Anesthesiology
59:459–462, 1983

Safety and Efficacy of Atracurium in Adolescents and Children Anesthetized with Halothane

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ATRACURIUM (BW 33A) is a new nondepolarizing neuromuscular blocking agent that has a short-to-intermediate duration of action. It is a bisquaternary compound designated chemically 2,2-(3,11-dioxo-4,10-dioxatridecamethylene) bis (2-methyl-1,2,3,4-tetrahydropapaverium benzenesulphonate).

Preclinical safety studies in animals and initial adult human studies have shown that atracurium is devoid of toxicopathologic effects and has considerable advantages over commonly used muscle relaxants.[1–4] Its duration of action is one-third to one-half that of *d*-tubocurarine and it has no cumulative properties.[2,3] These features are assumed to be due to its unique mode of elimination, either via Hofmann elimination, a *p*H and temperature-dependent degradation, or ester hydrolysis independent of plasma cholinesterase.[4] In adults, cardiovascular stability is maintained at doses up to 2 × ED_{95} (0.4 mg/kg), while larger doses (0.5–0.6 mg/kg) occasionally cause a minimal drop in blood pressure (13–21%) and a slight rise in heart rate (5–8%).[5] Renal and hepatic function tests are unaffected by its administration.

Since its safety and efficacy have been established in adults, the present study was designed to study its effects in adolescents and children.

METHODS

This protocol was approved by the Subcommittee on Human Studies, Committee on Research of the Massachusetts General Hospital; parental written informed consent was obtained for each patient.

Forty children and adolescents (ASA Class I and II) 2–17 years of age who required neuromuscular relaxation during surgical procedures were studied. Premedication consisted of rectal methohexital (25 mg/kg) in children less than eight years of age; older children and adolescents were given either diazepam (0.2–0.4 mg/kg po) or no premedication. Anesthesia was induced in the younger children using a 2:1 mixture of nitrous oxide and oxygen followed by halothane. Intravenous thiopental (5–7 mg/kg) was used to induce anesthesia in older children. Anesthesia was maintained in all patients with N_2O/O_2 and 1.5% inspired halothane. The electrocardiogram, auscultatory blood pressure, and esophageal temperatures were monitored in each patient. Changes in blood pressure and heart rate were recorded directly in three children who had indwelling arterial lines. End-expired carbon dioxide concentration was maintained between 35–45 mmHg (Datex CO_2 monitor).

The ulnar nerve was stimulated at the wrist via surface electrodes. Supramaximal train-of-four (2 Hz for 2 s) stimuli were generated by a Grass S88® stimulator at a rate of 0.1 Hz. The duration of each stimulus was 0.2 ms. The response of the adductor of the thumb was recorded through a Grass FT-03® force displacement transducer on a Grass®-Polygraph. Baseline readings of blood pressure, heart rate and neuromuscular response were obtained in each patient prior to administration of atracurium. Cardiovascular changes and onset of neuromuscular blockade were evaluated in the absence of surgical stimulation.

Patients were divided into four groups according to age and the mode of drug administration regimen. Atracurium was evaluated first in adolescents.

Group 1 (n = 9) consisted of male adolescents 11–17 years of age. Incremental doses of 0.1 mg/kg atracurium were given intravenously until more than 95% muscle twitch suppression occurred. Subsequent doses of atracurium were given after the peak effect of the previous dose had been reached. In some cases a final incremental dose 0.05 mg/kg was administered to obtain the desired degree of neuromuscular suppression. A cumulative dose

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Received from the Department of Anaesthesia, Harvard Medical School, at the Massachusetts General Hospital, Boston, Massachusetts, and Wellcome Research Laboratories, Burroughs Wellcome Company, Research Triangle Park, North Carolina. Accepted for publication April 4, 1983. Supported by a grant from Wellcome Research Laboratories. Presented in part at the American Society of Anesthesiologists Annual Meeting, October 1982.

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Key words: Neuromuscular relaxants: atracurium. Anesthesia: pediatric.

response curve for neuromuscular blocking effect then was constructed using the log–probit method.[6] The median ED_{95} value for the group was adopted as representative of the sample patient.

Group 2 (n = 10) consisted of male adolescents 11–17 years of age. These patients received a single intravenous bolus of 0.4 mg/kg atracurium, approximately 2 × ED_{95} dose established for Group 1 patients. Following this dose blood pressure and heart rate were recorded at 1-min intervals for 3–5 min. Endotracheal intubation was attempted 3–5 min after atracurium injection. At this time, the twitch response was suppressed completely.

Group 3 (n = 11) consisted of male and female children 2–10 years of age. They were studied in a fashion similar to Group 1.

Group 4 (n = 10) consisted of male or female children 2–10 years of age who were studied according to the same method as Group 2.

For patients in Groups 2 and 4, clinical conditions for endotracheal intubation were rated according to the ease with which the tube was passed and the patient's response (vocal cord movement, coughing, movement of the chest or abdomen). Conditions were rated excellent when the jaw muscles were relaxed and no movement of the vocal cords, diaphragm, or abdominal muscles was detected during or following intubation. When jaw muscles were relaxed but some movement of the vocal cords or abdominal muscles was detected, conditions were rated as satisfactory.

The muscle twitch response to train-of-four stimulation was monitored throughout the surgical procedure. If the surgical condition warranted, additional doses of atracurium were given when the twitch height had recovered to 25% of control. At the end of the procedure, residual neuromuscular blockade was antagonized with atropine 10–20 μg/kg and neostigmine 30–60 μg/kg. If the twitch height and train-of-four were at 95% of their control values, no reversal agents were administered.

The time to maximum depression of muscle twitch height was determined by measuring the time from the initial administration of atracurium to the onset of maximum depression. Recovery time was determined by measuring the time from the onset of maximal neuromuscular blockade to the return of twitch height to 5, 10, 25, 50, 75, and 95% of control. The data for comparison of adolescents and children were analyzed by Student's *t* test and analysis of variance.

Twitch heights (T1) at recovery to 10, 25, 50, 75, and 95% of control (fig. 1) were correlated with train-of-four values using the correlation coefficient.

In 14 patients, the preoperative and 24–48 h postoperative laboratory values for hemoglobin, hematocrit, complete white count, electrolytes, total calcium, creatinine, SGOT, and urine analysis were determined.

Results

Maximal changes in blood pressure and heart rate following atracurium administration are summarized in table 1. There were no significant changes in pulse rate, systolic and mean blood pressure. Two adolescents experienced a moderate change in diastolic pressure, the pressure decreasing from 75 mmHg to 60 mmHg in one patient and from 52 mmHg to 39 mmHg in the other. These changes were not considered clinically significant. None of the patients had a 20% or greater change in either mean arterial pressure or heart rate.

In Groups 1 and 3 there was no significant difference in the cumulative dose response curve of children compared with that of male adolescents. The ED_{50}, ED_{90}, and ED_{95} were estimated for each patient and these determinations then were used to estimate the medians for both Groups 1 and 3. The median derived ED_{50}, ED_{90}, and ED_{95} values of Group 1 patients were 0.12 mg/kg, 0.16 mg/kg, and 0.18 mg/kg, respectively; for Group 3 patients they were 0.11 mg/kg, 0.15 mg/kg and 0.17 mg/kg, respectively.

In Groups 2 and 4, after a bolus dose of 0.4 mg/kg atracurium, the twitch response to train-of-four stimulation was abolished in 2.0 ± 0.2 min (mean ± SE).

In the 10 adolescents, intubating conditions were considered to be excellent in four and satisfactory in five. One adolescent could not be intubated on the first trial (3.2 min after injection) because of inadequate exposure of the larynx. However, 2 min later, intubation was accomplished without difficulty. In children, conditions were excellent in eight and satisfactory in two.

One patient showed marked resistance to the actions of atracurium. He required approximately three times more drug than the other children to achieve the same degree of neuromuscular depression. The ED_{50} and ED_{95} of this patient were 0.27 mg/kg and 0.7 mg/kg, respectively. Despite a long anesthetic course requiring 10 0.2 mg/kg incremental doses, his recovery from neuromuscular block was similar in duration to that of the other adolescents. Because his response to the neuromuscular blocking effects of atracurium differed so greatly from that of any other patient, the data spuriously would have affected the cumulative dose–response curve and were not included in the calculation.

Times from maximal neuromuscular depression to full recovery of control twitch height are summarized in table 2. No significant difference was observed in recovery times between children (Group 3) and adolescents (Group 1) who received incremental doses of atracurium or between children (Group 4) and adolescents (Group 2) who received a 0.4 mg/kg bolus dose. For all patients who received 0.4 mg/kg, mean recovery time from the point of injection to 5% of control height was 26.2 ± 2.1 min,

TABLE 1. Maximal Changes in Blood Pressure and Pulse Rate (Mean ± SE) after the Administration of Atracurium in Adolescents and Children

	Before Atracurium (mmHg)		After Atracurium (mmHg)	
	BP systolic/ diastolic	Heart Rate beats/min	BP systolic/ diastolic	Heart Rate beats/min
Group 1	104 ± 7 / 68 ± 3	78 ± 4	103 ± 7 / 66 ± 2	77 ± 3
Group 2	99 ± 3 / 61 ± 3	81 ± 5	98 ± 3 / 57 ± 3*	79 ± 4
Group 3	91 ± 4 / 57 ± 4	106 ± 7	89 ± 4 / 56 ± 3	101 ± 7
Group 4	97 ± 3 / 63 ± 3	99 ± 6	98 ± 4 / 65 ± 3	101 ± 7

*Significantly different from control ($P < 0.05$).

from 5% to 25% of control was 9 ± 0.4 min, and from 25% to 95% it was 21.9 ± 1.5 min.

The train-of-four ratios (fourth twitch in the train-of-four to the first twitch) were evaluated when twitch height (T_1) had recovered to 10%, 25%, 50%, 75%, and 95% of control. When the train-of-four ratios were plotted against the percentage of depression of twitch height, the correlation coefficient was highly significant (r = 0.91; $P < 0.001$); the y-intercept corresponded to a twitch height of 19% of control (fig. 1).

Thirty-two of the 40 patients studied recovered spontaneously to at least 95% of control twitch height. In eight patients, the mean twitch height at the end of surgery was 64 ± 7% of control. After receiving atropine 15 ± 10 μg/kg and neostigmine 35 ± 8 μg/kg, these patients recovered to more than 95% of control twitch height in 5 + 2 min.

In three adolescents, a slight diffuse flushing was detected on the skin of the upper chest and neck after a bolus dose of 0.4 mg/kg. In two the flush was quite mild,

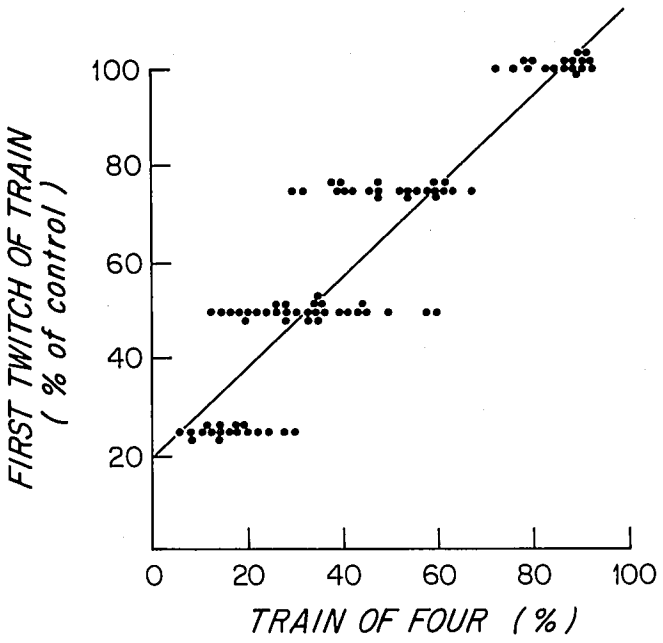

FIG. 1. Correlation between train-of-four values and the first twitch of train-of-four (percentage of control) at 0.1 Hz during recovery from the neuromuscular effects of atracurium in children anesthetized with halothane. (slope = 0.93, y-intercept = 19, r = 0.91)

whereas in the third it was somewhat deeper in color. Within 15-min the flushing disappeared spontaneously. No clinically significant changes in heart rate or in arterial pressure accompanied the flushing.

There was no significant difference between the preoperative and 24–48-h postoperative hemoglobin, hematocrit, complete white blood count, SGOT and serum creatinine, electrolytes, and calcium.

DISCUSSION

We elected to study male adolescents instead of both males and females because of the possibility of pregnancy

TABLE 2. Changes in the Neuromuscular Parameters after the Administration of Atracurium in Adolescents and Children Anesthetized with Halothane

				Mean Recovery Time from Atracurium in Minutes					
	Dose Administered (mg/kg)	Inject ⟶ Maximum Effect (min)	Max Block (%)	From Maximum Depression to 5% of Control Twitch Height	From 5–10% of Control Twitch	From 10–25%	25–50%	50–75%	75–95%
Group 1 (11–17 yr)	0.23 ± 0.02 incremental	9.2 ± 0.4 (n = 9)	98.7 ± 1.0	8.9 ± 1.0 (n = 9)	3.0 ± 0.2 (n = 9)	4.7 ± 0.4 (n = 9)	5.9 ± 0.5 (n = 6)	6.4 ± 1.0 (n = 5)	7.2 ± 1.2 (n = 3)
Group 2 (11–17 yr)	0.4 bolus	2.0 ± 0.2 (n = 10)	100%	24.6 ± 2.3 (n = 9)	3.0 ± 0.2 (n = 9)	5.3 ± 0.2 (n = 10)	7.7 ± 1.1 (n = 10)	5.8 ± 0.5 (n = 8)	9.0 ± 1.1 (n = 8)
Group 3 (2–10 yr)	0.23 ± 0.1 incremental	7.3 ± 0.6 (n = 10)	99.1 ± 0.4	11.5 ± 1.2 (n = 9)	3.1 ± 0.3 (n = 10)	5.6 ± 0.5 (n = 10)	5.8 ± 0.5 (n = 7)	5.3 ± 0.5 (n = 7)	6.4 ± 0.8 (n = 6)
Group 4 (2–10 yr)	0.4 bolus	2.0 ± 0.3 (n = 10)	100%	27.8 ± 2.5 (n = 9)	3.5 ± 0.3 (n = 9)	6.3 ± 0.5 (n = 9)	7.2 ± 0.7 (n = 8)	6.8 ± 0.7 (n = 8)	6.9 ± 0.8 (n = 10)

in females and the impracticality of performing preoperative pregnancy tests in these patients. We chose to begin our study by using small incremental doses of the drug rather than a larger bolus dose in order to minimize the risk of possible overdose or untoward side effects that could result from the larger dose. Because a dose of 0.1 mg/kg produced 66% twitch suppression in adults, this dose was selected as the first incremental dose.

In 20 patients who received atracurium as a bolus dose of 0.4 mg/kg, complete suppression of twitch occurred in a mean time of 2 min following injection. This suggests that halothane-anesthetized children and adolescents can be intubated endotracheally 2 min after the administration of the drug. Recovery to 95% of control twitch height from time of administration was 60.1 min in children. In similarly studied adults, a dose of 0.4 mg/kg produced complete twitch suppression in 1.3 min and 95% twitch recovery was achieved in 65.2 min.[2] These differences between adults and children are not significant and indicate that children older than 2 years seem to respond to atracurium in a fashion similar to adults.

A comparison of recovery times after an intubating dose of pancuronium (0.13 mg/kg), metocurine (0.5 mg/kg) and *d*-tubocurarine (0.8 mg/kg)[7] with that of atracurium (0.4 mg/kg) indicates that the latter is a shorter-acting agent. The mean recovery time of the twitch height to 5% of control of these three intubating doses of the long acting agents is 56 ± 6 min, whereas with atracurium it is 26.2 ± 2.1 min. (mean ± SE). Furthermore, recovery of the twitch in halothane-anesthetized children from 5–25% is 25 ± 2.0 min with *d*-tubocurarine[8] or metocurine[9] while with atracurium it is only 8.6 ± 0.6 min. These data indicate that the duration of action of atracurium in children is ⅓–½ that of long-acting nondepolarizing muscle relaxants.

In the clinical situation an adequately anesthetized patient will need more relaxation when the twitch height recovers to 25% of control.[7] Following an intubating dose of 0.4 mg/kg atracurium, we found that adequate surgical relaxation was maintained for about 35 min. Thereafter, a dose of 0.1 mg was needed every 8–10 min to maintain relaxation. Eight of the 40 patients studied required additional doses of atracurium; as few as one and as many as 24 additional doses were given. The consistent pattern of block and recovery following each supplemental dose suggests that there is no cumulative effect of the drug.

Recovery of the twitch (T_1) correlated satisfactorily ($r = 0.91$) with train-of-four values (fig. 1). A linear relationship similar to that observed for other nondepolarizing muscle relaxants in children[8,9] or adults[10] was found. The y-intercept point in this relationship corresponded to a twitch height of 19% of control, indicating that when the first twitches of the train-of-four can be felt or seen, then twitch height is about 19% of control. At this point relaxation probably will be satisfactory for only a few more minutes and an additional dose of relaxant will be required. The appearance of the fourth twitch generally indicates the need for more relaxation.

The stability of the cardiovascular system during the administration of atracurium (table 1) offers an important advantage over the other nondepolarizing relaxants. An intubating dose produces little or no cardiovascular changes. However, this dose may release histamine as manifested clinically by a rash in some patients. In adults, histamine levels are lower after atracurium administration than after comparable doses of *d*-tubocurarine or metocurine.[11] For this reason, atracurium probably will be more desirable than *d*-tubocurarine or metocurine.

The results of this study of children and adolescents under halothane anesthesia indicate that atracurium is a potent neuromuscular blocking agent with a rapid onset and an intermediate duration of action. At a dose of 2 × ED_{95}, endotracheal intubation may be accomplished 2 min after injection. Atracurium does not appear to have cumulative properties and its action is antagonized easily by neostigmine. The administration of atracurium was not associated with any significant cardiovascular changes. We conclude that it may be used safely in healthy children 2 years of age or older.

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