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Two-dose Technique to Create an Individual Dose–Response Curve for Atracurium

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While monitoring the thenar EMG response to ulnar nerve stimulation, the authors gave either 105, 150, 210, or 300 μg/kg of atracurium to 60 patients. The maximal neuromuscular responses were plotted on a log-probit paper. The individual second dose required to produce 95% neuromuscular block (NMB) was estimated from a graph drawn on the paper. The maximal response following this second dose was then plotted. The mean maximal response following the second atracurium dose was 95.5% (SD range, 92.6–97.4%) NMB. The two dose–response points thus acquired resulted in the individual two-dose dose–response curve. The ED_{50} and ED_{95} and slope of the two-dose dose–response curve were compared with the single-dose dose–response curve. The average ED_{50} and ED_{95} determined by the two-dose and the single-dose techniques were nearly identical [160 μg/kg (SD range, 126–201 μg/kg) *vs.* 164 μg/kg (SD range, 150–179 μg/kg) and 302 μg/kg (SD range, 251–363 μg/kg) *vs.* 336 μg/kg (SD range, 274–411 μg/kg) respectively]. Also, the slopes of the curves were similar [6.2 (SD range, 5.2–7.2) *vs.* 5.4 (SD range, 4.5–6.4) probit/log]. It is therefore possible to construct an individual dose–response curve for atracurium within 7–9 min and to determine individual pharmacodynamic characteristics of atracurium from this curve. (Key words: Measurement techniques: neuromuscular blockade. Neuromuscular relaxants: atracurium. Pharmacodynamics.)

IN MOST STUDIES describing the use of the cumulative dose technique to determine the potency of atracurium or vecuronium, the ED_{95} is greater with the cumulative technique than with the single-dose method.[1–4] This occurs because it is not possible to prevent elimination of some of the earliest doses of these relaxants by the time the maximum response occurs following the final cumulative dose. However, single-dose dose–response curves, determined by log-probit analysis in adults and children, have been found to be parallel for atracurium, vecuronium, pancuronium, and *d*-tubocurarine (*d*Tc) (the slopes range from 6.0 to 6.8 probit/log).[3,5–8] We therefore speculated that it should be possible to create an individual dose–response curve by using only one predetermined dose and another individually calculated incremental dose to achieve the desired final level of neuromuscular blockade (NMB). To test this hypothesis, we studied in 60 pediatric patients a two-dose dose–response technique for atracurium and compared the slope, the ED_{50}, and ED_{95} values with those obtained using the conventional single-bolus dose technique.

Materials and Methods

Sixty ASA Physical Status 1–2 patients between 2 and 10 yr of age (mean age, 6.1 yr, body weight of 24.3 kg, and body surface area of 0.88 m^2) who were undergoing elective surgery were studied. The study protocol was approved by the Ethical Committee of the Children's Hospital, University of Helsinki. The patients had no diseases or medications known to affect neuromuscular function. They were premedicated with 0.07 mg/kg of oral flunitrazepam. Induction of general anesthesia was carried out (after glycopyrrolate 5 μg/kg) with fentanyl 3 μg/kg and thiopental 3–4 mg/kg. Ventilation was then manually controlled with nitrous oxide in oxygen 2:1 to maintain end-tidal CO_2 at 5.0–5.5%. Normothermia was maintained. No volatile inhalational agent was used.

Two surface electrodes were applied over the ulnar nerve near the wrist: one over the adductor pollicis muscle on the thenar eminence and one on the proximal area of the middle finger. The forearm and the fingers were supported by a dorsal splint, and the neuromuscular monitor (Relaxograph, Datex, Helsinki, Finland) was calibrated. The ulnar nerve was stimulated supramaximally with train-of-four stimuli (2 Hz every 20 s) and the evoked compound electromyogram (EMG) was recorded. The calibration was continued until constant responses were recorded for at least 3 min.

The first 30 patients were given 150 μg/kg of atracurium. The ensuing NMB was monitored until no change in successive EMG responses was noticed (fig. 1).[5] This maximal effect was plotted on log-probit paper on which parallel lines with slopes of 6.5 probit/log had been drawn (fig. 2). From this graph, an individual incremental dose that would produce 95% NMB was estimated by assuming that the individual dose–response curves are parallel and that the slopes are 6.5 probit/log. This incremental second dose was then given, and the maximum NMB was recorded (fig. 1). This maximum effect was then plotted on the log-probit paper. The line drawn *via* the two dose-response points is the individual two-dose dose-response curve.

From the data derived from the first part of the study, the average atracurium dose–response curve of these 30 patients was divided by four cut points into three equal parts to cover that portion of the curve where responses

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lay between 5% and 95% NMB. The division was performed so that the response to 150 μg/kg constituted one of the points. Consequently, doses of 105, 150, 210, and 300 μg/kg on the horizontal axis became the cut points. These doses are at equal intervals on a logarithmic scale. The remaining 30 patients were then given either 105, 210, or 300 μg/kg of atracurium in random order. The maximum NMB following these doses was recorded, and the patients were given a second dose to achieve the desired final 95% NMB. The estimate of the magnitude of the second dose was based on the same graph as in the first part of the study. The individuals who manifested a >90% NMB following the initial dose of atracurium did not receive additional doses.

The maximum NMB was calculated after both doses of atracurium. An individual two-dose dose–response curve was drawn by log-probit transformation and the individual slope, ED_{50}, and ED_{95} determined by least-square linear regression analysis. The single-dose dose–response curve was drawn by log-probit transformation of the maximum NMB after the first doses of atracurium (*i.e.*, 105, 150, 210, and 300 μg/kg).[9] The effective doses were calculated on the basis of body weight (μg/kg) and body surface area (mg/m^2).

ANOVA, with the Welch modification in cases of unequal variances, was employed for statistical analysis (BMDP Statistical Software 7D of 1987, Berkeley, California). The Tukey studentized range method was used to compare the mean slope and ED_{50} and ED_{95} values of the two-dose dose–response groups. The method described by Litchfield and Wilcoxon was used to compare the ED_{50}, ED_{95} and the slope of the single-dose dose–response curve with the mean values of the separate and pooled two-dose dose–response groups.[9] The power of this study is determined by the confidence limits for the NMB achieved following the second dose of atracurium. $P < 0.05$ was considered statistically significant. Mean values are expressed with SEM, or in case of log-scale with 1 SD range. For the single-dose dose–response curve, 1 SD is expressed so that the 95% confidence limits would represent the range of 2 SD.

Results

The mean onset time of atracurium induced block after the initial dose (time from administration to maximum effect) was 5.3 ± 0.8 min (mean ± SEM). Three unchanged train-of-four responses were monitored before the second atracurium dose was administered. The maximal NMB was obtained 2.4 ± 0.5 min after the second dose. This time was not dependent on the amount of the first dose. Thereafter the NMB remained unchanged for 4.3 ± 0.1 min before it began to recover.

The effects of the first doses of atracurium are shown in table 1. One SD range of the NMB produced by 105, 150, 210, and 300 μg/kg of atracurium was 9–30%, 16–60%, 64–84%, and 82–96%, respectively. The patients given 300 μg/kg of atracurium as the first dose did not receive the second dose because their maximum NMB became >90% after the first dose (table 1).

The ED_{50} and ED_{95}, calculated from the single-dose dose–response curves, were 164 (SD range, 150–179) and

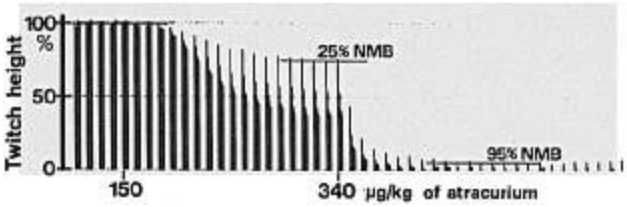

FIG. 1. An individual evoked EMG recording from a patient given two doses of atracurium. The first dose was 150 μg/kg and the second dose was 190 μg/kg (total dose 340 μg/kg). The maximum neuromuscular responses following atracurium were 25% and 95% NMB, respectively.

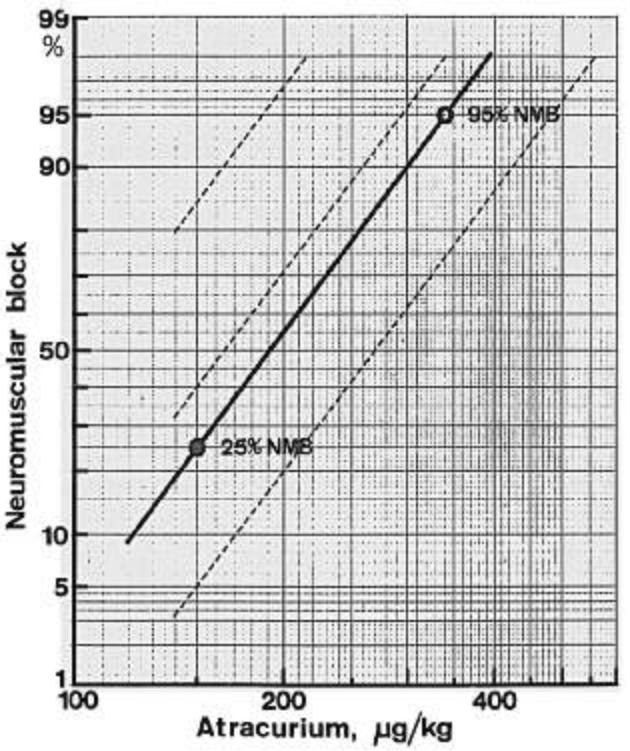

FIG. 2. The log-probit paper for plotting the individual dose–response relationship of atracurium. Broken lines have a slope of 6.5 probit/log. The 25% NMB response following the 150 μg/kg atracurium dose of the figure 1 patient is marked with closed circle. A line drawn *via* this circle and parallel to the broken lines crosses the 95% NMB response at the dose level of 340 μg/kg. Therefore, the second atracurium dose was 190 μg/kg. The subsequent NMB was exactly 95% (open circle). The line drawn *via* the circles is the individual two-dose dose–response curve.

TABLE 1. The Neuromuscular Block Achieved Following Administration of Atracurium

First Dose			Total Dose		
N	μg/kg	NMB (%)	N	μg/kg	NMB (%)
10	105	17 ± 4	10	271 ± 12	95.8 ± 0.6
30	150	35 ± 4	30	321 ± 12	95.7 ± 0.5
10	210	75 ± 3	10	306 ± 10	94.6 ± 0.5
10	300	91 ± 2		—	—
	ANOVA	$P = 0.000$		NS	NS

The values are mean ± SEM. Total dose is the sum of the first dose and the individual second dose.

336 (SD range, 274–411) μg/kg, respectively. The slope of the single-dose dose–response curve was 5.4 (4.5–6.4) probit/log (table 2; fig. 3).

The average maximal NMB after the individual second dose of atracurium was 95.5 ± 0.3%, without any difference between the three patient groups (table 1; fig. 4). In these 50 patients given second atracurium dose the maximum response was 6.695 probits with an SD of 0.25 probits. At 95% NMB (6.645 probits) the power to detect a difference of 0.10 probits is[10]: (standardized normal deviate) × $(-1.645 + 0.1 \times \sqrt{50}/0.25)$ = (standardized normal deviate) × (1.183) = 88%, or a beta error of 12%. Thus, there would be a 12% chance of failing to detect a difference from the precalculated 95% NMB if the mean maximum NMB following the second atracurium dose had been <93.88% (0.1 probits < 95% NMB) or >95.95% (0.1 probits > 95% NMB).

The slopes of the two-dose dose–response curves and the ED_{50} and ED_{95} values (calculated on the basis of both body weight and body surface area) were comparable between the three patient groups (table 2; fig. 4). The values of any two-dose dose–response group did not differ from the values produced by the single-dose dose–response technique. When the average ED values of all 50 patients given two doses of atracurium were calculated, they were almost identical with those obtained by the single-dose technique (table 2). Also, the slope of the average two-dose dose–response curve was similar to the slope of the single-dose dose–response curve (table 2).

Discussion

This investigation suggests that it is possible to create an individual dose–response curve of atracurium using only one predetermined dose and one increment individually calculated to produce a 95% NMB. By this method in an average of 8.5 min an individual dose–response curve could be drawn, from which it might be possible to determine the individual slope of the curve and the ED_{50} and ED_{95} of atracurium.

In children and adults, the distribution and elimination half-lives of atracurium are 2–3 and 19–20 min, respectively,[11–13] and the onset time (time between administration and maximum effect) is 6–7 min.[6,14,15] Therefore, if the cumulative dose dose–response curves are created by the method described by Donlon *et al.*,[5] it is not possible to prevent elimination of the first doses at the time of maximum EMG response following the later doses. Consequently, the calculated ED_{95} becomes too large and the slope of the dose–response curve becomes too small.

If the dose–response curve of atracurium or vecuronium is created by the single-dose technique, hundreds of patients would have to be studied if several patient groups were to be compared with each other. Therefore, it is valuable to have a reliable technique that may be used to construct an individual dose–response curve for every patient. This technique would be extremely valuable in determining individual response to NMB drugs in patients in whom an unpredictable response to NMB agents is likely.

The average onset time of the first atracurium dose in the present study was 5.3 min, which is similar to that documented in adults.[6,14,15] Interestingly, the time elapsed between injection of the second atracurium dose and its

TABLE 2. ED_{50}, ED_{95}, and the Slope of the Dose–Response Curve for Atracurium in the Study Groups

First Dose (μg/kg)	N	ED_{50} (μg/kg)	ED_{95} (μg/kg)	ED_{50} (mg/m²)	ED_{95} (mg/m²)	Slope (probit/log)
105	10	146 (126–169)	261 (223–305)	4.1 (3.4–5.0)	7.4 (6.1–9.0)	6.5 (6.0–7.0)
150	30	168 (132–215)	312 (258–378)	4.4 (3.3–5.9)	8.2 (6.4–10.5)	6.3 (5.3–7.3)
210	10	149 (117–190)	315 (279–356)	3.7 (2.8–4.9)	7.8 (6.3–9.7)	5.7 (4.2–7.2)
Two-dose	50	160 (126–201)	302 (251–363)	4.2 (3.2–5.6)	8.0 (6.3–10.0)	6.2 (5.2–7.2)
Single-dose	60	164 (150–179)	336 (274–411)	4.5 (4.2–4.9)	8.6 (6.9–10.5)	5.4 (4.5–6.4)
P		NS	NS	NS	NS	NS

The values are expressed as means, with 1 SD range given in parentheses.

maximal effect was only 2.4 min. Because the maximum NMB remained unchanged for an average of 4.3 min following the second atracurium dose, it is unlikely that the effect from the first dose had disappeared at the time of maximal NMB from the second dose. This is consistent with the finding that the slopes of the two-dose dose–response curves were not less than the slope of the single-dose dose–response curve (figs. 3 and 4). Furthermore, the maximum 95.5% NMB following the second atracurium dose was close to the precalculated level of 95%.

There were no differences in the slopes or ED_{50} or ED_{95} values between the present single-dose dose–response curve and any of the two-dose dose–response curves, even though the values were calculated on the basis of either body weight or body surface area. The slope, ED_{50} and ED_{95} values in our study are similar to those obtained by Brandom *et al.* in children 2–10 years of age.[16,17] Goudsouzian *et al.*, using the tension measurement in children 1–9 years of age, found identical ED_{50} but somewhat smaller ED_{95}.[18]

For statistical purposes, three types of comparisons were made: 1) The ED_{50} and ED_{95} values and the slopes of the dose–response curves were compared among the three groups of patients given two doses of atracurium. No differences were found by using ANOVA. 2) The mean ED_{50} and ED_{95} values and the slope of the dose–response curves of all the 50 patients given two atracurium doses were compared with the respective values derived by the single-dose dose–response technique. The values were almost identical (table 2). That the patients receiving the two-dose technique were also included in the single-dose group should not affect the slopes of the dose–response curves or the maximum response following the second atracurium dose. It may, however, reduce the difference especially between the ED_{50} values derived by different techniques. 3) The mean ED_{50} and ED_{95} values and the slopes of the dose–response curves of each two-dose technique group were compared with the respective values derived by the single-dose dose–response technique. No statistical differences were noted. Because the nature of the single-dose technique is such that a type II error analysis cannot be carried out, we determined the power of the study on the basis of maximal recorded response following the second atracurium dose. The chance of failing to detect even minor difference from the targeted 95% NMB was minimal.

When compared with the single-dose results, the ED_{95} tended to be somewhat smaller and the slope of the dose–response curve somewhat steeper in patients given the smallest initial atracurium dose. The direction of these changes is opposite to those found by using a cumulative dose dose–response technique. This tendency has to be reevaluated in larger patient populations in future "screening" studies before the two-dose technique is applied to evaluate pharmacodynamic characteristics of new NMB agents or new disease states. This is especially important because the slope of the dose–response curve may vary between different NMB agents and between individual patients.[19,20]

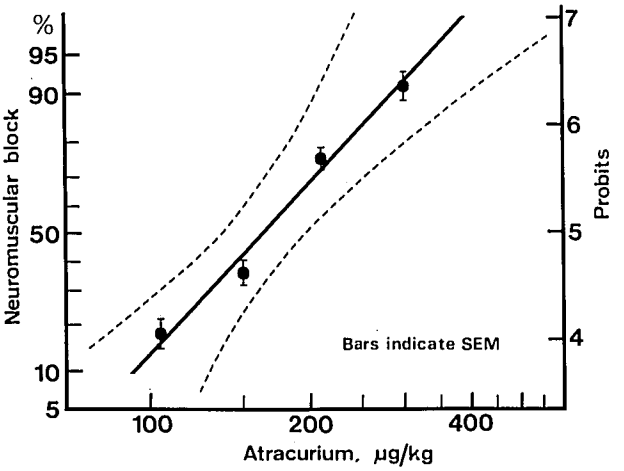

FIG. 3. The single-dose dose–response curve for atracurium. The 95% confidence limits are shown by broken lines. Calculated ED_{95} is 336 μg/kg.

A two-dose technique described here may be useful in several situations. First, for studies involving an NMB agent with intermediate duration of effect in small groups of patients, it is possible to construct a dose–response curve for each patient and to calculate the mean slope, ED_{50}

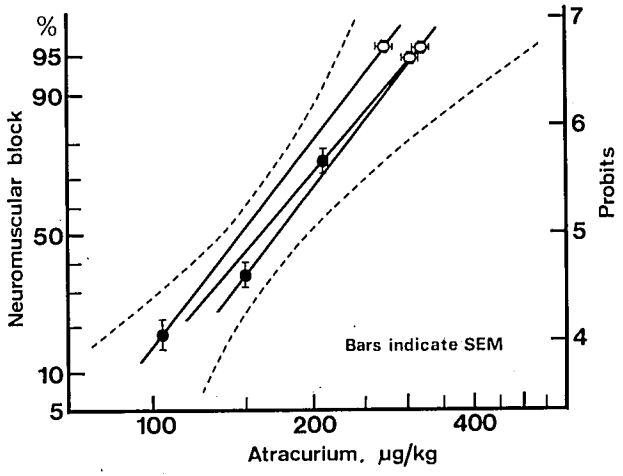

FIG. 4. The average two-dose dose–response curves for atracurium in the three patient groups given either 105, 150, or 210 μg/kg of atracurium as the first dose. Mean neuromuscular responses following the first and second doses of atracurium are marked with closed and open circles, respectively. Broken lines indicate the 95% confidence limits of the single-dose dose–response curve (see fig. 3). There are no differences between the calculated ED_{50}s, ED_{95}s, and the slopes of these dose–response curves.

and ED_{95} of all patients. Second, if an individual patient does not manifest the estimated NMB after administration of the first dose of atracurium, it would be possible to give a second dose that will produce the level of NMB desired. This is possible by using log-probit paper on which the slopes of the dose–response curves are drawn, as in figure 2. Third, the following method can be used in a patient with unpredictable response to NMB agents: the first atracurium dose might be 50 μg/kg. Thereafter, succeeding doses are doubled and administered every 2–3 min until a recordable NMB is achieved. The final dose is then determined from the graph, as in figure 2. The maximum number of doses would be 3 or 4 (the third and fourth logarithmic doses are 200 and 400 μg/kg, respectively), and the time to reach the 95% NMB would not exceed 8–12 min. Concurrently, the last increment constitutes at least 50% of the total cumulative atracurium dose. In this way, the possible elimination of first doses at the time of maximum NMB following the last increment contributes only slightly on the individual dose–response curve.

This method is based on our findings that if the given dose of atracurium is to be effective, its effect becomes recordable in 1–3 min and the maximum neuromuscular effect is obtained in 3–7 min. The 6.5 probit/log slope of the dose–response curve means that when the total dose of atracurium is doubled, it produces a 2.0 probit change in the NMB. This probit change is comparable to an increase in NMB from *e.g.*, 4% to 60% or from 40% to 96%. Therefore, it is not necessary to wait for the maximum effect of a slight neuromuscular response because doubling the dose does not produce an unpredictable profound NMB. We did not use any volatile inhalational agents, but these agents have not been found to alter the slope of the dose–response curves of muscle relaxants.[14,16,18]

In conclusion, we have developed a reliable method for determining individual dose–response curve for atracurium. From this curve it is possible to calculate the individual slope of the curve and the individual ED_{50} and ED_{95} values. This two-dose technique may in all likelihood be used in adults and in pediatric patients when the objective is to determine the individual response to an NMB agent having intermediate duration of effect.

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