

Atracurium, Vecuronium, and Pancuronium Do Not Alter the Minimum Alveolar Concentration of Halothane in Humans

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The authors studied 64 unpremedicated, healthy surgical patients, aged 42 ± 14 yr, to determine the effects of atracurium, vecuronium, and pancuronium on the minimum alveolar concentration (MAC) of halothane. Anesthesia was induced using halothane/nitrous oxide/oxygen *via* a mask without the administration of other drugs. Nitrous oxide was discontinued, the trachea was intubated without prior administration of neuromuscular blocking drugs, and anesthesia was maintained with halothane in oxygen. Participating patients were assigned to one of five groups: 1) no neuromuscular blocking drug (control group, $n = 9$); 2) atracurium 0.5 mg/kg ($n = 10$); 3) atracurium 1.0 mg/kg ($n = 15$); 4) vecuronium 0.1 mg/kg ($n = 20$); or, 5) pancuronium 0.1 mg/kg ($n = 10$). Tourniquets, inflated to 300 mmHg immediately before iv administration of neuromuscular blocking drug and 15-30 min prior to skin incision, were used to isolate extremities from circulating neuromuscular blocking drug in all patients. A positive response to stimulation was defined as movement of at least one extremity occurring distal to the tourniquet within 1 min following skin incision. The first patients in the control and atracurium groups were studied at an end-tidal halothane concentration of 0.95%. The first patient in the pancuronium group was studied at a halothane concentration of 0.75%, and the first patient in the vecuronium group at 0.70%. Subsequent patients were studied at end-tidal halothane concentrations 0.10% above or below that of the preceding patient, depending on the presence or absence of movement with skin incision. Control MAC for halothane was $0.74\% \pm 0.09\%$ (mean \pm SEM). Atracurium, 0.5 and 1.0 mg/kg, did not significantly change the MAC of halothane ($0.74\% \pm 0.08\%$ and $0.77\% \pm 0.05\%$, respectively). The MAC of halothane was also unchanged from control in the patients given vecuronium and pancuronium ($0.78\% \pm 0.04\%$ and $0.74\% \pm 0.12\%$, respectively). Thus, clinical doses of atracurium, vecuronium, and pancuronium do not change the MAC of halothane in humans. (Key words: Anesthetics, volatile: halothane. Metabolism: laudanosine. Neuromuscular blocking drugs: atracurium; pancuronium; vecuronium. Potency, anesthetic: MAC.)

In 1979 Forbes *et al.*¹ reported that pancuronium decreased the MAC of halothane by 25% in adult surgical patients. The authors postulated that pancuronium either exerted a direct effect on the CNS or that it relaxed muscle spindles, producing a "deafferentation" of the CNS. Ve-

curonium is a nondepolarizing neuromuscular blocking drug structurally similar to pancuronium and may thus also reduce the MAC of halothane. In contrast, a metabolite of atracurium, laudanosine, increases the MAC of halothane in rabbits, and administration of atracurium produces arousal EEG changes in dogs given subanesthetic concentrations of halothane.^{2,3} Thus, atracurium may produce a dose-dependent increase in the MAC of halothane. We tested the hypotheses that atracurium increases, and that vecuronium decreases, the MAC of halothane in humans. MAC in patients given atracurium or vecuronium was compared with MAC in unparalyzed patients and in those given pancuronium.

Materials and Methods

Following approval by the UCSF Committee on Human Research and informed consent, we studied 64 patients, aged 18-65 yr, scheduled for elective surgery. They were not premedicated and were ASA physical status 1 or 2. Anesthesia was induced using halothane/nitrous oxide/oxygen *via* a mask without the administration of other drugs. Nitrous oxide was discontinued, and the trachea was intubated without prior administration of neuromuscular blocking drugs or additional anesthetics. Anesthesia was maintained with halothane in oxygen. Ventilation was controlled to maintain end-tidal carbon dioxide at 30-35 mmHg, which, along with the end-tidal halothane concentration, was measured by mass spectrometry (Medspect®, St. Louis, Missouri).

Participating patients were assigned to one of five groups: 1) no neuromuscular blocking drug (control group, $n = 9$); 2) atracurium 0.5 mg/kg ($n = 10$); 3) atracurium 1.0 mg/kg ($n = 15$); 4) vecuronium 0.1 mg/kg ($n = 20$); or, 5) pancuronium 0.1 mg/kg ($n = 10$). Tourniquets were used to isolate extremities from circulating muscle relaxant. They were placed around one arm and one calf (atracurium, pancuronium, and control groups) or one arm and both calves (vecuronium group), and inflated to 300 mmHg immediately before iv administration of muscle relaxant and 10-30 min before skin incision. Isolation of these extremities from circulating relaxant was assumed when the responses to tetanic stimulation of the ulnar and posterior tibial nerves distal to the tourniquets were unaltered. To assure that patients remained paralyzed, complete absence of adductor pollicis movement in response to tetanic stimulation of the ulnar

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TABLE 1. Demographic Characteristics of the Patients

| Relaxant | No. of Male/No. of Total | Age (yr) |
|-----------------------|--------------------------|----------|
| Control | 5/9 | 31 ± 5 |
| Atracurium 0.5 mg/kg | 6/10 | 35 ± 10 |
| Atracurium 1.0 mg/kg | 1/15 | 40 ± 9 |
| Vecuronium 0.1 mg/kg | 3/20 | 46 ± 13 |
| Pancuronium 0.1 mg/kg | 1/10 | 36 ± 7 |

nerve of the arm without a tourniquet was documented a few minutes before skin incision.

A positive response to stimulation was defined as movement of one or more of the extremities on which the tourniquets had been placed, occurring within 1 min following skin incision, and was assessed by observation of the extremities by the investigators and other members of the operating room staff. In the control group (no neuromuscular blocking drug), only movement distal to the tourniquets was considered a positive response.

The first patients in the control and atracurium groups were studied at an end-tidal halothane concentration of 0.95%. The first patient in the pancuronium group was studied at a halothane concentration of 0.75%, and the first patient in the vecuronium group at 0.70%. Subsequent patients were studied at end-tidal halothane concentrations 0.10% above or below that of the preceding patient, depending on the presence or absence of movement with skin incision. To minimize the alveolar-brain halothane gradient, end-tidal concentrations were main-

tained constant for at least 15 min before skin incision. End-tidal halothane concentrations were adjusted for age (concentrations decreased by 16% in patients > 55 yr, and increased by 11% in those < 30 yr).⁴

The MAC of halothane for each group was determined by the quantal analysis technique of Waud.⁵ MAC and age in the groups given muscle relaxants were compared with those in the control group using one-way ANOVA. MAC in patients given pancuronium was compared with that previously reported¹ using two-tailed, unpaired *t* test. Statistical significance was assumed when *P* < 0.05.

Results

The mean age of the patients was 39 yr (±11 yr, SD), and did not differ significantly among the five groups (table 1). Twenty-five percent of the subjects were males, ranging from 7% to 60% within each group. Individual patient data with respect to administered halothane concentration and movement are shown in figure 1. The MAC of halothane in the control group was 0.74% ± 0.09% (mean ± SEM). Atracurium, in doses of 0.5 and 1.0 mg/kg, did not significantly increase the MAC of halothane (0.74% ± 0.08% and 0.77% ± 0.05%, respectively). The first patient who received 1.0 mg/kg atracurium moved with skin incision at an end-tidal halothane concentration of 0.95%. No other patient in our study demonstrated movement at or above this end-tidal halothane concentration. Vecuronium and pancuronium did

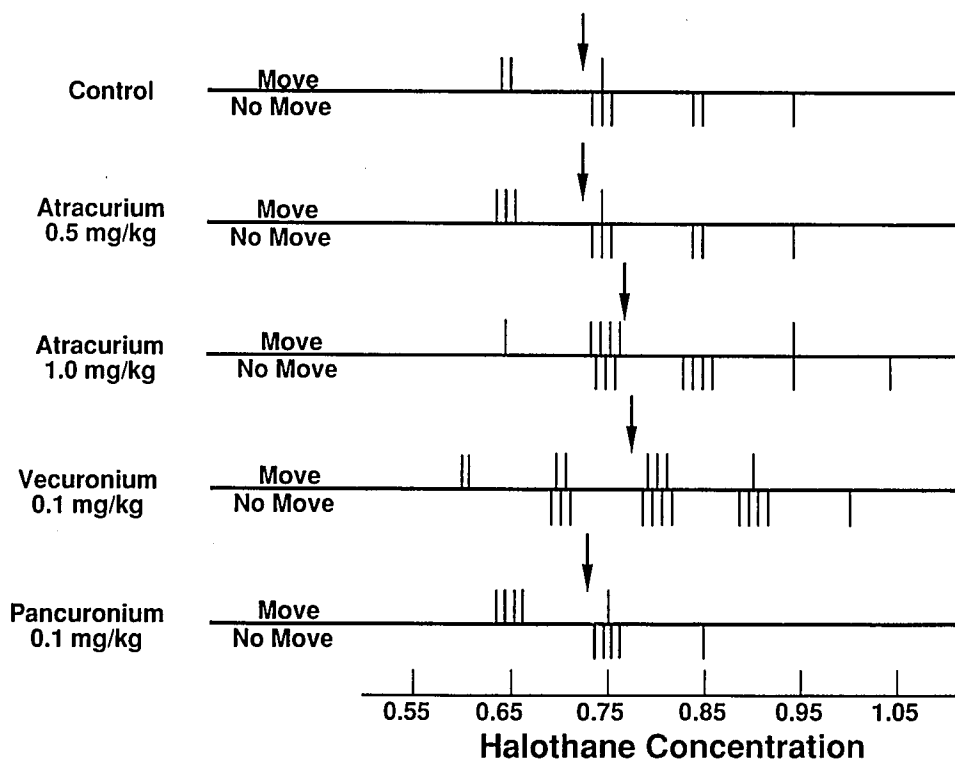


FIG. 1. Individual patient responses to surgical incision in control, atracurium, vecuronium, and pancuronium patient groups. Vertical arrows indicate the calculated MAC of halothane in each group. MAC was not significantly altered by any of the neuromuscular blocking drugs. End-tidal halothane concentration for each patient was adjusted for age (increased 11% for age < 30 yr and decreased 16% for age > 55 yr; individual responses are after age adjustment).

not significantly decrease the MAC of halothane ($0.78\% \pm 0.04\%$ and $0.74\% \pm 0.12\%$, respectively). MAC in patients given pancuronium differed significantly from that reported previously.¹

Discussion

A previous study, similar to ours, showed that pancuronium decreased the MAC of halothane by 25% in surgical patients.¹ The authors suggested that the decrease in MAC might result from a direct effect of pancuronium on the brain, or from muscle "deafferentation." In contrast to the other nondepolarizing neuromuscular blocking drugs, atracurium may increase the MAC of halothane *via* its metabolite laudanosine, which is a known CNS stimulant.

A direct CNS effect of neuromuscular blocking drugs is unlikely because ionized molecules with large steroidal nuclei do not easily pass through the blood-brain barrier. Although *d*-tubocurarine (4 ng/ml) has been detected in the cerebrospinal fluid of surgical patients 5 min after iv administration, these patients had CNS pathology, which may have increased the permeability of the blood-brain barrier.⁶ A study in humans, using atracurium, which has a similar chemical structure to that of *d*-tubocurarine, could not demonstrate measurable concentrations (≥ 2 ng/ml) of atracurium in cerebrospinal fluid during a 45-min sampling period after the iv administration of 0.5 mg/kg of the drug.⁷ Other studies have demonstrated that only trace amounts of nondepolarizing muscle relaxants pass the blood-brain barrier in mice, rats, and dogs.⁸⁻¹⁰ These studies suggest that pancuronium does not alter MAC by acting at a central site.

Neuromuscular blocking drugs may alter cerebrocortical activity by changing proprioceptive afferent activity from muscles. There is ample evidence that muscle spindle input to the cerebral cortex, as well as EEG activity, is influenced by the use of many different muscle blockers. Intravenous administration of depolarizing neuromuscular blocking drugs in humans (succinylcholine, decamethonium, carbolinium) but not of nondepolarizing agents (gallamine, alcuronium) during halothane anesthesia has been demonstrated to induce an arousal response in the EEG, accompanied by increases in heart rate and blood pressure.¹¹ These responses were later shown to be similar to the ones produced by skin incision during light halothane anesthesia (0.5–0.75%).¹² In dogs anesthetized with 1 MAC halothane, the administration of succinylcholine was accompanied by increases in intracranial pressure and cerebral blood flow and immediate EEG arousal following fasciculations.¹³ The investigators hypothesized that these changes resulted primarily from increased afferent muscle spindle activity.

Afferent muscle activity has been quantified in dogs

anesthetized with 1 MAC halothane, given a "defasciculating" dose of pancuronium before administration of succinylcholine.¹⁴ This study demonstrated that cerebral activation paralleled the increase in afferent muscle activity. It also showed that fasciculations were not a determinant of afferent muscle activity, indicating that "hyperafferentation" may result from a direct effect of depolarizing neuromuscular blocking drugs on the intrafusal muscle fibers (innervated by gamma-motoneurons), rather than indirectly by contraction of extrafusal muscle fibers (innervated by alpha-motoneurons).

These results with depolarizing neuromuscular blocking drugs suggest that nondepolarizing agents might have the opposite effect, producing "deafferentation." Gallamine and *d*-tubocurarine were found to induce electrocortical synchronization (associated with increased anesthetic effect) in cats when administered intravenously. Because no such effect was observed after injection of these drugs into the carotid arteries, the synchronizing effect presumably was due to eliminating from the cerebral cortex "extensive, proprioceptive influences."¹⁵ In contrast, EEG was unchanged following iv administration of pancuronium in dogs anesthetized with 1 MAC of halothane.³

Studies in animals suggest that laudanosine, a metabolite of atracurium, might increase MAC. Lanier *et al.* demonstrated in dogs given subanesthetic concentrations of halothane and having a control "anesthetized" EEG pattern, that 1 mg/kg atracurium produced a desynchronization of the EEG consisting of a reduction in amplitude and an increase in frequency.³ They interpreted these changes as representing "cerebral stimulation." However, EEG evidence of arousal did not occur in dogs given ≤ 1 mg/kg atracurium and 1 MAC of halothane, conditions comparable to those in our patients. Changes consistent with awakening from halothane anesthesia have been observed following administration of laudanosine in dogs.¹⁶ Similarly, an infusion of laudanosine increased the MAC of halothane by about 30% in rabbits, in proportion to plasma laudanosine concentration.²

We tested vecuronium because it is structurally similar to pancuronium, and would therefore be expected to reduce MAC in a similar fashion. Because it did not, we also evaluated the effect of pancuronium on MAC and, surprisingly, could not demonstrate any effect of pancuronium on the MAC of halothane.

The previous study in humans of pancuronium's effect on MAC contained only men, whereas our pancuronium group, though not by design, contained mostly women. Unpublished results in humans and animals indicate that there is either no difference in MAC between the sexes or that MAC in female mice may be slightly higher than in male mice.¹⁷ Our study also differs in that halothane was measured using mass spectrometry rather than an

infrared analyzer. We used two extremity tourniquets, whereas three were sometimes used in the previous study. We studied only ten patients given pancuronium, but five of ten patients in our study moved in response to surgical incision at concentrations of halothane at or above 0.65%, as opposed to 1 of 17 reported previously.¹ In summary, we have shown that clinical doses of vecuronium, atracurium, and pancuronium do not alter the MAC of halothane in healthy surgical patients.

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