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Effect of Lidocaine–Ketamine Infusions Combined with Morphine or Fentanyl in Sevoflurane-Anesthetized Pigs

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Providing lidocaine, ketamine, and an opioid greatly decreases the minimum alveolar concentration (MAC) of volatile anesthetics in dogs. However, the efficacy of this combination shows marked interspecies variation, and opioids are likely to be less effective in pigs than in other species. The aim of the study was to determine the effects of constant-rate infusion of lidocaine and ketamine combined with either morphine or fentanyl on the MAC of sevoflurane in pigs. In a prospective, randomized, crossover design, 8 healthy crossbred pigs were premedicated with ketamine and midazolam, and anesthesia was induced and maintained with sevoflurane. Pigs then received ketamine (0.6 mg/kg/h) and lidocaine (3 mg/kg/h) combined with either morphine (0.24 mg/kg/h; MLK) or fentanyl (0.0045 mg/kg/h; FLK) after a loading dose; the control group received Ringers lactate solution. The anesthetic-sparing action of the 2 infusion protocols was calculated according to the MAC, by using dewclaw clamping as the standard noxious stimulus. The sevoflurane MAC (mean ± 1 SD) was 2.0% ± 0.2%, 1.9% ± 0.4%, and 1.8% ± 0.2% in the control, MLK, and FLK groups, respectively. No differences among groups or treatments were found. In conclusion, the administration of MLK or FLK at the studied doses did not reduce the MAC of sevoflurane in pigs.

Abbreviations: FLK, fentanyl–lidocaine–ketamine; MAC, minimum alveolar concentration; MLK, morphine–lidocaine–ketamine

Analgesic drugs used in veterinary medicine include opioids, ketamine and local anesthetics. These drugs not only promote analgesia but also allow reduction of the necessary doses of anesthetics, with associated reduction in their dose-dependent side effects. This anesthetic-sparing action achieved can be estimated through measurement of the minimum alveolar concentration (MAC) of the inhalant anesthetic.[6] Drugs that reduce the MAC of inhalant anesthetics in various species include the opioids morphine and fentanyl;[1,15,17] ketamine, an antagonist of N-methyl-D-aspartate receptors;[2,25,34] and the local anesthetic lidocaine.[10,29,33,39] These drugs can be combined, and multimodal analgesia is increasingly used during veterinary surgery.[9] The intraoperative efficacy of analgesic combinations depends largely on their ability to reduce inhalant anesthetic requirements through an additive or synergistic action. In dogs and horses, the combination of morphine, lidocaine, and ketamine (MLK), when infused at a constant rate, produces perioperative analgesia and reduces the amount of inhalant anesthetic required by at least 40%.[2,26,40] The administration of fentanyl instead of morphine with lidocaine–ketamine (that is, FLK) may decrease anesthetic requirements by as much as 97% in dogs.[2] In ruminants, a constant-rate infusion of lidocaine–ketamine reduced the MAC of isoflurane.[7]

However, the effects achieved in one species do not necessarily predict those in others, and relevant interspecies differences in the ability of opioids to reduce anesthetic requirements have been determined. Although the doses of fentanyl required to reduce the Isoflurane MAC by 20% to 50% are reportedly higher in pigs (10- to 20-fold) [24,35,36] than in dogs, we hypothesized that a combination of an opioid with lidocaine and ketamine would produce a clinically relevant decrease in the MAC of sevoflurane in pigs. Therefore, the aim of the present study was to determine the sevoflurane-sparing effects of MLK and FLK in pigs at doses highly effective in dogs.[2]

Materials and Methods

A prospective, randomized, crossover study was performed. Each pig was anesthetized 3 times with sevoflurane and received each of the 3 treatments (MLK, FLK, and control) in random order (www.randomization.com) at intervals of at least 1 wk. The study was approved by the Institutional Animal Care and Use Welfare Committee (La Paz University Hospital, Madrid, Spain, CEBA-18-2012, 01 October 2012).

Animals. The study was performed in 8 healthy large white female pigs (age, 3 to 4 mo; weight [mean ± 1 SD], 31.2 ± 7.6 kg) purchased from an authorized research pig breeding facility (Agropardal de Almendros, Almendros, Spain). Pigs were considered healthy on reception at our facility by the designated veterinarian and were allowed to acclimate to the facility for at least 1 wk before experiments began. The pigs were housed individually in pens measuring 2 m^2 with plastic floors and were kept within sight and sound of one another. After an acclimation period of at least 72 h, pigs were clinically examined and weighed. A 12:12-h light:dark cycle was used, and the room temperature were set to 20 ± 2 °C. The pigs were fed a commercial finisher diet without growth promoter (1.3 kg daily; Complete Diet for Adult Miniswine, Safe, Augy, France) twice daily (0800 and 1600) and had free access to water. Food, but not water, was withdrawn overnight prior to the experiment. According to previous data from similar studies, a total of 6 to 8 pigs per group was considered sufficient to detect a difference between treatment group means of at least 15% (0.3% sevoflurane) with a power of 80% and a P value of 0.05.[5]

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Analgesic combination. The MLK solution was made daily by diluting morphine, lidocaine, and ketamine into 500 mL Ringers lactate solution;[26] fentanyl replaced morphine to create the FLK solution. The doses used in the pigs were the same as those used successfully in dogs in a previous study,[2] in which MLK achieved a 45% reduction in the isoflurane MAC and FLK reduced the isoflurane MAC by 97%. Briefly, loading doses of morphine (2%, B Braun, Barcelona, Spain), fentanyl (0.05 mg/mL, Fentanest, Kern Pharma, Barcelona, Spain), lidocaine (5%, B Braun), and ketamine (Ketolar 50, Pfizer, Madrid, Spain) were 0.24, 0.0045, 3, and 0.6 mg/kg IV, respectively, and were given over a 4-min period at 15 to 30 min after anesthetic induction; maintenance doses of 0.24, 0.0045, 3 and 0.6 mg/kg/h IV, respectively, were achieved through continuous-rate infusion (3 mL/kg/h; Infusomat, B Braun). In addition, Ringers lactate solution (7 mL/kg/h) was administered. The control group received the equivalent volume of a Ringers lactate solution (10 mL/kg/h). At the end of experiment, constant-rate infusion was discontinued, and postoperative analgesia was provided in all groups by using flunixin meglumine (2.2 mg/kg IM; Feverxin, Chemical Iberica, Salamanca, Spain).

Anesthetic procedure. Pigs were premedicated intramuscularly with a combination of ketamine (8 mg/kg) and midazolam (0.3 mg/kg, B Braun). At 15 min after premedication, the pigs were transferred to the operating room and preoxygenated through a face mask for at least 2 to 3 min. The auricular veins were catheterized (20- to 18-gauge; Insyte Autoguard, Becton Dickinson, San Agustin de Guadalix, Spain) for administration of drugs and fluids. Body temperature was maintained by using a circulating-water blanket (37 to 38 °C; MediTherm II, Gaymar, Orchard Park, NY).

Anesthesia was induced with sevoflurane (5% Sevorane, Abbott Laboratories, Madrid, Spain) vaporized in 100% oxygen at a flow of 4 L/min through a face mask. The pigs were endotracheally intubated (inner diameter, 6.5 to 7.5 mm) and maintained at an end-tidal sevoflurane concentration of 2.0% (50% oxygen, 0.9 L/min) delivered through a circular breathing circuit. Mechanical ventilation (Primus, Dräger, Lübeck, Germany) was set to maintain normocarbia (end-tidal CO_2, 35 to 40 mm Hg). Subsequently the femoral artery was catheterized, and a 20-gauge catheter (Insyte Autoguard, Becton Dickinson) was connected by rigid tubing to a pressure transducer to measure arterial pressures. Pigs were positioned in lateral recumbency and monitored. Oxygen saturation (pulse oximetry), heart and respiratory rates, invasive and noninvasive blood pressures, and esophageal temperature (Primus, Dräger; Cardiocap II, Datex-Ohmeda, Helsinki, Finland) were recorded every 15 min. In addition, the presence of shivering was recorded.

Determination of the MAC. The MAC was determined for each pig on 3 occasions by using, as the standard noxious stimulus, a clamp (8-in. Rochester Dean Hemostatic Forceps, Martin, Tutlingen, Germany) on a dewclaw for a maximum of 60 s or until a purposeful movement occurred.[11,28] The site of the stimulations was changed slightly each time to prevent sensitization or desensitization to subsequent stimuli. The MAC determination started just after the loading dose was administered.

When the nociceptive stimulus induced response movement (withdrawal of the clamped foot or gross movements of either legs or head), the sevoflurane end-tidal concentration was increased by 0.2%. When there was no purposeful movement in response to the stimulus, the sevoflurane end-tidal concentration was decreased by 0.2%; the sevoflurane end-tidal concentration was maintained at each level for 15 min before noxious stimulation and the next 0.2% change in concentration. The number of crossovers was recorded, and the average value of the inhaled anesthetic concentration of the pigs involved in the crossing was calculated. After 2 independent crosses (duplicate measures), the experiment was ended, and the MAC value was determined as the arithmetic mean of the concentrations of sevoflurane at the midpoints of these crosses.

Statistical analysis. Data are reported as mean ± 1 SD and were tested for normality by using the Shapiro–Wilk test. Repeated–measures ANOVA and Bonferroni posthoc tests were used to determine differences between groups. Differences between groups were considered significant at a P value of less than 0.05. All analyses were performed by using SPSS statistical software (version 19 for Windows 2010, IBM, Chicago, IL).

Results

The sevoflurane MAC was 2.0% ± 0.2%, 1.9% ± 0.4%, and 1.8% ± 0.2% in the control, MLK, and FLK groups, respectively; MAC did not differ significantly among groups or treatments. Data regarding the time required for MAC determination (beginning from the administration of the premedicants), heart and respiratory rates, noninvasive mean arterial blood pressure, oxygen saturation, and body temperature are shown in Table 1. None of these parameters differed among treatments. Shivering was increased ($P < 0.05$) when pigs received MLK or FLK (Table 2) compared with Ringers lactate solution (control).

Discussion

Opioids are known to be less effective in swine compared with other species, and higher doses are required in swine to produce effects similar to those in other species.[24,35,36] However, we expected that combining an opioid with local anesthetics and ketamine would increase the analgesic effect of the opioid. Unexpectedly, the 2 analgesic infusions MLK and FLK failed to reduce the anesthetic requirements of pigs. In contrast, these same infusion schemes achieved a 45% (MLK) or 97% (FLK) reduction in the amount of isoflurane needed in dogs[2,26] and a 43% reduction (MLK) in horses.[40] These differences reflect both interspecies variation in drug responses and the reduced efficacy of opioids in pigs. In one study, the intravenous administration of 2 mg/kg morphine to rhesus macaques, dogs, and pigs reduced the isoflurane MAC by 55%, 50%, and 13%, respectively.[36] In addition, fentanyl doses in pigs are comparatively higher than those commonly used in other species; doses of 50, 100, and 200 μg/kg/h decreased the isoflurane MAC of swine by 25%, 30%, and 46%, respectively.[24] However, fentanyl doses of 4.5 to 6.5 μg/kg/h, similar to that of the FLK combination used in the current study, reportedly were effective during inhalation anesthesia in pigs.[20] Alternatives to high-dose opioids include their combination with other analgesic drugs, which would be expected to potentiate the anesthetic-sparing effect. In our study, FLK reduced the sevoflurane MAC in pigs by 7%; however, we expected a reduction of at least 15%, similar to that in dogs given FLK and MLK although to a lesser extent.[2] The degree of reduction we observed has limited clinical utility in any species and is within the normal variability of the MAC method. Therefore we consider that both MLK and FLK infusions lacked sufficient clinical effect at the doses evaluated.

The reported sevoflurane MAC in swine ranges between 2.1% and 4.4%,[16,18,23] perhaps reflecting factors such as age, body temperature, preanesthetic protocol, type and site of noxious stimulus, and a defined end point for determination of purposeful movement in response to the applied stimulus.[11,30] In a previous study, pigs were premedicated with ketamine

Table 1. Parameters obtained from 8 pigs anesthetized with sevoflurane and receiving Ringers lactate solution (control), morphine–lidocaine–ketamine (MLK), or fentanyl-lidocaine–ketamine (FLK) by constant-rate infusion

	Control	MLK	FLK
Minimum alveolar concentration (MAC; %)	2.0 ± 0.2	1.9 ± 0.4	1.8 ± 0.2
MAC change (%)	0	−3 ± 21	−7 ± 9
Time to MAC determination (min)	133 ± 39	134 ± 24	147 ± 36
Heart rate (bpm)	111 ± 19	93 ± 27	108 ± 9
Systolic arterial pressure (mm Hg)	118 ± 21	117 ± 17	101 ± 35
Mean arterial pressure (mm Hg)	81 ± 14	77 ± 14	68 ± 15
Diastolic arterial pressure (mm Hg)	61 ± 11	61 ± 15	54 ± 15
Temperature (°C)	37.7 ± 1.5	37.3 ± 1.1	37.8 ± 0.6
SPO_2 (%)	100 ± 1	100 ± 0	100 ± 1

Data are expressed as mean ± 1 SD.

Table 2. Presence of shivering in 8 pigs anesthetized with sevoflurane and receiving Ringers lactate solution (control), morphine–lidocaine–ketamine (MLK), or fentanyl–lidocaine–ketamine (FLK) by constant-rate infusion

	Control	MLK	FLK
Absent	7	2	1
Present	1	6[a]	7[a]

[a]Value significantly ($P < 0.05$) different from that for control.

(10 mg/kg) and propofol, tested by using the same nociceptive stimulus as that in the present study, and demonstrated a sevoflurane MAC of 2.4%,[3] which is close to the MAC of 2.0% that we obtained by using 8 mg/kg ketamine and midazolam. Midazolam likely contributed to the effect on the MAC value, although midazolam is considered to have a shorter duration of effect than does ketamine.[19,21]

Premedication likely contributed to the observed decrease in the MAC, and a slightly higher MAC should be expected in nonpremedicated swine. We chose to premedicate swine, rather than determine the actual effects of MLK or FLK in nonmedicated swine, to better mimic the clinical situation, where pigs typically are premedicated before inhalational anesthetics are provided. The actual effect of the premedicants on MAC is likely to be related with the time from drug administration to the time of MAC determination. However, these times were similar between groups and therefore likely did not modify the conclusion drawn regarding the studied infusion schemes.

In dogs, ketamine at 3 mg/kg/h reduces the MAC of sevoflurane by 40%,[40] and the lower dose of 0.6 mg/kg/min decreased the MAC of isoflurane by 25%[26] in a dose-dependent, but nonlinear, manner. To our knowledge, similar data have not been reported for the pig. Lidocaine at 3 and 12 mg/kg/h reduced the MAC of isoflurane in dogs between 15% to 29% and 37% to 43%, respectively.[22,26,39,41] The lidocaine dose (3 mg/kg IV) we used in the current study produced no relevant effects on the MAC of sevoflurane in pigs even though we combined it with ketamine and an opioid. In horses, lidocaine at 3 mg/kg/h decreased isoflurane requirements by 25%,[10] and in ponies given doses of 3 to 6 mg/kg/h, halothane requirements were decreased by 20% to 70%.[8] The coadministration of lidocaine and ketamine by continuous-rate infusion further decreased the isoflurane requirements by 49% in horses, which is consistent with previous reports suggesting an additive effect of lidocaine and ketamine on the MAC.[12] However, coadministration of morphine with lidocaine and ketamine to horses yielded no further reduction in the anesthetic requirement.[40]

Overall, the effects of both MLK and FLK in our pigs are not in agreement with those reported for other species, including dogs or horses. Whether higher doses of these drugs will produce relevant effects on the sevoflurane MAC as well as various side effects in pigs is unknown. Morphine has been shown to produce histamine release[13] and excitatory reactions.[4,31] These behavioral reactions might be less likely to occur when other drugs such as sedatives are coadministered,[27,32] and none of our pigs displayed such behaviors during recovery from anesthesia. Another finding was the increased shivering of the pigs when they received either MLK or FLK. Previous data confirm the antishivering action of anesthetics and opioids, and pethidine has been used to block or prevent shivering by increasing the threshold body temperature at which shivering begins.[32] To our knowledge, opioids have not been reported to induce shivering in pigs during the intraoperative period, although we have repeatedly observed this response in our laboratory. In addition, neither FLK nor MLK administration led to any adverse cardiovascular effects in our pigs, perhaps because of the relatively low doses we used. Opioids can induce bradycardia[38] and hypotension, which is mediated at least in part through histamine release.[13] The absence of a painful surgical stimulus may account for the limited effect of the studied combinations in the pigs. In the current study, the absence of a continuous pain stimulus combined with the preanesthetic administration of midazolam–ketamine administration might have biased the MAC data. Furthermore, the use of opioids, which cause central nervous system stimulation rather than analgesia, might have confounded the interpretation of the MAC in opioid-treated pigs.[35]

In conclusion, the administration of MLK or FLK in pigs at doses highly effective in dogs did not provide a clinically relevant reduction in the MAC of sevoflurane, thus confirming marked interspecies differences in the anesthetic-sparing effect of ketamine–lidocaine–opioid infusion regimens.

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