Effects of morphine, lidocaine, ketamine, and morphine-lidocaine-ketamine drug combination on minimum alveolar concentration in dogs anesthetized with isoflurane

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Objective—To determine the effects of constant rate infusion of morphine, lidocaine, ketamine, and morphine-lidocaine-ketamine (MLK) combination on end-tidal isoflurane concentration (ET-Iso) and minimum alveolar concentration (MAC) in dogs anesthetized with isoflurane and monitor depth of anesthesia by use of the bispectral index (BIS).

Animals—6 adult dogs.

Procedure—Each dog was anesthetized with isoflurane on 5 occasions, separated by a minimum of 7 to 10 days. Individual isoflurane MAC values were determined for each dog. Reduction in isoflurane MAC, induced by administration of morphine (3.3 µg/kg/min), lidocaine (50 µg/kg/min), ketamine (10 µg/kg/min), and MLK, was determined. Heart rate, mean arterial blood pressure, oxygen saturation as measured by pulse oximetry (SpO₂), core body temperature, and BIS were monitored.

Results—Mean ± SD isoflurane MAC was 1.38 ± 0.08%. Morphine, lidocaine, ketamine, and MLK significantly lowered isoflurane MAC by 48, 29, 25, and 45%, respectively. The percentage reductions in isoflurane MAC for morphine and MLK were not significantly different but were significantly greater than for lidocaine and ketamine. The SpO₂, mean arterial pressure, and core body temperature were not different among groups. Heart rate was significantly decreased at isoflurane MAC during infusion of morphine and MLK. The BIS was inversely related to the ET-Iso and was significantly increased at isoflurane MAC during infusions of morphine and ketamine, compared with isoflurane alone.

Conclusions and Clinical Relevance—Low infusion doses of morphine, lidocaine, ketamine, and MLK decreased isoflurane MAC in dogs and were not associated with adverse hemodynamic effects. The BIS can be used to monitor depth of anesthesia. (Am J Vet Res 2003;64:1155–1160)

Providing adequate analgesia before, during and after anesthesia and surgery is believed to minimize patient stress and maximize patient well-being. Opioids (morphine, butorphanol) α₂-agonists (eg, medetomidine), dissociative anesthetics (ketamine), benzodiazepines (diazepam), local analgesics (lidocaine), and nonsteroidal anti-inflammatory drugs (NSAIDS) have been administered to dogs as single drug treatment or as part of preanesthetic drug combinations to provide analgesia and reduce the amount of injectable or inhalant anesthetic required for surgical anesthesia. Results of studies conducted in dogs anesthetized with isoflurane or enflurane suggest that clinically relevant dosages of morphine can reduce the minimum alveolar concentration (MAC) of inhaled anesthetic required to maintain general anesthesia by as much as 60%. Similar studies in dogs and cats have revealed the anesthetic sparing (MAC lowering) and adjunctive analgesic effects of systemically administered lidocaine and ketamine. Results of these same studies suggest that a reduction in inhalant anesthetic requirements should improve cardiorespiratory function, thereby improving the safety of general anesthesia. The IV coadministration of morphine and lidocaine or morphine and ketamine has been found to be synergistic and to prevent CNS hypersensitivity when administered to humans with inflammatory or neuropathic pain. Combining drugs that induce analgesia by different pharmacologic mechanisms is termed multimodal or balanced analgesia.

Preemptive analgesic treatment is the administration of single or multiple analgesic drugs before the painful stimulus in an attempt to prevent or reduce subsequent pain. Preemptive multimodal analgesia is thought to be more effective than traditional unimodal (single drug) treatment for postoperative pain because of improved efficacy, the potential for drug synergism, and a reduction in drug-related adverse effects.

Lowering the inhalant anesthetic MAC is a method used to determine whether a test substance supplements anesthetic-induced CNS depression, induces analgesia, or both. The bispectral index (BIS) is a number from 0 to 100 that is used in humans and animals to monitor the depth of anesthesia (level of consciousness) and guide anesthetic requirements during general anesthesia. The BIS number is derived from an analysis of the electroencephalogram (EEG) and represents the degree to which multiple EEG waveforms are in phase, the EEG power in the δ versus β range, and the proportion of the EEG that is isoelectric. The BIS is inversely related to the depth of anesthesia, and values from 40 to 60 are generally considered to represent surgical anesthesia (unconscious patient), whereas values > 60 are considered to represent increasing levels of consciousness. Because BIS monitors changes in anesthetic depth, it has been used to differentiate sedative from analgesic effects during inhalant anesthesia in humans.

The purpose of the study reported here was to determine the effects of constant rate infusion of morphine, lidocaine, ketamine, and a morphine-lidocaine-
ketamine (MLK) combination on end-tidal isoflurane concentration (ET-Iso) and MAC in dogs anesthetized with isoflurane and monitor the depth of anesthesia by use of the BIS.

Materials and Methods
Animal care and instrumentation—The study was approved by the Animal Care and Use Committee of The Ohio State University and was performed according to the Ethical Guidelines of the International Association for the Study of Pain. Six healthy Beagles (3 males and 3 females) judged to be in excellent health on the basis of physical examination, auscultation, CBC, fecal analysis for parasites, and an ECG were included in the study. The dogs ranged in age from 10 months to 2 years and weighed from 7.8 to 13.0 kg.

Each dog was anesthetized on 5 separate occasions and administered 5 separate treatments. Each anesthetic event was separated by a minimum of 7 to 10 days, and all 6 dogs were administered all 5 treatments in random order. The 5 treatments included IV infusion of the following: 10 mL/kg/h of lactated Ringer's solution; 10 mL/kg/h of lactated Ringer's solution containing 0.02 mg of morphine sulfate/mL; 10 mL/kg/h of lactated Ringer's solution containing 0.06 mg of ketamine hydrochloride/mL; (50 mg/kg/min); and 10 mL/kg/h of lactated Ringer's solution containing 0.06 mg of ketamine hydrochloride/mL. All solutions were determined and maintained from 37.5 to 38°C with a warm-air blanket.

Anesthesia was maintained with isoflurane i in oxygen delivered by an anesthetic circle rebreathing system. The initial oxygen flow rate was 2 L/min, and the ET-Iso was maintained from 1.7 to 2.0%. The oxygen flow rate was maintained at 1 L/min. Ventilation was controlled to maintain a constant end-tidal anesthetic concentration and a PaCO2 from 38 to 43 mm Hg. Inspired and expired (end-tidal) gas samples were continuously collected and analyzed for ET-Iso (%), oxygen,(%) and end-tidal carbon dioxide (ETCO2, mm Hg). The anesthetic analyzer was calibrated before and after each anesthetic event. A lead II ECG, pulse oximeter, and indirect oculometric arterial blood pressure were used to continuously monitor heart rate (bradycardia defined as < 60 beats/min) and rhythm, oxygen saturation as measured by pulse oximetry (SpO2), and systolic, diastolic, and mean arterial blood pressure, respectively. Respiratory rate, SpO2, ETCO2, inspired isoflurane concentration, ET-Iso, heart rate, core body temperature, and systolic, diastolic, and mean arterial pressures were recorded. Venous blood samples were occasionally obtained to confirm blood gas status and the absence of nonrespiratory acidosis.

Determination of isoflurane MAC—The ET-Iso was maintained at 1.3% for each dog the first time isoflurane MAC was determined and at 1.3% the isoflurane MAC value for each dog during the instrumentation period and for a minimum of an additional 30 minutes. Two 24-gauge, 10-mm insulated stimulating electrodes were inserted 1 cm apart into the buccal mucosa at a location dorsal and caudal to the incisors. The opposite ends of the electrodes were connected to an electrical stimulating device that delivered a supramaximal stimulus for determination of isoflurane MAC. The MAC for isoflurane was determined by delivering a predetermined stimulus of 50 V, 5 Hz, and 10 ms duration to the preplaced buccal mucosa electrodes for a period of 1 minute. The stimulus was discontinued when the dog had gross purposeful movement before completion of the 1-minute stimulation. Lifting of the head and repeated movement of the limbs were considered gross purposeful movement. Slight paw movement, arching of the back, chewing, swallowing, blinking, opening of the eyes, and nystagmus were not considered gross purposeful movement (negative response). If there was a negative response, the isoflurane concentration was decreased by 20% until the dog responded with gross purposeful movement. The inhalant anesthetic concentration was then increased by 10% of the preceding ET-Iso. The dog was allowed a minimum of 15 minutes for equilibration at each new anesthetic concentration before retesting. The MAC was taken as the value midway between a positive (purposeful movement) and negative response, as determined by calculating the mean of multiple determinations for each dog.

Determination of BIS—Electroencephalogram activity was obtained by use of a 2-channel referential montage from platinum subdermal needle electrodes arranged in a bifrontal configuration with the reference electrode positioned on the midline of the head rostral to the median canthus of the eyes. The ground electrode was positioned on the midline in the atlantooccipital region. All EEG activity and the BIS were continuously acquired and recorded by use of a specifically designed BIS monitor with the high-frequency filter set at 70 Hz and the low-frequency filter set at 2 Hz. The BIS number was automatically calculated and digitally displayed every 5 seconds and represented the EEG activity during the previous 60 seconds. Eight BIS values were recorded during a 2-minute period before and after buccal mucosal stimulation.

Statistical analyses—Data are reported as mean ± SD, and differences were considered significant at P < 0.05. The effect of each test drug and the MLK drug combination on isoflurane MAC, cardiorespiratory variables, and body temperature were determined by ANOVA for repeated measures. The Dunnett and Tukey posttests were performed to identify differences within and among groups, respectively, when differences were detected.
Results

Isoflurane MAC for the 6 dogs was 1.38 ± 0.08%. Dogs that had gross purposeful movement during isoflurane MAC determinations did so within the first 30 seconds of the electrical stimulus. Heart rate and respiratory rate increased at lower ET-Iso throughout the electrical stimulus. The most common positive response to the electrical stimulus was lifting or shaking the head and pawing at the muzzle. The infusion of morphine, lidocaine, ketamine, and their combination reduced isoflurane MAC in all dogs (Fig 1). Mean reduction of ET-Iso during morphine, lidocaine, ketamine, and MLK infusion was 48, 29, 25, and 45%, respectively. The BIS increased as ET-Iso decreased in all dogs, independent of the drug infusion administered (Table 1).

Mean arterial blood pressure decreased minimally during lidocaine, and MLK drug infusions and increased during ketamine infusion but was not significantly different from baseline (isoflurane alone) values. Heart rate was significantly decreased during morphine and MLK drug infusions and significantly increased during ketamine infusion, compared with baseline values. The SpO2 remained above 90% in all dogs, and core body temperature, pH, and blood gases did not change in any dog during any treatment.

Discussion

Our results confirm and extend results of other studies, which indicated that morphine, lidocaine, and ketamine reduce the concentration of inhalant anesthetic required to maintain anesthesia in dogs. The infusion of low doses of morphine, lidocaine, ketamine, or their combination reduced isoflurane MAC in dogs without adversely affecting hemodynamics or inducing obvious adverse effects.

Minimum alveolar concentration was originally developed as a standard of anesthetic potency and is defined as the minimum steady-state alveolar concentration of an inhalation anesthetic required to prevent gross purposeful movement to a noxious stimulus in 50% of patients. The MAC for isoflurane in dogs is reported to range from 1.30 ± 0.10 to 1.80 ± 0.21% at sea level. The identification of a specific MAC value for an individual animal is dependent on age, physical status, temperature, and adjuvant treatments; most of all, it is dependent on the magnitude and duration of the noxious stimulus. The determination of MAC in humans is made on the basis of their response to skin incision, whereas similar determinations in animals have used a variety of noxious stimuli, including the animals’ responses to tracheal intubation, airway obstruction, muscle squeeze, tail clamping, electric stimulation, and skin incision. These different stimulation procedures must be well defined, easy to perform, repeatable with minimal variability, and cause no harm to the patient. Our technique for determining MAC was identical to that reported by others and yielded similar results (1.38 ± 0.08 vs 1.28 ± 0.06%) for dogs anesthetized with isoflurane. Importantly, we determined BIS as a quantitative measure of anesthetic depth and used it as an index of each dog’s anesthetic depth. The prestim-
individual-animal variability. Our study found that poor gastrointestinal absorption, resulting in large ability because of substantial first-pass metabolism and duration of effect but are hampered by low bioavailability. Formulations should theoretically provide a longer responsive to naloxone. We could not assess the constant rate infusion of low doses of morphine. This resulted with bolus administration of much larger doses of morphine (2 mg/kg, IV). This effect was accompanied by a substantial increase in BIS, suggesting that the decrease in ET-Iso was caused by analgesia. Intravenous administration of bolus doses of morphine induce mild respiratory depression (Paco₂, 57.4 ± 2.0 mm Hg) and bradycardia that is responsive to naloxone. We could not assess the effects of our morphine infusion on ventilation, because our dogs were mechanically ventilated. Heart rate decreased, but no dog developed bradycardia. Our results combined with results of previous reports suggest that substantial reductions in ET-Iso can be caused by infusion of low doses of morphine. The low dose of morphine should minimize the potential for adverse cardiorespiratory effects associated with IV bolus or IM administration.

Local anesthetics cause local analgesia by blocking individual sodium channels in sensory nerve fibers, thereby inhibiting the production or conduction of electrical impulses. This effect is dose dependent and occurs rapidly in the small, thinly myelinated Aδ and unmyelinated C nerve fibers that are responsible for transmitting pain sensations. An IV bolus administration or infusion of lidocaine is used clinically to cause antihypertensive, perioperative analgesic, gastrointestinal promotility, and antishock effects and is known to reduce the requirement for injectable and inhalant anesthetics. Infusion of dosages ranging from 15 to 400 µg/kg/min reduced halothane and enflurane MAC from 10 to 37% in a dose-dependent manner. We observed a 29% decrease in isoflurane MAC during infusion of lidocaine (50 µg/kg/min), which is similar to results of other investigations in dogs anesthetized with halothane or enflurane. The decrease in ET-Iso did not cause changes in heart rate or mean arterial blood pressure, which suggested little or no change in cardiovascular function. The potential adverse effects of IV administration of lidocaine include disorientation, signs of anxiety, vocalization, mild sedation, seizures, vomiting, defecation, muscle twitching, and, rarely, respiratory depression and hypotension. These adverse effects are most commonly reported after IV administration of large bolus doses of lidocaine. The seizure threshold is reported to be 11.2 mg of lidocaine/kg following IV bolus administration in dogs. We did not observe neurologic or cardiovascular effects during the infusion of lidocaine in any dog during our studies. Our observations, in conjunction with another study investigating lidocaine plasma concentrations in cats, a species known to be much more susceptible to the neurologic and cardiotoxic effects of lidocaine than dogs, suggest that infusion of low doses of lidocaine (50 µg/kg/min) are unlikely to cause toxic effects.

Ketamine is a phencyclidine analogue that has been found to cause anesthetic, analgesic, psychotomimetic, anticonvulsant, neuroprotective, and in humans, amnesic effects. Ketamine prevents the exaggerated response (wind-up) and activity (central sensitization) of wide dynamic-range neurons in the dorsal horn of the spinal cord to nociceptive stimuli carried by afferent pain neurons (C fibers) by acting as a non-competitive N-methyl-D-aspartic receptor antagonist. Other proposed analgesic effects include opioid receptor agonist and partial activation of CNS noradrenergic and serotonergic neurons. The administration of low dosages of ketamine (< 20 µg/kg/min) to humans and dogs augments analgesia in the postoperative surgical period and is believed to play an important role in postoperative pain management when used in conjunction with local anesthetics, opioids, and inhalational anesthesia. Ketamine has also been found to attenuate and reverse morphine tolerance in rodents and humans, thereby yielding an opioid-sparing effect and providing superior analgesia, compared with administration of either drug alone. Our study found that low doses of ketamine administered by infusion reduced isoflurane MAC by approximately 25%. The decrease in ET-Iso was accompanied by a significant increase in the BIS. This change might suggest a decrease in the depth of anesthesia, although larger doses of ketamine than used in our study are known to cause paradoxical increases in BIS in humans. Therefore, we do not know whether ketamine lowered ET-Iso by inducing analgesia or depressing consciousness. The decrease in ET-Iso was accompanied by no change or a significant increase in heart rate and mean arterial blood pressure, suggesting an improvement in cardiovascular function. This finding requires further investigation with more sensitive and selective mea-
sures of cardiovascular activity. Our findings support and extend those of other studies\textsuperscript{1,2,4,13} that compared postoperative pain and behavior in dogs administered ketamine IV (10 μg/kg/min) or epidurally. Those studies did not evaluate ET-Iso but did find improved postoperative analgesia and quality of recovery, with minimal changes in cardiovascular function. We did not expect or observe adverse effects associated with infusion of low doses of ketamine, similar to investigations in rats,\textsuperscript{14} dogs,\textsuperscript{15} and humans.\textsuperscript{16}

One of the potential advantages of preemptive analgesia and infusion of multimodal analgesic drug combinations is the potential to reduce the amount of inhalant anesthetic required to maintain general anesthesia and thereby reduce the risk of cardiorespiratory depression.\textsuperscript{2,16} We did not observe significant changes in mean arterial blood pressure in any dog, although this was not the focus of our study. We did observe a decrease in heart rate in dogs administered morphine and MLK, an increase in heart rate in dogs administered ketamine, and no change in heart rate in dogs administered lidocaine. We did not determine cardiac output and, therefore, do not know the consequence of the observed drug-related effects on systemic blood flow. The absence of a significant change in venous pH or blood gas values suggests minimal alteration in tissue perfusion because of drug-related cardiovascular depression. We used controlled ventilation during all of our treatments and, therefore, cannot comment on the potential for the development of respiratory depression during our drug infusions. The drug dosages we selected were considerably less than those reported\textsuperscript{4,5,8,14} by others to induce important hemodynamic or respiratory complications, leading us to conclude that cardiorespiratory effects in spontaneously breathing dogs would be minimal.

The combined use of drugs to reduce anesthetic requirements, facilitate pain treatment, minimize adverse autonomic nervous system reflexes, and reduce or prevent adverse events is the basis of preemptive, multimodal, or balanced analgesia.\textsuperscript{2,16} We chose to combine drugs known to be compatible and synergistic so that we could use lower dosages and minimize or eliminate known adverse effects. Our inability to detect a significant difference in MAC reduction between morphine and MLK most likely reflects the insensitivity of MAC determination for quantifying subtle differences in drug-related analgesic effects and mechanism of drug action. Our studies suggest that the administration of low dosages of the MLK drug combination resulted in a significant reduction in isoflurane MAC and that BIS can be used to assess and differentiate drugs that change the level of consciousness.

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