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The Effects of Age on the Dose–Response Curves for Vecuronium in Adults

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Vecuronium is a nondepolarizing muscle relaxant for which d'Hollander *et al.*[1,2] reported age-related differences. The time to onset of maximum neuromuscular block from 70 μg/kg was longer with increasing age.[1] In another group of patients the infusion rate of vecuronium required to maintain 90% depression of the twitch response was decreased in patients older than 60 yr of age. When this infusion was terminated, these older patients had a slower recovery time (time for recovery of the twitch height from 25%–75% of control).[2] In a recent review of vecuronium and atracurium, Miller *et al.*[3] noted that further study is required to better define the effects of age on vecuronium-induced neuromuscular blockade. The purpose of our study was to compare the dose–response curves constructed for older and younger patient groups, using single iv doses of vecuronium.

MATERIALS AND METHODS

Sixty-four adults (ASA PS I–III) entered the study after providing written institutionally approved informed consent. Patients selected for the study were either aged 20–40 years (Group 1) or older than 70 years (Group 2). All patients were free of symptomatic systemic or neurologic disease. Drugs known to affect neuromuscular function were not administered in the immediate preoperative period. Patients were within 25% of normal body weight.[4]

Morphine sulfate, 0.1 mg/kg, and atropine, 0.4 mg, were given im approximately 1 hr before induction of anesthesia. Anesthesia was induced with thiopental 3–4 mg/kg and fentanyl 50–100 μg iv. Anesthesia was maintained with 67% N_2O in O_2 and small incremental iv doses of thiopental and fentanyl during the study period. Ventilation to normocarbia was maintained (monitored by end-tidal CO_2) while a baseline recording of train-of-four response was obtained. Each patient received a single dose of vecuronium, either 10, 20, 30, or 40 μg/kg, injected over 5 s into a rapidly running iv infusion. Before the administration of vecuronium, neuromuscular blockade was measured continuously with a linear force transducer (Devices ST-10®) fixed to an arm board and attached to the thumb with a preload of approximately 300 g. A Grass S48® stimulator with a stimulus isolator (SIU 5) delivered four supramaximal stimuli of 0.2 ms duration, at 2 Hz, to the ulnar nerve at the elbow via surface electrodes every 12 s. The train-of-four response was displayed on a Hewlett-Packard 7754B® chart recorder.

Time to onset of block (first depression of T_1 below control), time to maximum block, per cent maximal block and T_4/T_1 ratio at the time of maximum block were measured. Between-group comparisons were made with the unpaired Student's *t* test. Descriptive statistics are expressed as mean ± standard deviation (SD).

Dose–response curves were obtained by computer fitting of the individual response at each dose (weighted as the reciprocal sum of the square of the dose) in each group to the Hill equation:

$$\% \text{ paralysis} = \frac{100\% \times \text{Dose}^P}{ED_{50}{}^P + \text{Dose}^P}$$

(The superscript "P" is a derived power value to fit the Hill equation, which defines the sigmoidicity of the curve.) Dose–response curves also were constructed by linear regression analysis of log dose–probit response data. The lines of best fit to the log dose–probit response data for the two groups were compared by analysis of covariance. A P value of less than 0.05 was considered statistically significant.

RESULTS

The age (years) of patients in Group 1 ranged from 20 to 40 (29 ± 4.7) (mean ± SD) and in Group 2 from 70 to 88 (76 ± 5.0). There were 17 men and 15 women in Group 1 and 14 men and 18 women in Group 2. For Group 1, weights and heights were 68.6 kg (±12.2) and 168.5 cm (±11.8), respectively, and for group 2, 64.2 kg (±10.6) and 163.4 kg (±8.0). These were not statistically different.

Mean per cent blockade, time of onset, time to maximum block, and T_4/T_1 ratio for each group at each dose are shown in table 1. None of the comparisons between groups reached significance ($P > 0.05$).

The iterative nonlinear least-squares regression solutions to the Hill equation are shown in table 2. The derived ED_{50} and power functions then were fitted to the equation to obtain the values for ED_{90} and ED_{95} (table 2).

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TABLE 1. Neuromuscular Effects*

Dose (μg/kg)	Young				Old			
	Per cent Block	Onset Time (min)	Time to Max Block (min)	T_4/T_1	Per cent Block	Onset Time (min)	Time to Max Block (min)	T_4/T_1
10	6 (6.4)	4.0 (0.9)	6.5 (1.6)	90 (12)	7.5 (9.4)	3.4 (1.5)	6.9 (1.1)	93 (5)
20	54 (28.8)	2.2 (1.5)	5.1 (1.3)	37 (20)	55 (25.6)	1.9 (1.2)	5.3 (0.6)	35 (10)
30	73 (28.0)	1.6 (0.6)	4.8 (1.0)	16 (11)	88 (13.8)	1.5 (0.6)	5.3 (0.9)	26 (13)
40	93 (5.9)	1.3 (0.4)	4.9 (1.2)	17 (24)	94 (4.0)	1.3 (0.2)	4.9 (0.6)	14 (16)

Note: None of the comparisons between groups reached significance. * Mean (SD).

The linear regression analyses following log-probit transform for the young and older patients gave similar slopes and intercepts (table 2); the slopes of regression lines were not shown to be different (fig. 1). The values of ED_{90} and ED_{95} from log-probit analysis also are shown in table 2.

DISCUSSION

The ED_{50} is the most commonly reported value in dose–response studies. Previously published studies using a thiopental–narcotic–nitrous oxide technique[5–12]§ estimate ED_{50} for vecuronium at 20.8–35.2 μg/kg and ED_{90} at 32–53.8 μg/kg. Our results, with both groups of patients, fall within this range. Although age apparently does not affect the dose–response curve for vecuronium, inhaled anesthetics shift it to the left.[5,6,15] Studies using various inhaled anesthetics[5,6,13–17] estimate ED_{50} from 12.8–31 μg/kg with all but two studies showing ED_{50}s of below 20 μg/kg. Many of the studies were performed using cumulative dose techniques, which produce different potencies than when single doses are administered.[5]

All of the dose–response studies cited used the log dose, and some used probit transformation. When there are many points on the dose–response curve, the log probit curve yields results that are not different than those of the linear regression method.[18] This would not be true, however, if the dosages were all in the upper range of the sigmoid curve. Fitting the data to the equation for a sigmoid curve using a least-squares technique does not involve either log or probit transformation. The data are used to derive the optimal solution for the ED_{50} and an exponent that describes its shape.

The log-probit analysis is a least-squares regression of the probit transformation of each data point. Without probit transform, the sigmoid (log) dose–response curve is linear between 20 and 80% effect. For data in this range, both methods yield essentially the same result. With probit transform, the range becomes 1–99%. Differences between the two methods of analysis include the following: the log probit has a unique solution, whereas the Hill equation iteratively minimizes the sum of the squares; the log probit is linear because of its transforms, while the Hill is sigmoid without transforms; and the Hill equation employs a weighting factor.

There does not appear to be an age-related change in the sensitivity of neuromuscular transmission to the effects of vecuronium; younger and older patients were shown to have similar steady state concentrations that result in 50% paralysis.[19] The above study differed from ours in its use of stable end-tidal halothane anesthesia, where ours used a barbiturate–nitrous oxide–narcotic technique given to clinical effect only. It is possible that there could be age-related effects with the latter technique, but they should be small.

Dose–response data do not include a time factor. A number of studies have assessed onset times to peak neuromuscular block after a single initial dose. In adults, with a dose of 30 μg/kg, onset times have been calculated at 3.3–5.0 min[22,23] and with doses of 43–50 μg/kg at 3.7–6.7 min.[6,9,12,20–22] Our results at 30 μg/kg are within this range. Unlike d'Hollander *et al.*,[1] we found no difference in onset time to maximum block in elderly patients. The likely reasons for this difference include the use of two

TABLE 2. Least-squares Solutions to the Dose–Response Data

		Young	Old
Statistical results			
Hill	ED_{50}†	20.4	18.7
	Power	3.05	3.85
	R^2*	0.70	0.86
Log-probit	Slope (±SE)	5.5 (±0.4)	5.8 (±0.8)
	Intercept	−2.3 (±0.6)	−2.5 (±1.5)
	R^2*	0.76	0.88
Selected dose–response points			
ED_{50}†	Hill	20.4	18.7
	Log-probit	20.6	19.5
ED_{90}†	Hill	41.9	33.1
	Log-probit	35.3	32.6
ED_{95}†	Hill	53.6	40.2
	Log-probit	41.2	37.8

* R^2 is the square of the correlation coefficient.
† Dose in μg/kg.

§ Nagashima H, Yun H, Radnay PA, Duncalf D, Kaplan R, Foldes FF: Influence of anesthesia on human dose–response of ORG-NC 45 (abstract). ANESTHESIOLOGY 55:A202, 1984.

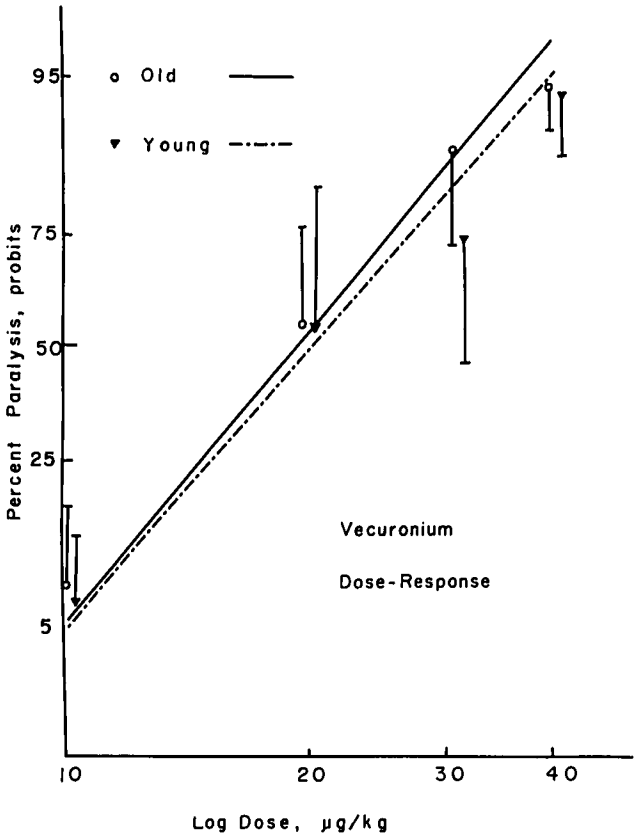

FIG. 1. Log dose-probit response relationships for vecuronium in young and elderly patient groups. The means (SD) at each of the four doses are indicated.

distinct age groups in our study rather than an age range from 15 to 85, our lower doses of 10–40 µg/kg, and our method of statistical analysis.

In summary, when single dose–response curves for vecuronium were constructed for younger or older patient groups, there were no differences detected between the groups. The ED_{50}s were 20.4 and 18.7 µg/kg, respectively, for the younger and older patients, and the ED_{90}s were 41.9 and 33.1 µg/kg, respectively. Therefore, the initial dose of vecuronium should not be decreased for elderly patients.

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