

*Potency Determination for Vecuronium (ORG NC45):**Comparison of Cumulative and Single-dose Techniques*

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To compare two methods of estimating the potency of neuromuscular relaxants of medium duration, the authors determined the potency of vecuronium (ORG NC45) using cumulative dose-response (CDR) techniques, and compared these data with published values from our group obtained using the single bolus technique. During 60% N₂O-halothane anesthesia, patients received 10 µg/kg vecuronium; additional incremental doses of vecuronium, 5 µg/kg, were given when no change occurred in the height of three successive twitches. Using these dose-response data, the authors determined least-squares regression lines and ED₂₀, ED₅₀, and ED₈₀. These results were compared to values obtained by the single bolus technique under comparable conditions. The CDR and single bolus technique yielded ED₅₀ values of 19.9 and 15.0 µg/kg, respectively. All potency estimates by CDR were larger than those obtained by the single bolus dose technique. It was concluded that, for vecuronium, a medium duration neuromuscular relaxant, CDR yields potency estimates which are larger than those obtained by the traditional single bolus dose technique. Because the single bolus dose technique is the accepted method for construction of dose-response curves, the authors recommended that CDR not be used for potency determination of muscle relaxants of medium and short duration such as vecuronium. (Key words: Pharmacology: dose-response curves: Neuromuscular relaxants: vecuronium (ORG NC45).)

VECURONIUM (ORG NC45), an analogue of pancuronium, is a nondepolarizing muscle relaxant undergoing extensive clinical evaluation. Determination of potency by cumulative dose response (CDR) rather than the single bolus technique would simplify these studies, since fewer patients are required with CDR.¹ Although these two techniques yielded comparable results for two long-acting neuromuscular relaxants,² pancuronium and *d*-tubocurarine, the methods have not been compared and validated with shorter acting drugs such as vecuronium. Thus, we compared the dose-response curve for vecuronium obtained with CDR to that previously reported for the single bolus dose technique.³

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Methods

The study was approved by the local committee on human research and informed consent was obtained. To determine potency by CDR, we studied ten patients (20–56 years of age), ASA class I or II, scheduled for elective surgery. Anesthesia was induced with intravenous 50–75 mg thiopental, and maintained with nitrous oxide, 60% inspired, and halothane, 0.4–1.0% end-tidal, as determined by mass spectrometer. The trachea was intubated without the aid of muscle relaxants, and ventilation was controlled to maintain an end-tidal P_{CO₂} of 30–40 mmHg. Esophageal temperature was maintained at 35–37° C with warming blankets. After induction of anesthesia, the ulnar nerve was stimulated at 0.15 Hz with supramaximal square wave pulses of 0.15-ms duration; evoked tension was measured with a Grass FT-10 force transducer. After the end-tidal anesthetic concentration and twitch heights were stable for at least 10 min, 10 µg/kg vecuronium was given as a bolus. When no further change occurred in the height of three successive twitches, 5 µg/kg vecuronium was administered. Additional doses of vecuronium, 5 µg/kg, were then administered by the same criteria until the twitch height was depressed greater than 90%. This CDR technique for studies with

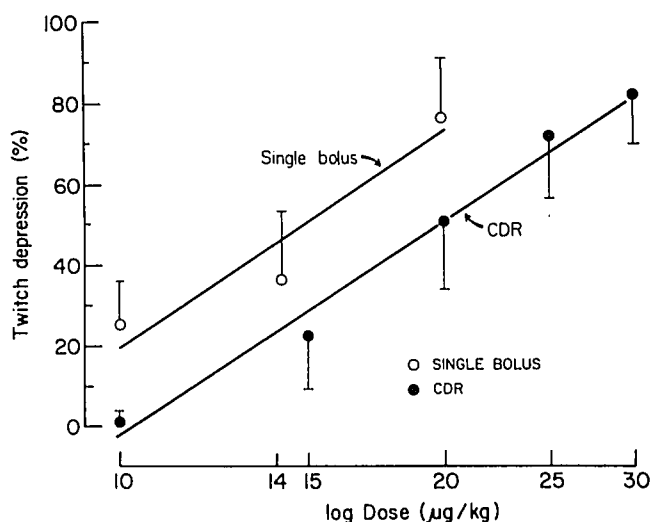


FIG. 1. Dose-response curves for CDR (n = 45) and single bolus dose (n = 20).³ Values plotted are means ± SD of the twitch depression at each dose.

TABLE 1. Dose-response Regression Lines for Vecuronium: Comparison of CDR and Single Bolus Dose Techniques

	CDR	Single Bolus Dose*
Patients	10	20
Data Points	45	20
r	0.82	0.80
Slope \pm SE	175 \pm 12	172 \pm 30
y-intercept (% Twitch depression)	-177 \dagger	-153
ED ₂₀ (μ g/kg)	13.4 \dagger	10.0
ED ₅₀ (μ g/kg)	19.9 \dagger	15.0
ED ₈₀ (μ g/kg)	29.6 \dagger	22.4

* From previous study.³ \dagger Different from single bolus dose, $P < 0.05$.

pancuronium and *d*-tubocurarine has been described by Donlon *et al.*²

For each patient, four or five data points (10, 15, 20, 25, and 30 μ g/kg) were available from the cumulative doses. The per cent twitch depression versus logarithm of the dose was analyzed by least-squares linear regression, and ED₂₀, ED₅₀, and ED₈₀ were calculated from this regression line.⁴

We previously reported potency determinations by the single bolus method in twenty patients, ASA class I or II (18–71 years old).³ Each of these patients received only one dose of vecuronium, 10, 14, or 20 μ g/kg. A least-squares regression line and ED₂₀, ED₅₀, and ED₈₀ were determined.⁴

The slopes of the two regression lines were compared by Student's *t* test and the position of the lines compared by analysis of covariance.⁴ A $P < 0.05$ was considered to be statistically significant.

Results

The regression lines for CDR and single bolus dose techniques are displayed in figure 1 and the slopes, intercepts, and correlation coefficients are shown in table 1. The dose-response regression lines obtained by the two techniques do not deviate from parallelism. ED₂₀, ED₅₀, and ED₈₀ were 13.4, 19.9, and 29.6 μ g/kg, respectively, determined by CDR, and 10.0, 15.0, and 22.4 μ g/kg, respectively, by the single bolus dose technique. By analysis of covariance, potency estimates by CDR differed from those obtained by the single bolus dose technique.

Discussion

CDR was introduced as a means to simplify evaluation of the potency of muscle relaxants.¹ Subsequently, Donlon *et al.*² have demonstrated that for two long-acting neuromuscular relaxants, *d*-tubocurarine and pancuronium, CDR yields results similar to those obtained by the

single bolus dose technique. Donlon *et al.*² emphasized that with CDR, all doses must be administered within a brief period relative to the duration of action. For *d*-tubocurarine and pancuronium, whose duration of action following 90% neuromuscular blockade is 45–60 min, they recommended that all doses be given within 10–12 min.

We determined dose-response curves for vecuronium, a relaxant whose duration of action is shorter than that of *d*-tubocurarine and pancuronium, and found that CDR yields potency estimates which differ from those obtained by the traditional single bolus technique. The difference between potency estimates can be explained by two factors. First, Fahey *et al.*³ demonstrated that following a single dose of 10 μ g/kg vecuronium, maximal twitch depression does not occur until 6.7 min after drug administration. With CDR, second and subsequent doses are given at 2- to 4-min intervals when there is no change in the height of three successive twitches¹ or when twitch height changes less than 2.5% during one minute.² While these criteria are necessary to permit administration of repeated doses in a brief period, additional doses may be given before the maximal effect of previous doses has been achieved. As a result, with CDR, twitch depression following the initial 10 μ g/kg may be less than that seen with a single dose of the same magnitude.

In addition, with CDR, additional doses are administered as long as 10–12 min after the first dose. Fahey *et al.*³ demonstrated that 90% recovery occurs 14 min after the administration of a single dose of 10 μ g/kg vecuronium. Ten to twelve minutes following the initial dose, significant recovery will have occurred. Thus, with vecuronium, the effect of cumulative doses should be less than the effect following bolus administration. This is consistent with our results.

In summary, we have demonstrated that CDR and the single bolus technique yield different potency estimates for vecuronium. We would recommend that CDR not be used in the evaluation of the potency of vecuronium. A similar caution applies to the use of CDR in the evaluation of other muscle relaxants of medium and short duration.

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