาที่แมวได้รับ การกระตุ้นเริ่มด้วยความร้อนที่เพิ่มขึ้นจนกระทั่งแมวแสดงอาการตอบสนอง ได้แก่ ผิวหนังกระตุก หันไปมองที่เครื่องมือ และกระโดดไปข้างหน้า จึงหยุดการกระตุ้น และ บันทึกอุณหภูมิ ณ จุดที่แมวแสดงอาการตอบสนอง และถือเป็นระดับความร้อนที่ทำให้แมวเริ่มมีการตอบสนอง โดยวัดค่าปกติของแมวแต่ละตัวก่อนได้รับยา ทำซ้ำกัน 3 ครั้ง ห่างกัน 15 นาที และกระตุ้นภายหลังที่แมวได้รับยาเป็นเวลา 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 480 และ 720 นาที ตามลำดับ ขณะทำการทดลองแมวสามารถทนต่อการกระตุ้นด้วยความร้อนซ้ำๆ ได้ตลอดการทดลอง และแมวแสดงพฤติกรรมเป็นปกติระหว่างทำการทดลอง แมวสามารถ กินอาหาร กินน้ำ ถ่ายอุจจาระ ปัสสาวะ เล่น เลียทำความสะอาดตัวเอง และตอบสนองต่อการสัมผัสของมนุษย์ได้ตามปกติ โดยค่าเฉลี่ย±ค่าเบี่ยงเบนมาตรฐาน ของระดับความร้อนที่ทำให้แมวเริ่มมีการตอบสนองตลอด 12 ชั่วโมงมีค่า 42.0±0.5°ซ. ในกลุ่มควบคุม, 43.2±0.9°ซ. ในกลุ่มมอร์ฟีน และ 44.2±1.6°ซ. ในกลุ่มทรามาดอล ซึ่งพบว่ามีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p<0.05$) ของค่าเฉลี่ยของระดับความร้อนที่ทำให้แมวเริ่มมีการตอบสนองตลอด 12 ชั่วโมงระหว่างกลุ่มทดลองกับกลุ่มควบคุม และค่าเฉลี่ยของระดับความร้อนที่ทำให้แมวเริ่มมีการตอบสนองแตกต่างกันอย่างมีนัยสำคัญทางสถิติกับก่อนให้ยา ($p<0.05$) ระหว่างเวลา 15-270 นาที และ 330-360 นาที ภายหลังฉีดมอร์ฟีน และระหว่างเวลา 45-90 นาที, 180-210 นาที และ 270-300 นาที ภายหลังฉีดทรามาดอล จากการศึกษาครั้งนี้สรุปว่า ทรามาดอลมีประสิทธิภาพในการระงับปวดที่เกิดจากการกระตุ้นด้วยความร้อนในแมว โดยระดับความร้อนที่ทำให้แมวเริ่มมีการตอบสนองหลังได้รับทรามาดอลเพิ่มขึ้นแตกต่างจากก่อนได้รับยา

คำสำคัญ: การระงับปวด แมว ระดับความร้อนที่เริ่มมีการตอบสนอง ทรามาดอล

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Introduction

The recognition, assessment and effective alleviation of pain in animals is necessary for proper clinical management and veterinary medicine. Furthermore, untreated pain generates physiological damage. Animals recovering from disease or surgical intervention are subject to increased metabolic demands and if this is not met by an increase in caloric intake, severe weight loss with a negative nitrogen balance develops. It may further compromise their medical condition (Wright, 2002).

Nowadays, cats are popular pets although feline perioperative and traumatic pain have been underestimated and under treated (Hansen and Hardie 1993; Lascelles et al., 1999; Watson et al., 1996; Robertson, 2005[a]). Pain management and pain score have been treated subjectively by veterinarians, but many cats have not received analgesics after surgery or trauma (Dohoo and Dohoo, 1996). Although veterinary surgeons have scored the pain from exploratory laparotomy equally in dogs and cats, 71% of dogs and only 56% of cats have received analgesics (Lascelles et al., 1999). The reasons for under treating pain in cats are the difficulty in assessing pain because cats do not exhibit behavior related to overt pain (Lascelles and Waterman, 1997; Lamont, 2002). There are no pain assessment scales validated for use in cats and there is no correlation between physiologic variable, plasma cortisol levels and pain scores in cats (Cambridge et al., 2000). Analgesic dosing has been extrapolated from other species because of the limited number of studies in cats (Taylor and Robertson, 2004). Drug options to provide analgesia in cats are limited for the fear of the side effects and toxicity of analgesics. Cats are known to be deficient in a number of excretory and metabolic pathways. For example,

cats have a low capacity for hepatic glucoronidation which has often led to toxicity.

Opioids are the most efficacious analgesic drugs in veterinary medicine (Pascoe, 2000). In the past, opioids were withheld from cats because they induced mania and excitement. However, recent studies have shown that opioids rarely cause excitement and can provide excellent analgesia at clinical doses in cats (Dixon et al., 2002; Dobbins et al., 2002; Robertson et al., 2003; Robertson, 2005[b])

Morphine is the prototype opioid and the agent of choice for the treatment of severe pain in dogs and cats (Lascelles and Waterman 1997; Gaynor, 1999). Tramadol is used widely in humans because in equipotent doses it has the same analgesic effect as morphine in relieving mild-to-moderate pain (Houmes et al., 1992; Tarradel et al., 1996; Mildh et al., 1999). In addition, tramadol, a synthetic analog of codeine, is a centrally acting opioid analgesic drug that has been used to manage pain in humans with a low incidence of adverse effects (Raffa et al., 1993; Wilder-Smith and Bettiga, 1997; Scott and Perry, 2000). Tramadol has weak mu-opioid agonist and lower affinity for delta and kappa receptors. Moreover, tramadol has an effect on the descending pain inhibitory systems by preventing reuptake and enhancing the release of serotonin and norepinephrine. The main metabolite of tramadol is O-desmethyltramadol (M1) that metabolites by cytochrome P-450 in the liver.

Pain can not be monitored directly in animals, but can only be estimated by examining their response to nociceptive stimuli. The monitored reactions are almost always motor responses (Bars et al., 2001). Furthermore, objectively, pain assessment depends on the ability to produce pain in controlled trials and to measure grades of response in order to compare analgesics. A thermal threshold-testing device (Dixon et al., 2002) has proved effective for the assessment of the analgesic effects of many opioids in cats and is relevant to clinical practice.

The purpose of the study was to characterize the antinociceptive action of tramadol in cats using thermal threshold testing.

Materials and Methods

Animals: All studies were approved by the Institutional Animal Care and Use Committee at the Faculty of Veterinary Science, Chulalongkorn University with license No. 0831002. Eight adult cats (3 castrated males and 5 neutered females) were studied by consent of their owners. The cats were determined to be healthy based on physical examination and the results of a complete blood count and serum chemistry analysis. All cats had previously been well handled and were familiarized with the procedures before the experiments.

Thermal threshold testing device: The cats' thermal thresholds were measured by applying a mild, transient heat stimulus to elicit pain. The cats were observed until they reacted; the probe's temperature

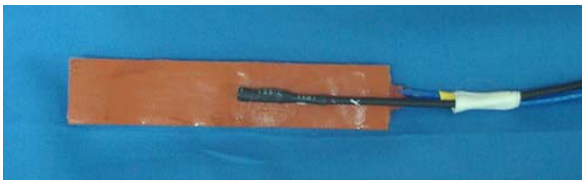

Figure 1 Probe containing a heater element, 12.5 cm long, 2.5 cm wide and 0.1 cm deep and a center temperature sensor.

was recorded at this point and the heater was turned off simultaneously. Thermal stimulation was provided by a probe which contained a heater element, 12.5 cm long, 2.5 cm wide and 0.1 cm deep at increments of 0.5°C/sec and a center temperature sensor (Fig 1). The heater element was a silicon 15 Watt resistor. The heater voltage was variable between 0-12 volts and set to 10 volts (V) for all tests, giving 0.5°C/sec temperature rise. A digital temperature sensor, SILA AP-101 version 1.1, detected the temperature between -55^{0}C to 125^{0}C in atmosphere with a 0.5^{0}C sensitive display. This was connected to a control unit and a temperature digital monitor by flexible cable (Fig 2). To prevent skin damage when higher temperatures were reached an automatic safety cut-off operated at 55^{0}C if not stopped earlier.

Procedures: On the day before testing, the craniolateral thorax was shaved. On the day of testing, the cats were transported to the laboratory and housed individually in cages with a litter tray and positioned in a quiet environment. The probe was held against the shaved thoracic skin of the cat with a 2 inches wide flexible cohesive bandage (Fig 3). A minimum of 5 min was allowed for the probe to reach skin temperature. The thermal thresholds were measured on eight unrestrained cats as described by Dixon et al. (2002), and recorded by activation of the heater until the cat showed a positive response (e.g. skin flicks, turning and looking at the probe and jumping forwards). Three baseline measurements

Figure 2 A temperature digital monitor showing an increase in thermal temperature with 0.5°C/sec increments and a control unit providing safety for cats from skin thermal stimulation by an automatic safety cut-off switch.

Figure 3 For the tests, cats were moved into laboratory and housed singly in cages. The probe is placed in contact with cat's shaved skin by placing an elastic band around cat's thorax.

were made at 15 min intervals before any drugs were administered and their mean values were taken as the basal thermal thresholds. Each cat randomly received an intramuscular administration of tramadol (Tramal®100, Grünenthal GmbH, Germany) 2 mg/kg (tramadol group), morphine 0.2 mg/kg (morphine group) and saline 0.04 ml/kg (control group) as a three period cross-over study with a weekly interval from an observer unaware of the treatment.

All cats were conditioned to the testing protocol. A washout period of 7 days was left between each administration. The thermal thresholds were measured at 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 480 and 720 min after the drug administration. Observations of behavior and side effects, including nausea, vomiting, mydriasis and changes in activity and awareness were made throughout the testing period.

Statistical analysis: A normal threshold reference range for the cats not treated with an analgesic was obtained by taking the mean of threshold temperatures measured in each cat over 12 hours after it had been injected with saline. The thresholds from different treatment groups were compared using one-way ANOVA followed by Dunnett's test and an unpaired t-test. Within-group changes with time were analyzed using a paired t -test. A p value < 0.05 was accepted as having significant differences.

Results

All cats tolerated repeated thermal stimuli well and continued normal activities (e.g. eating, drinking, urination, defecation, grooming, and playing) throughout the testing period. One cat vomited after the morphine administration and another after the tramadol administration. Minor skin lesions were found a few days after the testing in one cat after the tramadol administration and one cat after the morphine administration. No adverse excitatory behavioral effects related to drug administration were noted during the study. The cats did not remove or play with the bands. Threshold responses to heat stimulus included skin flicks, turning, looking and licking at the probe, jumping forwards and occasional vocalisation. There was marked variation in response to opioid administration among the cats, with some responding very little and the others responding enthusiastically.

There were no significant changes in the thermal thresholds over time after saline injection. The mean thermal thresholds over 12 hours were significantly different (p<0.05) between the experimental and control groups (Table 1). The mean thermal thresholds over 12 hours±SD were 42.0±0.5°C (placebo), 43.2±0.9°C (morphine) and 44.2±1.6°C (tramadol).

Table 1 Mean thermal thresholds over 12 hours±SD (°C) obtained from 8 cats during thermal threshold testing.

Treatments	Mean thermal thresholds over 12 hours±SD (°C)
Pre-injection	42.2±0.9[a]
NSS	42.0±0.5
Morphine	43.2±0.9*
Tramadol	44.2±1.6*

[a] *Mean pre-injected thermal thresholds from all treatments.*
** Significant difference when compared to NSS*

Both analgesics increased the thresholds significantly above the pre-injection basal thermal thresholds. The mean thermal thresholds of both morphine and tramadol were significantly increased (p<0.05) from the pre-injection baseline (basal thermal threshold) between 15-360 min after administration (Table 2) when dividing the time after injection into 3 periods as 15-60 min, 90-360 min and 480-720 min.

The mean thermal thresholds were significantly increased (p<0.05) from the pre-injection baseline (basal thermal threshold) between 15-270 min and 330-360 min after the morphine administration and between 45-90 min, 180-210 min and 270-300 min after the tramadol administration (Fig 4). The maximum thermal thresholds increasing from basal thermal thresholds was 1.7±2.2°C at 2.5 hour after the morphine adminstration and 2.4±2.7°C at 1.5 hour after the tramadol administration.

Table 2 Mean thermal thresholds±SD (°C) obtained from 8 cats during thermal threshold testing.

	Mean thermal threshold temperature±SD (°C)		
	NSS	Morphine	Tramadol
Pre-injection	41.7±0.7	42.2±0.9	42.7±0.9
Post-injection (min)			
15-60	41.9±0.6	43.1±1.1*	44.3±1.6*
90-360	42.0±0.7	43.3±1.2*	44.4±2.1*
480-720	41.8±0.8	42.9±0.7	42.3±0.8

**Significant difference (p<0.05) when compared to pre-injection thermal thresholds*

Discussion

Tramadol is a centrally acting analgesic that exerts its effect through opioid, serotonin, and adrenergic pathways. For example, an alpha-2 adrenergic effect was shown by the inhibition of the antinociceptive effect of tramadol after yohimbine administration in cats (Desmeules et al., 1996). Preemptive administration of tramadol (2 mg/kg IV) in dogs has shown a similar analgesic effect to morphine (0.2 mg/kg IV) and can provide safe control of early pain after ovariohysterectomy without significant adverse effects (Mastrocinque and Fantoni, 2003).

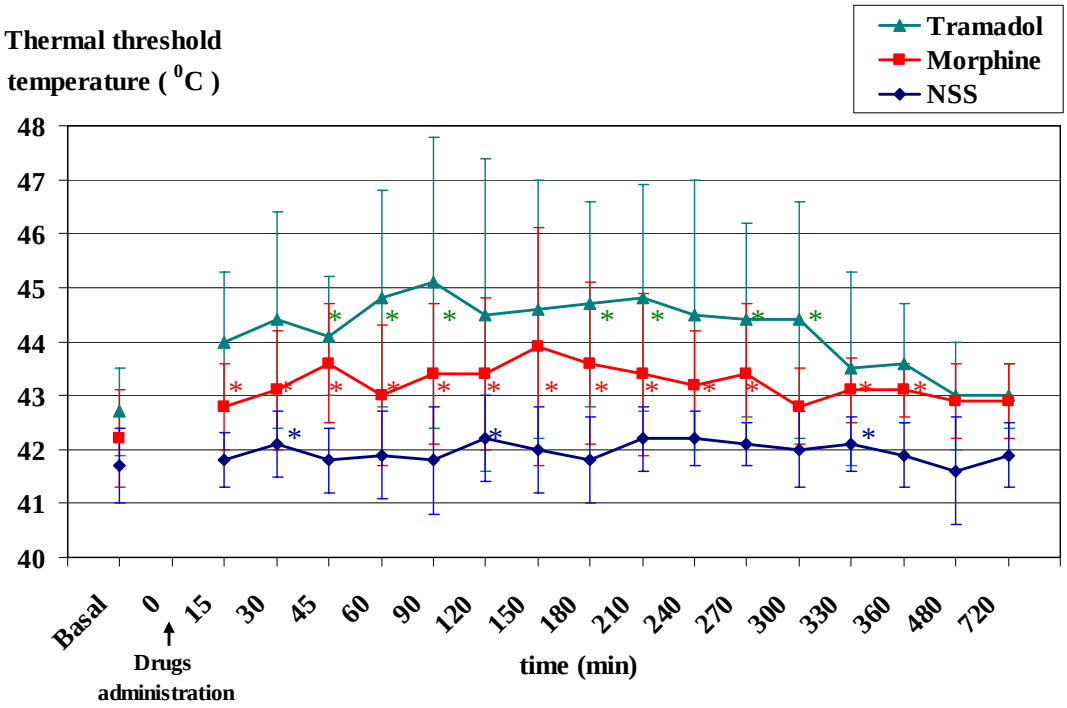

Figure 4 Mean thermal thresholds±SD (^{0}C) obtained from 8 cats during thermal threshold testing.

In addition, cats have a lower clearance of tramadol results in a longer elimination half-life 3.4 hours (Pypendop and Ilkiw, 2007) than in dogs 1.71 hours (KuKanich and Papich, 2004). Furthermore, tramadol (1-4 mg/kg IV) in cats has caused a dose-dependent respiratory depressant effect on the increase in the apneic thresholds. Naloxone (0.1 mg/kg IV) has completely reversed the depressant effects which are mediated by an action on opioid receptors (Teppema et al., 2003). However, no adverse effect was observed after administration of tramadol and morphine in this report.

Pain assessment depends on the ability to produce pain in controlled trials and to measure grades of response in order to compare analgesics. The thermal threshold system has been developed specifically for the evaluation of analgesics in cats. In addition, this system has proved effective 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, 2004).

In this study, an evaluation of tramadol via the thermal threshold model showed the analgesic effect of tramadol on cats. Both tramadol and morphine increased the thermal thresholds significantly when compared to the pre-injection basal thermal thresholds. The mean thermal thresholds were significantly increased (ρ<0.05) from the pre-injection baseline between 15 min-6 hours after taking morphine and between 45 min-5 hours after taking tramadol.

A previous study of morphine (0.2 mg/kg IM) in cats showed an increased in the thermal threshold between 4-6 hours (Robertson et al., 2003), whereas this study showed an increase in the thermal thresholds of between 15 min–6 hours. The increased thermal thresholds of this study were related to the pharmacokinetics of morphine (0.2 mg/kg) in cats, which the times to peak plasma concentration (t_{max}) were 15 min after intramuscular administration (Taylor et al., 2001). The peak analgesic effect of morphine of the previous study was about 4 hours, whereas that of this study was about at 2.5 hours later. Moreover, morphine's duration of action was shorter in the previous study by about 2 hours.

The mean thermal thresholds in the previous study of tramadol (1 mg/kg SC) in cats did not change significantly from baseline (p>0.05) (Steagall et al., 2008) and there was no efficient analgesic effect in cats. However, the mean thermal thresholds of the present study increased significantly from 45 min - 5 hours after the intramuscular tramadol (2 mg/kg) administration. Moreover, tramadol produced dose-related antinociception in the hot-plate test in rats. The effects of tramadol in the hot-plate test were apparent between 45-120 min (20 mg/kg IP) and between 60-120 min (10 mg/kg IP). In contrast, tramadol (5 mg/kg IP) did not produce a significant antinocieptive effect at all time points (ρ>0.05) (Guneli

et al., 2007). It is conceivable that higher doses and a different route of administration might produce a greater analgesic effect.

The thermal threshold system detected that the analgesic effects of opioids in cats for example buprenorphine (0.01 mg/kg IM) that increase the thermal threshold significantly (Robertson et al., 2003) are clinically efficacious (Stanway et al., 2002; Robertson et al., 2005) and the duration of the effect of pethidine (5 mg/kg IM) that increases the thermal threshold significantly from 30-60 min (Dixon et al., 2002) correlated closely with clinical trial (Slingsby and Waterman-Pearson, 1998). Therefore, the analgesic effect testing results of the opioid drugs on the thermal thresholds in cats tend to be good predictors of the drugs' clinical performance and tramadol may possibly have a good clinical analgesic effect in cats. However, recent studies and this study have shown that cats may display marked variations in analgesic response to opioids in Thermal threshold response (Robetson et al., 2003; Lascelles and Robertson, 2004; Steagall et al., 2008) and postoperative analgesia (Slingsby and Waterman-Pearson). To illustrate, the thermal thresholds were high in some cats after opioid administration, but did not increase at all in others. Moreover, the pharmacokinetic data for opioids such as morphine (Taylor et al., 2001) and tramadol (Pypendop and Ilkiw, 2007) show considerable inter-individual variation. The maximal plasma concentration (C_{max}) and the time for the administration to reach the maximal plasma concentration (t_{max}) were variable among cats. For example, the time for tramadol administration to reach the maximal plasma concentration (t_{max}) ranges from 20-90 min (5 mg/kg PO) and 15-119 min (2 mg/kg IV) (Pypendop and Ilkiw, 2007). In addition, the longer terminal half-life after oral administration and the lower rate of formation of the metabolite after oral rather than after i.v. tramadol administration may suggest that the kinetics for tramadol are dose dependent (Pypendop and Ilkiw, 2007).

Therefore, there is the necessity for a careful approach to pain management in cats because one analgesic at a set dose is unlikely to be equally effective in all patients. Further clinical studies comparing different doses and routes of administration of tramadol should be investigated to establish the best dosing protocols in clinical feline pain management.

In conclusion, tramadol had an efficacy comparable to morphine on the antinociceptive effect by increasing thermal threshold response in cats when compared to the pre-injection basal thermal threshold.

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