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Intrathecal Morphine Reduces the Minimum Alveolar Concentration of Halothane in Humans

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The authors hypothesized that the analgesia provided by intraspinal opiates would decrease anesthetic requirement. To test this hypothesis, 20 women undergoing major gynecologic surgery were divided randomly into two groups. One group received 0.75 mg morphine sulfate intrathecally, and the other, the same dose intramuscularly (control), prior to the induction of anesthesia with halothane. MAC for halothane was 0.81% in the control group and 0.46% in the intrathecal morphine group ($P = 0.024$). The reduction in anesthetic requirement due to intrathecal morphine is greater than that produced by low to moderate doses of systemically administered opiates. (Key words: Analgesics, intrathecal: morphine. Anesthesia, volatile: halothane. Anesthetic requirement: MAC. Anesthetic techniques: spinal.)

SYSTEMIC ADMINISTRATION of opiates decreases the anesthetic requirement in both animals and humans.[1–5] We hypothesized that the inhibition of spinal nociceptive transmission resulting from administration of intraspinal opiates might decrease the need for volatile anesthetics. We demonstrated recently that intrathecal morphine significantly reduced anesthetic requirement in rats.[6] However, quantitation of an effect in humans has not been made. The present study was designed to determine whether intrathecal morphine would decrease the anesthetic requirement in humans.

Methods

We studied 20 women (ASA P.S. I or II) undergoing major abdominal gynecologic surgery with approval from our Committee on Human Research and informed consent from each patient. Women receiving medication known to affect anesthetic requirement were excluded from study.

Patients were divided randomly into two groups. Prior to induction of anesthesia, patients in group 1 received an intrathecal injection of 0.75 mg of preservative-free morphine sulfate (Duramorph®). The morphine solution was diluted 1:1 with a 10% dextrose solution to a total volume of 3 ml, and was injected at the L3–4 or the L4–5 level. Patients in group 2 (the control group) received the same dose of morphine sulfate administered into the deltoid muscle. No other premedication was given.

MAC was determined as in previous studies.[7] Anesthesia was induced with halothane, oxygen, and nitrous oxide. Following induction, *d*-tubocurarine (3 mg iv) and succinylcholine (100 mg iv) were administered, nitrous oxide was discontinued, and the patient's trachea was sprayed with 4 ml of 4% lidocaine and intubated. A stethoscope with a temperature probe was inserted into the esophagus. After tracheal intubation, oxygen flow was set at 5 l/min, and halothane concentration was adjusted to maintain a preselected end-tidal concentration adjusted to account for differences in MAC due to patient age.[8] Blood pressure was monitored noninvasively (Ohio® 2100 Monitor). Ventilation was controlled to obtain an end-tidal P_{CO_2} between 27 and 34 mmHg.

Gas samples obtained from a catheter located at the endotracheal tube connection site were analyzed by a mass spectrometer (SARA® PPG Biomedical). Halothane and CO_2 concentrations were displayed on a strip-chart recorder and the wave forms examined to ensure that a plateau phase in gas concentration had been obtained. Before each patient was studied, the mass spectrometer system was calibrated independently using a standardized tank containing 0.76% halothane in oxygen.

The preselected end-tidal halothane concentration was maintained for a minimum of 20 min prior to skin incision. A nerve stimulator was used to ensure that no significant residual succinylcholine paralysis persisted at the time of skin incision. The presence or absence of movement was determined by an observer blinded to the method of morphine administration. The criterion for a positive response was that of "gross purposeful" movement as defined by Eger *et al.*[9] Heart rate, blood pressure, and esophageal temperature were recorded immediately before skin incision. Following skin incision, anesthetic management was left to the discretion of the anesthesiologist. Postoperative monitoring of all patients included respiratory rate determinations for a period of 24 h postinjection. Over the first 12 h patients were checked every 30 min, and for the last 12 h, every 60 min.

End-tidal halothane concentrations were preselected using a modification of Dixon's method for sequential

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sampling of quantal–response data.[10] This sampling technique uses the results of each trial to dictate the concentration sampled on the subsequent trial. In the present study, if a patient did not move at skin incision, the next patient in the same treatment group was tested at a 0.1% lower halothane concentration. If movement was apparent, the halothane concentration was adjusted upward 0.1%.

The MAC of halothane for each group was calculated and compared using logistic regression.[11] Differences between groups in age, temperature, pre-incision blood pressure, end-tidal CO_2, duration of anesthesia, and times from injection and tracheal intubation to incision were compared using Student's t test. $P < 0.05$ defined significant differences.

Results

Intrathecal administration of 0.75 mg morphine sulfate significantly reduced halothane anesthetic requirement ($P = 0.024$; fig. 1). MAC of halothane for the control group was 0.81%, and for the intrathecal morphine group, 0.46%. No patient given intrathecal morphine moved at an end-tidal halothane concentration greater than 0.50%. In contrast, all patients in the control group moved at an end-tidal concentration of less than 0.78%.

There were no significant differences between the groups in age, temperature, pre-incision blood pressure, end-tidal CO_2, duration of anesthesia, or times from injection and tracheal intubation to incision (table 1).

Nine hours after injection, one patient in the intrathecal morphine group had a respiratory rate of 8 breaths/min. Two iv boluses of naloxone (0.2 mg) were administered 3 h apart to maintain her respiratory rate above 10 breaths/min.

Discussion

The 40% reduction in halothane MAC due to intrathecal morphine could be the result of analgesia produced solely by a direct action at opiate receptors within the dorsal horn of the spinal cord, activation of brain stem receptors, or activation of both spinal and supraspinal opiate-sensitive sites.

Activation of opiate receptors restricted to the spinal cord is sufficient to produce analgesia.[12–16] Because MAC does not vary with stimulus intensity once a certain supramaximal intensity has been achieved,[9] intrathecal morphine could have acted solely at the spinal cord to inhibit afferent nociceptive input, such that the stimulus was no longer supramaximal.

Although intrathecal morphine analgesia does not appear to be dependent upon an action at opiate-sensitive sites in the brain stem, it is likely that supraspinal opiate-sensitive sites contributed to the observed reduction in halothane requirement. In the present study, the average time from intrathecal injection of morphine to skin incision was 128 min. The concentration of morphine at relevant brain stem sites alone was likely to be too low[17–20] to produce the profound reduction we observed in halothane MAC. However, brain stem and spinal cord opiate-sensitive sites are known to interact multiplicatively or synergistically to produce analgesia.[21] Thus, even very limited activation of brain stem sites could have contributed significantly to the effect on MAC.

Because topical lidocaine was administered to both the intrathecal and intramuscular morphine groups, it cannot account for the observed difference in anesthetic requirement. Moreover, the MAC of halothane for the control group agrees with previously reported values.[3,8]

The observed reduction in halothane MAC due to intrathecal administration of 0.75 mg morphine sulfate

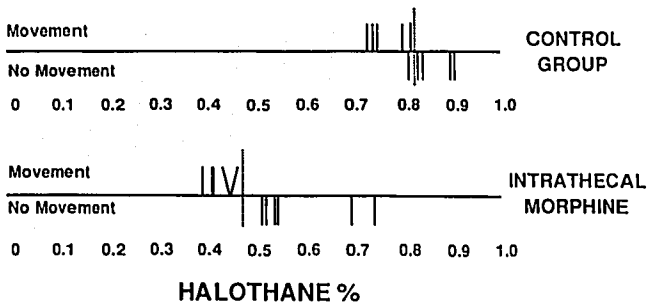

FIG. 1. Individual patient responses to skin incision. The horizontal axis represents alveolar halothane concentration at the time of skin incision. An upward deflection represents movement, and a downward deflection represents no movement in response to skin incision. Dashed line indicates calculated MAC value.

TABLE 1. Comparative Patient Data

	Intrathecal Morphine	Control
Age (yr)	38.0 ± 9.9	40.6 ± 11.0
Hematocrit (%)	38.8 ± 2.6	36.0 ± 4.2
Time from		
Injection to incision (min)	128.0 ± 42.0	105.0 ± 40.0
Induction to incision (min)	38.4 ± 4.2	40.5 ± 7.4
Intubation to incision (min)	27.2 ± 6.1	29.0 ± 5.8
Temperature (° C)	36.1 ± 0.6	36.3 ± 0.2
$\frac{FI - FE}{FE} \times 100$* (%)	15.2 ± 5.0	16.3 ± 6.1
End-tidal P_{CO_2} (mmHg)	30.1 ± 2.1	29.9 ± 2.2
Pre-incision systolic blood pressure (mmHg)	100.0 ± 16.3	95.2 ± 9.4

Values are given as mean ± SD.
* FI is inspired and FE is end-tidal halothane concentration.

is greater than the effect achieved with low to moderate doses of systemic opiates. In patients premedicated with 8–15 mg of intramuscular morphine sulfate, Saidman and Eger observed a 9% decrease in halothane MAC.[3] Using a similar dose range of intramuscular morphine for premedication, Munson *et al.* reported a 20% reduction in MAC for fluroxene.[4] In a study of volunteers in which electrical current was used as the test stimulus, Tsunoda *et al.* observed a 28% reduction in halothane MAC with iv administration of 0.2 mg/kg of pentazocine.[5]

The present study demonstrates that intrathecal administration of morphine decreases volatile anesthetic requirement in humans. Clinically, this effect may prove beneficial, particularly in patients who may not tolerate the hemodynamic changes associated with volatile anesthetics. However, because the present study incorporated only a single dose, the optimal dose as well as the advantages of this technique have yet to be established.

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