

The Effects of Gabapentin on Acute Opioid Tolerance to Remifentanil Under Sevoflurane Anesthesia in Rats

Delia Aguado, DVM,*† Mariana Abreu, DVM,*† Javier Benito, DVM,‡
Javier Garcia-Fernandez, MD, PhD,§ and Ignacio A. Gómez de Segura, DVM, PhD, DECLAM, DECVAA*

BACKGROUND: Tolerance to remifentanil during sevoflurane anesthesia may blunt the ability of this drug to reduce anesthetic requirements. Gabapentin has been shown to be effective in reducing postoperative narcotic usage, a reduction that may be associated with a reduction in opioid-induced tolerance and hyperalgesia. We sought to determine whether gabapentin might prevent the observed acute opioid tolerance (AOT) produced by remifentanil in sevoflurane minimum alveolar concentration (MAC).

METHODS: Wistar rats were anesthetized with sevoflurane and the effects of gabapentin alone on sevoflurane MAC were determined at doses of 150 and 300 mg · kg⁻¹. In a second experiment, gabapentin 300 mg · kg⁻¹ was administered before remifentanil (120 and 240 μg · kg⁻¹ · h⁻¹). The MAC was determined before gabapentin administration and 3 more times at 1.5-hour intervals after drug administration to assess AOT. MAC was determined from intratracheal gas samples using a sidestream gas analyzer; tail clamping was used as a supramaximal stimulus. Statistical analysis was performed with the 1-way analysis of variance test.

RESULTS: Remifentanil reduced MAC (2.5% ± 0.2%) by 16% ± 5% and 36% ± 6% (120 and 240 μg · kg⁻¹ · h⁻¹, respectively, *P* < 0.01) with a further reduction produced by coadministration with gabapentin 300 mg · kg⁻¹ to 39% ± 12% and 62% ± 14%, respectively (*P* < 0.01 versus remifentanil alone). Gabapentin given alone at 150 and 300 mg · kg⁻¹ reduced MAC by 26% (both doses, *P* < 0.01). AOT was observed with remifentanil and characterized by a lower degree of MAC reduction, approximately 1.5 hours later (*P* < 0.05). However, when remifentanil was administered with gabapentin, the AOT to remifentanil was not observed (*P* > 0.05).

CONCLUSIONS: Gabapentin reduced the sevoflurane MAC and enhanced the MAC reduction produced by remifentanil. This enhancement may limit AOT in rats. (*Anesth Analg* 2012;115:40–5)

Remifentanil is a potent opioid analgesic used during the perioperative and critical care period¹ for its favorable pharmacokinetic characteristics, including the rapid and predictable onset and offset of the analgesic effect. However, evidence suggests that opioid analgesic effectiveness may be limited by tolerance and opioid-induced hyperalgesia,² leading to increased postoperative pain and morphine consumption.³ Studies performed in volunteers showed an early (3 hours) development of acute opioid tolerance (AOT) to the analgesic action of remifentanil.⁴ However, a lack of tolerance to remifentanil has also been reported.⁵ A recent study in rats showed that AOT blunted the sevoflurane minimum alveolar concentration

(MAC) reduction produced by remifentanil,⁶ suggesting a perioperative decrease in analgesic efficacy.

Gabapentin, frequently used as an antiepileptic drug, is also used in the treatment of neuropathic pain,⁷ perioperative pain management,⁸ and opioid-induced hyperalgesia.⁹ Gabapentin has also been shown to inhibit the development of morphine tolerance.^{10–12} There is little information describing the potential interactions among gabapentin, inhaled anesthetics, and opioids. Therefore, we hypothesized that gabapentin might prevent AOT to remifentanil during inhaled anesthesia in terms of MAC reduction. Our aim was to determine whether gabapentin might prevent the observed AOT produced by remifentanil in the sevoflurane MAC.

METHODS

After obtaining approval from the Institutional Animal Care Committee (La Paz University Hospital, Madrid, Spain), the reduction of the sevoflurane MAC in response to gabapentin and remifentanil was evaluated in rats. Sevoflurane was obtained from Abbott (Sevorane; Madrid, Spain); gabapentin was obtained from Pharmagenus (Gabapentina; Uriach Group, Barcelona, Spain); and remifentanil was obtained from Glaxo-Wellcome (Ultiva; Madrid, Spain).

Forty-two adult male Wistar rats (Charles River Laboratories, Barcelona, Spain) weighing 331 ± 42 g were housed in groups of 4 to 6 animals per cage (Macrolon type

Author affiliations are provided at the end of the article.

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Address correspondence to Ignacio A. Gómez de Segura, DVM, PhD, DECLAM, DECVAA, Department of Animal Medicine and Surgery, Veterinary Faculty, Complutense University of Madrid, Avda. Puerta de Hierro s/n, 28040 Madrid, Spain. Address e-mail to iagsegura@vet.ucm.es.

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IV) with a 12-hour light/12-hour dark cycle at a relative humidity of 40% to 70% and $20^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ambient temperature. Food (B&K Universal, Grimston, UK) and water were provided ad libitum. Animals were allowed to acclimatize for at least 1 week. All of the studies were performed during the morning (starting at 8:30 AM).

Rats were placed in an induction chamber into which 8% sevoflurane was directed in a continuous oxygen flow of $3 \text{ L} \cdot \text{min}^{-1}$ (sevoflurane vaporizer, Sevoflurane, Dragër Vapor 2000; Dragër Medical, Lubeck, Germany). Endotracheal intubation was performed using a 14-gauge polyethylene catheter (Terumo Surflo IV Catheter; Terumo Europe NV, Leuven, Belgium) with the animal positioned in sternal recumbency. A flexible, blunt-tipped wire guide was inserted into the trachea with an otoscope and used to direct the endotracheal catheter. After the catheter was properly positioned, it was connected to a small T piece breathing system with minimum dead space. Fresh gas flow to the T piece was adjusted to $1 \text{ L} \cdot \text{min}^{-1}$ of oxygen (100%), and the sevoflurane concentration was adjusted to $1.5 \times \text{MAC}$ (3.5%–4% vol). Rats were kept under spontaneous ventilation throughout the experiment. Gabapentin capsules were diluted in saline and administered per os (orally) by gavage using a polyvinyl chloride catheter (suction catheter 2.0 mm \times length 270 mm; Vygon, Ecouen, France). Remifentanyl was administered IV with an infusion pump (syringe pump, model Sep11S; Ascor SA, Warsaw, Poland) using a 22-gauge polyethylene catheter inserted in a tail vein.

Monitoring

Heart rate and arterial oxygen hemoglobin saturation (via pulse oximetry) as well as respiratory rate were recorded continuously (RGB; Medical Devices, Madrid, Spain). Rectal temperature was also monitored and maintained between 37.0°C and 38.5°C using a water-circulating warming blanket (Heat Therapy Pump, model Tp-220; Gaymar, Orchard Park, NY) and a heating light.

Determination of the MAC

Intratracheal gas sampling was used to measure the anesthetic gas concentration and to determine the MAC. A fine catheter with a 0.9-mm external diameter was inserted through the endotracheal catheter with the fine catheter tip located at the level of the carina, and gas samples were assayed using a sidestream infrared analyzer (Capnomac Ultima; Datex-Ohmeda, Hertfordshire, UK).

A supramaximal noxious stimulus was applied with a long hemostat (8-in. Rochester Dean Hemostatic Forceps) clamped to the first ratchet lock on the tail for 60 seconds, or until positive response was observed, immediately before the gas sample was obtained from the trachea. The tail was always stimulated proximally to a previous test site when the previous response was negative, or it was stimulated more distally if the response was positive, starting 6 cm from the tail base. A positive response was considered to be a gross purposeful movement of the head, extremities, or body. A negative response was considered to be the lack of movement or grimacing, swallowing, chewing, or tail flicking. When a negative response was seen, the sevoflurane concentration was reduced in decrements of 0.2% vol

until the negative response became positive. Similarly, when a positive response was seen, the sevoflurane concentration was increased by 0.2% vol until the positive response became negative. The MAC was considered to be the concentration midway between the highest concentration that permitted movement in response to the stimulus and the lowest concentration that prevented such movement. Determination of the MAC was performed in a laboratory 650 m above sea level, which decreases the barometric pressure and results in MAC values that are higher than those obtained at sea level. Therefore, MAC values were corrected to the barometric pressure at sea level using the following formula: $\text{MAC} (\%) \text{ at sea level barometric pressure (760 mm Hg) (altitude adjusted MAC)} = \text{measured MAC} (\%) \times \text{measured ambient barometric pressure (700 mm Hg in Madrid) / sea level barometric pressure (760 mm Hg)}$.

Experimental Design and Drug Groups

The MAC was determined 4 times in each animal (MAC-1, MAC-2, MAC-3, and MAC-4) (Fig. 1). In the first experiment, 3 groups of animals ($n = 6$ per group) were anesthetized, instrumented, and administered gabapentin (150 and 300 $\text{mg} \cdot \text{kg}^{-1}$ orally) or saline (1 mL, control group) just after induction. Periods of 30 minutes were allotted between MAC determinations, and periods of 40 to 60 minutes were usually necessary to determine the MAC value. Overall, each experiment lasted >6 hours.

In the second experiment, to evaluate the interaction of gabapentin with remifentanyl during AOT, another 4 groups of animals ($n = 6$ per group) were administered both drugs. Gabapentin (300 $\text{mg} \cdot \text{kg}^{-1}$) or saline was given orally combined with remifentanyl (120 or 240 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, low and high doses, respectively) administered IV without an initial loading dose using a constant rate of infusion into the tail. A baseline MAC was determined (MAC-1), and each animal acted as its own control. Gabapentin or saline was then administered, and the MAC was redetermined (MAC-2). Next, remifentanyl (120 or 240 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was administered, and MAC was redetermined twice (MAC-3 and MAC-4). Animals were euthanized with an overdose of potassium chloride given IV while they were still deeply anesthetized.

Doses of drugs used in rats are frequently higher compared with humans and their extrapolation between species should be based on allometric escalation.¹³ Gabapentin doses were based on their ability to produce analgesia in rats¹⁴ and block AOT or hyperalgesia^{9,10,15}; otherwise, remifentanyl doses were those previously reported to achieve a significant MAC reduction.⁶

Statistical Analysis

Sample size calculations indicated that an n value of 6 was necessary to determine differences in MAC reduction produced by remifentanyl and the remifentanyl-induced AOT with a power of 80% and a P value of 0.05 to determine at least a 10% change in MAC.⁶ The mean and SD were obtained from a previous study,⁶ and the statistical package used was N Query Advisor (version 2.0; Statistical Solutions, Saugus, MA).

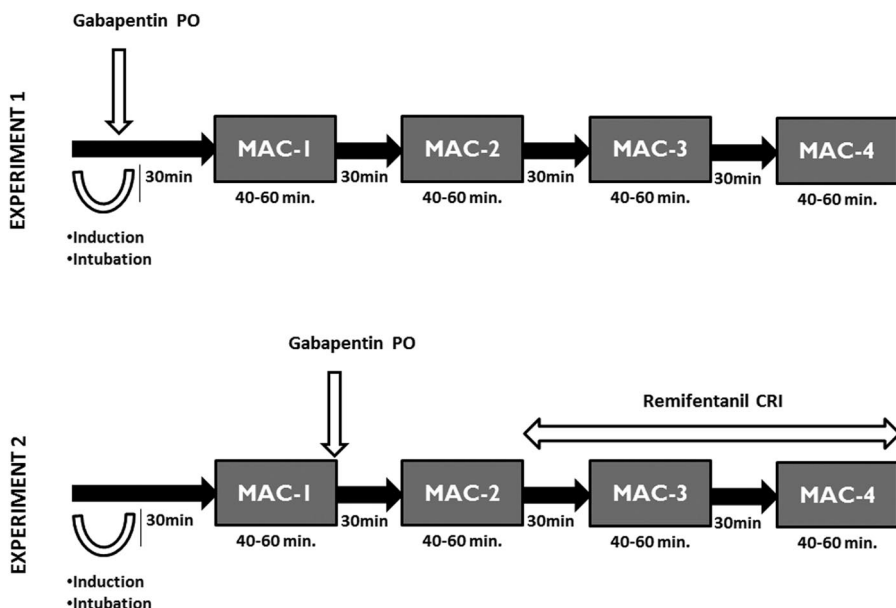


Figure 1. Experimental design. PO = per os; MAC = minimum alveolar concentration; CRI = constant rate infusion.

Results are presented as the mean \pm SD. Rats in each experiment were randomly allocated using a random number generator (Excel 2007, Microsoft Office). The data were tested for normality with the Kolmogorov-Smirnov test. To assess the effects of remifentanyl, gabapentin, and the combination of both drugs on the absolute and relative (percentage of variation) MAC values, the repeated-measures analysis of variance, with dose as the between-subjects factor, was used. To assess the appearance of AOT, a 1-way analysis of variance was used to compare MAC-3 and MAC-4. The Bonferroni post hoc test was used to compare groups. A *P* value of <0.05 was set to indicate statistical significance. All analyses were performed using the SPSS statistical package (version 19 for Windows, 2010; SPSS Inc., Chicago, IL).

RESULTS

Gabapentin Reduced the MAC

The MAC determined in the group administered saline alone ($n = 6$) was $2.3\% \pm 0.2\%$ vol, with no difference over time (MAC-1 to -4; $P > 0.05$) (Fig. 2). Gabapentin reduced the MAC by 26% at MAC-3 ($1.7\% \pm 0.3\%$ vol and $1.7\% \pm 0.1\%$ vol, with 150 and $300 \text{ mg} \cdot \text{kg}^{-1}$ orally, respectively), and by 25% to 30% at MAC-4 ($1.6\% \pm 0.2\%$ vol and $1.7\% \pm 0.2\%$ vol, with 150 and $300 \text{ mg} \cdot \text{kg}^{-1}$ orally, respectively). There were no differences between the MAC values (MAC-1 to -4) at either gabapentin dose (150 or $300 \text{ mg} \cdot \text{kg}^{-1}$ orally).

Gabapentin Enhanced the Remifentanyl-Induced MAC Reduction

The baseline MAC (MAC-1) determined in all rats was $2.2\% \pm 0.3\%$ vol ($n = 24$) and was similar between groups ($P > 0.05$) (Fig. 3, A and B). When administered alone, remifentanyl dose-dependently reduced the MAC (MAC-3) by $16\% \pm 5\%$ and $36\% \pm 6\%$ when given at the low and high doses, respectively ($P < 0.01$). When gabapentin ($300 \text{ mg} \cdot \text{kg}^{-1}$) was administered before the remifentanyl infusion, the MAC reduction was enhanced to $39\% \pm 12\%$ and $62\% \pm 14\%$ when

remifentanyl was given at the low and high doses, respectively ($P < 0.01$ versus remifentanyl group).

Gabapentin Blunted the Remifentanyl-Induced AOT in the MAC

A remifentanyl-induced AOT was observed approximately 1.5 hours later with a lower MAC reduction (MAC-3 versus MAC-4; $P = 0.03$, $P < 0.01$) when remifentanyl was administered alone at either dose (Fig. 3, A and B). When gabapentin was administered before the remifentanyl infusion, the MAC reduction was not different (MAC-4 versus MAC-3; $P = 0.511$, $P = 0.051$ at the low and high remifentanyl dose, respectively), suggesting a lack of remifentanyl-induced AOT.

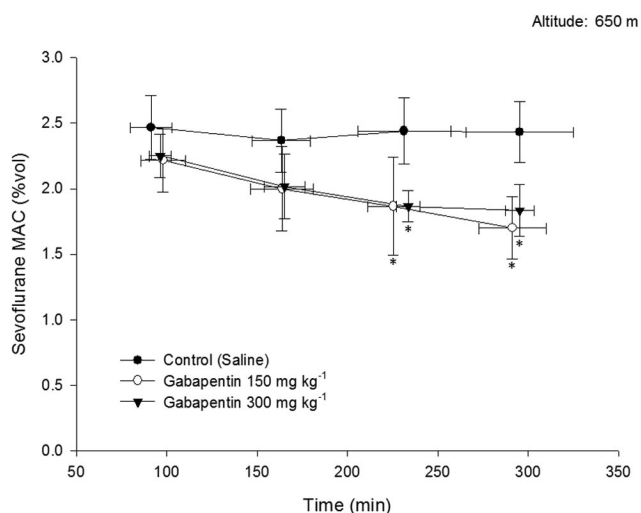


Figure 2. Reduction of the minimum alveolar concentration (MAC) of sevoflurane (% vol) produced by gabapentin (150 and $300 \text{ mg} \cdot \text{kg}^{-1}$ orally) or saline. Data are expressed as the mean \pm SD. The *n* value is always 6 animals per group. *Significantly different from control group (saline instead of gabapentin); $P < 0.01$.

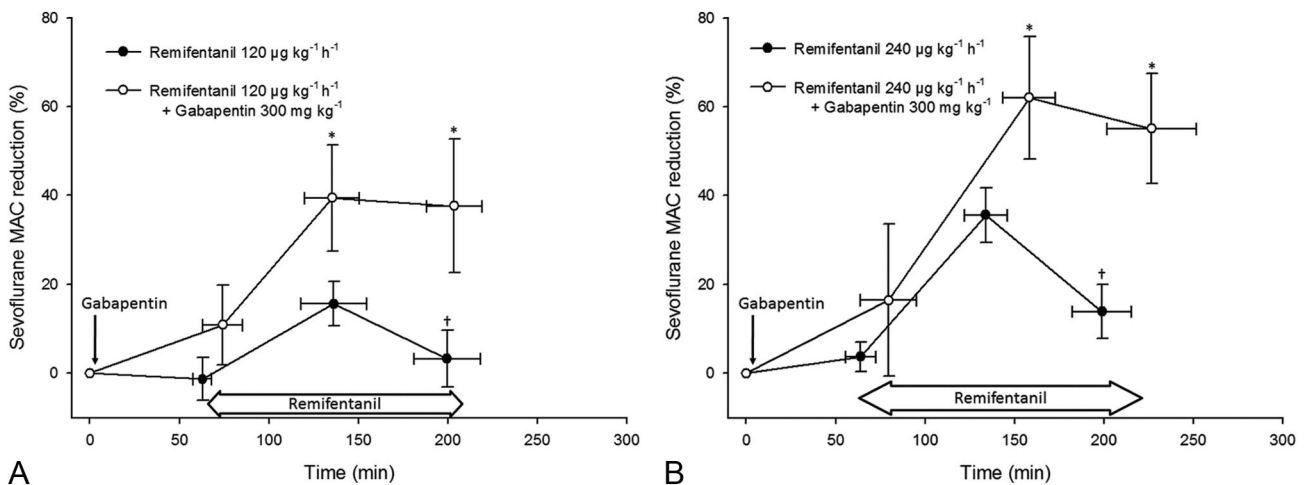


Figure 3. Reduction of the minimum alveolar concentration (MAC) of sevoflurane (%) produced by gabapentin ($300 \text{ mg} \cdot \text{kg}^{-1}$ orally) or saline administered before MAC-2, and remifentanyl (A: $120 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$; B: $240 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) administered just after MAC-2 determination. Data are expressed as the mean \pm SD. The n value is always 6 animals per group. *Significantly different from remifentanyl group; $P < 0.01$. †MAC-4 significantly different from MAC-3 (acute opioid tolerance effect); $P < 0.05$.

DISCUSSION

Gabapentin reduces the MAC in rats (25%–30%) to a clinically significant extent with a delayed onset and without differences between the 2 doses assessed. However, gabapentin similarly decreased the MAC in an additive manner when it was combined with remifentanyl at either dose studied. Furthermore, preemptive gabapentin administration prevented or blunted remifentanyl-induced AOT, although an additive effect of both drugs on the MAC cannot be excluded. The combined effects of gabapentin and remifentanyl in the intraoperative period have not been determined previously nor has the potential preventive or therapeutic effect of gabapentin in hyperalgesia or remifentanyl-induced opioid tolerance.

An analgesic effect of gabapentin has been described in rodents¹⁰ and humans,¹⁶ although there are also reports in which no analgesic effect could be established.¹¹ Preemptive gabapentin administration has been reported to reduce postoperative pain and analgesic consumption.^{17,18} No previous studies have demonstrated a potential anesthetic-sparing effect of gabapentin on the MAC in humans, but it has been recently determined in rats.¹⁹ In fact, the MAC reduction determined in this study was lower and may reflect differences in the timing of drug administration because gabapentin was given only 15 minutes before MAC determination, probably before maximum blood levels and the effect on MAC were achieved. A previous work in cats failed to demonstrate this sparing effect,²⁰ unlike the results in rats in the present study. The lack of effect could have been due to several reasons, such as an insufficient plasma concentration of gabapentin or delayed onset of the effect on the MAC, although steady-state plasma concentrations in past studies were maintained similar to studies performed in humans for up to 2.5 hours.²⁰ Nevertheless, in our study in rats, 2 doses of gabapentin were used and produced a similar effect on the MAC, suggesting that no further reduction in the MAC would be expected by increasing the dose. It is likely that the saturable absorption of gabapentin may account for this finding.²¹

The MAC reduction produced by gabapentin gradually increased over the course of the experiment. Gabapentin was given orally 40 minutes before starting the MAC determination, and the last MAC determination was measured approximately 4 hours later. Therefore, this drug should be given well in advance of anesthetic induction to ensure maximum plasma levels²⁰ and effects on the MAC. In fact, most clinical studies have reported that gabapentin was administered 1 to 2 hours before the induction of anesthesia.^{18,22,23}

Gabapentin administration has been reported for perioperative pain management⁸ in a multimodal analgesic approach.²⁴ The drug may enhance the analgesic effect of morphine,²⁵ decreasing its consumption during the postoperative period.²⁶ However, there are also studies in which gabapentin failed to produce these effects on postoperative pain.^{27,28} In animal models, the combination of gabapentin and opioids also produced contradictory results. An enhancement of the analgesic action has been determined with tramadol²⁹ and morphine³⁰ using the tail-flick test, but not with fentanyl using the paw pressure test.⁹ The additive action of gabapentin and remifentanyl in the MAC in this study may also suggest an enhancement of the analgesic effect.

A preventive effect of gabapentin in the development of opioid-induced hyperalgesia^{9,31} and delayed opioid tolerance^{10–12,32} has been assessed in animals, but only a few studies have assessed a similar action in humans, and the results are controversial.^{16,33}

Remifentanyl administered alone dose-dependently reduces the MAC in rats, although an AOT rapidly develops, characterized by a smaller MAC reduction approximately 1.5 hours later.⁶ This lower efficacy of remifentanyl for reducing the MAC of sevoflurane in the short term was determined in this study, but the administration of gabapentin prevented the phenomenon. Nevertheless, it could not be determined whether this lack of tolerance to remifentanyl was attributable to an additive effect between the 2 drugs or by some impairment in the development of

tolerance. However, a gradual increase in the MAC values despite the maintenance of the remifentanyl infusion (MAC-3 versus MAC-4, $P = 0.051$ with the high dose of gabapentin and remifentanyl) suggests that a tolerance effect may be still present.

The possibility of interference of gabapentin in the development of tolerance could not be excluded. Gabapentin has been shown to interact with receptors directly involved in the development of hyperalgesia and AOT by interacting with a subunit of voltage-gated calcium channels,³⁴ involved in pain transmitters into the spinal cord,³⁵ or with glutamate receptors,³⁶ such as *N*-methyl-D-aspartate receptors,³⁷ involved in opioid-tolerance and hyperalgesia mechanisms.³⁸

Extrapolation of the results of the present study to the clinical setting has limitations. The effects of gabapentin and remifentanyl on the MAC were assessed in rats, and potential differences may account for the efficacy of this drug when combined with opioids in reducing the MAC and blunting AOT in humans. Nevertheless, there are certain similarities between rats and humans; the pharmacokinetics of gabapentin are similar in both rats and humans, achieving a maximum concentration in the blood within 2 to 3 hours,^{21,39} suggesting that it should be administered in advance for optimal results, i.e., before remifentanyl induces AOT^{4,6} at approximately 1.5 hours. Unfortunately, the plasma levels of the drugs used in this study were not determined. Therefore, further studies should be conducted to determine whether the interaction observed in the rat is of clinical relevance.

Another limitation of the study is the method used to determine the interaction of gabapentin and remifentanyl (MAC reduction).⁴⁰ A direct link between analgesic potency and MAC reduction cannot be established intraoperatively during inhaled anesthesia. Potent analgesic drugs, such as opioids,⁴¹ and sedatives,^{42,43} decrease the MAC to a clinically relevant extent. Therefore, anesthetic immobility and analgesia are not necessarily linked,⁴⁴ and a variable effect on the MAC has been determined when different types of analgesic drugs are considered. Nevertheless, the MAC method mimics the intraoperative period and is of clinical relevance.

In conclusion, gabapentin enhanced the effect of remifentanyl, preventing AOT in the rat. Further studies are needed to determine the clinical relevance of these findings. ■■

AUTHOR AFFILIATIONS

From the *Department of Animal Medicine and Surgery, Veterinary Faculty, Complutense University of Madrid, Madrid; †Department of Experimental Surgery, La Paz University Hospital, Madrid, Spain; ‡Comparative Pain Research Laboratory, Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina; and §Department of Anesthesiology and Critical Care, Puerta de Hierro University Hospital, Madrid, Spain.

DISCLOSURES

Name: Delia Aguado, DVM.

Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.

Attestation: Delia Aguado has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

Name: Mariana Abreu, DVM.

Contribution: This author helped conduct the study.

Attestation: Mariana Abreu has seen the original study data and approved the final manuscript.

Name: Javier Benito, DVM.

Contribution: This author helped design the study and write the manuscript.

Attestation: Javier Benito has seen the original study data and approved the final manuscript.

Name: Javier Garcia-Fernandez, MD, PhD.

Contribution: This author helped design the study and write the manuscript.

Attestation: Javier Garcia-Fernandez approved the final manuscript.

Name: Ignacio A. Gómez de Segura, DVM, PhD, DECLAM, DECVA.

Contribution: This author helped design the study, analyze the data, and write the manuscript.

Attestation: Ignacio A. Gómez de Segura has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

This manuscript was handled by: Marcel E. Durieux, MD, PhD.

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