Epidural morphine reduces halothane MAC in the dog

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Morphine, 0.1 mg · kg^{-1} was administered epidurally on two different occasions to ten dogs to determine the effect of two different volumes of saline dilution, 0.13 and 0.26 ml · kg^{-1}, on the minimum alveolar concentration (MAC) of halothane as determined by subcutaneous electrical current applied to the fore and hind limbs in a random order. Following MAC determination with halothane alone, epidural morphine was administered and MAC was redetermined. Epidural morphine significantly reduced, $P < 0.001$, the MAC of halothane for fore and hind legs in both volume groups; from 1.04 ± 0.038 to 0.68 ± 0.034 and 0.60 ± 0.017 for fore and hind limbs, respectively, in the large volume group, and from 0.96 ± 0.038 to 0.66 ± 0.088 and 0.60 ± 0.030 for fore and hind limbs, respectively, in the small volume group. The reduction in MAC was significantly greater, $P < 0.025$, in the hind limb. This study indicates that epidural morphine reduces the halothane requirements in the dog in a segmental manner. The volume of administration was not shown to be critical. Epidural morphine, 0.1 mg · kg^{-1}, diluted in 0.13 to 0.26 ml · kg^{-1} saline produces significant analgesia in the dog as far forward as the fore limb and will reduce the halothane requirement to permit surgery.

Key words

ANAESTHETICS, VOLATILE: halothane; ANAESTHETIC TECHNIQUES: epidural; ANALESICS: morphine; POTENCY, ANAESTHETIC: MAC

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The use of spinal opioids in the intraoperative period and the resultant requirement for inhalational anaesthetics has not been thoroughly investigated in humans or animals. Recent studies in humans[1,2] using morphine intrathecally reported conflicting results. Although epidural morphine is used clinically for postoperative pain control in dogs and cats, no quantitative evaluation of the analgesia achieved has been done. This study was designed to determine the influence of epidural morphine and the volume of administration on the anaesthetic requirements for halothane.

Methods

Phase I

Ten mongrel dogs (nine males, one female), weighing 25–31 kg, were used for this study. Anaesthesia was induced with halothane in oxygen (O_2) and nitrous oxide (1:2 ratio) using a face mask. The trachea was intubated and thereafter anaesthesia was maintained with halothane in O_2 using a coaxial (Bain Breating Circuit, Ormond Veterinary Supply Ltd., Hamilton) circuit system with an O_2 flow of 3 L · min^{-1}. End-tidal halothane and carbon dioxide (CO_2) concentrations were monitored using an infrared gas analyser (Datex Instrumentation Corp, Helsinki) calibrated before each experiment with a standardized calibration gas mixture (Datex Instrumentation Corp, Helsinki) designed for the analyser. This calibration was verified each time using a known halothane concentration (Matheson Gas Products Canada, Whitby, Ottawa) (2.97 per cent halothane in nitrogen). Mechanical ventilation was used and the end-tidal CO_2 concentration was maintained between 30 and 40 mmHg. Body temperature was monitored electronically and maintained between 38 and 39° C which corresponds to normal limits in the dog. A 16-g Tuohy needle was inserted into the lumbosacral space and a 19-g Vialon catheter was advanced through it approximately 2–3 cm cephalad into the epidural space for the subsequent administration of morphine.

Determinations of the minimum alveolar concentration (MAC) for halothane were carried out using well-established techniques.[3] After an initial equilibration period of at least 30 minutes at a constant end-tidal halothane concentration thought to be near the MAC

TABLE I Minimum alveolar concentration (MAC) of halothane before and after epidural administration of morphine (0.1 mg·kg^{-1}) in ten dogs using different volumes of diluent saline

	Volume I (0.26 ml·kg^{-1})			*Volume II (0.13 ml·kg^{-1})*		
		Post-epidural			*Post-epidural*	
n	*Pre-epidural fore & hind limb*	*fore limb*	*hind limb*	*Pre-epidural fore & hind limb*	*fore limb*	*hind limb*
1	0.95	0.65	0.55	0.95	0.75	0.65
2	1.05	0.65	0.55	1.05	0.55	0.55
3	0.95	0.85	0.65	0.95	0.65	0.65
4	1.05	0.65	0.55	0.95	0.65	0.55
5	1.25	0.85	0.65	1.05	0.75	0.75
6	0.95	0.55	0.55	0.85	0.55	0.55
7	1.15	0.65	0.65	1.15	0.75	0.65
8	0.85	0.55	0.55	0.75	0.65	0.45
9	1.05	0.65	0.65	1.05	0.75	0.65
10	1.15	0.75	0.55	0.85	0.55	0.55
mean ± SEM	1.04 ± 0.038	0.68 ± 0.034*	0.60 ± 0.017*†	0.96 ± 0.038‡	0.66 ± 0.088*	0.60 ± 0.30*†

*Significantly different ($P < 0.001$) from pre-epidural MAC value. †Significantly different from ($P < 0.025$) post-epidural MAC value for the fore limb. ‡Significantly different ($P < 0.05$) from pre-epidural MAC value of volume I.

level, a supramaximal electrical stimulus (50 volts at 50 cycles·sec^{-1} for 10 msec)[3] using a Grass SD9 Stimulator was applied subcutaneously to the proximal third of the fore and hind limb in a random order. Once the presence or absence of purposeful movement was determined the end-tidal halothane concentration was increased or decreased by ten per cent. The new end-tidal concentration was kept constant for at least 15 minutes following the adjustment and the stimulus procedure was repeated. This process was continued until purposeful movement ceased or returned, respectively. The end-tidal anaesthetic concentration midway between the highest value permitting purposeful movement and the lowest value preventing the same was recorded as the MAC value for halothane for that animal, and was determined for both the fore and hind limbs. Purposeful movement was taken as a jerking or twisting motion of the head or running motion of the extremities.[3,4] These determinations were completed in approximately 80 minutes.

Following the determination of halothane MAC, morphine at a dose of 0.1 mg·kg^{-1} diluted in 0.26 ml·kg^{-1} saline was injected into the epidural space. The MAC redeterminations were started 30 minutes following morphine administration and completed in approximately 80 minutes or less after the epidural injection.

Following complete recovery from anaesthesia and at six and 24 hours postanaesthetic, the dogs were monitored for the appearance of adverse side effects, including vomiting, pruritus, respiratory depression and inability to urinate. Proprioceptive reflexes were also evaluated using standard postural reaction tests for dogs, including proprioceptive positioning, hopping, wheelbarrowing, and extensor thrust reaction.[5]

Phase II

Two weeks after testing, each dog was anaesthetized as described in Phase I and halothane MAC was again determined. Epidural morphine, 0.1 mg·kg^{-1}, was then administered diluted in a reduced volume of saline, 0.13 ml·kg^{-1}, and MAC for halothane was determined in order to compare the effect of this volume with the previous injectate volume used in the Phase I study.

Statistical analysis

Statistical comparisons of the halothane MAC values for the fore and hind limbs were carried out using a paired Student's t test. A similar evaluation was used to assess the response of epidural morphine, and to compare the response to the two volumes of injectate.

Results

Phase I

The mean halothane MAC value for the dogs was 1.04 ± 0.038 (SEM) for both the fore and hind limb (Table, Figure). Epidural administration of morphine significantly, $P < 0.001$, decreased the MAC of halothane in the fore limb to 0.68 ± 0.034, and the MAC of halothane in the hind limb to 0.60 ± 0.017. After epidural morphine administration the MAC level for hind limb stimulation was significantly, $P < 0.025$, lower than for the fore limb.

Phase II

In this study the mean halothane MAC value was 0.96 ± 0.038 for both the fore and hind limbs (Table, Figure). After epidural administration of morphine at the same

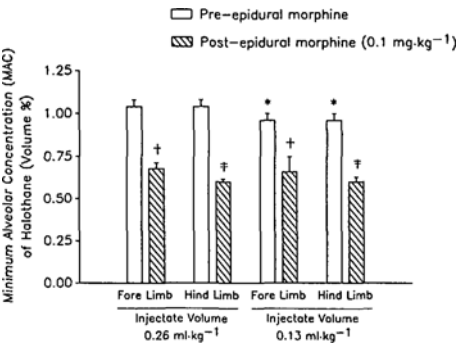

FIGURE Effect of epidural morphine on the minimum alveolar concentration (MAC) of halothane.

dose but with half of the injectate volume as was used in the phase I study the MAC value was decreased significantly, $P < 0.001$, to 0.66 ± 0.088 and 0.60 ± 0.030 for the fore and hind limbs. The MAC value for hind limb stimulus was significantly lower, $P < 0.025$, than that of the fore limb, as in the phase I study.

When the results from both phases were compared, there was a significant difference between the pre-epidural halothane MAC levels, $P < 0.05$, but not between the post-epidural values.

A problem was encountered in determining the halothane MAC level after epidural administration of morphine as the large decrease in the halothane requirement to abolish a limb stimulus was not matched by any apparent central sedative effect from the morphine. This meant that the dogs were very close to a level of returning consciousness when MAC determinations were carried out after epidural morphine administration. When consciousness returned before purposeful limb movement, the fore and hind limb MAC levels were taken as the midway point between the lowest end-tidal halothane concentration at which the animals did not respond to the supramaximal stimulus with purposeful movement or returning consciousness and the concentration when they woke up. This occurred in three out of ten animals for fore limb MAC determination and in eight out of ten for the hind limb in the first study, and in five out of ten and nine out of ten animals for similar determinations in the second study.

Once full recovery from halothane anaesthesia occurred (less than ten minutes), the dogs could stand and walk without assistance. No proprioceptive deficits were detectable at this time or over the next 24 hours, nor were any other adverse side effects noted.

Discussion

This study demonstrated that epidural morphine produced a significant reduction in halothane MAC for the fore and hind limbs.

The difference observed, between the pre-epidural halothane MAC levels from both phases, was expected as variations of up to ten per cent have been found between repeated determinations within the same animal.[3] Other factors were controlled to reduce this variability, as the same investigator was responsible for determining MAC by assessing purposeful movement of each animal. The reliability of the infrared gas analyser has also been documented.[6,7] Interestingly, the MAC determinations for the fore and hind limb with epidural morphine were very similar regardless of the volume used. One study in humans[8] compared 6 mg of morphine in 3 and 30 ml solutions, and the degree of analgesia was slightly better for the larger volume, although the absorption of morphine from the epidural space, as reflected by measured plasma concentrations was similar for both volumes. Our 50 per cent reduction in volume may not have duplicated the difference shown by the 90 per cent volume reduction used in their study. Also precise determination of MAC in the dogs was limited by their tendency to awaken and resist tracheal intubation at the low levels of halothane anaesthesia required under these circumstances. Awakening did not necessarily indicate reduced analgesia but rather reduced sedation.

The reduction in halothane MAC was significantly more pronounced in the hind limb than in the fore limb in both phases of the study. This segmental analgesia has also been demonstrated in humans[9] and in the cat.[10] Studies in the conscious cat[10] with different opioids administered epidurally, suggested that the analgesia occurred earliest and lasted longest in the somatic segment exposed to the largest amount of drug.

Differences in drug polarity are responsible for differences in the absorption and cephalad migration of opioids administered epidurally.[10,11] Lipid soluble opioids including meperidine, methadone, and fentanyl have a rapid onset of action and a short duration of effect.[10,11] The hydrophilic characteristics of morphine are responsible for its slow onset of action, approximately 30 to 60 minutes.[9,10,12] The determination of MAC for the fore limb and for the hind limb following epidural administration of morphine took on average 70 and 74 minutes, respectively, in phase I, and 61 and 69 minutes, respectively, in phase II which ensured that the onset of morphine's action had occurred. The analgesia was not tested beyond this point, and no conclusions were drawn as to the duration of action; however, epidural morphine has been reported to produce a long-lasting analgesic effect for up to 20 to 24 hours in other human and animal studies.[9,10,12,13]

The absence of observed adverse side effects in the present study is in contrast to human studies where respiratory depression, pruritus, nausea, vomiting and urinary retention have been reported.[12,14,15] Vomiting has been reported in conscious cats shortly after epidural injection of morphine.[10] However, this was not observed in this study nor in our clinical experience in dogs utilizing the technique in over 250 operations (Ontario Veterinary College medical records). Anaesthesia could have abolished this side effect.

In conclusion, this study demonstrated that morphine administered epidurally at 0.1 $mg \cdot kg^{-1}$ and diluted in 0.13–0.26 $ml \cdot kg^{-1}$ of saline reduced the anaesthestic requirement for halothane in the dog in a segmental manner, and this reduction was clinically significant for the fore and hind limbs. Therefore, epidural morphine could be used to provide intraoperative and postoperative analgesia for surgery involving procedures as far anterior as the fore limb.

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Résumé

Nous avons observé en deux fois l'effet du volume de dilution (0,13 et 0,26 $ml \cdot kg^{-1}$) d'une dose de morphine péridurale (0,1 $mg \cdot kg^{-1}$) sur la modification de la concentration alvéolaire minimale (MAC) de l'halothane de dix chiens, mesurée par application d'un courant électrique sous-cutané aux pattes avant et arrière, en ordre variable. Peu importe le volume de dilution, le MAC diminuait de façon significative ($P < 0,001$) aprés l'injection de morphine péridurale et ce, pour les pattes avant et arrière. Respectivement pour les membres antérieurs et postérieurs, le MAC passait de 1,04 ± 0,038 à 0,68 ± 0,034 et 0,60 ± 0,017 avec le grand volume de dilution et de 0,96 ± 0,038 à 0,66 ± 0,088 et 0,60 ± 0,030 avec le petit volume. En fait, la baisse du MAC était plus marquée aux membres postérieurs ($P < 0,025$) et cela semble indiquer un effet segmentaire de la morphine péridurale. Cependant, qu'on utilise 0,13 ou 0,26 $ml \cdot kg^{-1}$ de salin pour diluer 0,1 $mg \cdot kg^{-1}$ de morphine péridurale importe peu chez le chien, car la réduction du MAC de l'halothane et l'atteinte d'une analgésie englobant les membres antérieurs est la même.