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Vecuronium-induced Neuromuscular Blockade during Enflurane, Isoflurane, and Halothane Anesthesia in Humans

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To determine the effect of the commonly used volatile anesthetics on a vecuronium-induced neuromuscular blockade, the authors studied 54 patients anesthetized with 1.2 MAC or 2.2 MAC enflurane, isoflurane, or halothane (MAC value includes contribution from 60% nitrous oxide). During 1.2 MAC enflurane, isoflurane, and halothane, the ED_{50}s (the doses depressing twitch tension 50%) for vecuronium were 12.8, 14.7, and 16.9 μg/kg, respectively. During 2.2 MAC enflurane, isoflurane, and halothane, the ED_{50}s for vecuronium were 6.3, 9.8, and 13.8 μg/kg, respectively ($P < 0.05$). Time from injection to peak effect was the same for each anesthetic group (6.5 ± 0.5 min, mean ± SD), except for the group given 2.2 MAC enflurane (9.7 ± 0.6 min) ($P < 0.05$). The duration of a 50% block from injection to 90% recovery was the same for each group (mean 20 ± 4 min), except for the group given 2.2 MAC enflurane (46.5 min) ($P < 0.05$). The authors conclude that enflurane is the most potent volatile anesthetic, followed by isoflurane and then halothane, in augmenting a vecuronium-induced neuromuscular blockade. Increasing the concentration of volatile anesthetic has less effect on a neuromuscular blockade produced by vecuronium than on one produced by other nondepolarizing relaxants (*e.g.*, pancuronium and *d*-tubucurarine). (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Neuromuscular relaxants: vecuronium. Potency, anesthetic: ED_{50}; MAC.)

VOLATILE ANESTHETICS augment the neuromuscular block produced by nondepolarizing muscle relaxants. Also, the neuromuscular blocking ability of vecuronium (Org NC45), a new nondepolarizing muscle relaxant having an intermediate duration of action, is greater during enflurane anesthesia than during neurolept[1] or halothane anesthesia.[2] However, no studies have made quantitative comparisons of the effects of the volatile anesthetics on the neuromuscular block produced by vecuronium. Therefore, we not only quantitated and compared the neuromuscular blocking effects of vecuronium during equipotent concentrations of enflurane, isoflurane, and halothane, but also compared the effects of increasing the concentration of each volatile anesthetic on the neuromuscular blockade induced by vecuronium.

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Materials and Methods

We obtained approval from our local committee on human research and informed consent to study 54 ASA I and II patients undergoing elective surgery. Patients were premedicated with diazepam, 10 mg orally. We induced anesthesia with thiopental, 2–4 mg/kg intravenously, and one of the inhaled volatile anesthetics (enflurane, isoflurane, or halothane) with 60% nitrous oxide. The trachea was sprayed with 4 ml 4% lidocaine and intubated without the use of muscle relaxants. The concentrations of the volatile anesthetics, nitrous oxide, oxygen, and carbon dioxide were determined continuously using mass spectrometry. We controlled ventilation to keep end-tidal P_{CO_2} between 30 and 40 mmHg and maintained esophageal temperature above 35.5° C. A Grass S-44 stimulator delivered supramaximal square-wave bipolar impulses of 0.15 ms duration and 0.15 Hz to thin-walled, 27-gauge steel-needle electrodes placed 3 cm apart near the ulnar nerve at the wrist. The resultant force-of-thumb adduction was measured by a Grass FT-10 force-displacement transducer and was recorded continuously on a polygraph.

We divided the patients into six groups. In three groups, the anesthesia was kept at 1.2 MAC, which included a 0.6 MAC contribution from the 60% nitrous oxide.[3] The resulting mean (±SD) end-tidal concentrations were 1.02 ± 0.01% for enflurane, 0.71 ± 0.01% for isoflurane, and 0.44 ± 0.02% for halothane. To allow maximum separation between the anesthetic levels while avoiding significant cardiovascular depression, we used 2.2 MAC (which included the MAC contribution from 60% nitrous oxide) in Groups 4–6. The resulting end-tidal concentrations were 2.82 ± 0.02% for enflurane, 1.82 ± 0.03% for isoflurane, and 1.20 ± 0.02% for halothane. After end-tidal concentration was stable for 30 min, we administered vecuronium intravenously. The maximum percentage of depression of twitch tension (peak effect), the time from administration to peak effect (onset time), and the time from injection until muscle twitch tension returned to 90% of control (duration of action) were determined. Data for eight patients were not analyzed for duration of action because of the clinical need to administer more muscle relaxant or antagonist before twitch tension could recover to 90% of control.

Using linear regression, we determined the dose–response relationship (log dose *vs.* peak effect) for vecuronium for each of the six groups. All regression lines

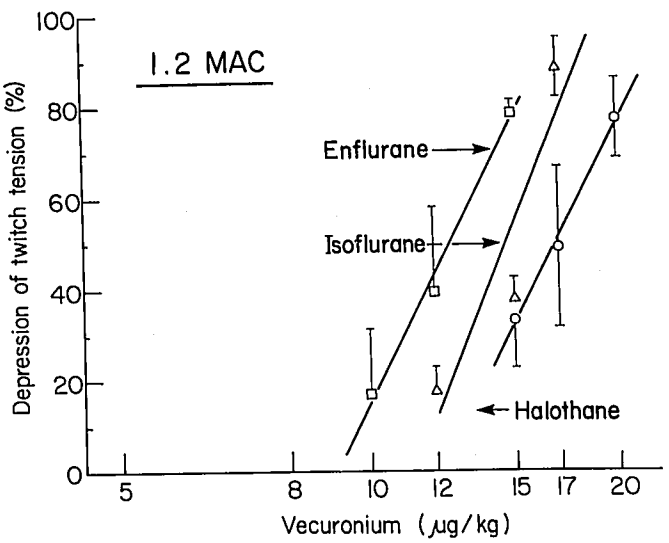

FIG. 1. Dose–response relationships for vecuronium during 1.2 MAC anesthesia: 0.6 MAC from 60% nitrous oxide and 0.6 MAC from enflurane, isoflurane, or halothane. The dose–response relationship for enflurane differed significantly ($P < 0.05$) from that for isoflurane or halothane.

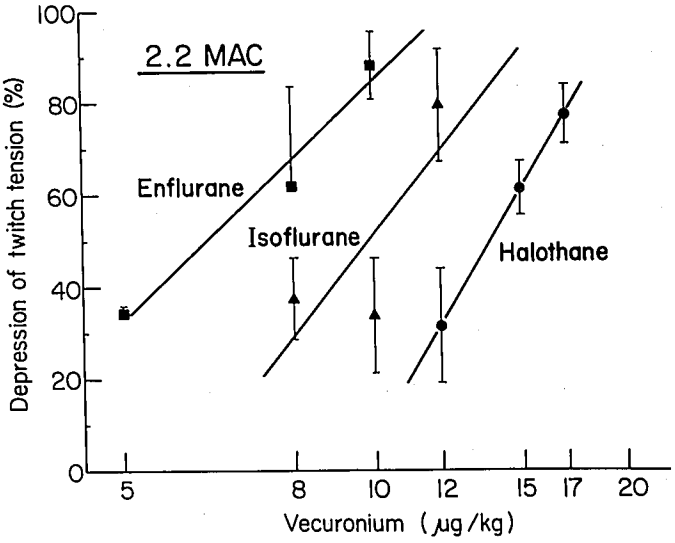

FIG. 2. Dose–response relationships for vecuronium during 2.2 MAC anesthesia: 0.6 MAC from 60% nitrous oxide and 1.6 MAC from enflurane, isoflurane, or halothane. All dose–response relationships differed significantly ($P < 0.05$).

were compared using analysis of covariance.[4] First, we tested the lines to determine if they deviated from parallelism. If they did not, an F test was applied to determine if the elevations were different. If so, the Student–Newman–Keuls test was applied to determine which lines differed in elevation. To compare the potency of vecuronium between groups, we calculated an ED_{50} (the dose causing 50% depression of twitch tension) for each group from the regression analysis. Comparisons of ED_{50} were made only after regression lines were found not to deviate from parallelism. Using analysis of variance, we compared onset time between groups. Duration of action was compared between groups by plotting duration of action *vs.* peak effect for each group, after which an analysis of linear regression was performed. These regressions then were compared, as were dose–response relationships. The latter comparison was made because doses producing little neuromuscular block have a shorter duration of action than those producing near maximal neuromuscular blockade. Thus, an error could be made in comparing mean duration between groups if their mean peak effects (and thus the mean duration) differed considerably. $Duration_{50}$ (the duration of a 50% block) is reported for each anesthetic group and was determined by interpolating the plots of duration *versus* depression of twitch tension (as was done in determining ED_{50}s). Again, $duration_{50}$s were compared only after lines were found not to deviate from parallelism. Analysis of variance determined whether differences existed between the six groups for age, body weight, sex, esophageal temperature, dose of thiopental, or end-tidal P_{CO_2}.

For all statistical comparisons, differences were considered significant when $P < 0.05$.

Results

At both 1.2 (fig. 1) and 2.2 MAC (fig. 2), enflurane was the most potent volatile anesthetic in augmenting the peak effect of vecuronium ($P < 0.05$) (table 1). Isoflurane and halothane followed, in that order. However, differences between the two were statistically significant only at 2.2 MAC. For all groups, the regression analyses of peak depression of twitch tension *versus* log dose for vecuronium did not deviate from parallelism.

TABLE 1. Potency, Onset, and Duration of Action for Three Volatile Anesthetics at Two Levels of Potency

Anesthetic*	ED_{50}† (μg/kg)	Mean ± SD Onset (min)	$Duration_{50}$‡ (min)
1.2 MAC enflurane	12.8§	7.0 ± 0.5	23.6
1.2 MAC isoflurane	14.7	6.1 ± 0.3	15.2
1.2 MAC halothane	16.9	6.2 ± 0.2	19.7
2.2 MAC enflurane	6.3¶	9.7 ± 0.6¶	46.5¶
2.2 MAC isoflurane	9.8¶	6.9 ± 0.5	24.3
2.2 MAC halothane	13.8	6.1 ± 0.2	17.0

* All MAC values include a MAC contribution from 60% nitrous oxide.

† Dose producing 50% depression of twitch tension.

‡ Duration to 90% recovery of a dose producing 50% depression of twitch tension.

§ Different from all other groups ($P < 0.05$) except 2.2 MAC halothane.

¶ Different from all other groups ($P < 0.05$).

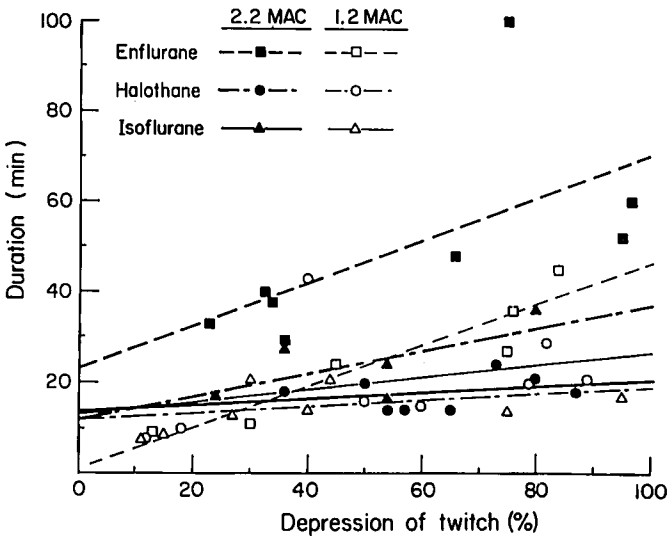

FIG. 3. Regression analyses of duration of action (time from injection to 90% recovery) *versus* peak effect (maximum percentage depression of twitch tension) are shown. Analysis of covariance revealed that all lines were not significantly different except the line representing 2.2 MAC enflurane ($P < 0.05$).

Increasing the dose of anesthetic from 1.2 to 2.2 MAC shifted the dose–response curve to the left, *i.e.*, decreased the ED_{50} of vecuronium (table 1): 51% for enflurane ($P < 0.05$), 33% for isoflurane ($P < 0.05$), and 18% (not significant) for halothane.

Onset time was not related to the anesthetic or dose of anesthetic except for the group given the 2.2 MAC enflurane (table 1); for this group, onset time was 50% greater than for all other groups ($P < 0.001$). In the dose range studied, onset time also did not relate to the dose of vecuronium.

The regression lines representing duration *versus* peak depression of twitch tension did not deviate from parallelism (fig. 3). Values for $duration_{50}$ did not differ significantly between groups, except for the group given 2.2 MAC enflurane (table 1). Its value for $duration_{50}$ was 2.3 times greater than the mean $duration_{50}$ values for the other five groups ($P < 0.01$).

No significant differences existed among all six groups in age, body weight, sex, esophageal temperature, dose of thiopental, or end-tidal P_{CO_2}.

Discussion

Volatile anesthetics interact differently with vecuronium than with other nondepolarizing muscle relaxants in two important ways. First, at both MAC levels of anesthesia, enflurane was more potent than isoflurane or halothane in augmenting a vecuronium-induced neuromuscular blockade. In contrast, enflurane and isoflurane equally augmented a neuromuscular blockade induced by pancuronium or *d*-tubocurarine, and both anesthetics were roughly twice as potent as halothane.[5-7] Furthermore, isoflurane and halothane were similar in enhancing a vecuronium-induced neuromuscular blockade, especially at the 1.2 MAC level. Our *in vivo* human findings are consistent with the *in vitro* findings of Chaudry *et al.*,[8] who found that isoflurane and halothane equally enhanced the neuromuscular blocking effects of vecuronium and that both anesthetics were less potent than enflurane. We cannot explain why volatile anesthetics interact differently with vecuronium than with pancuronium or *d*-tubocurarine.

Second, increasing the concentration of volatile anesthetic had less effect on a neuromuscular blockade produced by vecuronium than on blockades produced by pancuronium or *d*-tubocurarine. Using anesthetic conditions almost identical to ours, Miller *et al.*[9] found that increasing the end-tidal concentration of halothane from 0.4% to 1.2% (that is, from 1.2 MAC to 2.2 MAC, which included the MAC contribution from 70% nitrous oxide) reduced the ED_{50} for *d*-tubocurarine by 62% and the ED_{50} for pancuronium by 57%. Similarly, increasing the end-tidal concentration of isoflurane from 0.5% to 1.5% (that is, from 1.1 MAC to 2.0 MAC, which included the MAC contribution from 70% nitrous oxide) reduced the ED_{50} of *d*-tubocurarine by 39% and the ED_{50} of pancuronium by 70%.[9] Data for enflurane are not available. Thus, while the neuromuscular blockade induced by *d*-tubocurarine and pancuronium are markedly enhanced by increasing the end-tidal concentration of halothane and isoflurane, this effect is minimal on the neuromuscular block produced by vecuronium (particularly when the anesthetic is halothane).

The twofold reduction in vecuronium's ED_{50} during enflurane anesthesia when MAC is increased from 1.2 to 2.2 is consistent with enflurane's ability to depress single twitch tension when administered alone in end-tidal concentrations exceeding 2.5%.[10] Neither halothane nor isoflurane depresses single twitch when given in concentrations equipotent to such a dose of enflurane.[6] This characteristic of enflurane also may account for the fact that $duration_{50}$ was 2.3 times greater for the group given 2.2 MAC enflurane than for the other five groups. Thus, the prolonged duration of action of vecuronium during 2.2 MAC enflurane may be due more to enflurane's neuromuscular effect at this concentration than to some unusual interaction between vecuronium and enflurane. Data on other nondepolarizing relaxants at this concentration of enflurane are not available.

At 2.2 MAC, enflurane prolongs the onset time of a vecuronium-induced neuromuscular blockade by 50%, perhaps because blood flow was diminished due to depressed cardiac output. Alternatively, altered neuromuscular receptor affinity during deep enflurane anesthesia may have delayed the binding of vecuronium and

thus prolonged onset time. The exact mechanism for prolonged onset time is not known.

In conclusion, we found differences in the manner in which volatile anesthetics enhance a neuromuscular block produced by vecuronium, as compared with other nondepolarizing muscle relaxants (*e.g.*, *d*-tubocurarine, pancuronium). Most important, the peak effect of vecuronium is less dependent on the concentration of volatile anesthetic than is the peak effect of other nondepolarizing drugs. The clinical advantage of this is that neuromuscular blockade will be more predictable if the end-tidal concentration of anesthesia is estimated or unknown. The disadvantage is that an existing block would not easily be enhanced by increasing the inspired concentration of the volatile anesthetic. Whether this characteristic is unique to vecuronium or is true for all the new nondepolarizing muscle relaxants having an intermediate duration of action (*e.g.*, atracurium) remains to be determined.

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