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Epidural morphine reduces halothane MAC in humans

The effect of epidural morphine sulphate (4 mg in 10 ml saline) on the minimum alveolar concentration of halothane was investigated in a double-blind, randomized fashion in ten adult patients undergoing abdominal surgery, and compared with the minimum alveolar concentration of halothane after epidural administration of 10 ml saline in a similar group of patients. Morphine sulphate, administered through the epidural catheter 98 ± 33 min before to skin incision reduced the minimum alveolar concentration of halothane by 28% (0.57% vs 0.78%, $P < 0.05$).

Cette étude randomisée à double-aveugle évalue l'effet du sulfate de morphine en injection épidurale (4 mg dans 10 ml de soluté physiologique) sur la concentration alvéolaire minimum de l'halothane chez dix adultes subissant une intervention abdominale. La comparaison se fait avec un group contrôle identique recevant 10 ml de soluté physiologique par la même voie. Le sulfate de morphine, administré par le catheter péri-dural 98 ± 33 min avant l'incision réduit la concentration alvéolaire minimum d'halothane par 28% (0,57% vs 0,78%, $P < 0,05$).

Systemic administration of opiates reduces the minimum alveolar concentration (MAC) of volatile anaesthetics in animals and humans.¹⁻³ Intrathecal administration of morphine has been shown to reduce isoflurane MAC in the rat⁴ and halothane MAC in humans.⁵ Recently, however, in a randomized double-blind study, Licina *et al.*⁶ were unable to confirm these results and observed that intrathecal morphine did not reduce halothane MAC in humans.

Key words

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

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Epidural morphine is in current use at our institution as an adjuvant to volatile anaesthetics for major abdominal surgery because it may provide a more stable intraoperative course and offers a smoother transition into the postoperative period and better postoperative analgesia. Our clinical experience suggests that epidural administration of morphine reduces the anaesthetic requirement. In an attempt to answer this question, the present double-blind, randomized study was designed to determine whether an epidural administration of morphine would decrease the MAC of halothane in humans.

Methods

After obtaining institutional approval and informed consent, 20 adult ASA Physical Status I and II patients scheduled to undergo major abdominal surgery that included midline incision entered the study. Patients receiving medication known to affect anaesthetic requirement were excluded.

Patients were randomly allocated to one of two groups. No premedication was given. Before induction of anaesthesia, an epidural catheter was inserted cephalad in the L₂-L₃, or L₃-L₄ space (after infiltration with 2-3 ml 1% lidocaine) with the patient in the right decubitus position, and tested with a 3 ml solution of 1:200,000 epinephrine in saline for intravenous placement. Patients in the morphine group (M) then received 4 mg morphine sulphate diluted in 10 ml saline, and patients in the control group (C) received 10 ml saline through the epidural catheter by an anaesthetist blinded to the nature of the administered solution. Care was taken to blind all patients to the administration of morphine so as to avoid bias. The MAC was determined as in previous studies.⁵⁻⁷ Anaesthesia was induced with halothane in oxygen and nitrous oxide. After the induction, succinylcholine 1.5 mg · kg⁻¹ was administered, nitrous oxide discontinued, the trachea intubated, oxygen flow set at 4 L · min⁻¹, and the halothane concentration was adjusted to maintain a preselected end-tidal concentration corrected for age-related differences in MAC.⁸ Ventilation was controlled to obtain an end-tidal CO₂ between 3.5 and 4 kPa.

Gas samples were obtained from a catheter located at the proximal end of the endotracheal tube and analyzed by an infrared multigas sensor (Capnomac, Datex). The

apparatus was calibrated automatically before the beginning of each study according to the manufacturer's instructions. End-tidal concentration of halothane was preselected by using an "up-down method" for sequential sampling of quantal-response data.⁹⁻¹² This technique uses the result of each trial to determine the concentration sampled on the subsequent trial. In this study, if a patient moved at skin incision, the next patient in the same treatment group was tested at 0.1% higher halothane concentration. If movement did not occur, the halothane concentration was decreased by 0.1%. The preselected end-tidal halothane concentration was maintained for a minimum of 20 min before skin incision. The lack of residual succinylcholine paralysis at the time of skin incision was assessed by a train-of-four obtained with a nerve stimulator. The absence or presence of gross purposeful movement as defined by Eger *et al.*¹³ was determined by a neutral observer, blinded to the nature of the epidural administration.

Arterial, central venous, and urinary catheters were inserted. Neuromuscular blockade, heart rate, mean arterial blood pressure, oesophageal temperature, and oxyhaemoglobin saturation measured by pulse oximetry were monitored throughout the study and recorded at five-minute intervals. An oesophageal stethoscope and temperature probe were inserted. Following skin incision, anaesthetic management was left to the discretion of the anaesthetist.

After surgery, all the patients were transferred, after tracheal extubation, to the recovery room for surveillance until the next morning. Epidural placement of the catheters was verified by administering 6 ml bupivacaine, 0.25%, through the epidural catheter in all the patients and assessing their reaction to thermal and pinprick stimuli. Epidural opiates were then used for postoperative analgesia.

The MAC of halothane for each group was calculated and compared using a modification of Dixon's method for sequential sampling of quantal-response data,⁹⁻¹² and these results were verified with probit analysis. Student's *t* test was used where appropriate. Values for *P* < 0.05 were considered significant.

Results

Twenty patients consented to participate in the study. Cephalad insertion of the epidural catheters was uneventful. The "up-down" method was scrupulously followed. Postoperative administration in the recovery room of 6 ml bupivacaine, 0.25%, through the epidural catheter confirmed correct positioning of the catheter in the epidural space in all 20 patients.

There were no differences between the groups with respect to age, weight, sex, or preoperative haemoglobin concentration; preincision temperature, mean arterial blood pressure, heart rate, oxygen saturation, or end-tidal

TABLE Demographic data (mean $\pm$ SD)

	Morphine (<i>n</i> = 10)	Control (<i>n</i> = 10)
Age (yr)	58 $\pm$ 25	58 $\pm$ 16
Weight (kg)	71 $\pm$ 13	67 $\pm$ 15
Preoperative Hb (g $\cdot$ dl ⁻¹)	14 $\pm$ 1	14 $\pm$ 2
Injection to incision time (min)	98 $\pm$ 33	92 $\pm$ 21
Temperature at incision ($^{\circ}$ C)	35.8 $\pm$ 0.8	36.3 $\pm$ 0.5
FETCO ₂ at incision (KPa)	4.3 $\pm$ 0.4	4.4 $\pm$ 0.3
Preincision heart rate (BPM)	68 $\pm$ 18	78 $\pm$ 13
Preincision systolic blood pressure (mmHg)	108 $\pm$ 7	109 $\pm$ 4

FIGURE Each dot represents an individual response to skin incision (determination of MAC). The horizontal axis represents alveolar halothane concentrations (%) at the time of MAC determinations. Dots placed above the horizontal line represent movement to skin incision, and those below the line represent no movement in response to skin incision. Dashed lines represent calculated MAC values.

CO₂ concentration. Similarly, the time from epidural administration of morphine or saline to skin incision was not different between groups (98 $\pm$ 33 min vs 92 $\pm$ 21 min respectively; Table).

The MAC of halothane in patients receiving 4 mg epidural morphine sulphate was lower than the MAC ($\pm$ SE) of halothane in the patients receiving saline (0.57 $\pm$ 0.05 vs 0.78 $\pm$ 0.04 respectively; *P* < 0.05; Figure). Probit analysis confirmed these results: MAC in the M group was lower (*P* < 0.05) than in the C group (0.54 vs 0.73 respectively; with 95% confidence limits of 0.49 and 0.59 for the M group, and 0.69 and 0.78 for the C group).

Recovery for all patients was uneventful, and none developed complications due to epidural administration of morphine sulphate.

Discussion

Systemic administration of opioids has been shown to reduce the MAC of volatile anaesthetics by 20 to 60%,

depending on the dose and method of administration, in both animals and humans.¹³ This study was undertaken to determine whether preoperative administration of epidural morphine modified anaesthetic requirement and showed that the MAC of halothane was reduced.

The 28% reduction in the MAC of halothane after administration of epidural morphine probably resulted from binding with spinal opiate receptors and impairment of rostral transmission of nociceptive impulses^{14–15} as well as activation of supraspinal opiate-sensitive sites.¹⁵ Vascular absorption of morphine, on the other hand, only contributed a fraction of the analgesic effect since the appearance of morphine in plasma is transient after epidural injection.^{16–17}

Drasner *et al.*⁵ administered intrathecal morphine sulphate (0.75 mg) diluted 1:1 with 10% dextrose solution to a volume of 3 ml to ten patients and observed a reduction in the MAC of halothane. More recently, Licina *et al.*⁶ administered intrathecal undiluted morphine sulfate (15 $\mu\text{g} \cdot \text{kg}^{-1}$; range 0.75–1.4 mg) to 11 patients, observed no reduction in the MAC of halothane, and raised the possibility that the addition of glucose in the former study may have diluted the local sodium concentration in the subarachnoid space and therefore contributed to the observed reduction in MAC. In the present study, morphine sulphate 4 mg diluted in 10 ml saline was used. Dilution of subarachnoid sodium concentration was unlikely, and the effect of baricity on the narcotic effect of epidural or intrathecal opioids is not known.

Doses of epidural morphine used to relieve postoperative pain after major abdominal pain ranging from 2 mg to 0.1 $\text{mg} \cdot \text{kg}^{-1}$ have been evaluated.¹⁹ The best compromise between analgesia and an acceptable incidence of side effects seems to be 3–4 mg^{20} which corresponds to the morphine dose administered in the present study. The accepted potency ratio between epidurally and intrathecally administered morphine is 10:20:1;²¹ our epidural dose of morphine (4 mg or approximately 0.06 $\text{mg} \cdot \text{kg}^{-1}$) corresponds to an intrathecal dose of 0.2–0.4 mg and is less than half the doses used by Drasner *et al.*¹⁵ or Licina *et al.*⁶

The MAC of halothane in the control group corresponded to previously published values.^{2,8} The analgesic effect of epidural morphine has been shown to appear 20 min after its administration and maximum pain relief occurs after 40–60 min.^{22–25} Since the mean time from epidural injection to skin incision in the present study was 98 ± 33 min in the morphine group and 92 ± 21 min in the control group, this delay respected the pharmacodynamic properties of epidurally administered morphine.^{22–25}

Although the standard for halogenated anaesthetic agent monitoring remains the mass spectrometer,^{26,27} new single room gas monitors measure volatile anaesthetics by infra-

red analysis. These more modern monitors, such as the one used in the present study, have been shown to provide accurate and reliable measurements of end-tidal anaesthetic concentrations between 0.5% and 4%.

In conclusion, the present study demonstrated that epidural administration of morphine 4 mg in 10 ml of saline decreased the minimum alveolar concentration of halothane in humans.

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