Gabapentin is a structural analogue of GABA, which was originally developed as an antiepileptic drug.1 Gabapentin was also found to be effective in the treatment of some chronic pain syndromes in people, such as postherpetic neuralgia, postpoliomyelitis neuropathy, and reflex sympathetic dystrophy.1 More recently, gabapentin also decreased signs of pain and opioid consumption after surgery in various clinical studies,2–9 suggesting that it may be effective in the treatment of acute pain in humans.

Although gabapentin resembles GABA, it does not appear to interact with GABA_A or GABA_B receptors or inhibit GABA uptake. It is not metabolized into GABA or a GABA receptor agonist. Data suggest that it binds to the α2δ accessory subunit of voltage-dependent calcium channel complexes and has an inhibitory effect on voltage-gated calcium channels.10 Gabapentin has been shown to affect nociception in rats in various experimental pain models.11–14 However, in most of those studies, the effect of gabapentin was thought to be attributable to decreased hyperalgesia rather than direct antinociception. Nevertheless, it is unclear whether gabapentin is devoid of antinociceptive effect. In 1 study,15 local administration of gabapentin decreased acute thermal nociception in rats. Whether those results can be extrapolated to systemic administration remains to be elucidated.

The purpose of the study reported here was to characterize the effect of oral administration of gabapentin on the nociceptive thermal threshold in cats and the dose dependence of that effect, and to examine the relationship between plasma gabapentin concentration and antinociceptive effect. We hypothesized that oral administration of gabapentin would increase the thermal threshold in cats in a dose-dependent manner.

**Objective**—To determine the thermal antinociceptive effect of various single doses of gabapentin administered orally in cats.

**Animals**—6 healthy adult domestic shorthair cats.

**Procedures**—Baseline skin temperature and baseline thermal threshold were determined via application of a thermal probe to the thorax of each cat prior to oral administration (in random order) of an empty capsule (placebo) or a capsule containing 5, 10, or 30 mg of gabapentin/kg (4 experiments/cat). After each treatment, thermal threshold was determined at intervals during an 8-hour period. Plasma gabapentin concentration was measured prior to and at 1-hour intervals after drug administration. Dose and time effects were analyzed by use of a repeated-measures ANOVA.

**Results**—Peak plasma gabapentin concentration increased with increasing gabapentin dose. After administration of the 5, 10, and 30 mg/kg doses, median interval until the greatest gabapentin concentration was detected was 60, 120, and 90 minutes, respectively (interval ranges were 60 to 120 minutes, 60 to 120 minutes, and 60 to 180 minutes, respectively). In the experiments involving administration of the placebo or increasing doses of gabapentin, mean ± SD baseline skin temperature and thermal threshold were 36.8 ± 1.21°C and 45.8 ± 4.4°C, 36.9 ± 1.1°C and 43.1 ± 2.4°C, 37.0 ± 0.7°C and 44.0 ± 1.5°C, and 36.1 ± 1.7°C and 43.3 ± 3.3°C, respectively. There was no significant effect of treatment on thermal threshold.

**Conclusions and Clinical Relevance**—At the doses evaluated, orally administered gabapentin did not affect the thermal threshold in healthy cats and therefore did not appear to provide thermal antinociception. (Am J Vet Res 2010;71:1027–1032)

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**Abbreviations**

GABA γ-Aminobutyric acid
LC Liquid chromatography
MS Mass spectrometry

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Thermal antinociceptive effect of orally administered gabapentin in healthy cats

Bruno H. Pypendop, DrMedVet, DrVetSci; Kristine T. Siao, BS; Jan E. Ilkiw, BVSc, PhD

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**Conclusions and Clinical Relevance**—At the doses evaluated, orally administered gabapentin did not affect the thermal threshold in healthy cats and therefore did not appear to provide thermal antinociception. (Am J Vet Res 2010;71:1027–1032)
Cats were deemed healthy on the basis of physical examination findings and the lack of clinical signs of disease for at least 3 months prior to the study. Each cat was used in 4 experiments with a minimum interval of 2 weeks between successive experiments. The study was approved by the Institutional Animal Care and Use Committee at the University of California-Davis. Cats were observed for behavioral changes and other visible drug effects during the study period.

**Instrumentation and drug administration**—The day before an experiment, food was withheld from each cat for at least 4 hours before it was anesthetized with isoflurane in oxygen delivered in an acrylic chamber. After anesthesia was induced, the trachea was intubated and anesthesia was maintained with isoflurane in oxygen delivered via a coaxial Mapleson F circuit. A 22-gauge, 10-cm-long catheter was aseptically placed in a jugular vein. The catheter was capped with an infusion plug and sutured to the skin. A light bandage was placed over the catheter insertion site. The lateral aspect of the thorax (between the caudal aspect of the scapula and the last rib, and from the sternum to the vertebral column) was clipped, and the cat was allowed to recover from anesthesia.

Gabapentin (90.7% pure [no excipient]) was packaged into gelatin capsules in doses of approximately 5, 10, and 30 mg/kg. The day of an experiment (ie, at least 12 hours after anesthesia), gabapentin (1 of the 3 doses/d) or placebo (empty gelatin capsule) was administered orally. Cats were under continuous observation for at least 1 hour after capsule administration to ensure that vomiting would be witnessed if it occurred. For each cat, the order of administration of the 4 study doses was randomly selected by use of a computer-generated random list.

**Thermal threshold determination**—For each experiment, each cat was placed in an individual cage (80 × 60 × 65 cm) that had a transparent acrylic door and mirrors on each sidewall. Cats had been acclimatized to the cage and placement of the thermal threshold probe prior to the study. During acclimatization, each cat was brought to the laboratory 2 to 3 times a week for at least 4 weeks and an elastic band and pressure cuff similar to those used during the study were placed on the lateral aspect of the thorax; the cat remained in a cage used for the study for several hours with intermittent interaction with an investigator. The thermal threshold testing system used in the study was identical to that previously developed and validated for use in cats and used in various investigations of the effects of analgesic drugs in that species.36-38

A probe containing a heater element and an adjacent temperature sensor, both of which were embedded in epoxy, was attached to a pressure cuff and held in position over the lateral aspect of the thorax by use of an elastic band. The pressure cuff was inflated to 100 mm Hg to ensure good contact between the probe and skin. The cuff bladder was visually inspected before each measurement and reinflated if necessary. Before each measurement, the probe was connected to a control unit by a flexible cable. Each cat was allowed to move freely in the cage and had free access to food and water during the experiments.

Skin temperature was measured, and the heater was activated (rate of temperature increase, 0.6°C/s). The cat was observed until a reaction (eg, jumping, turning the head toward the probe, or licking or biting the probe area or cable) was detected or a maximal temperature (35°C) was reached. When a reaction was observed before the cutoff temperature was achieved, the temperature was recorded and considered the thermal threshold, and the heater was turned off. Thermal thresholds were always determined by the same investigator (BHP), who was unaware of treatment assignments. Before drug administration, at least 30 minutes were allowed for equilibration between probe and skin temperatures, then baseline skin temperature and baseline thermal threshold values were determined in duplicate at 20-minute intervals. Ten minutes after determination of baseline values, 1 of the 4 treatments was administered (designated as 0 minutes). Following capsule administration, skin temperature and thermal threshold were determined every 20 minutes for 1 hour and then at 1-hour intervals for an additional 7 hours. A single thermal threshold determination was performed at each time point.

Thermal probes were calibrated weekly during the study. For calibration, the probe was securely attached on top of a 9.0 × 9.0 × 0.5-cm aluminum plate. A thermocouple was placed in a previously drilled horizontal hole so that the tip was directly below the probe and was connected to a digital thermometer, the accuracy of which had been verified against a certified thermometer. The aluminum block was placed on a standard laboratory hotplate that was heated to approximately 85°C and then allowed to cool to 30°C. As the hotplate temperature changed from 65° to 30°C, measurements from the probe and thermocouple were recorded at decrements of 5.0°C. The probe response was linear within that range (linear regression correlation coefficient [R²], > 0.998). A calibration curve was constructed by use of linear regression, and temperatures recorded during the treatment experiments were mathematically corrected by use of the most recent curve for that probe.

**Blood sample collection**—A blood sample (2 mL) was obtained from each cat via the jugular catheter prior to placebo or gabapentin administration and at 1-hour intervals thereafter until completion of each experiment. At least 5 mL of blood was scavenged in a syringe containing heparin prior to collection of the sample. Scavenged blood was injected back through the catheter after sample collection, and the catheter was flushed with 2 mL of physiologic saline (0.9% NaCl) solution containing heparin (1 U of heparin/mL). The catheter was removed immediately after the last thermal threshold determination. Blood samples were transferred to tubes containing EDTA and immediately placed on ice. Within 10 minutes after collection, samples were centrifuged at 3,901 × g for 10 minutes at 4°C; the plasma was separated and stored at −20°C until analysis.

**Assessment of plasma gabapentin concentration**—Plasma gabapentin concentration was not measured in the blood samples collected after placebo administration. Gabapentin was quantitated in feline plasma by LC-MS analysis of extracted plasma samples. The cali-
ibration standards were prepared; stock solutions were prepared by dissolving 10.0 mg of gabapentin standard\(^c\) in 10.0 mL of acetonitrile,\(^d\) and working solutions were prepared by dilution of the gabapentin stock solution with acetonitrile to achieve concentrations of 10.0, 1.0, and 0.1 mg/mL. Plasma calibrators were prepared by dilution of the working gabapentin solutions with drug-free feline plasma to achieve concentrations of 0.5, 2.0, 5.0, 10, 25, 50, 100, 500, 1,000, 2,000, 5,000 10,000, 20,000, and 30,000 ng/mL. Calibration curves and negative control samples were prepared fresh for each quantitative assay. In addition, quality-control samples (plasma fortified with analytes at concentrations at the mid-point of the standard curve) were routinely included as an additional assessment of accuracy.

The concentration of gabapentin in each sample was determined with the internal standard (baclofen\(^f\)) method by use of the peak area ratio and linear regression analysis. Quantitative analyses were performed on an MS unit\(^g\) coupled with an LC system.\(^h\) Chromatography involved use of a 50 × 2.1-mm, 3-m column\(^i\) and a linear gradient of acetonitrile in water with 0.2% formic acid\(^i\) at a constant flow rate of 0.4 mL/min. The acetonitrile concentration was held at 2% for 0.3 minutes and increased to 98% during a 2-minute period. Prior to analysis, all plasma samples were extracted via solid-phase extraction. Aliquots of 0.4 mL of plasma were each treated with 2.0 mL of phosphate buffer (pH, 7.0), fortified with 4 ng of internal standard, and subjected to an extraction procedure that was developed to elute gabapentin and baclofen in a single fraction. Injection volumes were each 30 µL. Detection and quantification used full-scan LC-MS-MS transitions of initial product ions for gabapentin (mass-to-charge ratio, 172.1). The response for the major product ion for gabapentin (mass-to-charge ratio, 154.1) was plotted, and peaks at the proper retention time were integrated by use of a computer program.\(^j\) The same software program was used to generate calibration curves and quantitate the analyte concentrations in all samples.

The concentration of gabapentin in each plasma sample (eg, in calibrators, quality-control samples, and study samples) was determined by use of an internal standard method involving the peak area ratio and linear regression analysis. The response for gabapentin was linear with correlation coefficients \(R^2 ≥ 0.99\). The technique was optimized to provide a limit of detection of 0.5 ng/mL and limit of quantitation of 2.0 ng/mL. Intraday accuracy (percentage of nominal concentration) was 94% and 98% for 25 and 500 ng of gabapentin/mL, respectively. Interday accuracy (percentage of nominal concentration) was 92% and 96% for 25 and 500 ng of gabapentin/mL, respectively. Intraday precision (percentage of relative SD) was 2.7% and 1.8% for 25 and 500 ng of gabapentin/mL, respectively. Interday precision (percentage of nominal concentration) was 6.4% and 5.3% for 25 and 500 ng of gabapentin/mL, respectively. Precision and accuracy were expected to be similar or better for higher concentrations within the calibration curve (ie, up to 30,000 ng/mL).

### Statistical analysis

Power analysis that was based on the results of other thermal threshold studies\(^18,19\) previously conducted by our group suggested that 6 cats were needed to detect a thermal threshold increase of 5°C, with an \(α\) level of 0.05 and a power of 0.8. Skin temperature, thermal threshold, and thermal excursion (ie, the difference between thermal threshold and skin temperature at a given time point) data were analyzed for time and treatment effects by use of a repeated-measures ANOVA. A Dunnett test for pair-
wise comparisons with baseline values or a Tukey test for pairwise comparisons was used when appropriate to detect differences in skin temperature, thermal threshold, or thermal excursion. Statistical significance was set at a value of $P < 0.05$. Data are reported as mean ± SD, except where indicated otherwise.

**Results**

None of the cats had an exaggerated response to the stimulus or developed signs of skin burns. No behavioral effect following administration of gabapentin or placebo was observed. Actual mean ± SD gabapentin doses in the placebo and 5, 10, and 30 mg/kg treatments were 0 ± 0 mg/kg, 5.1 ± 0.11 mg/kg, 10.18 ± 0.08 mg/kg, and 30.19 ± 0.2 mg/kg, respectively. Mean ± SD baseline skin temperature, baseline thermal threshold, and baseline thermal excursion were 36.8 ± 1.1°C, 45.8 ± 4.4°C, and 9.0 ± 4.8°C, respectively, for the placebo treatment; 36.9 ± 1.1°C, 43.1 ± 2.4°C, and 6.2 ± 1.9°C, respectively, for the 5 mg/kg treatment; 37.0 ± 0.7°C, 44 ± 1.5°C, and 7.0 ± 1.7°C, respectively, for the 10 mg/kg treatment; and 36.1 ± 1.7°C, 43.3 ± 3.3°C, and 7.2 ± 2.3°C, respectively, for the 30 mg/kg treatment. Baseline values did not differ significantly among treatments. A significant time effect on skin temperature was detected when the cats received the 10 mg/kg treatment (maximum and minimum mean skin temperature were 37.0°C and 36.1°C, respectively). Pairwise comparisons of data obtained after treatment with baseline values did not reveal any significant differences. No significant treatment or time effect was detected for thermal threshold or thermal excursion (Figure 1).

Plasma gabapentin concentrations were proportional to the dose administered to the cats. Peak concentrations were 6,337 ± 1,334 ng/mL, 10,834 ± 2,839 ng/mL, and 25,464 ± 8,634 ng/mL following administration of 5, 10, and 30 mg/kg of gabapentin, respectively. After administration of the 5, 10, and 30 mg/kg doses, median intervals until the greatest gabapentin concentration was detected were 60, 120, and 90 minutes, respectively (interval ranges were 60 to 120 minutes, 60 to 120 minutes, and 60 to 180 minutes, respectively). Plasma gabapentin concentration significantly decreased over the 8-hour period following oral administration of any of the 3 drug doses (Figure 2).

**Discussion**

In the present study, gabapentin administered orally at doses of 5, 10, and 30 mg/kg had no effect on the thermal threshold in a group of 6 healthy cats. There are several possible explanations for this finding. The evaluated doses of gabapentin may have been inadequate (ie, subtherapeutic). Appropriate dosages of gabapentin to provide an analgesic effect have not been established in cats. Anecdotal reports recommend oral administration of 2.5 to 50 mg of gabapentin/kg 2 to 3 times a day, with an initial dosage of 2.5 to 10 mg/kg twice a day. Although the dose range in our study did not include the highest of those recommended doses, it did encompass the most common and clinically accepted doses. Nevertheless, it is possible that gabapentin would result in thermal antinociception at higher doses. Another consideration is that absorption of gabapentin may have been inadequate. Commercial gabapentin formulations were not used in the study; instead, pure gabapentin was inserted in gelatin capsules. This may have resulted in poor or erratic absorption of the drug. Commercial formulations are indeed often optimized to maximize absorption. Peak plasma gabapentin concentration following administration of 600 mg to human volunteers that resulted in significant enhancement of morphine-induced analgesia was approximately 3,700 to 4,600 ng/mL. In the present study, peak plasma gabapentin concentration following administration of the lowest (ie, 5 mg/kg) dose in cats was 1.4 times as great as the high value in the range of achieved concentrations in the human volunteer study, and the 2 higher doses resulted in approximately proportionally higher plasma concentrations. It is therefore deemed unlikely that poor gabapentin absorption had a role in the lack of effect observed in the present study.

Also, thermal threshold testing may be an inadequate model with which to test the analgesic effect of gabapentin. Drugs may affect different types of pain (ie, thermal, mechanical, visceral, or inflammatory pain) differently, and it is possible that gabapentin induces analgesia for pain types other than that which is thermally induced. Although thermal antinociception after local administration of gabapentin in rats was detected in 1 study, it is unclear whether that effect can be extrapolated to the systemic administration of clinically relevant doses. It is indeed possible that the local tissue concentration was much higher following local application than after systemic administration. Moreover, in several pain studies involving various species, gabapentin appeared to provide antinociception, but in most of those studies, the effect could be attributed to an antihyperalgesic effect rather than to a direct effect on nociception. The thermal threshold experimental method is likely inadequate to test the effects of drugs on hyperalgesia, even after induction of

![Figure 2](image-url)
mild inflammation. Other experimental methods may be more likely to detect an analgesic effect of gabapentin in cats, if the drug induces such an effect. 26–31

Additionally, it is possible that gabapentin may potentiate the effect of other antinoceptive drugs without directly inducing antinoception. Although gabapentin decreased postoperative pain scores in people in several clinical studies, 2,3,5–9, all patients treated with gabapentin also received opioids. In healthy humans undergoing a nociceptive cold pressor test, gabapentin increased the analgesic effect of morphine but, when administered alone, it did not have a significant effect. 23 Finally, the lack of significant effect could be attributable to a type II statistical error. Prospective power analysis showed that the study reported here had adequate power (ie, power = 0.8); however, although adequate power limits the risk of a type II error, it does not eliminate that risk. The fact that no pattern of effect could be detected by examining the thermal threshold and thermal excursion data is compatible with—but cannot prove—a true lack of effect, particularly in a small study such as that reported here.

It is unclear why a significant decrease in skin temperature was detected over time in the cats following treatment with 10 mg of gabapentin/kg. The effect was of small magnitude (maximum and minimum mean skin temperatures were 37.0° and 36.1°C, respectively) and deemed unlikely to affect the results. It has been reported that the reproducibility of skin temperature measurements is affected by the quality of the hair clipping and by the pressure in the inflatable bladder of the blood pressure cuff. 16 In the present study, attention was paid to clip each cat’s hair as short as possible without damaging the skin, to test the thermal threshold within 1 day after clipping (as previously recommended), and to clip a wide area so that if the probe moved slightly during the study, hair would not insulate the skin. 16 In addition, poor clipping would be expected to affect all measurements rather than to cause a change in temperature over time. The inflatable bladder of the blood pressure cuff was inspected visually before each measurement and reinflated if it appeared deflated. Dixon et al 16 have reported that loss of pressure in the cuff bladder is a potential cause for measurement inaccuracy and is easily detected by visual inspection. Finally, it is possible that the probe moved slightly during the study and that this resulted in an alteration in the skin temperature. Skin temperature could have been included as a covariate in the analysis of thermal excursion; it was deemed unnecessary because a decrease in skin temperature would increase the thermal excursion at a constant thermal threshold, and results of thermal excursion data analysis were not significant without taking into account that change in skin temperature.

In the present study, no effect of orally administered gabapentin on the thermal threshold in cats was detected. The results suggest that gabapentin is unlikely to affect thermal nociception in cats. Further studies involving other nociceptive models, experimental models adapted to detect an antihyperalgesic effect, and combinations of gabapentin and other analgesic drugs are necessary to determine the role of gabapentin in the treatment of pain in cats, and to establish therapeutic doses.

References


