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Potency of Atracurium: A Comparison of Single Dose and Cumulative Dose Techniques

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It has been shown previously that the potency of a relatively short acting drug like vecuronium is greater when a single-dose method is used in contrast to a cumulative dose technique.[1]§ Atracurium is another recently introduced muscle relaxant with a duration of action similar to that of vecuronium.[2,3] The reported ED_{95} has varied from 200 μg/kg to 279 μg/kg.[4,5] Although Katz and his colleagues[2] pointed out that a given dose of atracurium produced a greater degree of block when administered as a bolus rather than in increments, there is no information as to the comparative potency of the drug with the two techniques. This was the object of the present investigation.

METHODS

Patients conforming to ASA grade I scheduled to undergo elective surgery were included in the study. All gave informed consent, and the investigation was approved by the regional Ethical Committee. Following premedication with diazepam 10–15 mg orally, anesthesia was induced with thiopental 4–5 mg/kg and maintained with 70% nitrous oxide in oxygen and increments of fentanyl and additional thiopental as required. Ventilation was assisted as required to maintain an end-tidal CO_2 of around 4.5–5.0% using a nonrebreathing circuit.

The ulnar nerve was stimulated at the wrist with supramaximal square wave stimuli of 0.2 ms duration at 0.1 Hz using surface electrodes. The resultant force of thumb adduction was measured and recorded using a force displacement transducer and a neuromuscular function analyzer (Myograph 2000®, Biometer Limited).[6]

The control twitch height was allowed to stabilize for at least 10 min. The patients were divided randomly into two groups, the cumulative dose group and the single dose group. In the cumulative dose group, patients were administered increments of 50 μg/kg of atracurium every time there was no change in the twitch height in response to three consecutive stimuli as described by Donlon and his colleagues.[7] Increments were administered until a reduction in twitch height of at least 95% (ED_{95}) was attained. Ten patients were studied in this manner.

In the group being studied using the single-dose technique, patients were further allocated randomly to receive 50, 100, 150, 200, or 250 μg/kg atracurium. The maximal depression in twitch height obtained in each patient was noted irrespective of the time taken. The certainty of this end point was assured when the block had started to recover. A total of 30 patients was studied with the single dose technique, 6 patients being studied with each dose.

The twitch height data were subjected to an arc-sine transformation as described by Armitage[8] for responses involving the two extreme points (0 and 100%) on the dose–response curves. Regression analysis of the data was carried out using the method of least squares and dose–response curves constructed for each of the two groups. The lines were tested for any difference in their slopes and intercepts and the doses producing 50 and 95% block (ED_{50} and ED_{95}) compared using a Student's *t* test. The average maximum block and the time taken to attain it in the single dose group patients was subjected to an analysis of variance.

RESULTS

The two groups did not differ in their physical characteristics. The dose–response curves obtained using the cumulative and single dose techniques are shown in figure 1. The lines did not differ significantly in their slopes, but the intercepts were significantly different (*P*

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§ Nagashima H, Yun H, Radnay PA, Duncalf D, Kaplan R, Foldes FF: Influence of anesthesia on human dose–response of Org-NC45 (abstract). ANESTHESIOLOGY 55:A202, 1981.

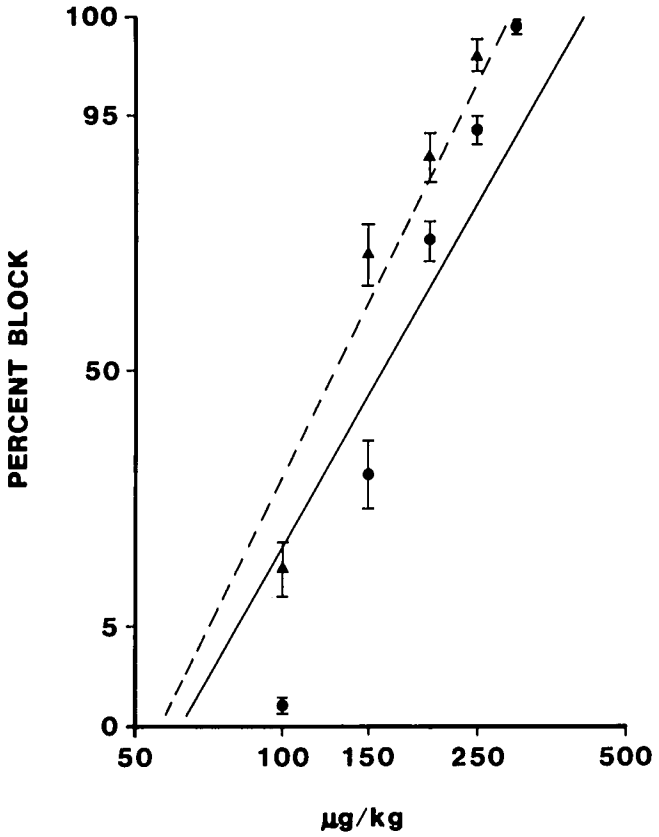

FIG. 1. Dose–response curves for atracurium using a cumulative ●——● or single dose ▲- - -▲ technique. Values plotted are mean ± SEM of the twitch height depression. Cumulative dose group—equation: arcsine of response = $-14.8 + 117 \log_{10}$ (no. of increments); r = 0.88; slope = 117; intercept on the x-axis = 66.6. Single dose group—equation: arcsine of response = $-220.3 + 126 \log_{10}$ (dose); r = 0.96; slope = 126; intercept on the x-axis = 55.6. Difference in the slopes insignificant; difference in the intercepts significant ($P < 0.005$).

< 0.005). The dose–response curve with the single-dose technique was to the left of the one obtained using the cumulative dose technique, indicating a greater potency

TABLE 1. Comparison of Cumulative Dose and Single Dose Techniques

	Cumulative Dose Technique	Single Dose Technique
Age (yr ± SEM)	40.7 ± 4.26	39.8 ± 3.34
Weight (kg ± SEM)	64.1 ± 3.72	65.0 ± 2.37
ED_{50} (µg/kg)	162	126*
(95% confidence limits)	(149–175)	(115–137)
ED_{95} (µg/kg)	305	226*
(95% confidence limits)	(275–336)	(207–246)

* Significantly different ($P < 0.005$) from the cumulative dose technique for both end points.

TABLE 2. Average Maximum Block and the Time Taken to Attain it in the Single-dose Group

µg/kg	Maximum Block (%) (±SEM)	Time Taken to Attain Maximum Block (min ± SEM)
50	0	—
100	16 ± 5.7*	6.6 ± 0.97†
150	70 ± 8.0*	6.2 ± 0.69†
200	88 ± 3.3*	5.9 ± 0.43†
250	98 ± 1.3*	5.9 ± 0.86†

* Differences significant ($P < 0.01$).
† Differences insignificant.

of the drug when evaluated by the single-dose method. The actual ED_{50} and ED_{95} along with their 95% confidence limits with the two techniques are given in table 1. For the single dose, the ED_{50} and ED_{95} were 126 µg/kg and 226 µg/kg, respectively, in contrast to 162 µg/kg and 305 µg/kg obtained with the cumulative dose method. These are significantly different for both end points ($P < 0.005$). The averge maximum block attained in the single dose group (table 2) increased significantly ($P < 0.01$) as the size of the boluses increased from 100 to 250 µg/kg, 50 µg/kg produced no measurable block. The corresponding times taken to attain this block decreased from 6.6 to 5.9 min, but this was not significant.

DISCUSSION

Donlon and his colleagues[9] showed that the dose–response curves did not differ when either the single dose or the cumulative dose technique was used to determine the potency of relatively long-acting relaxants like pancuronium and tubocurarine. The present study, however, shows atracurium, a relatively shorter acting drug in comparison to pancuronium and tubocurarine, seeming to be more potent when assessed by a single-dose method. The ED_{95} of 305 µg/kg obtained by the cumulative dose method in the present study is similar to that reported by Gramstad and Lilleaasen.[5] The ED_{95} of 226 µg/kg with the single dose method also is similar to that of 200 µg/kg reported by Basta and his colleagues[4] using the same method of evaluation. These findings confirm the observations of Katz and his colleagues,[2] who had observed that a total dose of 0.25 mg/kg of atracurium produced an average block of only 70% when administered in the form of smaller increments in comparison to a block of 95% or more in every patient when the same dose was administered as a single bolus.

These findings with atracurium are similar to those reported with vecuronium,[1] where the single dose technique showed it to be more potent than when assessed

using a cumulative dose method. This has been explained on the basis of the relatively short action of vecuronium, particularly in small doses, in relation to the time it takes to administer further increments in a cumulative dose technique.[1] Similar considerations perhaps apply to atracurium, an agent with a short half-life[10] and which begins to be metabolized from the time of administration via the Hoffman elimination reaction.

An obvious disadvantage of the single dose method is the larger number of patients required to establish potency of a drug. It is, however, clear that the results with relatively shorter acting agents like atracurium and vecuronium are influenced by the technique of evaluation, although this does not seem to matter when longer acting agents like pancuronium and tubocurarine are evaluated. It is perhaps preferable to determine potency of such agents by a single-dose technique, since this is the way in which anesthetists administer the muscle relaxants, particularly the initial dose.

In conclusion, our results show the potency of atracurium to be significantly greater ($P < 0.005$) when assessed using a single-dose method. The ED_{50} and ED_{95} were determined to be 162 and 305 $\mu g/kg$, respectively, using the cumulative dose technique, and 126 and 226 $\mu g/kg$, respectively, using the single-dose technique.

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Emergency Management of the Infant with an Obstructed Airway at Birth

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Congenital subglottic stenosis is the third most common obstructive airway lesion in infancy and childhood[1] and the most common congenital laryngeal lesion requiring tracheotomy.[2] Such infants usually present with stridor and/or repeated respiratory infections in the first few months of life. We describe a neonate with total subglottic obstruction, symptomatic from birth. Differential diagnosis of the newborn with an apparently obstructed airway along with suggestions for acute airway management of such infants is discussed.

Report of a Case

This 2,780-g female infant was born at 37 weeks' gestation to a 33-year-old gravida 8 para 3 mother. Four spontaneous first-trimester abortions had occurred between the last live birth and the current pregnancy. Ultrasound at 24 weeks' gestation performed for evaluation of polyhydramnios revealed fetal ascites but no other anomalies. Antibody screen of mother's blood was negative. Fetal heart rate was noted to be 180 bpm. With the presumption that the ascites represented congestive heart failure secondary to supraventricular tachycardia,[3] digitalis was administered to the mother. Follow-up sonograms showed resolution of ascites, but polyhydramnios remained.

Delivery was accomplished by repeat Cesarean section in labor under general anesthesia. The infant had good tone and made two or three attempts at inspiration, then became apneic. Efforts to ventilate her lungs with help of a bag and mask were unsuccessful; the infant's chest did not expand, nor did her bradycardia or cyanosis improve. During an attempt by an experienced neonatologist to intubate the trachea, first with a 3.0 and then with a 2.5 endotracheal tube, the cords were easily visualized, but the endotracheal tube

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