Prior determination of baseline minimum alveolar concentration (MAC) of isoflurane does not influence the effect of ketamine on MAC in rabbits

Giacomo Gianotti, Alexander Valverde, Melissa Sinclair, Doris H. Dyson, Thomas Gibson, Ron Johnson

Abstract

The objective of this study was to compare the effect on the minimum alveolar concentration (MAC) of isoflurane when ketamine was administered either after or without prior determination of the baseline MAC of isoflurane in rabbits. Using a prospective randomized crossover study, 8 adult, female New Zealand rabbits were allocated to 2 treatment groups. Anesthesia was induced and maintained with isoflurane. Group 1 (same-day determination) had the MAC-sparing effect of ketamine [1 mg/kg bodyweight (BW) bolus followed by a constant rate infusion (CRI) of 40 μg/kg BW per min, given by intravenous (IV)], which was determined after the baseline MAC of isoflurane was determined beforehand. A third MAC determination was started 30 min after stopping the CRI. Group 2 (separate-day determination) had the MAC-sparing effect of ketamine determined without previous determination of the baseline MAC of isoflurane. A second MAC determination was started 30 min after stopping the CRI. In group 1, the MAC of isoflurane (2.15 ± 0.09%) was significantly decreased by ketamine (1.63 ± 0.07%). After stopping the CRI, the MAC was significantly less (2.04 ± 0.11%) than the baseline MAC of isoflurane and significantly greater than the MAC during the CRI. In group 2, ketamine decreased isoflurane MAC (1.53 ± 0.22%) and the MAC increased significantly (1.94 ± 0.25%) after stopping the CRI. Minimum alveolar concentration (MAC) values did not differ significantly between the groups either during ketamine administration or after stopping ketamine. Under the study conditions, prior determination of the baseline isoflurane MAC did not alter the effect of ketamine on MAC. Both methods of determining MAC seemed to be valid for research purposes.

Résumé

L'objectif de la présente étude était de comparer l'effet de la concentration alvéolaire minimale (MAC) d'isoflurane lorsque de la kétamine était administrée soit après ou sans détermination préalable de la MAC de base d'isoflurane chez les lapins. Au moyen d'une étude prospective aléatoire croisée, huit lapines adultes de race Nouvelle-Zélande ont été réparties dans deux groupes de traitement. Une anesthésie a été induite et maintenue avec de l'isoflurane. Le groupe 1 (détermination le même jour), a eu l'effet atténuant sur la MAC de la kétamine [bolus de 1 mg/kg de poids corporel (BW) suivi d'une infusion à taux constant (CRI) de 40 μg/kg BW par minute, administré par voie intraveineuse (IV)], déterminé après que la MAC de base de l'isoflurane fut déterminée préalablement. Une troisième détermination de la MAC a débuté 30 min après l'arrêt de la CRI. Le groupe 2 (détermination lors de jours distincts) a eu l'effet atténuant de la kétamine déterminé sans détermination préalable de MAC de base de l'isoflurane. Une deuxième détermination de la MAC fut débutée 30 min après l'arrêt de la CRI. Dans le groupe 1, la MAC d'isoflurane (2,15 ± 0,09 %) était significativement réduite par la kétamine (1,63 ± 0,07 %). Après l'arrêt de la CRI, la MAC était significativement moindre (2,04 ± 0,11 %) que la valeur de MAC de base d'isoflurane et significativement plus élevée que la MAC durant la CRI. Dans le groupe 2, la kétamine diminua la MAC d'isoflurane (1,53 ± 0,22 %) et la MAC augmenta de manière significative (1,94 ± 0,25 %) après l'arrêt de la CRI. Les valeurs de MAC n'ont pas différé significativement entre les groupes durant soit l'administration de kétamine ou après l'arrêt de kétamine. Dans les présentes conditions expérimentales, la détermination préalable de la MAC de base d'isoflurane n'a pas altéré l'effet de la kétamine sur la MAC. Les deux méthodes pour déterminer la MAC ont semblé être valides pour des besoins de recherche.

(Traduit par Docteur Serge Messier)

Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Ontario N1G 2W1.

Address all correspondence to Dr. Giacomo Gianotti; telephone: (215) 450-4648; fax: (215) 573-9578; e-mail: gianotti@vet.upenn.edu

This study was presented as an abstract at the 15th International Veterinary Emergency and Critical Care Symposium and Annual Conference of the American College of Veterinary Anesthesiologists, Chicago, Illinois in 2009.

Received September 28, 2011. Accepted October 31, 2011.

Introduction

Minimum alveolar concentration (MAC) is defined as the end-tidal concentration of an inhalational anesthetic that prevents purposeful movement in 50% of the study population in response to a supramaximal noxious stimulus and is considered the standard method for comparing the potency of inhalational anesthetics (1). Determination of MAC method is a useful tool to quantify the sparing properties of sedatives and analgesics on inhalational anesthetics.

The application of the noxious stimulus is repetitive during MAC determinations and thus local tissue trauma may activate or inactivate specific pain conduction mechanisms (2,3). A short interval between application of the noxious stimulus or an increase in the intensity of the stimulus can generate movement by inducing temporal summation (4) and thereby affect values obtained during MAC studies since purposeful movement is the endpoint during MAC determinations. Therefore, the timing and intensity of stimulation during MAC determinations should be considered.

Historically, studies that investigate the effect of injectable drugs on MAC have been designed using 1 of 2 distinct methods. The first method (same-day determination) consists of determining the baseline MAC for the inhalational anesthetic, followed immediately by administering the drug of interest and then re-determining the MAC (5–8). The second method (separate-day determination) consists of obtaining the baseline MAC value for the inhalational anesthetic and the MAC after administering the test drug during different experiments on separate days (9,10). A variation of this method is to use a population mean MAC that has already been determined for that specific population in a separate study (11).

There is no scientific evidence supporting the hypothesis that these 2 methods are equivalent. On the contrary, there is conflicting information. For example, 2 independent studies of cats that received epidural morphine yielded different results when inhalational and inhalational/epidural morphine MAC values were determined on the same day or on separate days. There was a significant decrease in isoflurane MAC after epidural morphine was administered if the MAC determinations were completed on the same day (5), while there was no difference if each MAC was determined individually on different days (9). Despite some differences in the design of those 2 studies, it was also suggested that a plausible justification for these results may be that, in order to obtain a MAC-sparing effect of an analgesic drug such as morphine, it is necessary to induce prior activation of pain pathways from repetitive noxious stimulation. This may have occurred in the study that first determined the MAC of isoflurane alone (12).

The MAC-sparing effect of ketamine has been reported in several species, including dogs, cats, and horses (7,13–17), but not in rabbits. The 2 methodologies used to determine the sparing effect of injectable drugs have not been compared in a controlled study. The objective of this study was therefore to first determine the effect of ketamine on the MAC of isoflurane in rabbits and then to determine if the effect of ketamine on MAC was influenced by determining the baseline MAC immediately before administering ketamine. Our hypotheses were that ketamine would cause a significant decrease in the MAC of isoflurane in rabbits and that both methods of MAC determination would yield similar results.

Materials and methods

Animals

Eight female New Zealand rabbits, approximately 1 y of age and weighing 4.1 to 4.7 kg, were used in this study. All rabbits had normal physical examination findings before inclusion in the study. Each rabbit was studied on 2 occasions using a crossover design, with 4 to 6 days between treatments and the order of treatment was randomized. Food and water were available *ad libitum* before anesthesia. This study was approved by the Institutional Animal Care and Use Committee of the University of Guelph.

Anesthesia and instrumentation

Anesthesia was induced with isoflurane (Isoflo; Baxter Corporation, Mississauga, Ontario, Canada) in 100% oxygen using a facemask attached to a coaxial non-rebreathing system (Bain Circuit) with an oxygen flow rate of 200 to 300 mL/kg per minute. When unconscious, the rabbit was positioned in right lateral recumbency and blindly intubated with a low-pressure, high-volume cuffed endotracheal tube. Intermittent positive pressure ventilation was immediately established using an electronically controlled, time-cycled, pressure-limited ventilator (Model 2000; Hallowell EMC, Pittsfield, Massachusetts, USA), with a rate of 10 to 12 breaths/min and a tidal volume of 10 to 15 mL/kg in order to maintain end-tidal carbon dioxide (CO_2) between 30 and 40 mmHg. Rabbits were instrumented for monitoring during the first 30 min of anesthesia, during which time end-tidal isoflurane concentration was 2.5%. The end-tidal isoflurane and CO_2 were monitored using a side-stream infrared gas analyzer (Datex-Ohmeda S/5 Anesthesia Monitor; GE Healthcare Finland, Helsinki, Finland) attached between the endotracheal tube and the breathing system, with a sampling rate of 200 mL/min. The anesthesia monitor was calibrated each morning using a calibration gas designed specifically for this purpose (DOT-34 NRC 300/375M1014; Datex-Ohmeda Division, Helsinki, Finland).

Rectal temperature was monitored every 10 min with a digital thermometer and maintained between 37°C and 38.5°C with the use of a fan heater device (Lancaster; Trileaf Distribution, Toronto, Ontario, Canada). Indirect systolic arterial blood pressure (Doppler; Parks Medical Electronics, Aloha, Oregon, USA), electrocardiogram and heart rate (Datex-Ohmeda S/5 Anesthesia Monitor, GE Healthcare, Helsinki, Finland) were monitored continually and recorded before and after each MAC determination. In addition, the left auricular artery of 2 rabbits in each group was catheterized with a 24-SWG (0.75-in) catheter and direct blood pressure was measured using an electronic pressure transducer (Becton Dickinson Infusion Therapy Systems, Sandy, Utah, USA). The transducer was zeroed at the level of the sternum and interfaced with the anesthesia monitor in order to verify the accuracy of the Doppler readings. Arterial blood was collected twice from each rabbit from the arterial catheter into heparinised syringes (Gastlyte; Marquest Medical Products, Englewood, Colorado, USA) for blood gas analysis (CCX; Nova Biomedical, Waltham, Massachusetts, USA) to verify the end-tidal CO_2 readings.

The left auricular vein was catheterized with a 22-SWG (1.00-in) catheter (BD Insyte-W; Becton Dickinson Infusion Therapy Systems)

for administration of ketamine and a balanced electrolyte solution (Plasmalyte A; Baxter Corporation). Ketamine was mixed with the electrolyte solution into a 3 mg/mL concentration and administered at 3 mL/kg BW per hour using a syringe pump (Graseby 3500 Anesthesia Pump; Smiths Medical International, Wartford, Herts, UK).

MAC determinations

Minimum alveolar concentration (MAC) was determined using previously published techniques (2). The noxious stimulation consisted of 50 volts at 50 cycles/s for 10 ms (S48 Stimulator; Astro-Medical, West Warwick, Rhode Island, USA) applied via two 25-gauge hypodermic polypropylene hub, 0.75-in needles (Tyco Healthcare Group, Mansfield, Massachusetts, USA) inserted subcutaneously 3 cm apart in the left forelimb and at the level of the ulna. The sequence of noxious stimulation consisted of applying 2 single stimuli, followed by 2 continuous stimuli applied for 2 to 3 s, with 5-second intervals between all 4 stimuli. If gross purposeful movement, defined as jerking or twisting motions of the head or running motion of the limbs, was elicited at any time during the cycle, the stimulation was immediately stopped and the event was recorded as a positive response. The end-tidal isoflurane concentration was then increased by 0.1%; conversely, if a negative response was obtained initially, the end-tidal concentration was decreased by 0.1%. The noxious stimulation was repeated after 15 to 20 min of equilibration at the new end-tidal concentration and, if the opposite response to the previous stimulation was obtained after a 15 to 20 min equilibration process, the end-tidal concentration was returned to the initial value to verify the first response (duplicate MAC measurement). Minimum alveolar concentration (MAC) was always determined in duplicate. The mean value midway of the lowest end-tidal concentration that prevented purposeful movement and the highest end-tidal concentration that allowed movement was recorded as the MAC value for that rabbit.

Experimental design

After the instrumentation phase, the end-tidal isoflurane concentration of rabbits in group 1 (same-day MAC determinations) was decreased to approximately 2.0%, which corresponds to the MAC value reported for rabbits (2,18,19). It was maintained at this value for at least 30 min to establish equilibration before starting MAC determinations. During this period, a bolus and CRI of a balanced electrolyte solution were administered at the same volume rate as the ketamine infusion to be used later. In group 2 (separate-day MAC determination), the end-tidal isoflurane concentration of rabbits was decreased to approximately 1.7% for the same time duration (30 min) after receiving a bolus of 1 mg/kg BW of ketamine IV (Vetalar; Bioniche Animal Health Canada, Belleville, Ontario), followed immediately by a CRI at 40 μg/kg BW per min using a syringe pump. The CRI was maintained until the MAC determination was completed.

After the first MAC determinations were completed in each group, rabbits in group 1 were given the ketamine bolus and CRI, as previously described. The end-tidal isoflurane concentration was decreased to 1.7% and after 30 min of the infusion, the MAC was determined again. At this time, the CRI of ketamine was stopped in group 2, the end-tidal isoflurane concentration was increased to 2.0%, and the MAC determinations were started again 30 min later. During this time, the infusion of the balanced electrolyte solution was continued at 3 mL/kg BW per hour. Rabbits in group 2 were allowed to recover from anesthesia when the second MAC determination was completed. In rabbits in group 1, the CRI of ketamine was stopped and replaced by an infusion of the balanced electrolyte solution after the second MAC determination. The end-tidal isoflurane concentration was increased to 2.0% during this time and the third MAC determination was started 30 min later. Rabbits were allowed to recover from anesthesia after the third MAC determination. At the end of the experiment before recovery, 0.2 mg/kg BW of meloxicam (Metacam; Boehringer Ingelheim, Burlington, Ontario) was administered by IV to all rabbits.

The time required to complete each MAC determination was recorded as the time elapsed from the beginning of the equilibration phase until the MAC value was determined. Total anesthesia time corresponded to the time the rabbit was connected to the anesthetic machine until the last MAC was determined.

Data analysis

The MAC values were calculated by using mathematical averaging of 2 subsequent concentrations of isoflurane at which gross purposeful movement and no gross purposeful movement were observed. The 2 groups were statistically compared for MAC values after administering ketamine, after stopping ketamine, and for time to MAC determinations using a paired Student's *t*-test (Version 11.2.1; MedCalc Software, Mariakerke, Belgium). Normality of the data was verified by use of the D'Agostino-Pearson and Kolmogorov-Smirnov tests. The MAC values and time of determination are reported as mean ± standard deviation (SD). Minimum alveolar concentration (MAC) values within the 2 groups were also compared with a paired Student's *t*-test (Version 11.2.1; MedCalc Software). Mean values for indirect systolic blood pressure, end-tidal CO_2 concentrations, heart rate, and rectal temperature were compared between groups using an independent samples *t*-test. Values of $P < 0.05$ were considered significant.

Results

Cardiorespiratory parameters were within acceptable limits for MAC determinations for all rabbits and they recovered uneventfully from the experiments. End-tidal CO_2, heart rate, indirect systolic blood pressure, and rectal temperature values for group 1 were 34 ± 2.8 mmHg, 295 ± 29 beats/min, 78 ± 12 mmHg, and 38.7 ± 0.6°C, respectively; and 34 ± 3.7 mmHg, 292 ± 39 beats/min, 74 ± 8 mmHg and 38.5 ± 0.7°C, respectively for group 2 throughout the experiment.

In group 1, the MAC for isoflurane was 2.15 ± 0.09%, which decreased by 24% when ketamine was administered. The MAC value after administering ketamine in group 2 was also less than the baseline MAC value for isoflurane obtained in group 1 (Table I). Similarly, in both groups after ketamine was discontinued, the MAC value was significantly less than the baseline MAC for isoflurane obtained in group 1 and significantly greater within each group than the MAC value obtained during the ketamine CRI (Table I). There was no difference in MAC values between groups 1 and 2 while

Table I. MAC values and time for MAC determinations after administering ketamine (1 mg/kg BW bolus IV followed immediately by a CRI of 40 μg/kg BW per min) in 8 rabbits with same-day prior determination of baseline MAC of isoflurane (Group 1) or without same-day prior determination of baseline MAC of isoflurane (Group 2)

	Isoflurane baseline	Isoflurane + ketamine	After stopping ketamine	Total anesthesia time (min)
Group 1				
MAC (%)	2.15 ± 0.09	1.63 ± 0.07*	2.04 ± 0.11†	
Time (min)	80 ± 26	75 ± 16	80 ± 14	249 ± 15
Group 2				
MAC (%)	ND	1.53 ± 0.22*	1.94 ± 0.25†	
Time (min)	ND	103 ± 37	81 ± 20	205 ± 56

Values expressed as mean ± standard deviation (SD).

MAC — minimum alveolar concentration; BW — body weight; CRI — constant rate infusion; ND — not determined.

* Significantly different within the group.

† Significantly different ($P < 0.05$) from baseline isoflurane value.

ketamine was being administered or in MAC isoflurane values after ketamine was discontinued.

There were no significant differences in times required for MAC determinations between the 2 groups. The time of ketamine CRI administration was the same time as for MAC determination of the isoflurane and ketamine combination (Table I).

Discussion

This study determined that ketamine decreases the MAC of isoflurane in rabbits and the magnitude of this decrease was not affected by whether a baseline MAC was determined before ketamine was administered. Few studies have determined MAC values for isoflurane in rabbits. The baseline MAC value determined for isoflurane in the present study, 2.15 ± 0.09%, is within the range (2.04% to 2.49%) reported in other studies (2,18–20).

The decrease in the baseline MAC of isoflurane (group 1) with the ketamine CRI corresponded to a 24% reduction, which is similar to reported values in dogs (25%) using a loading dose of 0.6 mg/kg BW and a CRI of 10 μg/kg BW per min (15) or the same as the dose used in this study (13). The decrease is also in the range (11% to 39%) of that achieved by targeting plasma concentrations of 1000 ng/mL with a loading dose of 3 mg/kg BW and a CRI based on the pharmacokinetic rate constants of individual dogs (14). The decrease in the MAC of isoflurane in the present study is less than the decrease in the MAC of sevoflurane in dogs given a loading dose of 3 mg/kg BW and a CRI of 50 and 100 μg/kg BW per min, which resulted in a 40% and 45% decrease, respectively (16). It is also less than the decrease obtained in cats administered a loading dose of 2 mg/kg BW and a CRI of 23 μg/kg BW per min (45%) or 46 μg/kg BW per min (63%) (7).

In 2 previous independent studies in cats that received epidural morphine, effects on the MAC of isoflurane were different. In 1 study, epidural administration of morphine decreased the MAC of isoflurane after prior determination of the baseline MAC of isoflurane on the same day (5). When morphine was administered epidurally without prior determination of the baseline MAC, however, it had no effect on MAC (9). Due to the unexpected lack of effects of epidural morphine on MAC in the latter study, it was suggested that along with possible differences in the methodology of the 2 studies, the lack or less intense prior activation of pain pathways from repetitive noxious stimulation when MAC determinations are completed on separate days prevented morphine's analgesic actions (9). In our study using ketamine IV, prior noxious stimulation did not influence the results in rabbits.

The sample size (N = 8) used in the study could have contributed to our findings of no significant differences between the 2 groups. We anticipated a ketamine-sparing effect of 30%, based on published information for other species, and assumed standard deviations (SDs) not to exceed 0.25 of the mean to obtain at least 95% confidence for a Type I error (α value) at 0.05 and 80% power to detect a difference in MAC values for the expected degree of MAC reduction. The slightly less MAC-sparing effect of ketamine demonstrated in this study (24%) and the narrow difference of 6% in MAC values for the ketamine-isoflurane combination in both groups (1.63% ± 0.07 for group 1 versus 1.53% ± 0.22 for group 2) with a wider variation in the SD of group 2 did not allow significant differences. In another study using dogs with the same experimental design and ketamine doses, there was a significant difference between groups 1 and 2, due to a greater difference (10%) in MAC values and tighter SD in both groups (13).

Several other factors may contribute to the variability in MAC values obtained in different studies and their sometimes contradictory results, including methodology used for MAC determinations and repeatability of MAC determinations. Minimum alveolar concentration (MAC) values for isoflurane in rabbits differ by up to 22% (from 2.04% to 2.49%) (2,18–20), which slightly exceeds expected intra- and interspecies variations of 10% to 20% (21,22). This variation also occurs with halothane, up to 42% for rabbits (0.82% to 1.42%) (2,18,19,23), and is common in other species with different inhalant anesthetics, in dogs up to 22% for halothane (0.81% to 1.04%) (1,2,24) and up to 42% for isoflurane (1.27% to 1.80%) (2,6,25), whereas in

cats there are variations of up to 64% for isoflurane (1.24% to 2.03%) (7,9,10,26). It has also been determined that individual variation due to genetics influences MAC values (26,27), which is rarely considered in studies. Using 15 different mouse strains with different genotypes, variations in MAC values for desflurane, isoflurane, and halothane were 39%, 44%, and 55%, respectively (27). Such variations have not been determined in other species. The factors discussed previously, in addition to the power of the study, could be partly responsible for the results obtained in this investigation.

Variability was minimized in the present study by using a crossover design that involved the same animals acting as their own controls. Factors such as age, gender, and variations in the interpretation of movement in response to noxious stimulation can therefore be excluded, whereas other factors that may affect MAC determinations, such as type of noxious stimulation, body temperature, cardiovascular status, and blood gases, were maintained constant throughout the study (1,2,21). The MAC method used in this study consisted of bracketing isoflurane concentrations up and down by 0.1% to 0.2%. We used 0.1% consistently to avoid variability since MAC values reported often use combinations (28), 0.1% (2), or 0.2% (29). The use of single, duplicate, or even triplicate measurements during MAC determination is also optional and not clearly described by researchers in their methodology. Values derived from single measurements that are not corroborated within the study may therefore not be equivalent to those confirmed from more than 1 response.

Plasticity of pain pathways (30) from repetitive noxious stimulation is likely and often not considered as a process that could affect MAC determinations. The type and intensity of noxious stimulation used during MAC studies may result in desensitization of nerve fibers or in changes in plasticity that lead to sensitization and generate different MAC values. Both sensitization and desensitization have been associated with trauma from repetitive noxious stimulation either by enhanced tissue sensitivity and plasticity of nociceptive mechanisms or by damage and perineural inflammation that prevents impulse conduction (18). Increasing the voltage (10, 15, 20, and 40 volts) during electrical stimulation results in desensitization after fewer attempts with higher voltages so that a positive response becomes negative sooner (4), even though MAC values are slightly greater at the higher voltage (3). In the original description of MAC methodology, 10 volts was considered a submaximal noxious stimulus, but 30 and 50 volts were both supramaximal and equivalent (1).

The method of MAC determination used in this study is a variation of the original method described, in which the electrical stimulus of 50 volts at 50 cycles/s for 10 ms was applied (1,21). The duration and mode of stimulation were altered, however, according to a validation study in which the stimulus is applied using a sequence of 2 single stimuli, followed by 2 continuous stimuli applied for 2 to 3 s, with 5-s intervals between all 4 stimuli (2), instead of applying a single stimulus for up to 60 s or less if a positive response is observed. This variation was chosen since it compared well with clamping techniques and minimizes trauma to the tissue (2), which may avoid plasticity changes from repetitive stimulation.

Another important factor in MAC studies is the likelihood of developing sensitization from frequent stimulation of single synapses. This can eventually result in temporal summation (4), which contributes in part to the movement produced in response to noxious stimulation. Under normal circumstances, lack of movement may result from suppression of mechanisms underlying the summation process itself since blockade of temporal summation decreases the isoflurane concentration required to suppress movement (4). Sensitization originates from intense stimulation during temporal summation to multiple fibers that synapse in the same post-synapses, which results in spatial summation. Temporal and spatial summation mechanisms can lead to "wind-up" and "central sensitization" (31) and can influence the results obtained in MAC studies. Temporal summation occurs when the interval between stimuli and/or the intensity of the stimulus is shortened. Since temporal summation leads to movement, which constitutes the end-point for assessment during MAC studies, values could feasibly be overestimated during those studies in which conditions for sensitization have occurred. Theoretically, sensitization is more likely to occur when using end-tidal isoflurane concentrations that correspond to MAC levels lower than 1 (MAC-1) because isoflurane produces immobility in part by disrupting mechanisms underlying temporal summation, which implies that an insufficient amount of isoflurane will facilitate a response and movement (4). Because MAC values are derived using end-tidal concentrations that are below 1-MAC at least 50% of the time, it appears to be important to minimize the number of stimuli during MAC studies. This is best accomplished during separate day studies.

The choice of ketamine to test our hypothesis in this study may have influenced the results, because wind-up and eventually central sensitization depend on activation of N-methyl d-asparate (NMDA) receptors (32,33). Ketamine is an NMDA antagonist and has the ability to block these receptors and prevent sensitization from repeated stimulation. It has also been shown that ketamine prevents movement through glutamate receptor blockade by inhibiting descending motor responses to repeated noxious stimuli through a decrease in ON-cell activity. These cells are responsible for allowing a permissive effect of nocifensor reflexes (movement) in response to noxious stimuli, through projections from the rostral ventromedial medulla of the cells to the spinal cord (34).

Plasma concentrations of ketamine were not measured in this study. Based on the half-life of ketamine in rabbits (0.74 h) (35) and the time required to complete MAC determinations after ketamine (75 and 103 min in groups 1 and 2, respectively); however, plasma concentrations were probably relatively constant. The MAC values that were determined at approximately 80 min in both groups after discontinuing the CRI of ketamine were also less than the baseline MAC value for isoflurane in group 1. It is possible that not enough time was allowed for plasma concentrations of ketamine to decrease to values that have no influence on MAC. In a similar study using dogs and the same ketamine dose, plasma concentrations of ketamine were still measurable after the CRI was discontinued, which had an effect in decreasing the MAC of isoflurane and prevented it from returning to baseline values (13).

In conclusion, ketamine significantly decreased the MAC of isoflurane in rabbits and this effect does not appear to be influenced by prior determination of the baseline MAC of isoflurane within the same experiment.

Acknowledgment

This work was funded by a grant from the Ontario Veterinary College Pet Trust Fund.

References

1. Eger EI 2nd, Saidman L, Brandstater B. Minimum alveolar anesthetic concentration: A standard of anesthetic potency. Anesthesiology 1965;26:756–763.
2. Valverde A, Morey TE, Hernández J, Davies W. 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.
3. Laster MJ, Liu J, Eger EI 2nd, Taheri S. Electrical stimulation as a substitute for the tail clamp in the determination of minimum alveolar concentration. Anesth Analg 1993;76:1310–1312.
4. Dutton RC, Zhang Y, Stabernack CR, Laster MJ, Sonner JM, Eger EI 2nd. Temporal summation governs part of the minimum alveolar concentration of isoflurane anesthesia. Anesthesiology 2003;98:1372–1377.
5. Golder FJ, Pascoe PJ, Bailey CS, Ilkiw JE, Tripp LD. The effect of epidural morphine on the minimum alveolar concentration of isoflurane in cats. Vet Anaesth Analg 1998;25:52–56.
6. Valverde A, Doherty TJ, Hernández J, Davies W. Effect of lidocaine on the minimum alveolar concentration of isoflurane in dogs. Vet Anaesth Analg 2004;31:264–271.
7. Pascoe PJ, Ilkiw JE, Craig C, Kollias-Baker C. The effects of ketamine on the minimum alveolar concentration of isoflurane in cats. Vet Anaesth Analg 2007;34:31–39.
8. Seddighi MR, Egger CM, Rohrbach BW, Cox SK, Doherty TJ. Effects of tramadol on the minimum alveolar concentration of sevoflurane in dogs. Vet Anaesth Analg 2009;36:334–340.
9. Pypendop BH, Pascoe PJ, Ilkiw JE. Effects of epidural administration of morphine and buprenorphine on the minimum alveolar concentration of isoflurane in cats. Am J Vet Res 2006;67:1471–1475.
10. Ferreira TH, Aguiar AJ, Valverde A, Neto FJ, Steagall PV, Soares JH. Effect of remifentanil hydrochloride administered via constant rate infusion on the minimum alveolar concentration of isoflurane in cats. Am J Vet Res 2009;70:581–588.
11. Pypendop BH, Solano A, Boscan P, Ilkiw JE. Characteristics of the relationship between plasma ketamine concentration and its effect on the minimum alveolar concentration of isoflurane in dogs. Vet Anaesth Analg 2007;34:209–212.
12. Fields H. State-dependent opioid control of pain. Nature Rev Neurosci 2004;5:565–575.
13. Gianotti G, Valverde A, Hathway A. Effect of prior noxious stimulation on the minimum alveolar concentration of isoflurane with ketamine and correlation with ketamine plasma concentrations in dogs. Vet Anaesth Analg 2011;38:4–5. Abstract available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1467-2995.2010.00587a.x Last accessed July 22, 2012.
14. Solano AM, Pypendop BH, Boscan PL, Ilkew JE. Effect of intravenous administration of ketamine on the minimum alveolar concentration of isoflurane in anesthetized dogs. Am J Vet Res 2006;67:21–25.
15. Muir WW 3rd, Wiese AJ, March PA. Effects of morphine, lidocaine, ketamine, and morphine-lidocaine-ketamine drug combination on minimum alveolar concentration in dogs anesthetized with isoflurane. Am J Vet Res 2003;64:1155–1160.
16. Wilson J, Doherty TJ, Egger CM, Fidler A, Cox S, Rohrbach B. Effects of intravenous lidocaine, ketamine, and the combination on the minimum alveolar concentration of sevoflurane in dogs. Vet Anaesth Analg 2008;35:289–296.
17. Muir WW 3rd, Sams R. Effects of ketamine infusion on halothane minimal alveolar concentration in horses. Am J Vet Res 1992; 53:1802–1806.
18. Sobair AT, Cottrell DF, Camburn MA. A mechanical stimulator for the determination of the minimum alveolar concentration (MAC) of halothane in the rabbit. Vet Res Commun 1993;17: 375–385.
19. Drummond JC. MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit: And a test for the validity of MAC determinations. Anesthesiology 1985;62:336–338.
20. Turner PV, Kerr CL, Healy AJ, Taylor WM. Effect of meloxicam and butorphanol on minimum alveolar concentration of isoflurane in rabbits. Am J Vet Res 2006;67:770–774.
21. Quasha AL, Eger EI 2nd, Tinker JH. Determination and applications of MAC. Anesthesiology 1980;53:315–334.
22. Eger EI. Physiological effect. In: Anesthetic Uptake and Action. Baltimore: Williams & Wilkins, 1974:371.
23. Davis NL, Nunnally RL, Malinin TI, Theodore I. Halothane MAC in the rabbit. Anesthesiology 1974;41:310–311.
24. Valverde A, Dyson DH, McDonell WN. Epidural morphine reduces halothane MAC in the dog. Can J Anaesth 1989;36: 629–632.
25. Hellyer PW, Mama KR, Shafford HL, Wagner AE, Kollias-Baker C. Effects of diazepam and flumazenil on minimum alveolar concentrations for dogs anesthetized with isoflurane or a combination of isoflurane and fentanyl. Am J Vet Res 2001;62: 555–560.
26. Barter LS, Ilkiw JE, Steffey EP, Pypendop BH, Imai A. Animal dependence of inhaled anaesthetic requirements in cats. Br J Anaesth 2004;92:275–277.
27. Sonner JM, Gong D, Eger EI 2nd. Naturally occurring variability in anesthetic potency among inbred mouse strains. Anesth Analg 2000;91:720–726.
28. Credie RG, Teixeira-Neto FJ, Ferreira TH, Aguiar AJ, Restitutti FC, Corrente JE. Effects of methadone on the minimum alveolar concentration of isoflurane in dogs. Vet Anaesth Analg 2010;37: 240–249.
29. Yamashita K, Iwasaki Y, Umar MA, Itami T. Effect of age on minimum alveolar concentration (MAC) of sevoflurane in dogs. J Vet Med Sci 2009;71:1509–1512.
30. Woolf CJ. Central sensitization: Uncovering the relation between pain and plasticity. Anesthesiology 2007;106:864–867.
31. You H, Mørch CD, Arendt-Nielsen L. Electrophysiological characterization of facilitated spinal withdrawal reflex to repetitive electrical stimuli and its modulation by central glutamate receptor in spinal anesthetized rats. Brain Res 2004;1009:110–119.
32. Svendsen F, Tjølsen A, Rygh LJ, Hole K. Expression of long-term potentiation in single wide dynamic range neurons in the rat

is sensitive to blockade of glutamate receptors. Neurosci Lett 1999;259:25–28.
33. Schaible HG, Grubb BD, Neugebauer V, Oppmann M. The effects of NMDA antagonists on neuronal activity in cat spinal cord evoked by acute inflammation in the knee joint. Eur J Neurosci 1991;3:981–991.
34. Jinks SL, Carstens EE, Antognini JF. Glutamate receptor blockade in the rostral ventromedial medulla reduces the force of multisegmental motor responses to supramaximal noxious stimuli. Neurosci Lett 2007;426:175–180.
35. Pedraz JL, Lanao JM, Dominguez-Gil A. Kinetics of ketamine and its metabolites in rabbits with normal and impaired renal function. Eur J Drug Met Pharmacokinet 1985;10:33–39.