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Onset and Duration of Neuromuscular Blockade Following High-dose Vecuronium Administration

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To determine the onset time and duration of high doses of vecuronium, 40 ASA Physical Status 1 and 2 patients were randomly assigned to receive either 100, 200, 300, or 400 μg/kg of vecuronium bromide for muscle relaxation during elective general surgery. Neuromuscular blockade was continuously quantitated by recording the electromyographic response to stimulation of the ulnar nerve train-of-four. The rate of onset of neuromuscular blockade, endotracheal intubating conditions, duration of neuromuscular blockade, and hemodynamic effects of vecuronium at each dose were evaluated and compared. The time from vecuronium administration to complete abolition of twitch tension (T1 = 0%) decreased from 208 ± 41 to 106 ± 35 s as the vecuronium dose was increased from 100 to 400 μg/kg ($P < 0.01$). Corresponding times to endotracheal intubation (T1 < 20%) also decreased from 183 ± 24 to 96 ± 31 s with increasing doses ($P < 0.01$). Recovery time (T1 = 25%) increased from 37 ± 13 to 138 ± 24 min with increasing doses ($P < 0.01$). No significant hemodynamic differences between the four groups were observed. Endotracheal intubating conditions were good or excellent in all patients. High doses of vecuronium may, therefore, be a useful alternative to succinylcholine when a rapid onset of neuromuscular blockade is required. (Key words: Induction: anesthesia. Neuromuscular relaxants: vecuronium.)

VECURONIUM BROMIDE is a nondepolarizing neuromuscular blocking drug with minimal effects on the autonomic nervous system and little or no histamine release.[1] The reported speed of onset of neuromuscular blockade of 100 μg/kg iv of vecuronium is 3 min compared to the 1 min required for 1.5 mg/kg of succinylcholine.[2] This longer onset time has limited the use of vecuronium in situations requiring a rapid onset of neuromuscular blockade. It would, however, be desirable to maintain the hemodynamic stability and nondepolarizing characteristics of vecuronium while decreasing its onset time.[3,4] Some investigators have found that as the dose of vecuronium is increased from its ED_{95} the onset time is decreased.[2] Therefore, increasing the dose of vecuronium to several times the ED_{95} may produce even a more rapid onset of neuromuscular blockade and acceptable intubating conditions within 1 min.

We, therefore, evaluated the onset time of neuromuscular blockade, endotracheal intubating conditions, neuromuscular recovery, and hemodynamics (*i.e.*, heart rate and arterial blood pressure) following doses of vecuronium ranging from 100 to 400 μg/kg when used for neuromuscular blockade during anesthesia produced by a combination of halothane, nitrous oxide, and fentanyl.

Methods

This study was approved by the institutional review board and written informed consent was obtained from each patient. Forty ASA Physical Status 1 and 2 patients, who were scheduled for elective orthopedic or gynecological surgery expected to last more than 2 h, were enrolled in the study. Patients with a history of gastroesophageal reflux, known neuromuscular, hepatic, or renal disease, potentially difficult endotracheal intubation, or who were taking medication known to affect neuromuscular blockade were excluded. Patients were randomly assigned into four groups of ten patients each. The groups received either 100, 200, 300, or 400 μg/kg iv of vecuronium after induction of general anesthesia.

Diazepam 5–10 mg was administered orally 60–90 min preoperatively. The left or right forearm and hand were immobilized and prepared for stimulation of the ulnar nerve at the wrist *via* surface electrodes and the evoked electromyogram (EMG) was recorded from the abductor digit minimi utilizing a Puritan Bennett™ Model 221 evoked electromyograph.[5]

General anesthesia was induced with a combination of fentanyl 1–2 μg/kg, followed 2–3 min later by thiopental 4 to 7 mg/kg. Following loss of consciousness, the electromyograph was calibrated to 100% reference T1 (of the train-of-four) with a supramaximal stimulating current. A bolus intravenous dose of vecuronium 100, 200, 300, or 400 μg/kg was then administered according to the assigned patient group. Ventilation was controlled manually *via* a face mask with 70% nitrous oxide in oxygen until tracheal intubation was performed. Additional incremental intravenous doses of fentanyl up to a total of 3 μg/kg were administered if indicated by physical movement or by a dramatic increase in heart rate or arterial blood pressure.

When T1 had fallen below 20% of control, laryngoscopy and endotracheal intubation was undertaken and the intubating conditions were assessed using a four-point scale. Intubating conditions were scored as "excellent" if the jaw was relaxed, the vocal cords were immobile, and there was no diaphragmatic movement; and "good" if all

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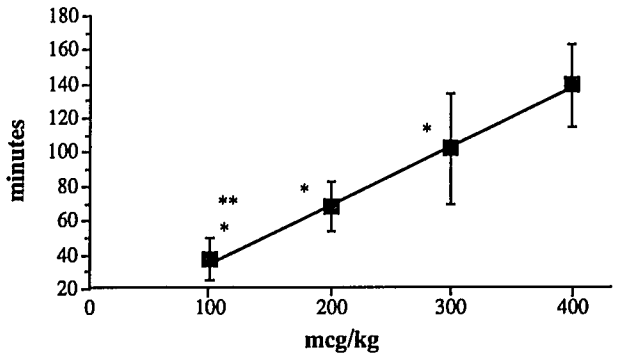

FIG. 1. Onset of neuromuscular blockade in seconds (T1 = 0%) following 100, 200, 300, and 400 μg/kg of vecuronium (r = 0.87). Mean ± SD (in seconds). $P < 0.01$ (*) when the 400 μg/kg is compared to the 100, 200, and 300 μg/kg dose and $P < 0.01$ (**) when the 200 and 300 μg/kg groups are compared to the 100 μg/kg group.

the above criteria were met except for diaphragmatic movement. Conditions were scored as "poor" if the vocal cords were moving and if there was coughing or bucking; and "inadequate" if in addition to the above criteria, the jaw was clinically not relaxed.

Systolic, diastolic, and mean arterial blood pressure and heart rate were recorded every 2 min from induction of anesthesia until 10 min after endotracheal intubation, and every 5 min thereafter utilizing a Dinamap™ oscillometric blood pressure monitor applied to the upper arm. Heat loss was limited during the study by utilizing a warming blanket, breathing circuit humidification, and an intravenous fluid warmer.

The time from the administration of vecuronium until intubation was completed was recorded as the "intubation time." Following intubation, anesthesia was maintained with 70% nitrous oxide and halothane (up to an inspired concentration of 0.5%) and incremental doses of fentanyl

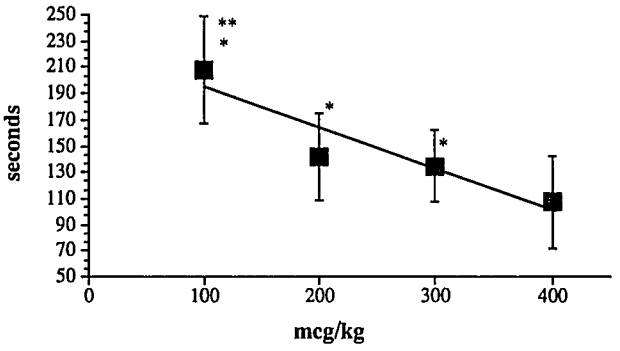

FIG. 2. Duration in minutes of neuromuscular blockade (T1 = 0–25%) following 100, 200, 300, and 400 μg/kg of vecuronium when combined with halothane (<0.5%), nitrous oxide, fentanyl anesthesia. Mean ± SD $P < 0.01$ (*) when the 400 μg/kg is compared to the 100, 200, and 300 μg/kg dose, and $P < 0.01$ (**) when the 200 and 300 μg/kg is compared to the 100 μg/kg group.

as needed in order to maintain heart rate and blood pressure within 15% of preinduction control values. Mechanical ventilation was adjusted so as to maintain the end-tidal CO_2 between 30 to 40 mmHg. Onset time was defined as the time from vecuronium administration until complete abolition of T1. Neuromuscular recovery was allowed to progress spontaneously, and the elapsed time from the vecuronium dose until T1 reached 10% and 25% was recorded for each patient. Duration of neuromuscular blockade was defined as the time from vecuronium administration until T1 recovered to 25%. Whenever clinically feasible, recovery was allowed to progress further spontaneously. The time until T1 reached 50% and 75% of control were recorded. If, however, further neuromuscular blockade was required each time T1 reached 25%, a supplemental dose of 20 μg/kg of vecuronium was administered. At the completion of surgery, any residual neuromuscular blockade was antagonized with intravenous neostigmine, 40 μg/kg, and atropine 20 μg/kg iv.

Analysis of variance was used for comparison between groups and when significant by Fisher protected least significant test. Linear regression analysis was used to estimate the dose response effect. A value of $P < 0.01$ was considered statistically significant. Results are stated as mean ± SD.

Results

There were no significant demographic differences between groups with respect to age, height, weight, and sex. Endotracheal intubating conditions were graded as either good or excellent in all patients in all groups. Time to intubation (T1 < 20%) varied from 183 ± 24 s in the 100 μg/kg group, to 96 ± 31 s in the 400 μg/kg group ($P < 0.01$). Increasing the dose of vecuronium also decreased the time to onset of neuromuscular blockade (T1 = 0%) from 208 ± 41 s to 106 ± 35 s in the 100 and 400 μg/kg groups, respectively ($P < 0.01$) (fig. 1). Onset was significantly different between all groups except the 200 μg/kg *versus* the 300 μg/kg group. T1 = 0% was reached in all patients in all groups.

Figure 2 illustrates the approximately linear increase (r = 0.87, $P < 0.01$) in duration (T1 = 0–25%) of neuromuscular blockade, from 37 ± 13 min in the 100 μg/kg group to 138 ± 24 min in the 400 μg/kg group as the dose of vecuronium was increased.

The number of patients who spontaneously recovered to T1 = 75% was 18. In these patients, the recovery time for T1 to progress from 10–50% and from 10–75% was linearly prolonged as the dose of vecuronium was increased (fig. 3). The duration of sequential repeated doses when T1 recovered to 25% did not vary significantly either within each dosage group or between different

groups (table 1). There were no clinical features of residual blockade observed in any patient after administration of a single dose of the neuromuscular antagonist.

Arterial blood pressure and heart rate at five times (baseline, postinduction, after vecuronium, and 2 and 4 min later), showed no statistical difference between dosage groups (fig. 4).

Discussion

This study has demonstrated that over the dosage range 100–400 μg/kg of vecuronium there is a dose-dependent decrease in time to onset of neuromuscular blockade and a predictable increase in duration. The onset of neuromuscular blockade (T1 = 0%) decreased from 208 ± 41 s to 106 ± 35 s and duration (T1 = 0–25%) increased from 37 ± 13 to 138 ± 24 min as the dose was increased from 100 to 400 μg/kg. In addition, the time for T1 to recover from 10–50% and 10–75% increased with increasing dose; however, the duration of supplemental maintenance doses did not increase.

A rapid, predictable onset of neuromuscular blockade is a prerequisite for a rapid sequence endotracheal intubation. Succinylcholine is the standard neuromuscular blocking drug for this purpose; however, its use is associated with numerous undesirable side effects[5–10] necessitating a search for a either a new nondepolarizing muscle relaxant with a rapid onset of action or a technique to enhance the onset of the available nondepolarizing muscle relaxants. Until a nondepolarizing muscle relaxant becomes available with a rapid onset of neuromuscular blockade, the alternatives to succinylcholine are either the priming technique[11–13] or, as demonstrated by this study, the use of a large dose of a nondepolarizing neuromuscular blocking agent. Martin *et al.*[16] found that with a 10 μg/kg priming dose and 90 μg/kg intubating dose of vecuronium intubation at T1 = 5% occurred in 158 ± 12 s with excellent intubating conditions in only 60% of patients. In comparison, we found with 200 and 400 μg/kg of vecuronium good or excellent intubating conditions at 133± and 96 ± 31 s, respectively. The priming technique is also associated with blurring of vision in 20–100% of cases,[14] even at a low dose of 5 μg/kg of vecuronium. Difficulty in breathing and swallowing occurs in 90% of patients with a priming dose of 20 μg/kg of vecuronium and maximum inspiratory pressures is reduced by up to 24% (12 μg/kg).[18] In addition to the psychological distress that this neuromuscular weakness can present to an awake patient, pulmonary aspiration has been a complication of this weakness.[19] The priming technique does hasten the onset of neuromuscular blockade, but at the expense of increased morbidity and possible mortality.

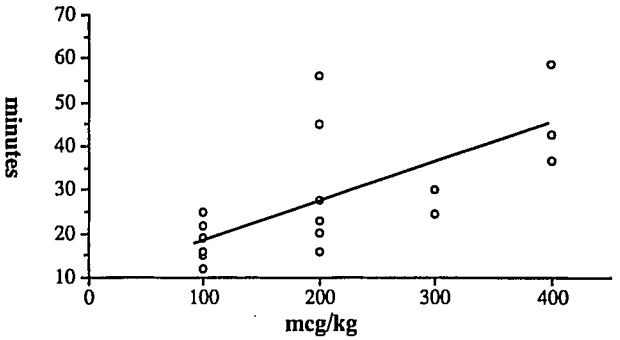

FIG. 3. Time for the recovery of neuromuscular blockade (T1 = 10–75%) following 100, 200, 300, and 400 μg/kg of vecuronium when combined with halothane (<0.5%), nitrous oxide, fentanyl anesthesia. Mean ± SD $P < 0.01$ and r = .66.

Doses of neuromuscular blocking agents in excess of their ED_{95} have been used to speed up the onset of the nondepolarizing agents. The use of pancuronium 150–200 μg/kg produces accentuated hemodynamic alterations and a prolonged paralysis (3–5 h).[20] This duration of neuromuscular blockade for pancuronium contrasts with a duration of 2–3 h following 400 μg/kg of vecuronium. Therefore, nondepolarizing neuromuscular blockers with an intermediate duration of action can more readily be used in high dose as the anticipated duration would not be as excessive as with a long lasting neuromuscular blocker. Doses of 0.5 mg/kg and 0.8 mg/kg of atracurium result in an onset of neuromuscular blockade

TABLE 1. Duration of Action of Maintenance Doses of Vecuronium

Dose	Maint # 1	Maint # 2	Maint # 3	Maint # 4	Maint # 5	Maint # 6
100 μg/kg	28.5 (±4.1)	36.2 (±5.6)	—	—	—	—
N	4	2				
200 μg/kg	21.7 (±9.8)	28.0 (±8.2)	25.2 (±5.9)	27.0 (±7.8)	29.9 (±9.9)	24.0 (±7.0)
N	4	4	4	4	4	2
300 μg/kg	23.2 (±6.9)	25.2 (±9.8)	26.5 (±6.6)	23.6 (±3.2)	23.0 (±9.8)	—
N	4	4	4	3	2	
400 μg/kg	35.5 (±13)	33.0 (±9.8)	42.5 (±24)	34.5 (±13)	35.5 (±14)	36 (±15)
N	2	2	2	2	2	2

Duration of action of maintenance doses (maint) of 20 μg/kg of vecuronium when T1 reached 25% of control after the four loading doses of 100, 200, 300, and 400 μg/kg of vecuronium. N = the number of patients in each group who received each subsequent maintenance dose.

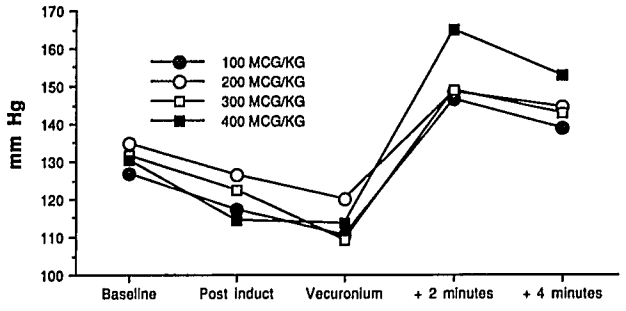

FIG. 4. Systolic arterial blood pressure (mmHg) following 100, 200, 300, and 400 μg/kg of vecuronium at: 1) baseline; 2) post induction; 3) post vecuronium; 4) 2 min postintubation; and 5) 4 min postintubation.

in 150 and 90 s, respectively, but there are significant hemodynamic alterations at the higher atracurium dose.[21] Atracurium 1.5 mg/kg results in the time to T1 = 5% in 56 ± 20 s, but this is accompanied with a 22% decrease in systolic blood pressure post endotracheal intubation.[22] Vecuronium at high doses (up to 400 μg/kg), unlike pancuronium or atracurium, did not have any effect on the simple hemodynamics (blood pressure and heart rate). Thus, when a high doses of nondepolarizing muscle relaxant is used, vecuronium has advantages both with respect to hemodynamic stability and duration of neuromuscular blockade.

Vecuronium has also been previously evaluated at high doses.[23] Our results, however, are in contrast to Casson and Jones[23] who did not show a linear increase in onset time from 50 μg/kg to 400 μg/kg. Casson and Jones[23] studied five groups of five patients each who received 50, 100, 150, 200, or 400 μg/kg of vecuronium. They reported onset times (T1 = 0%) that correlated with the results achieved in this study with the exception that the 200 μg/kg dose, in their study, was far more rapid and approximated that of our 400 μg/kg group. The reason for this discrepancy may be either due to the effect of 1% halothane (in Casson and Jones' study) prior to vecuronium administration on the onset of neuromuscular blockade, or due to the small number of patients in each group.[5] Halothane enhances the action of neuromuscular blocking drugs, but less than either isoflurane or enflurane.[24] Halothane administration was only started following intubation in our study, thus excluding any potentiation on the rate of onset of neuromuscular blockade, and the halothane was kept at a low concentration (<0.5% inspired) to limit its effect on recovery.

The utilization of a train-of-four stimulus every 20 s instead of every 10 s, which is more routinely used, may have delayed the detection of onset of neuromuscular blockade by up to 10 s. The evoked EMG is different in some respects from a mechanomyogram. A T1 = 0% level on the mechanomyogram is associated with activity on a simultaneous EMG recording.[25] Thus, if a mechanomyogram and a faster stimulus frequency had been used, the onset of neuromuscular blockade may have occurred even earlier.

The time for recovery T1 = 10–50% and 10–75% increased as the initial dose of vecuronium was increased, yet the duration of the 20 μg/kg maintenance dose remained constant, irrespective of the loading dose or number of repeat doses. This may be explained by the known pharmacokinetics of vecuronium.[26] Redistribution and elimination are both responsible for the recovery of neuromuscular function following a bolus dose of vecuronium. The prolongation of the time for T1 = 10–50% and 10–75%, as the dose of vecuronium is increased from 100–400 μg/kg, is probably the result of elimination contributing more to the decrease in vecuronium concentration during recovery in the higher dose range and redistribution being more important at the lower dose range. When small repetitive doses of equal size of vecuronium are given, the duration of neuromuscular blockade will increase until a steady state is achieved. Thereafter, vecuronium plasma concentration and the duration of neuromuscular blockade is dependent on the elimination time for vecuronium and will remain constant for each consecutive dose. If a large bolus dose is given followed by a small maintenance dose (as in this study), a steady-state plasma concentration is rapidly achieved, and thus, subsequent maintenance doses will all have the same duration. Therefore, as expected, the duration (T1 = 0–25%) of repeat doses of 20 μg/kg of vecuronium remained constant at 25–35 min, irrespective of the loading dose.

In summary, when the dose of vecuronium is increased from 100 μg/kg to 400 μg/kg, it still retains its favorable hemodynamic profile, shows no clinical features of histamine release, and provides a more rapid onset of neuromuscular blockade, therefore allowing earlier tracheal intubation, but with prolonged recovery. Thus, the predictable dose response obtained for onset and spontaneous recovery enables selection of the dose best suited to the clinical situation. High doses of vecuronium may provide an alternative means of achieving a rapid onset of neuromuscular blockade.

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