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# *The Enflurane Sparing Effect of Morphine, Butorphanol, and Nalbuphine*

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**The potencies of morphine and of the narcotic analgesic agonist-antagonists butorphanol and nalbuphine in terms of their ability to decrease enflurane MAC were studied. Following the determination of control MAC for enflurane in each dog, an intravenous bolus dose of either butorphanol tartrate, nalbuphine hydrochloride, morphine, or placebo was administered and enflurane MAC was redetermined. A higher dose of the same drug was then administered and enflurane MAC was redetermined up to a total of four doses in each animal. The successive doses for morphine and nalbuphine were 0.5, 1.5, 5.0, and 20.0 mg/kg; for butorphanol, 0.1, 0.3, 1.0, and 4.0 mg/kg; lactated Ringer's solution was used as a placebo. Both butorphanol and nalbuphine produced significant reductions of enflurane MAC (11 and 8%, respectively) at their lowest doses. No further reductions were produced by three- to forty-fold larger doses of either agonist-antagonist. Morphine produced a 17% reduction of enflurane MAC at the lowest dose with progressive decreases of enflurane MAC up to 63% at a dose of 5 mg/kg morphine. A fourfold increase in the morphine dose did not further decrease MAC. No change in enflurane MAC occurred in the animals given placebo. It was concluded that there is a "ceiling" to the potency of butorphanol and nalbuphine as anesthetic supplements. There is also a limit to the anesthetic sparing effect of morphine, but it is considerably greater than that of the agonist-antagonist narcotic analgesics. (Key words: Analgesics, narcotic: morphine; butorphanol; nalbuphine. Anesthetics, inhalational: enflurane; minimal alveolar concentration.)**

NARCOTIC ANALGESICS frequently are used as supplements to nitrous oxide or potent inhalational agents and have even been used in high doses as "anesthetics."[1] The use of high doses of narcotic analgesics as anesthetics is based primarily on their lack of cardiovascular depression; however, respiratory depression is a significant problem in the postoperative period. The agonist-antagonist analgesics, butorphanol and nalbuphine, have a plateau or "ceiling" effect in terms of respiratory depression, and this may be an advantage in the postoperative period.[2,3] However, their ability to serve as anesthetic supplements has not been quantitated.

This study was performed to determine the potency and efficacy of butorphanol and nalbuphine as anesthetic supplements in terms of their ability to decrease the anesthetic requirements (*i.e.*, MAC) of enflurane. For this purpose, they were compared with morphine, the drug for which they frequently are substituted, and one that has a similar onset and duration of action.[4–6]

## Materials and Methods

Mongrel dogs weighing 14–24 kg (mean 18 ± 0.6 SEM, N = 20) each were given an intravenous injection of succinylcholine chloride (0.10 ± 0.003 mg/kg) and atropine sulfate (0.10 ± 0.003 mg/kg), and anesthesia was induced immediately with 5% enflurane in oxygen, administered via a mask and a Bain anesthesia circuit. A cuffed endotracheal tube was introduced and the dog was ventilated with a Harvard® respirator to maintain a normal $Pa_{CO_2}$; blood *p*H was maintained in the normal range by the addition of sodium bicarbonate as needed. An intravenous catheter was placed in a foreleg vein and 5% dextrose in lactated Ringer's solution was administered at a rate of 11.6 ± 0.3 $ml \cdot kg^{-1} \cdot h^{-1}$. Body temperature was maintained at 37.4° ± 0.2 C. The electrocardiogram was monitored throughout the experimental period and a urinary catheter was inserted.

A femoral arterial cannula was utilized for continuous blood pressure recording and for periodic sampling of blood for gas analysis. When necessary, phenylephrine was used by bolus and/or infusion to maintain blood pressure at control levels in the case of morphine, which otherwise produces profound hypotension in the dog.[7] End-tidal enflurane was measured by a Beckman® LB-2 infrared analyzer. MAC determinations were made according to the technique of Eger *et al.*[8] Briefly, the base of the dog's tail was shaved. At least one hour after the induction of anesthesia and with a stable end-tidal enflurane concentration maintained for a minimum of 15 min, a "sponge stick" clamp was applied to the tail. The tail was moved continuously with the closed clamp for one min or until purposeful movement was elicited from the dog. Purposeful movement was defined as gross movement of the head or extremities, and did not include coughing, chewing, swallowing, or an increased respiratory effort. MAC was determined as the point midway between the end-tidal concentrations at which the animals would or would not move. MAC was determined to the closest 0.1% end-tidal enflurane concentration maintained for at least 15 min.

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TABLE 1. Effect of Butorphanol on Enflurane MAC

| Butorphanol Dose (mg/kg) | | Enflurane MAC (Mean % ET ± SEM) | Per Cent Reduction (Mean ± SEM) |
|---|---|---|---|
| Individual | Cumulative | | |
| Control | 0 | 2.28 ± 0.18 | —— |
| 0.1 | 0.1 | 2.04 ± 0.18* | 11 ± 2* |
| 0.3 | 0.4 | 1.92 ± 0.13* | 15 ± 4* |
| 1 | 1.4 | 1.93 ± 0.13* | 15 ± 4* |
| 4 | 5.4 | 1.90 ± 0.12* | 16 ± 3* |

* $P < 0.025$ *vs.* control or zero by paired $t$ test.
Analyses of variance without the control value shows no significant differences among the four butorphanol doses.

TABLE 3. Effect of Morphine on Enflurane MAC

| Morphine Dose (mg/kg) | | Enflurane (Mean % ET ± SEM) | Per Cent Reduction (Mean ± SEM) |
|---|---|---|---|
| Individual | Cumulative | | |
| Control | 0 | 2.16 ± 0.09* | —— |
| 0.5 | 0.5 | 1.81 ± 0.10 | 17 ± 3* |
| 1.5 | 2 | 1.46 ± 0.13 | 32 ± 7 |
| 5 | 7 | 0.79 ± 0.07† | 63 ± 3 |
| 20 | 27 | 0.69 ± 0.05† | 67 ± 3 |

* Significant reduction of enflurane MAC in relation to increasing morphine dosage by one-way analysis of variance ($P < 0.01$).
† MAC reduction by 5 and 20 mg/kg doses of morphine do not differ significantly by paired $t$ test ($P > 0.05$).

Approximately one hour after induction of anesthesia, control MAC determinations for enflurane were begun and took about one hour to complete. Following control determinations of enflurane MAC in each animal, an intravenous dose of either morphine, butorphanol, nalbuphine, or placebo was administered and enflurane MAC was redetermined. A higher dose of the same narcotic drug was then administered and enflurane MAC again determined. The sequence was repeated up to a total of four doses in each animal. Four dogs received morphine in successive doses of 0.5, 1.5, 5.0, and 20.0 mg/kg; five animals were given butorphanol tartrate, 0.1, 0.3, 1.0, and 4.0 mg/kg; six dogs received nalbuphine hydrochloride, 0.5, 1.5, 5.0, and 20.0 mg/kg; and five animals used as controls were given intravenous injections of lactated Ringer's solution as a placebo.

The drugs were administered over a 30-s period as an intravenous bolus. In the case of nalbuphine and butorphanol, enflurane MAC determinations were begun at 10 min and were completed by 60 min after the injection at which time another dose was given. Determinations of enflurane MAC were not begun until 30 min after the injection of morphine and were completed by 80 min in most instances. (Studies in human subjects indicate that the three drugs have a similar onset and duration of action, and produce a relatively stable analgesic effect between 10 and 90 min after an intravenous dose.[4–6]) The five placebo animals had four determinations of enflurane MAC (including their control) performed over an 8-h period.

Values are expressed as the means ± standard error of the mean unless designated otherwise. Significant differences were determined by analysis of variance and paired $t$ tests with $P < 0.05$ as the minimal limit of significance.

TABLE 2. Effect of Nalbuphine on Enflurane MAC

| Nalbuphine Dose (mg/kg) | | Enflurane MAC (Mean % ET ± SEM) | Per Cent Reduction (Mean ± SEM) |
|---|---|---|---|
| Individual | Cumulative | | |
| Control | 0 | 2.31 ± 0.08 | —— |
| 0.5 | 0.5 | 2.15 ± 0.15* | 8 ± 1* |
| 1.5 | 2 | 2.18 ± 0.15* | 7 ± 2* |
| 5 | 7 | 2.15 ± 0.17* | 8 ± 3* |
| 20 | 27 | 2.22 ± 0.17* | 6 ± 3* |

* $P < 0.001$ *vs.* control or zero by paired $t$ test.
Analysis of variance without the control value shows no significant differences among the four nalbuphine doses.

## Results

Butorphanol and nalbuphine both produced significant reductions of enflurane MAC at their lowest doses (tables 1 and 2), 11% for the 0.1 mg/kg dose of butorphanol, and 8% for 0.5 mg/kg dose of nalbuphine. However, no further reductions in enflurane MAC occurred after doses three- to forty-fold larger than the initial dose of either agonist-antagonist.

The lowest dose of morphine (0.5 mg/kg) produced a 17% decrease of enflurane MAC. Increasing doses of morphine produced progressive reductions of enflurane MAC up to the 5 mg/kg dose (table 3). The reduction of enflurane MAC for the 20 mg/kg dose of morphine (67%) was not significantly different than that produced by the 5 mg/kg dose (63%).

In five dogs, a placebo (lactated Ringer's solution) was administered over an 8-h period in a sequence similar to that used in the animals receiving one of the narcotics. The initial enflurane MAC was 2.26 ± 0.02% and it remained unchanged following the three placebo doses; MAC was 2.23 ± 0.06, 2.19 ± 0.10, and 2.19 ± 0.10% at 4, 6, and 8 h, respectively.

Three of the four dogs given intravenous bolus doses of morphine required phenylephrine to support their blood pressure after some of the doses. In most instances one to two small bolus doses (25–100 μg) immediately after the morphine sufficed to return the blood pressure to pre-study levels. However, in one of the animals, an

infusion of phenylephrine was required for a period of 20–70 min after each dose of morphine with multiple bolus doses of phenylephrine totalling 3.5 and 7 mg after the 5 and 20 mg/kg doses of morphine. In no instance was the decrease in systolic blood pressure greater than 16% of the control systolic pressure during the period of determination of MAC. The reductions of enflurane MAC in the animal not receiving phenylephrine were not different from those that did require phenylephrine.

## Discussion

Quasha *et al.*[9] noted in their review that studies in both animals and humans demonstrated reductions in the MAC of various inhalational agents when morphine was given as a pre-anesthetic medication. Hoffman and DiFazio[10] showed a linear decrease in cyclopropane MAC with increasing log doses of morphine and meperidine in rats. At the maximal doses of morphine (8 mg/kg) and meperidine (60 mg/kg) used in their study, there was a 55 and 70% decrease in cyclopropane MAC, respectively.

In our study of dogs, morphine produced increasing reductions of enflurane MAC with increasing doses up to a maximum reduction of 63% at 5 mg/kg. A fourfold greater dose failed to decrease enflurane MAC further. This "ceiling" effect for morphine has not been demonstrated previously. However, it is similar to the plateau seen with fentanyl.[11] Infusions of extremely high doses of fentanyl (up to 270 $\mu g/kg$ over 20 min with a maintenance rate of 3.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were unable to decrease enflurane MAC in the dog by more than 65%.

In three of the four dogs given morphine, phenylephrine was needed to maintain blood pressure at predrug levels. (Severe hypotension has been shown to reduce MAC.) Drugs that increase neurotransmitter levels in the central nervous system will have the effect of increasing MAC, while peripheral acting vasopressors have no effect on MAC.[9,12] It is doubtful that intravenous phenylephrine affected CNS neurotransmitter levels, and in fact, the dog that did not require the vasopressor for blood pressure support consistently fell within the high and low values for enflurane MAC reduction at each dose of morphine.

The ability of the agonist-antagonists, butorphanol and nalbuphine, to reduce enflurane MAC was very limited in our study. Butorphanol tartrate is approximately five times more potent than morphine sulfate as an analgesic, while nalbuphine hydrochloride is equipotent. At the lowest dose studied (equivalent to 0.5 mg/kg of morphine sulfate), butorphanol and nalbuphine had both reached their peak enflurane-sparing effect.

In the study by Hoffman and DiFazio,[10] pentazocine produced a 20% reduction of cyclopropane MAC at 20 mg/kg but a two- to fourfold greater dose produced no further decrease in MAC. Sederberg *et al.*[13] infused dogs (ventilated with oxygen only) with butorphanol at rates of 0.1 and 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ and found that 75% of the animals moved with tail-clamp stimulation at the lower dose and 25% at the higher dose. However, anesthesia was induced in the dogs with 15 to 20 mg/kg of sodium thiopental. Eger *et al.*[8] reported that induction of anesthesia with sodium thiopental (150–200 mg) in dogs reduced MAC by up to 20% for 2 to 4 h, and studies cited by Quasha *et al.*[9] showed decreases of inhalational anesthetic requirements of 27 to 77% with various barbiturates. Sederberg *et al.*[13] noted that in preliminary experiments, butorphanol infusions greater than 1 $mg \cdot kg^{-1} \cdot min^{-1}$ did not consistently prevent movement to a painful stimulus in their dogs.

In patients about to undergo aortocoronary bypass surgery, Moldenhauer *et al.*‡ found that butorphanol tartrate in doses of 0.15 and then 0.3 mg/kg (supposedly equivalent in analgesic terms to a 1.5 mg/kg dose of morphine sulfate) did not anesthetize the patients nor even render them unconscious. Even after anesthesia was induced with thiopental, diazepam, and nitrous oxide, there were marked hemodynamic responses to surgical stimulation in some of the patients. Similarly, Duckworth *et al.*§ found that nalbuphine hydrochloride in doses up to 3 mg/kg were not sufficient to anesthetize patients for coronary artery surgery. Although sleep was induced in some, others remained responsive.

In conclusion, the potency of the agonist-antagonists butorphanol and nalbuphine to decrease enflurane MAC is limited with a "ceiling" of efficacy similar to their "ceiling" of respiratory depression. In both respects the effects are similar to other agonist-antagonist narcotic analgesics. There appears to be no basis for the use of very large doses for anesthetic purposes. There is also a limit to the anesthetic sparing effect of morphine but it is considerably greater than for the agonist-antagonist and agrees closely with the effect found for another pure narcotic agonist, fentanyl.

‡ Moldenhauer CC, Hug CC Jr, Nagle DM, et al: High dose butorphanol (Stadol) in anesthesia for aortocoronary bypass surgery (ACB). Abstracts, 3rd Annual Meeting of the Society of Cardiovascular Anesthesiologists, San Francisco, May 10–13, 1981, pp 59–60.

§ Duckworth EN, Lake CL, DiFazio CA, et al: Cardiovascular effects of nalbuphine in patients with coronary artery disease. Abstracts, 3rd Annual Meeting of the Society of Cardiovascular Anesthesiologists, San Francisco, May 10–13, 1981, pp 61–62.

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