

Continuous Infusion of Vecuronium: The Effect of Anesthetic Agents

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The authors studied the effects of enflurane, isoflurane, and fentanyl, each in combination with 60% nitrous oxide, on the vecuronium infusion rate necessary to maintain constant 90% depression of control muscle twitch tension. Thirty healthy surgical patients were given an initial 0.1 mg/kg bolus of vecuronium, followed by an infusion of vecuronium at an initial rate of $1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. After 1 h of steady-state 90% twitch depression, plasma vecuronium concentrations (C_{590}) were measured by capillary column gas chromatography. Total plasma clearance of vecuronium was estimated using C_{590} values. Vecuronium infusion rates (mean \pm SD) were similar for patients given enflurane ($0.28 \pm 0.13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and isoflurane ($0.30 \pm 0.13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), but significantly higher in patients given fentanyl ($0.92 \pm 0.37 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Values for C_{590} in the patients receiving enflurane and isoflurane were similar (71 ± 34 and $72 \pm 44 \text{ ng/ml}$, respectively), but significantly higher in those receiving fentanyl ($165 \pm 48 \text{ ng/ml}$). Total plasma clearance was similar during enflurane, isoflurane, and fentanyl anesthesia (4.4 ± 2.6 , 4.6 ± 1.2 , and $5.6 \pm 1.9 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively). The authors conclude that patients receiving isoflurane and enflurane require markedly lower vecuronium infusion rates to achieve 90% neuromuscular blockade than those receiving fentanyl. The enhancement of neuromuscular blockade by isoflurane and enflurane represents a change in the pharmacodynamics of vecuronium-induced neuromuscular blockade, rather than a change in pharmacokinetics. (Key words: Anesthetics, intravenous: fentanyl. Anesthetics, volatile: enflurane; isoflurane. Anesthetic technique: infusion; inhalation. Neuromuscular relaxants: vecuronium. Pharmacokinetics: vecuronium.)

VECURONIUM BROMIDE is a nondepolarizing neuromuscular blocking drug with an intermediate duration of action.¹ It should, therefore, be possible to administer vecuronium by continuous infusion to provide precise control of neuromuscular blockade during long surgical procedures. The usefulness of this method could be further defined by knowing the effect of different anesthetics on vecuronium infusion rate require-

ments. Accordingly, we studied the effects of isoflurane, enflurane, and fentanyl anesthesia on neuromuscular blockade induced by vecuronium administered by continuous infusion.

Methods and Materials

Approval for this study was granted by the UCSF Committee on Human Research, and informed consent was obtained from 30 ASA PS I-II patients who were to undergo elective surgery. Patients were premedicated orally with diazepam, 10 mg, and anesthesia was induced with thiopental, 4–8 mg/kg iv, and 60% nitrous oxide by face mask. Neuromuscular blockade was assessed with a Grass® FT-10 force transducer, which measured adductor pollicis twitch tension in response to supramaximal stimulation of the ulnar nerve. A Grass® S44 stimulator (0.15 ms, 0.15 Hz) delivered the stimulating current through 27-gauge needles placed at the wrist. Esophageal temperature was maintained at 35–37° C by warming blankets and heated iv fluids.

Patients were randomly assigned to receive one of three anesthetic agents ($n = 10$ for each group), each of which was combined with 60% nitrous oxide in oxygen. Two were volatile agents, enflurane and isoflurane, administered at end-tidal concentrations of 1.6% and 1.2%, respectively. The third was fentanyl, administered as an initial iv bolus of 9 $\mu\text{g}/\text{kg}$ followed by an infusion of $0.09 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. After at least 10 min of stable anesthetic conditions, 0.1 mg/kg iv of vecuronium was administered to facilitate intubation of the trachea. Minute ventilation was mechanically controlled to maintain end-tidal CO_2 tension at 35–40 mmHg.

Vecuronium was prepared for infusion by dissolving 10 mg of the powdered commercial preparation in 50 cc of normal saline. Stability of vecuronium in this solution has been previously tested.² The infusion was delivered by a Harvard® volumetric infusion pump that was calibrated before each patient study to assure accurate delivery of the desired volume of vecuronium. When muscle twitch tension returned to 10% of control, vecuronium was infused initially at a rate of $1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, after which the rate was continually adjusted to maintain a stable 90% depression of control muscle twitch tension. After 1 h of 90% depression at a constant infusion rate, two heparinized blood samples were drawn, 15 min apart, to determine steady-state

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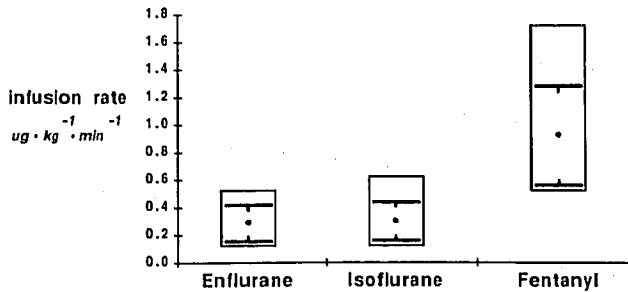


FIG. 1. Vecuronium infusion rates necessary to maintain constant 90% depression of control muscle twitch tension during three different anesthetics, ● = mean infusion rates; $\bar{\text{I}}$ = SD values; and \square = the range of infusion rates.

plasma vecuronium concentrations (C_{SS90}) for each patient. Infusion of vecuronium was then either discontinued and spontaneous recovery allowed, or continued as part of the anesthetic regimen. When necessary, neuromuscular blockade was antagonized by iv administration of edrophonium (0.5–1.0 mg/kg) and atropine (7.0 μg/kg).

Data for the following were obtained from each patient: (1) the time from initiation of vecuronium infusion to steady-state 90% depression of control twitch tension; (2) the rate of vecuronium infusion required to produce 90% depression; (3) the total duration of infusion; and (4) the time from 25–75% recovery of control muscle twitch tension. Total plasma clearance (Cl) of vecuronium in each patient was calculated using the formula:³

$$\text{DOSE IN} = \text{DOSE OUT} = Cl \times C_{SS90}$$

Blood samples for quantitative vecuronium analysis were kept at 0–4° C in the operating room and then centrifuged. Aliquots of plasma were acidified and stored at –70° C prior to analysis. For each aliquot, an organic ion-pair extraction of vecuronium from acidified plasma was analyzed by capillary gas chromatography using a nitrogen-sensitive detector.†† This assay is linear over the range of 2–5000 ng vecuronium/ml of plasma with a coefficient of variation of 3–15% over the linear range.

Mean values for patient groups were compared by analysis of variance and the Student-Newman-Keuls test.⁴ Differences were considered statistically significant when $P < 0.05$.

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Results

The vecuronium infusion rate (mean ± SD) required to maintain 90% depression of control muscle twitch tension in patients given fentanyl ($0.92 \pm 0.37 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was significantly greater ($P < 0.001$) than that in patients given enflurane ($0.28 \pm 0.13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or isoflurane ($0.30 \pm 0.13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). The mean infusion rates for the two volatile agents did not differ significantly (fig. 1). The coefficients of variation for the mean infusion rates were similar for the three groups: 45% for enflurane, 43% for isoflurane, and 40% for fentanyl anesthesia. The mean end-tidal enflurane and isoflurane concentrations maintained during vecuronium infusion were $1.39 \pm 0.24\%$ and $0.97 \pm 0.21\%$, respectively.

The mean times (±SD [range]) required to establish the vecuronium infusion rates necessary to achieve 90% depression of control twitch tension were 45.2 ± 48.3 [5–134] min for enflurane, 42.2 ± 37.7 [5–124] min for isoflurane, and 49.3 ± 28.5 [0–89] min for fentanyl; the differences between these mean values were not significant. The mean duration of vecuronium infusion during each anesthetic was 148 ± 82 min for enflurane, 109 ± 43 min for isoflurane, and 126 ± 61 min for fentanyl. Infusions were maintained for 3 h or longer in six patients (in one patient for 6 h) with adequate surgical relaxation.

When infusion of vecuronium was terminated, spontaneous recovery began within 60 s in all patients, eight of whom recovered spontaneously to 100% of control muscle twitch tension. Five of these eight patients were in the fentanyl group and had a mean time (±SD) from 25–75% recovery of control twitch of 10.8 ± 0.8 min. The mean time for 25–75% recovery time in patients who received edrophonium/atropine and had sufficient twitch data for analysis was 8.7 ± 9.3 min for enflurane ($n = 5$), 13.2 ± 22.6 min for isoflurane ($n = 7$), and 3.2 ± 1.8 min for fentanyl ($n = 4$). These differences were not statistically significant.

Plasma vecuronium concentrations were obtained for nine, seven, and eight patients in the enflurane, isoflurane, and fentanyl groups, respectively. Data from six patients were discarded because of errors in sample collection or analysis. A comparison of the two heparinized samples drawn for C_{SS90} determination revealed average absolute differences between the first and second samples of 7.6%, 15.0%, and 5.8% for enflurane, isoflurane, and fentanyl, respectively (table 1). C_{SS90} values for vecuronium were higher with fentanyl (165 ± 48 ng/ml) than with enflurane (71 ± 34 ng/ml) or isoflurane (72 ± 44 ng/ml). Values for the two volatile agents did not differ significantly. Total plasma clearance for vecuronium did not differ among the groups (fig. 2).

Discussion

We demonstrated in this study that enflurane and isoflurane could reduce vecuronium infusion rate requirements by as much as 70% when compared to infusion rate requirements during fentanyl anesthesia. Swen *et al.* found only a 37% reduction in vecuronium infusion rate requirement for halothane *versus* fentanyl anesthesia in a study similar to ours.⁵ This difference between volatile anesthetics has been reported previously by Rupp *et al.* using single dose-response determinations, and can be explained by the known effects of enflurane and isoflurane on muscular response to stimulation.⁶ In addition, Rupp *et al.* showed that the magnitude of these effects of enflurane and isoflurane varied with the end-tidal concentration, an effect not elucidated in our study because only one concentration of enflurane and isoflurane was studied. Thus, enflurane and isoflurane offer advantages to the clinician employing vecuronium infusions by lowering infusion rate requirements and providing significant and controllable potentiation of vecuronium neuromuscular blockade.

Not only can the choice of anesthetic alter the patient's response to drugs, as discussed above, but it also may alter the elimination of drugs. Vecuronium may undergo extensive uptake by the liver in humans, a process which could be altered by volatile anesthetics.⁷ Our study, using estimates of clearance, could not detect significant differences in vecuronium clearance among anesthetic groups. Stanski *et al.* found similar results with *d*-tubocurarine, and showed that pharmacokinetic estimates of distribution and elimination half-lives, volume of distribution at steady state, and clearance did not differ among patients anesthetized with fentanyl, halothane, or enflurane.^{8,9} Thus, the differences in vecuronium infusion rate requirements in the three groups in our study represent differences in how these anesthetics alter the pharmacodynamic response to vecuronium.

The variability in vecuronium infusion rates for all three anesthetic agents was similar, suggesting that no one agent allowed for more accurate prediction of the infusion rates necessary for stable neuromuscular blockade. Other investigators, notably Swen *et al.*, have reported that the vecuronium infusion rates necessary for 90% twitch depression varied more with fentanyl anesthesia than with halothane anesthesia.⁵ However, when we determined the coefficients of variation (SD/mean × 100%) for their vecuronium infusion requirements for both anesthetics, we found that these values were not significantly different: 21% during fentanyl anesthesia *versus* 20% during halothane anesthesia. Thus, clinicians may use the mean infusion rate results reported in our study and neuromuscular moni-

TABLE 1. Vecuronium Concentrations (ng/ml) at 90% Neuromuscular Blockade (C_{SS90})

Enflurane		Isoflurane		Fentanyl	
First Sample	Second Sample	First Sample	Second Sample	First Sample	Second Sample
124	114	20	22	120	115
70	68	70	49	188	188
113	94	73	69	170	160
29	28	57	52	268	207
109	84	173	152	80	77
81	79	73	73	186	193
19	19	52	73	181	179
48	48			162	169
85	72				

toring as guidelines for determining a vecuronium infusion rate that will provide continuous stable neuromuscular blockade.

The C_{SS90} values measured in this study also can be used by clinicians to establish similar concentrations rapidly in patients. Mitenko and Ogilvie have developed a method in which a bolus dose of drug (equal to C_{SS90} times volume of distribution) and a concomitant infusion of drug (equal to C_{SS90} times plasma clearance) rapidly produced plasma concentrations of drug equal to C_{SS90}.¹⁰ Clinicians using C_{SS90} data from this study and values for volume of distribution and clearance from previous studies^{11,12} could produce stable neuromuscular blockade with vecuronium using the Mitenko and Ogilvie method. Prior to this study, only indirectly determined estimates of C_{SS90} during fentanyl anesthesia have been available.^{13,14}

In summary, the present study has further defined the applicability of a vecuronium infusion technique to the routine administration of general anesthesia. Stable neuromuscular blockade can be achieved rapidly with this technique, and blockade can be quickly and easily antagonized following even prolonged vecuronium infusions. Although no one anesthetic agent proved the most ideal, vecuronium infusion requirements were

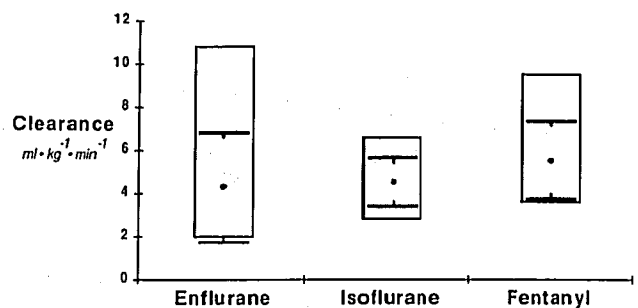


FIG. 2. Clearance of vecuronium calculated by dividing the vecuronium infusion rate by C_{SS90}. ● = mean clearance; I = SD values; and □ = the range for vecuronium clearance.

lower during enflurane or isoflurane anesthesia than during fentanyl anesthesia.

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