Effects of magnesium sulfate and propofol on the minimum alveolar concentration preventing motor movement in sevoflurane-anesthetized dogs

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OBJECTIVE
To evaluate the effect of $MgSO_4$, alone and in combination with propofol, on the minimum alveolar concentration preventing motor movement (MAC_{NM}) in sevoflurane-anesthetized dogs.

ANIMALS
6 healthy purpose-bred adult male Beagles (least squares mean ± SEM body weight, 12.0 ± 1.1 kg).

PROCEDURES
Dogs were anesthetized 3 times at weekly intervals. The MAC_{NM} was measured 45 minutes after induction of anesthesia (baseline; $MAC_{NM\text{-}B}$) and was determined each time by use of a noxious electrical stimulus. Treatments were administered as a loading dose and constant rate infusion (CRI) as follows: treatment 1, $MgSO_4$ loading dose of 45 mg/kg and CRI of 15 mg/kg/h; treatment 2, propofol loading dose of 4 mg/kg and CRI of 9 mg/kg/h; and treatment 3, $MgSO_4$ and propofol combination (same doses used previously for each drug). A mixed-model ANOVA and Tukey-Kramer tests were used to determine effects of each treatment on the percentage decrease from $MAC_{NM\text{-}B}$. Data were reported as least squares mean ± SEM values.

RESULTS
Decrease from $MAC_{NM\text{-}B}$ was 3.4 ± 3.1%, 48.3 ± 3.1%, and 50.3 ± 3.1%, for treatments 1, 2, and 3, respectively. The decrease for treatments 2 and 3 was significantly different from that for treatment 1; however, no significant difference existed between results for treatments 2 and 3.

CONCLUSIONS AND CLINICAL RELEVANCE
$MgSO_4$ did not affect MAC_{NM}, nor did it potentiate the effects of propofol on MAC_{NM}. Administration of $MgSO_4$ in this study appeared to provide no clinical advantage as an anesthetic adjuvant. (*Am J Vet Res* 2016;77:575–581)

Magnesium is the second most abundant intracellular cation and plays an integral role in several biological processes. It influences membrane potentials via modulatory effects on sodium and potassium currents and serves as a cofactor for protein synthesis, nucleic acid stabilization, and neuromuscular function.[1] Magnesium also acts as a calcium-channel antagonist and has inhibitory effects on the CNS, including antagonism of the *N*-methyl-D-aspartate glutamate receptor and suppression of catecholamine release from the adrenal medulla and adrenergic nerve endings.[1,2]

ABBREVIATIONS

CRI	Constant rate infusion
MAC	Minimum alveolar concentration
MAC_{NM}	Minimum alveolar concentration preventing motor movement
$MAC_{NM\text{-}B}$	Minimum alveolar concentration preventing motor movement measured at baseline
$MAC_{NM\text{-}T}$	Minimum alveolar concentration preventing motor movement measured after treatment
P_{ETCO_2}	End-tidal partial pressure of carbon dioxide
P_{ETSEVO}	End-tidal partial pressure of sevoflurane
TOF	Train-of-four

The administration of $MgSO_4$ has been associated with volatile and injectable anesthetic–sparing effects, augmentation of neuromuscular blockade, and attenuation of postoperative pain in human patients.[3–5] A volatile anesthetic–sparing effect of $MgSO_4$ has been found for human patients anesthetized with desflurane.[6,7] Injectable anesthetic– and analgesic-sparing effects of $MgSO_4$ have been reported for several agents, including propofol, fentanyl, remifentanil, and midazolam.[8–10] Postoperative administration of $MgSO_4$ decreases opioid consumption and pain scores in a variety of human surgical patients.[11–13] In particular, the propofol-sparing effect of Mg has been reported for several studies[14–16] of humans in which an infusion of Mg was used to decrease dose requirements of propofol during surgery and at the time of anesthetic induction. In dogs undergoing ovariohysterectomy, dose requirements of halothane and thiopental were decreased following anesthetic premedication and intraoperative infusion of $MgSO_4$.[17] The anesthetic- and analgesic-sparing properties of Mg have been attributed primarily to its antagonism of the *N*-methyl-D-aspar-

tate receptor[2]; thus, Mg may potentiate the effect of other agents (including volatile anesthetics, propofol, and ketamine) that act on the same receptor.[18–20]

On the basis of the proposed anesthetic-sparing mechanism of Mg and the reports of its volatile anesthetic– and propofol-sparing effects in humans, the objective of the study reported here was to evaluate the effects of IV administration of $MgSO_4$, alone and in combination with propofol, on the MAC_{NM} in sevoflurane-anesthetized dogs. The MAC_{NM} was used as an endpoint that corresponds to the lack of any motor movement in response to a noxious stimulation.[21–23] The hypothesis was that $MgSO_4$ would decrease the MAC_{NM} of sevoflurane and potentiate the MAC-sparing effect of propofol.

Materials and Methods

Animals

Six healthy adult (2 to 7 years old) purpose-bred male Beagles were selected for use in the study. Least squares mean ± SEM body weight was 12.0 ± 1.1 kg. The study was approved by an institutional animal care and use committee.

Experimental design

A computer-randomized[a] crossover (6 × 3) design was used. Each dog was anesthetized and evaluated 3 times. There was a minimum 7-day washout period between subsequent anesthetic episodes.

Anesthesia

Food was withheld from the dogs for 12 hours prior to anesthesia, but access to water was unrestricted. Anesthesia was induced by administration of sevoflurane[b] in oxygen (2 L/min) delivered via a mask attached to a circle system. An endotracheal tube was then inserted to the level of the thoracic inlet, and anesthesia was maintained with sevoflurane in oxygen (1 L/min) by use of a small animal anesthesia machine.[c] Anesthetized dogs were placed in right lateral recumbency and mechanically ventilated to maintain P_{ETCO_2} between 35 and 45 mm Hg. Values for P_{ETSEVO} and P_{ETCO_2} were monitored continuously (sampling rate, 200 mL/min) with an infrared gas analyzer[d] placed at the proximal end of the endotracheal tube. Before the start of each experiment, the gas analyzer was calibrated in accordance with the manufacturer's instructions by use of a manufactured calibration gas[e] containing known concentrations of desflurane, CO_2, nitrous oxide, and oxygen (2%, 5%, 33%, and 55%, respectively). A 20-gauge catheter[f] was placed in the right cephalic vein and used for infusion of lactated Ringer solution[g] (3 mL/kg/h), propofol,[h] and $MgSO_4$.[g] A second 20-gauge catheter was placed in the left jugular vein to facilitate blood collection for analysis of propofol and Mg concentrations. The ECG and heart rate were continuously monitored.[d] Blood pressure was noninvasively monitored by use of an oscillometric technique[d] with an appropriately sized cuff (width, approx 40% of the circumference of the limb) placed over the right dorsal pedal artery. Dobutamine was administered as a CRI, as necessary, if mean arterial blood pressure was < 60 mm Hg. An esophageal temperature probe[d] was used to monitor body temperature, and a circulating warm water blanket[i] and warm-air blanket[j] were used to maintain normothermia (37.5° to 38.5°C). The urinary bladder was manually expressed intermittently during anesthesia to prevent overdistention.

Acceleromyography

Acceleromyography[k] by use of the TOF ratio to monitor neuromuscular function was performed throughout the period of anesthesia. Two electrodes of the unit were attached to 2 needles inserted into the subcutaneous tissues over the common peroneal nerve of the left pelvic limb, and the accelerometer was affixed to the dorsal surface of the distal aspect of the metatarsal region. After anesthesia was induced but before each experiment was performed, the current for the supramaximal stimulus was determined by use of an automated function (ie, CAL2) of the unit, and 3 TOF ratios were determined every 15 minutes by use of a standard TOF stimulation (2 Hz for 0.2 milliseconds), as described elsewhere.[24] An interval of at least 10 minutes was allowed between each TOF stimulation and noxious electrical stimulation for MAC_{NM} determination to avoid interference between the 2 techniques. A TOF ratio > 90% was considered to be physiologically normal.[25]

Determination of $MAC_{NM\text{-}B}$

Determination of $MAC_{NM\text{-}B}$ was initiated 45 minutes after anesthetic induction (baseline). The P_{ETSEVO} was held constant at 2.4 vol% for a minimum of 15 minutes. A noxious electrical stimulus[l] (50 V at 50 Hz for 10 milliseconds) was delivered to the lateral aspect of the left forelimb via two 25-gauge needle electrodes inserted into the subcutaneous tissues 5 cm apart. The stimulation pattern included 2 initial single stimuli, which were followed by 2 continuous stimuli for 5 seconds; there was a 5-second interval between stimuli.[26] The MAC_{NM} was defined as the minimum P_{ETSEVO} that abolished motor movement in response to noxious stimulation. Withdrawal or twitching of the nonstimulated limbs, movement of the head, licking, chewing, swallowing, or blinking was considered a positive response; twitching of the stimulated limb was not considered a positive response.[21] After a positive response was obtained, P_{ETSEVO} was increased by 0.1 vol%; conversely, after a negative response was obtained, P_{ETSEVO} was decreased by 0.1 vol%. After a 15-minute equilibration period elapsed, the noxious stimulus was reapplied. The $MAC_{NM\text{-}B}$ was determined in duplicate, and the mean value was recorded as the $MAC_{NM\text{-}B}$ for that dog. Blood samples for analysis of propofol and Mg concentrations were collected at these duplicate time points, combined, and analyzed

to reflect the mean value. When the 2 MAC_{NM-B} values differed by > 10%, a third MAC_{NM-B} was determined, and the mean for all 3 values was used to determine MAC_{NM-B}. Time to MAC_{NM-B} was defined as the interval from anesthetic induction to the completion of the duplicate MAC_{NM-B} measurements.

Treatments

After MAC_{NM-B} was determined, dogs were initially arbitrarily assigned to receive 1 of the 3 treatments (loading dose followed by a CRI). Each treatment was administered IV. Treatment 1 was $MgSO_4$ (loading dose, 45 mg/kg; CRI, 15 mg/kg/h). Treatment 2 was propofol (loading dose, 4 mg/kg; CRI, 9 mg/kg/h). Treatment 3 was a combination of propofol and $MgSO_4$ at each of the aforementioned doses. The loading dose and CRI were started simultaneously. The loading dose was administered over a period of 20 minutes; the loading dose and CRI were administered with syringe pumps.[m] Blood samples were collected from dogs receiving treatments 1 and 3 into lithium-heparin tubes and used for measurement of the Mg concentration prior to starting administration of the loading dose. Magnesium concentrations were measured by use of a chemistry analyzer.[n]

The MAC_{NM-T} determination began 60 minutes after starting each treatment infusion. The Petsevo was held at each dog's MAC_{NM-B} for at least 15 minutes, and MAC_{NM-T} was determined in duplicate by use of the same technique described for MAC_{NM-B} determination. Time to MAC_{NM-T} was defined as the interval from the start of the treatment infusion to completion of the MAC_{NM-T} determination. Jugular blood samples (3 mL) were collected into a lithium-heparin tube from dogs receiving treatments 2 and 3 at the time of each MAC_{NM-T} determination and stored at –80°C; both samples subsequently were combined and used for analysis of propofol concentrations. Jugular blood samples were also collected from dogs receiving treatments 1 and 3 at the time of each MAC_{NM-T} determination; both samples were combined and used to measure the Mg concentration after treatment.

At the end of each experiment, sevoflurane and all infusions were discontinued, and the dogs were allowed to recover from anesthesia. Dogs were extubated after the swallowing reflex was detected. Time to extubation was defined as the interval from discontinuation of sevoflurane administration to extubation. Dogs were monitored continuously until they regained the ability to ambulate without assistance.

Dogs subsequently received the other 2 treatments. There was a 1-week interval between successive anesthetic episodes (ie, treatments).

Analysis of propofol concentrations

Propofol concentrations were analyzed by use of a reverse-phase high-performance liquid chromatography method; the system consisted of a separation module,[o] fluorescence detector,[p] and computer equipped with chromatography data software.[q] Propofol was extracted from blood samples by use of a liquid extraction technique. Frozen samples were thawed to room temperature (21°C) and mixed in a vortex device. Then, 400 µL was transferred to a new test tube, and 10 µL of an internal standard (2,4-ditert-butylphenol; 100 µg/mL) was added to each tube. One milliliter of a solution of acetonitrile-methanol (75:25 [vol/vol]) was added, and tubes were mixed in a vortex device, covered with paraffin film,[r] and placed in a refrigerator (4°C) for 10 minutes. Tubes were mixed again in a vortex device for 10 seconds and then centrifuged (1,000 × *g* for 15 minutes). Supernatant was removed and placed in a new tube. The procedure was repeated with an additional 0.5 mL of acetonitrile-methanol. Both supernatants for each dog were combined into a single tube; tubes were centrifuged (1,000 × g for 5 minutes). An aliquot (40 µL) of the resulting supernatant was harvested and placed in chromatographic vials for analysis.

Compounds were separated on a C18 column[s] (4.6 × 250 mm; 5 µm) with an accompanying guard column. The mobile phase was a mixture (31:69 [vol/vol]) of water (adjusted to pH 4.0 with glacial acetic acid) and acetonitrile. Flow rate was 1.5 mL/min, and the column was at room temperature. The fluorescence detector was set at an excitation wavelength of 276 nm and emission wavelength of 310 nm with the gain at 10×.

Standard curves for analysis of concentrations were prepared by fortifying untreated canine whole blood with propofol to create calibration samples that yielded a linear concentration range of 5 to 7,000 ng/mL. Calibration samples were prepared as described previously for unknown blood samples. Mean recovery for propofol was 95%; intra-assay and interassay variability ranged from 2.2% to 8.2% and 3.5% to 6.7%, respectively. The lower limit of quantification was 5 ng/mL.

Data analysis

The assumption that residuals from all models fit a normal distribution was assessed by use of the test statistic for the Shapiro-Wilk test. All data were reported as least squares mean ± SEM values.

The percentage change from MAC_{NM-B} was calculated by use of the following equation: $([MAC_{NM-B} - MAC_{NM-T}]/MAC_{NM-B}) \times 100$. The effect of treatment on the dependent variables MAC and Mg concentration were evaluated with a mixed-model ANOVA.[t] Class variables included in the model were dog, time of MAC measurement (baseline vs treatment), treatment, and treatment order (week). Independent variables included body weight of dog, treatment, time interval (time to MAC_{NM-B} or time to MAC_{NM-T}), and the interaction between treatment and time interval. Dog, week, and the 3-way interaction between dog, week, and treatment were included as random factors in the model. A second mixed model was used to assess the effect of treatment on time to extubation and effect of treatments 1 and 3 on blood propofol

concentration. Class variables in this model included dog, treatment, and week. Body weight, treatment, MAC_{NM}, and time intervals were included as independent variables, with dog as a random factor in the model. A third mixed model was used to assess the effect of treatment on time to measurement of MAC_{NM}. Class variables included in this third model were dog, time of measurement, treatment, and week. Body weight, treatment, MAC_{NM}, time of measurement, and the interaction between treatment and time of measurement were included as independent variables. Dog, week, and the interaction between dog, week, and treatment were included as random factors in the model.

Adjustment for multiple levels of independent variables in all models was performed by use of the Tukey method. Fit of models to the data was assessed with the –2 log-likelihood ratio. Values of $P < 0.05$ were considered significant.

Results

Dobutamine (1 to 5 µg/kg/min) was administered to 2 dogs during treatment 1, 4 dogs during treatment 2, and 5 dogs during treatment 3. Dobutamine was primarily administered 30 to 60 minutes after the start of treatment infusion to maintain mean arterial blood pressure ≥ 60 mm Hg; thus, blood pressure data were not statistically analyzed.

Overall, the least squares mean ± SEM value for MAC_{NM-B} for all treatments was 2.5 ± 0.1 vol%. The percentage decrease from MAC_{NM-B} was 3.4 ± 3.1%, 48.3 ± 3.1%, and 50.3 ± 3.1%, for treatments 1, 2, and 3, respectively **(Table 1)**. Significant decreases from MAC_{NM-B} were observed only for treatments 2 and 3. However, the percentage decrease from MAC_{NM-B} was not significantly different between treatments 2 and 3.

Blood propofol concentrations did not differ significantly between treatments 2 and 3 (Table 1). Administration of $MgSO_4$ for treatments 1 and 3 was associated with a significant increase in Mg concentration.

Neuromuscular function did not change during the course of the infusions, and all TOF ratios exceeded 90%. The times to determine MAC_{NM-B} and MAC_{NM-T} did not differ significantly among treatments.

Least squares mean ± SEM time to extubation was 6.3 ± 1.5 minutes, 10.0 ± 1.5 minutes, and 7.0 ± 1.5 minutes for treatments 1, 2, and 3, respectively; these values did not differ significantly among treatments. Recovery was uneventful after all anesthetic episodes.

Discussion

Despite significant increases in blood Mg concentration for the treatments, administration of $MgSO_4$ was not associated with a significant decrease in sevoflurane MAC_{NM}, nor did it potentiate the MAC_{NM}-sparing effect of propofol. Infusion of propofol provided a MAC_{NM}-sparing effect at blood propofol concentrations similar to those reported in a previous study[23] in which investigators used the same dosing regimen. The overall MAC_{NM-B} value of 2.5 vol% in the study reported here is consistent with reports of 2.7 vol%[21,22] by use of the same methods.

The selected infusion rates of $MgSO_4$ in the present study were based on evaluation of the propofol-sparing effects of Mg[27] and volatile anesthetic–sparing effects of Mg in humans[6] and dogs.[17] Infusion of $MgSO_4$ at a rate of 10 mg/kg/h to humans undergoing cholecystectomy resulted in a 2-fold increase in serum Mg concentrations and was associated with a decrease in desflurane MAC of 20%.[6] In another study,[8] $MgSO_4$ infusion at a rate of 8 mg/kg/h decreased propofol dose requirements by 50% and resulted in a 35% increase in baseline serum Mg concentrations. In dogs undergoing elective surgery, infusion of $MgSO_4$ at a rate of 12 mg/kg/h increased serum Mg concentrations and resulted in a decreased requirement for halothane.[17]

A volatile anesthetic–sparing effect of $MgSO_4$ has been detected in multiple studies. The MAC of desflurane in humans was decreased by 24% following $MgSO_4$ infusion at a rate of 10 mg/kg/h.[7] In another study[6] that involved administration of the same dose of $MgSO_4$ to humans, desflurane requirements were decreased by 22%. In those studies,[6,7] the serum Mg concentrations of the patients were increased from

Table 1—Effect of $MgSO_4$ and propofol infusion on MAC_{NM} of sevoflurane in dogs (n = 6).

Variable	Treatment 1	Treatment 2	Treatment 3
MAC_{NM-B}	2.5 ± 0.1	2.6 ± 0.1	2.3 ± 0.1
MAC_{NM-T}	2.4 ± 0.1[a]	1.4 ± 0.1*[b]	1.2 ± 0.1*[b]
Decrease from MAC_{NM-B} (%)	3.4 ± 3.1[a]	48.3 ± 3.1[b]	50.3 ± 3.1[b]
Mg_P (mmol/L)	0.7 ± 0.0	—	0.7 ± 0.0
Mg_T (mmol/L)	1.2 ± 0.0†	—	1.2 ± 0.0†
Blood propofol (µg/mL)	—	2.4 ± 0.3	2.4 ± 0.3

Data represent least squares mean ± SEM values. Treatment 1 was $MgSO_4$ (loading dose, 45 mg/kg; CRI, 15 mg/kg/h). Treatment 2 was propofol (loading dose, 4 mg/kg; CRI, 9 mg/kg/h). Treatment 3 was a combination of propofol and $MgSO_4$ at each of the aforementioned doses. Each dog was anesthetized 3 times; there was a 1-week interval between successive anesthetic episodes (ie, treatments). Percentage decrease in MAC_{NM} was calculated by use of the following equation: $([MAC_{NM-B} - MAC_{NM-T}]/MAC_{NM-B}) \times 100$.

*Within a column, value differs significantly ($P < 0.05$) from the value for MAC_{NM-B}. †Within a column, value differs significantly ($P < 0.05$) from the value for Mg_P. [a,b]Values in each row with different superscript letters differ significantly ($P < 0.05$).

Mg_P = Magnesium concentration prior to treatment. Mg_T = Magnesium concentration after treatment.

baseline values by 75% and 68%, respectively. In dogs undergoing elective surgery, $MgSO_4$ infusion at a rate of 12 mg/kg/h decreased halothane requirements by approximately 22% while increasing serum Mg concentrations by approximately 58%.[17] In the present study, no significant volatile anesthetic–sparing effect was evident despite a 71% increase in blood Mg concentrations.

Additionally, the dose-sparing relationship of Mg and propofol has been evaluated in several studies. In a study[8] of humans undergoing hysterectomy, an $MgSO_4$ infusion of approximately half the dose administered to the dogs of the study reported here resulted in a significant increase in serum Mg concentration and decreased propofol dose requirements by approximately 50%. In a study[14] of humans undergoing vertebral column surgery, $MgSO_4$ infusion at a lower rate (10 mg/kg/h) than was used in the dogs of the present study resulted in a decrease in propofol consumption by approximately 15%; in a similarly designed study[28] involving human orthopedic surgical patients, $MgSO_4$ infusion at 10 mg/kg/h decreased propofol requirements by 30%. However, because plasma propofol concentrations were not determined in any of the aforementioned studies, comparison of the results of the present study with results for those studies may be inconclusive. Additionally, the only report in which serum Mg concentration was determined in the aforementioned studies indicated an increase in baseline Mg concentrations of only 35%,[8] whereas baseline Mg concentrations in the dogs of the present study increased by approximately 70%.The higher serum concentrations of Mg in the dogs of the study reported here were clearly a result of the higher infusion rate for $MgSO_4$ (15 mg/kg/h) versus the rate (8 mg/kg/h) used for humans in that other study.[8]

A number of studies have supported the volatile and injectable anesthetic–sparing effects of Mg, whereas other studies have reported a lack of an anesthetic-sparing effect, which is similar to the findings of the present study. Administration of $MgSO_4$ at doses similar to the dose used in the study reported here did not cause an isoflurane-sparing effect in dogs undergoing elective surgery in another study[29] and, when used alone or in combination with an infusion of ketamine, had no effect on isoflurane MAC in goats.[30] Results of those studies[29,30] parallel the lack of a sevoflurane-sparing effect after $MgSO_4$ administration that was found in the present study. In humans undergoing hysterectomy, $MgSO_4$ administration at a rate of 30 mg/kg did not decrease the doses of propofol needed for anesthetic induction,[31] and infusion of $MgSO_4$ at a rate of 10 mg/kg/h did not result in significant changes in the requirement for sevoflurane in other studies.[32,33] Those studies[31–33] also corroborated findings of the present study, whereby $MgSO_4$ did not provide a decrease in the requirements for volatile or injectable anesthetics.

The exact reason for the lack of an anesthetic-sparing effect for Mg in the present study remains unknown; however, there are several possible explanations. Many of the reports describing the anesthetic-sparing effects of $MgSO_4$ in humans and dogs are based on clinical endpoints, such as changes in blood pressure, respiratory rate, and heart rate in patients undergoing surgical procedures.[8,10,17] Thus, results of those studies may have been influenced by the combined effects of multiple agents, including inhalational anesthetics, opioids, γ-aminobutyric acid agonists, and neuromuscular blockers; each of these drugs could have resulted in an additive or synergistic effect with Mg. Other factors may include differences in methods among studies, species differences, and the type of inhalation anesthetic used. For instance, $MgSO_4$ infusion (12 mg/kg/h) significantly reduced the requirement for halothane in dogs undergoing elective ovariohysterectomy in 1 study,[17] but a higher administration rate (15 mg/kg/h) failed to reduce the isoflurane requirement in dogs undergoing a similar surgical procedure[29] and did not change the MAC of isoflurane in goats.[30] Other studies in humans have reported that $MgSO_4$ infusion decreased desflurane requirements,[6,7] whereas it increased requirements for sevoflurane.[32]

The study reported here had some potentially limiting factors that may have influenced the results. Blood Mg concentrations significantly increased for both of the treatments that involved $MgSO_4$ infusion; however, total Mg concentration was measured, rather than the biologically active ionized form. However, the authors do not consider that this influenced the results because studies of dogs[34] and humans[35] have revealed that changes in total serum Mg concentrations are correlated with changes in ionized Mg concentrations. Another factor to consider was the potential effect of $MgSO_4$ on neuromuscular function because Mg can augment the effects of neuromuscular blockade associated with a decrease in acetylcholine release from motor nerve terminals,[3] which could have affected the response to noxious stimulation. Although neuromuscular blockers were not used in the present study, acceleromyography was performed to rule out the potential effect of Mg on neuromuscular function. The small sample size for the study reported here also could have predisposed to a type II error, but sample size calculations based on a 24% MAC reduction for desflurane following $MgSO_4$ infusion in humans[7] indicated that only 4 dogs/treatment were needed to detect (power, 90%) a similar MAC reduction for sevoflurane. The present study had 6 dogs/treatment; thus, it was sufficiently powered. However, the expected MAC reduction for sevoflurane may not be to the same scale as the 24% decrease for desflurane MAC in humans, which would mean that the present study could have been underpowered for the detection of smaller percentages of MAC-sparing effects.

In the present study, propofol significantly decreased the MAC_{NM} of sevoflurane. However, despite a significant increase in blood Mg concentrations, $MgSO_4$ infusion at the doses used in this study was not associated with a sevoflurane-sparing effect, and it did

not potentiate the anesthetic-sparing effect of propofol. These results do not support the use of $MgSO_4$ to decrease the anesthetic dose of sevoflurane or propofol. Nevertheless, evaluation of other potential beneficial effects of $MgSO_4$ infusion (eg, analgesic effects) that were beyond the scope of this study is warranted.

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Footnotes

a. SAS, version 9.4, SAS Institute Inc, Cary, NC.
b. Sevoflo, Abbott Laboratories, North Chicago, Ill.
c. DRE Premier XP, DRE Veterinary, Louisville, Ky.
d. Datex-Ohmeda S/5, Planar Systems, Beaverton, Ore.
e. Air Liquide Healthcare, Scott Medical Products, Plumsteadville, Pa.
f. ProtectIV, Johnson & Johnson, North Brunswick, NJ.
g. Hospira Inc, Lake Forest, Ill.
h. PropoFlo, Abbott Laboratories, North Chicago, Ill.
i. K-Mod 107, Allegiance Healthcare Corp, Waukegan, Ill.
j. Bair Hugger, Arizant, Healthcare Inc, Saint Paul, Minn.
k. TOF Watch SX, Organon Ltd, Dublin, Ireland.
l. Grass Instrument Co, Warwick, RI.
m. Medfusion 2010i, Medox Inc, Wilmington, NC.
n. COBAS c501, Roche Diagnostics, Indianapolis, Ind.
o. 2695 separations module, Waters Corp, Milford, Mass.
p. 2475 fluorescence detector, Waters Corp, Milford, Mass.
q. Empower Software, Waters Corp, Milford, Mass.
r. Parafilm, Sigma-Aldrich Corp, St Louis, Mo.
s. Waters XBridge C_{18}, Waters Corp, Milford, Mass.
t. PROC MIXED, SAS, version 9.4, SAS Institute Inc, Cary, NC.

References

1. Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth* 1999;83:302–320.
2. Herroeder S, Schönherr ME, De Hert SG, et al. Magnesium—essentials for anesthesiologists. *Anesthesiology* 2011;114:971–993.
3. Dubé L, Granry JC. The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. *Can J Anaesth* 2003;50:732–746.
4. Pinard AM, Donati F, Martineau R, et al. Magnesium potentiates neuromuscular blockade with cisatracurium during cardiac surgery. *Can J Anaesth* 2003;50:172–178.
5. Tramer MR, Schneider J, Marti RA, et al. Role of magnesium sulfate in postoperative analgesia. *Anesthesiology* 1996;84:340–347.
6. Olgun B, Oğuz G, Kaya M, et al. The effects of magnesium sulphate on desflurane requirement, early recovery and postoperative analgesia in laparascopic cholecystectomy. *Magnes Res* 2012;25:72–78.
7. Tomak Y, Tekin M, Kati I, et al. Analysis of the effect of perioperative magnesium sulphate on minimal alveolar concentration of desflurane using bispectral index monitoring. *Magnes Res* 2011;24:181–188.
8. Choi JC, Yoon KB, Um DJ, et al. Intravenous magnesium sulfate administration reduces propofol infusion requirements during maintenance of propofol-N_2O anesthesia. *Anesthesiology* 2002;97:1137–1141.
9. Ryu JH, Kang MH, Park KS, et al. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. *Br J Anaesth* 2008;100:397–403.
10. Lee D, Kwon I. Magnesium sulphate has beneficial effects as an adjuvant during general anaesthesia for Caesarean section. *Br J Anaesth* 2009;103:861–866.
11. Murphy JD, Paskaradevan J, Eisler LL, et al. Analgesic efficacy of continuous intravenous magnesium infusion as an adjuvant to morphine for postoperative analgesia: a systematic review and meta-analysis. *Middle East J Anaesthesiol* 2013;22:11–20.
12. Akarsu M, Tuncer S, Reisli R, et al. The role of magnesium in preventing postoperative hyperalgesia [in Turkish]. *Agri* 2012;24:15–22.
13. Albrecht E, Kirkham KR, Liu SS, et al. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. *Anaesthesia* 2013;68:79–90.
14. Altan A, Turgut N, Yildiz F, et al. Effects of magnesium sulphate and clonidine on propofol consumption, haemodynamics and postoperative recovery. *Br J Anaesth* 2005;94:438–441.
15. Khafagy HF, Osman ES, Naguib AF. Effects of different dose regimens of magnesium on pharmacodynamics and anesthetic requirements of balanced general anesthesia. *J Egypt Soc Parasitol* 2007;37:469–482.
16. Wu HL, Ye TH, Sun L. Calculated plasma medial effective concentration of propofol with and without magnesium sulfate at loss of consciousness. *Chin Med J (Engl)* 2011;124:997–1000.
17. Anagnostou TL, Savvas I, Kazakos GM, et al. Thiopental and halothane dose-sparing effects of magnesium sulphate in dogs. *Vet Anaesth Analg* 2008;35:93–99.
18. Liu HT, Hollmann MW, Liu WH, et al. Modulation of NMDA receptor function by ketamine and magnesium: part I. *Anesth Analg* 2001;92:1173–1181.
19. Hollmann MW, Liu HT, Hoenemann CW, et al. Modulation of NMDA receptor function by ketamine and magnesium. Part II: interactions with volatile anesthetics. *Anesth Analg* 2001;92:1182–1191.
20. Nastou H, Sarros G, Palta M, et al. Fluctuations in serum magnesium levels during total intravenous anaesthesia with propofol. *Magnes Res* 1996;9:47–53.
21. Seddighi R, Egger CM, Rohrbach BW, et al. The effect of midazolam on the end-tidal concentration of isoflurane necessary to prevent movement in dogs. *Vet Anaesth Analg* 2011;38:195–202.
22. Reilly S, Seddighi R, Egger CM, et al. The effect of fentanyl on the end-tidal sevoflurane concentration needed to prevent motor movement in dogs. *Vet Anaesth Analg* 2013;40:290–296.
23. Singsank-Coats J, Seddighi R, Rohrbach BW, et al. The anesthetic interaction of propofol and sevoflurane on the minimum alveolar concentration preventing motor movement (MAC_{NM}) in dogs. *Can J Vet Res* 2015;79:95–100.
24. Martin-Flores M, Lau EJ, Campoy L, et al. Twitch potentiation: a potential source of error during neuromuscular monitoring with acceleromyography in anesthetized dogs. *Vet Anaesth Analg* 2011;38:328–335.
25. Kopman AF. Surrogate endpoints and neuromuscular recovery. *Anesthesiology* 1997;87:1029–1031.
26. Valverde A, Morey TE, Hernández J, et al. Validation of several types of noxious stimuli for use in determining the minimum alveolar concentration for inhalation anesthetics in dogs and rabbits. *Am J Vet Res* 2003;64:957–962.
27. Seyhan TO, Tugrul M, Sungur MO, et al. Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery. *Br J Anaesth* 2006;96:247–252.
28. Ray M, Bhattacharjee DP, Hajra B, et al. Effect of clonidine and magnesium sulphate on anaesthetic consumption, haemodynamics and postoperative recovery: a comparative study. *Indian J Anaesth* 2010;54:137–141.
29. Rioja E, Dzikiti BT, Fossgate G, et al. Effects of a constant rate infusion of magnesium sulphate in healthy dogs anaesthetized with isoflurane and undergoing ovariohysterectomy. *Vet Anaesth Analg* 2012;39:599–610.
30. Queiroz-Castro P, Egger C, Redua MA, et al. Effects of ketamine and magnesium on the minimum alveolar concentration of isoflurane in goats. *Am J Vet Res* 2006;67:1962–1966.
31. Gupta K, Vohra V, Sood J. The role of magnesium as an adjuvant during general anaesthesia. *Anaesthesia* 2006;61:1058–1063.

32. Oguzhan N, Gunday I, Turan A. Effect of magnesium sulfate infusion on sevoflurane consumption, hemodynamics, and perioperative opioid consumption in lumbar disc surgery. *J Opioid Manag* 2008;4:105–110.
33. Durmus M, But AK, Erdem TB, et al. The effects of magnesium sulphate on sevoflurane minimum alveolar concentrations and haemodynamic responses. *Eur J Anaesthesiol* 2006;23:54–59.
34. Nakayama T, Nakayama H, Miyamoto M, et al. Hemodynamic and electrocardiographic effects of magnesium sulfate in healthy dogs. *J Vet Intern Med* 1999;13:485–490.
35. Lanzinger MJ, Moretti EW, Wilderman RF, et al. The relationship between ionized and total serum magnesium concentrations during abdominal surgery. *J Clin Anesth* 2003;15:245–249.