TABLE 4. Hemodynamic Changes Produced by the Surgery (Mean ± SD)

Group		Before Surgery	Five Minutes after the Start of Surgery	Per Cent Changes
D (n = 7)	H R	74 ± 6	89 ± 11*	+21 ± 19
	S A P	96 ± 17	136 ± 31*	+48 ± 18
	R P P	7.1 ± 1.3	12.5 ± 3.5†	+80 ± 51
LE (n = 14)	H R	85 ± 16	85 ± 16	+1 ± 2
	S A P	101 ± 18	100 ± 16	−1 ± 7
	R P P	8.7 ± 2.7	8.6 ± 2.7	0 ± 9
LED (n = 14)	H R	80 ± 12	80 ± 12	+1 ± 2
	S A P	97 ± 14	96 ± 12	−1 ± 4
	R P P	7.7 ± 1.5	7.7 ± 1.4	0 ± 5

HR, SAP, and RPP represent heart rate (beat/min), systolic arterial pressure (mmHg), and rate pressure product ($\times 10^3$), respectively.

* $P < 0.025$, † $P < 0.005$ as compared with the prior value.

epinephrine occurs in some cases when an epinephrine solution is injected for hemostatic purposes. The absorption of epinephrine into the blood is suppressed significantly by using 10% low-molecular-weight dextran instead of normal saline solution to dilute the epinephrine.

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Neuromuscular Effects of Atracurium in Infants and Children

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Atracurium is a new short–intermediate acting neuromuscular blocking drug that, with the usual clinical doses in pediatric patients, does not cause any appreciable change in heart rate or blood pressure.[1,2] Its relatively short duration of action makes it a suitable agent for short surgical procedures that are frequent in infants and children.

Previously we studied atracurium in adolescents and children anesthetized with halothane N_2O:O_2.[1] In the present study we evaluated the effects of atracurium in infants anesthetized with N_2O:O_2:halothane and in children anesthetized with N_2O:O_2 narcotic technique. We used the same methods of evaluation and measurement as in our previous study to facilitate the comparison between the responses of adolescents, children, and infants.

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Methods

The protocol was approved by our Subcommittee on Human Studies, Committee on Research. Parental written informed consent was obtained.

Nineteen infants, 4 weeks to 1 year of age, were anesthetized with N_2O:O_2: halothane, and 18 children (1–10 yr) anesthetized with N_2O:O_2 narcotic. Premedication consisted of rectal methohexital 25–30 mg/kg in children 10 months to 10 years: the smaller infants were not premedicated. In infants, anesthesia was induced by inhalation of a 2:1 mixture of nitrous oxide and oxygen followed by halothane. Anesthesia was maintained at a 1–1.5% inspired concentration of halothane. In the children, anesthesia was induced with a thiobarbiturate and maintained with nitrous oxide and oxygen and supplemented by iv increments of methohexital 2 mg/kg, thiopental 5 mg/kg, meperidine 1 mg/kg, and/or morphine 0.1 mg/kg. The ECG, auscultatory blood pressure, precordial or esophageal heart sounds, and esophageal temperature were monitored in each patient. End-expired carbon dioxide was maintained between 35–45 mmHg.

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. 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.

Group 1 (n = 9) consisted of infants 6 weeks to 1 year of age (mean ± SE, 4.8 ± 1.1 month) anesthetized with halothane. Incremental doses of 0.1 mg/kg atracurium were given iv until more than 95% muscle twitch suppression resulted. Subsequent doses of atracurium were given after the peak effect of the previous dose had been reached. In some cases a final incremental dose of 0.05 mg/kg was administered to obtain the desired degree of neuromuscular suppression. A cumulative dose–response curve for the neuromuscular blocking effect then was constructed using the log–probit method. The median ED_{95} value for the group was adopted as representative of the patient sample.

Group 2 (n = 10) consisted of infants 4 weeks to 1 year (4.4 ± 1.0 month) anesthetized with halothane. These patients received a single intravenous bolus of 0.4 mg/kg atracurium, approximately 2 times the ED_{95} dose estimated for Group 1 patients. Following this dose, arterial blood pressure and heart rate were recorded at 1-min intervals for 3 to 5 min. Endotracheal intubation was attempted 3–5 min after atracurium injection. At this time, the twitch response was suppressed completely.

Group 3 (n = 9) consisted of children 1–9 years of age (4.0 ± 0.8 yr) anesthetized with N_2O:O_2 narcotic and barbiturates. They were studied in a fashion similar to Group 1.

Group 4 (n = 9) consisted of children 1–5 years of age (2.5 ± 0.4 yr) who were anesthetized with N_2O:O_2 narcotic and barbiturates and studied according to the same method as Group 2. These children received an iv bolus dose of 0.5 mg/kg atracurium.

For patients in Groups 2 and 4, clinical conditions for endotracheal intubation were rated according to the ease with which the tube was passed (evaluated by the anesthesia resident) and the patient's response (vocal cord movement, coughing, movement of the chest or abdomen) (evaluated by the investigator and staff anesthesiologist). 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 of the trachea. When the jaw muscles were relaxed but some movement of the vocal cords or abdominal muscles was detected during or following intubation, conditions were rated as satisfactory.

The muscle twitch response to train-of-four stimulation was monitored throughout the surgical procedure. At the end of the procedure, residual neuromuscular blockade was antagonized with atropine 10 μg/kg and neostigmine 30 μg/kg. If the height of the first twitch of the train-of-four was 95% of its control value, no antagonists were administered.

The time to maximum depression of muscle twitch tension 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, 25, 75, and 95% of control. The data for comparison of adolescents and children were analyzed by the Student's *t* test and analysis of variance.

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

Results

In infants anesthetized with halothane (Group 1), the median effective doses of atracurium that caused 50% (ED_{50}) and 95% (ED_{95}) suppression of the first twitch

TABLE 1. The Effective Doses for 50 and 95% Suppression of the Twitch in Infants and Children

	ED_{50} (mg/kg)	ED_{95} (mg/kg)	ED_{95} ($mg \cdot m^{-2}$)
Infants (halothane)			
Median	0.10	0.17	3.3
Mean ± SE	0.12 ± 0.01	0.18 ± 0.02	
Children* (Halothane)			
Median	0.11	0.17	4.7
Mean ± SE	0.12 ± 0.01	0.19 ± 0.01	
Adolescents* (Halothane)			
Median	0.12	0.18	6.4
Mean ± SE	0.13 ± 0.01	0.20 ± 0.02	
Children (N_2O:O_2 Narcotic)			
Median	0.16	0.24	6.01
Mean ± SE	0.17 ± 0.01†	0.23 ± 0.01†	

* Data from our previous study[1] conducted in a manner similar to the present one.

† Significant difference with children anesthetized with halothane ($P < 0.005$).

during train-of-four stimulation were estimated to be 0.10 and 0.17 mg/kg, respectively. In children anesthetized with N_2O:O_2 narcotic (Group 2), the estimates were 0.16 and 0.24 mg/kg, respectively (table 1).

In infants (Group 2), a bolus dose of 0.4 mg/kg abolished the twitch height during train-of-four stimulation in 1.6 ± 0.3 min. In this group, conditions for endotracheal intubation were considered excellent in five of the infants and satisfactory in the remaining five. In children (Group 4) anesthetized with N_2O:O_2 narcotic, a bolus dose of atracurium 0.5 mg/kg abolished the twitch in 1.5 ± 0.1 min and provided excellent intubating conditions in five and satisfactory conditions in four.

The onset and times from maximal neuromuscular depression to full recovery of control twitch height are summarized in table 2. In general, the recovery times after 0.4 mg/kg of atracurium in infants anesthetized with halothane were similar to recovery times after 0.5 mg/kg in children anesthetized with N_2O/O_2 narcotic (table 3).

The train-of-four ratios (height of the fourth twitch in the train-of-four to the first twitch) were evaluated when the twitch height had recovered to 10, 25, 50, 75, and 95% of control. In both infants and children there was a highly significant correlation ($P < 0.001$) between the twitch height (per cent of control) and the train-of-four ratio (%). In children the correlation coefficient of this relationship (r) was 0.93 with a slope of 1.02. The standard error of the slope estimate was 0.07. The intercept of this linear regression was 16%, indicating that when three twitches were present during train-of-four stimulation, the twitch height had recovered to 16% (of control twitch height). For infants r was 0.87, slope 1.04 (SE 0.09), and the y-intercept of the relationship was at 9% of control twitch height.

Sixteen of the 37 patients recovered spontaneously to at least 95% of control twitch height. In the re-

TABLE 2. Changes in the Neuromuscular Variable (Mean ± SE) after the Administration of Atracurium in Infants Anesthetized with Halothane and Children Anesthetized With N_2O:O_2 Narcotic

	Dose Administered (mg/kg)	Inject to Maximum Effect (min)	Max Block (%)	From Maximum Depression to 5% of Control Twitch Height	Recovery of the Twitch Height (min)		
					From 5 to 25% of Control Twitch	25–75%	75–95%
Group 1							
Infants–halothane	0.23 ± 0.02 incremental	7.0 ± 0.7 (n = 9)	98.5 ± 0.7 (n = 9)	9.0 ± 1.2 (n = 8)	8.2 ± 1.6 (n = 8)	13.8 ± 1.5 (n = 3)	7.1 ± 1.0 (n = 3)
Group 2							
Infants–halothane	0.4 bolus	1.6 ± 0.3 (n = 10)	100 (n = 10)	28.4 ± 2.3 (n = 8)	8.5 ± 0.5 (n = 8)	12.4 ± 1.8 (n = 6)	6.8 ± 0.9 (n = 6)
Group 3							
Children N_2O:O_2 narcotic	0.3 ± 0.01 incremental	7.5 ± 0.8 (n = 9)	99.0 ± 0.5 (n = 9)	11.5 ± 1.5 (n = 8)	7.6 ± 0.7 (n = 8)	11.1 ± 1 (n = 6)	6.3 ± 1.3 (n = 4)
Group 4							
Children N_2O:O_2 narcotic	0.5 bolus	1.5 ± 0.1 (n = 9)	100 (n = 9)	29.3 ± 1.5 (n = 9)	7.3 ± 0.6 (n = 7)	9.2 ± 0.5 (n = 4)	5.5 ± 2.3 (n = 3)

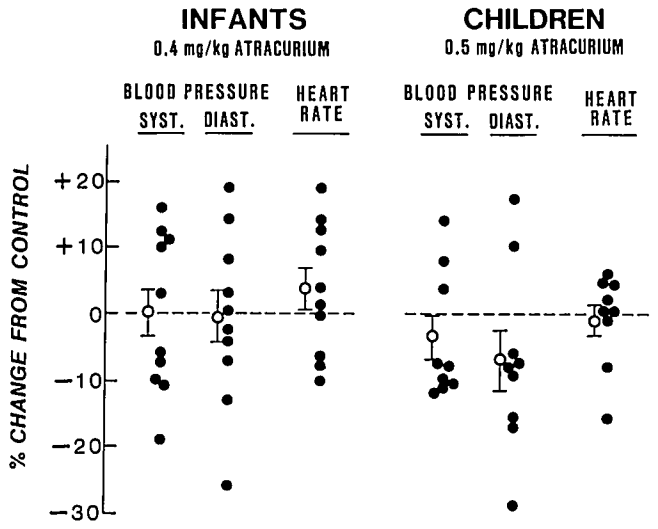

FIG. 1. A diagram indicating the maximum per cent change in systolic and diastolic blood pressures and heart rate upon the administration of 0.4 mg/kg atracurium in halothane-anesthetized infants (group 2) and 0.5 mg/kg atracurium in children anesthetized with N_2O:O_2 narcotic (Group 4). The bars indicate the mean ± SE.

mainding patients, the mean twitch height was 42 ± 9% of control at the end of the surgical procedure; in these patients, recovery to more than 95% of control twitch tension was obtained after the iv administration of atropine 10 μg/kg and neostigmine 30 μg/kg.

Administration of a bolus dose of 0.4 mg/kg atracurium in infants (Group 2) or 0.5 mg/kg in children (Group 4) did not cause any significant change in the mean heart rate or arterial systolic or diastolic blood pressure (fig. 1). Diastolic pressure decreased to more than 20% of control in one child and one infant. In the infant, the decrease in diastolic pressure (26%) was associated with a 19% drop in systolic pressure, whereas in the child, the decrease in diastolic pressure (29%) was associated with an 8% rise in systolic pressure. These effects on the blood pressure were transient and did not require any treatment.

None of the infants or children developed any flushing of the skin or rash following the administration of atracurium.

One infant 5 weeks of age accidentally received an initial dose of 1 mg/kg atracurium. This infant did not show any cardiovascular changes. The twitch response was abolished for 46 min and recovered to control values within 69 min. The data from this patient are not included in the above analysis.

DISCUSSION

The main purpose of the present study was to evaluate infants with the same techniques that we used to evaluate children in a previous study so that the results could be compared. In like manner, the same technique was used to compare the children anesthetized with N_2O/O_2 narcotic and the children anesthetized with halothane in a previous study.[1] In both studies the frequency of train-of-four stimulation was 0.1 Hz, the incremental technique was used, and the incremental doses were administered within approximately the same time interval (7 min). The two studies demonstrate that the onset of action, conditions for endotracheal intubation, and recovery times are comparable after 0.4 mg/kg atracurium in infants, children, and adolescents anesthetized with halothane. The ED_{50} and ED_{95} also were comparable for these three groups (table 1). While the effective doses of atracurium (ED_{50} and ED_{95}) determined by the incremental dose response technique are expected to be higher than the values obtained by the bolus method,[3,4] this should not affect the values of the results in the studies we are presently comparing since they were all performed with the same technique.

In adults anesthetized with halothane, a dose of 0.4 mg/kg atracurium abolished the twitch response during train-of-four stimulation in 1.3 ± 0.1 min.[5,6] Twitch recovered to 95% in 65.2 ± 2.2 min, a time slightly longer but not significantly different from that observed in our series of infants and children. However, a significantly faster recovery time was observed in children compared with adults anesthetized with N_2O/O_2 narcotic. Following a dose of 0.5 mg/kg atracurium, recovery to 95% of control required 52.6 ± 3.8 min in children and 67.6 ± 5.4 min in adults ($P < 0.02$).

Our results are slightly different from the findings of Brandom *et al.*[7] They found that when the ED_{50} and ED_{95} of atracurium was determined according to body weight these values were higher for children than for infants or adolescents. However, when they calculated the ED_{50} and ED_{95} based on surface area, infants required less atracurium than adolescents, whereas children and adolescents require similar doses.[7] Our results with atracurium indicate that infants, children, and adolescents require the same amount of atracurium when the dose is calculated on the basis of body weight. Infants have a relatively large surface area relative to body weight. Not surprisingly, therefore, when we calculated the dose of atracurium based on surface area, we found that infants are more sensitive to atracurium than adolescents or children (table 1). Whether atracurium has a larger distribution volume in infants and is effective at lower plasma concentration as is the case with *d*-tubocurarine[8] needs to be determined with pharmacokinetic studies. However, for practical purposes calculation by body weight proves to be a simple and a satisfactory means on which to base the dose of atracurium.

TABLE 3. The Clinical Profile of Endotracheal Intubating Doses of Atracurium in Infants and Children

	Dose (mg/kg)	Maximum Effect	Intubating Condition		Recovery of the Twitch Height (min)		
			Excellent	Satisfactory	From Maximum Depression to 5% of Control Twitch Height	From 5 to 25% of Control Twitch	Total from Injection to 95% Recovery
Infants (Halothane)	0.4	1.6 ± 0.3	60%	40%	28.4 ± 2.3	8.5 ± 0.5	56.2 ± 3.9
Children* (Halothane)	0.4	2.0 ± 0.3	80%	20%	27.8 ± 2.5	9.8 ± 0.4	59.5 ± 3.7
Adolescents* (Halothane)	0.4	2.0 ± 0.2	40%	60%	24.6 ± 2.3	8.3 ± 0.3	57.4 ± 3.8
Children (N_2O:O_2 narcotic)	0.5	1.5 ± 0.1	56%	44%	29.3 ± 1.5	7.3 ± 0.6	50.6 ± 3.8

Data are expressed mean ± SE.

* Data from our previous study[1] conducted in a similar manner.

Brandom[7] found that 0.3 mg/kg atracurium provided excellent conditions for intubation in nine out of 10 infants. We found that a larger dose, 0.4 mg/kg, provided excellent condition in only half of the infants and satisfactory in the other half. Endotracheal intubating condition were considered excellent in our study if there was no muscle movement during or after endotracheal intubation. We rated conditions as satisfactory if any muscular movement was detected during or after intubation. In our study muscular movement was observed only immediately after the endotracheal tube had been inserted. Several factors will affect the conditions of intubation, including premedication, the depth and duration of anesthesia, the intubating skill of the anesthesiologist, the anatomy of the airway of the patient, and the degree of hyperventilation. The difference in intubating conditions between the two studies also may be due to the difference in the ages of the infants in each study. Brandom[7] studied infants less than 6 months of age, whereas we studied infants up to 1 year of age. On reviewing the data, however, we could not identify a specific sensitity to atracurium in the small infants of our series.

In this present study, we found that the atracurium requirement of children anesthetized with N_2O:O_2 narcotic was higher (25–30%) than that of children anesthetized with halothane. This tendency frequently is seen with nondepolarizing muscle relaxants.[9] The higher dose of atracurium (0.5 mg/kg) in children anesthetized with N_2O/O_2 produced conditions of intubation and recovery times similar to those following 0.4 mg/kg atracurium in children anesthetized with halothane.

In summary, the requirement of atracurium in infants (4 weeks or older), children, and adolescents anesthetized with halothane is rather similar when the calculated doses are based on body weight. Atracurium 0.4 mg/kg provides satisfactory conditions for intubation in all patients within 3 min; the twitch height recovers to 95% of control within 1 h. The requirement of children anesthetized with N_2O/O_2 narcotic is moderately higher than in those anesthetized with halothane.

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