A comparative evaluation of intubating doses of atracurium, d-tubocurarine, pancuronium and vecuronium in children

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To determine the onset and recovery times and haemodynamic effects of intubating doses of atracurium (0.4 mg·kg^{-1}), d-tubocurarine (0.8 mg·kg^{-1}), pancuronium (0.12 mg·kg^{-1}), and vecuronium (0.07 mg·kg^{-1}), sixty-seven children aged one to eight years were studied under halothane and nitrous oxide anaesthesia. The time to maximum twitch depression and the time to recovery to T1/Tc 25 per cent were recorded with an integrated evoked EMG recorder. The heart rate and systolic blood pressure were recorded for five minutes after drug administration and prior to intubation. There was no difference in onset times between drugs. The recovery time to T1/Tc 25 per cent following vecuronium (25.5 ± 6.3 min) was shorter than following atracurium (37.5 ± 7.0 min). Recovery times for d-tubocurarine and pancuronium were greater than sixty minutes. Elevation of heart rate occurred after administration of pancuronium (+29.8 per cent to +38.6 per cent) and d-tubocurarine (+31 per cent to +34.9 per cent), but no change was observed after atracurium or vecuronium. Elevation of blood pressure was greatest following pancuronium (+10.8 to +14.8 per cent). No significant change was observed following atracurium or vecuronium. A transient lowering of blood pressure (−9.3 per cent) occurred following d-tubocurarine.

Key words

NEUROMUSCULAR RELAXANTS: atracurium, d-tubocurarine, pancuronium, vecuronium; ANAESTHESIA: paediatric; BLOOD PRESSURE: drug effects, intubation.

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It is reported that in addition to having a shorter duration of action, the neuromuscular blocking agents atracurium and vecuronium may provide more haemodynamic stability than d-tubocurarine and pancuronium.[1,2] A randomized comparative study in children of the four commonly used agents, atracurium, d-tubocurarine, pancuronium, and vecuronium, under identical anaesthetic management was undertaken. The onset and recovery times and haemodynamic effects of intubating doses were measured for each drug.

Methods

With institutional approval and parental consent, 67 ASA physical status I children, aged one to eight years were studied. The subjects had no known hepatic, renal, or neuromuscular disorders and were not on any medications known to affect neuromuscular function. All surgery was peripheral. No premedication was given. Monitoring included a precordial stethoscope, an ECG, a Dinamap vital signs monitor with appropriate cuff for blood pressure measurement, end-tidal CO_2 monitor and an axillary temperature probe.

After intravenous induction with thiopentone, 4–6 mg·kg^{-1} (without atropine), and during an equilibration period of 10 to 20 minutes with 1.5 per cent inspired halothane in 60 per cent nitrous oxide, neuromuscular response was monitored with surface electrodes using an integrated evoked electromyographic recorder (Puritan-Bennet Datex NMT 221) stimulating the ulnar nerve with train-of-four stimulation at 2 Hz every 20 seconds and recording the EMG response at the adductor pollicis. After appropriate calibration, one of the four muscle relaxants, randomly selected and blindly administered, was injected over 60 seconds. The dose of muscle relaxant given was twice the ED_{95} for children in this age group; i.e., atracurium 0.4 mg·kg^{-1}, d-tubocurarine 0.8 mg·kg^{-1}, vecuronium 0.07 mg·kg^{-1}, or pancuronium 0.12 mg·kg^{-1}.[2,3,4] Measurements of heart rate and blood

pressure were recorded each minute for five minutes after injection, using a Dinamap recorder. The end-tidal CO_2 was controlled by mask ventilation to between 35 and 45 mmHg and normothermia was maintained. Intubation was performed after the five minute study period, thus 5 minutes after administration of the muscle relaxant. The time to maximum twitch depression after completion of the injection of the drug and the recovery time to T1/Tc 25 per cent were recorded.

The patient was observed for local or generalized cutaneous flushing. Flushing was scored as mild (localized to IV site), moderate (involving the arm and partial chest), or severe (involving the chest and face). Intubating conditions were also scored as excellent (no movement and relaxed vocal cords), good (some cord or diaphragmatic movement), or poor (coughing or bucking). The haemodynamic data were expressed as mean (±SD) per cent-change from control. Onset and recovery times were expressed in minutes (±SD). Multiple group comparisons were analyzed using one-way ANOVA and Sheffe's F test. Intubating conditions and flushing were analyzed using the Chi-square test. P values < 0.05 were considered significant.

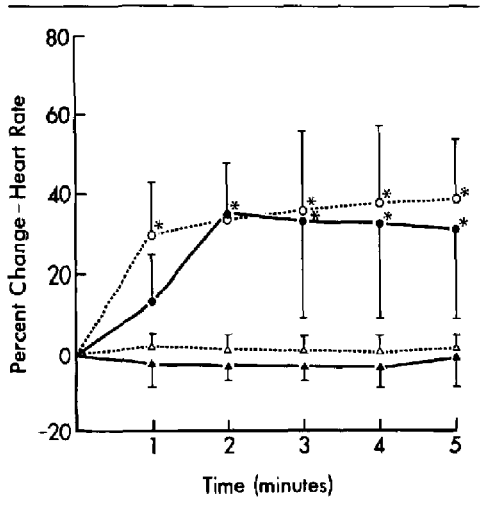

FIGURE 1 Change in heart rate expressed as per cent change from control: atracurium Δ--Δ; d-tubocurarine ●—●; pancuronium ○--○; and vecuronium ▲—▲; *significantly different from control (mean value ± SD).

Results

There were 16 patients in the atracurium and d-tubocurarine groups, 17 in the vecuronium group and 18 in the pancuronium group. There were no significant differences between groups in age, height, or weight (Table I). Control systolic blood pressures and heart rates under halothane and nitrous oxide anaesthesia, prior to drug administration were also not significantly different between groups (Table II).

Heart rate was significantly elevated following pancuronium (+29.8% to +38.6 per cent) at each minute study interval when compared to atracurium and vecuronium ($p<0.01$). Elevation of heart rate following d-tubocurarine (+31.0 to +34.9 per cent) was also significant from the second to the fifth minute ($p < 0.01$). A slight but insignificant slowing of heart rate was noted with vecuronium (−1.1 to −3.1 per cent). The least change occurred with atracurium (−0.2 to +1.7 per cent) (Figure 1). One patient (age six years) in the vecuronium group, required atropine 0.02 mg·kg^{-1} after the haemodynamic recording period and prior to intubation as the heart rate had fallen to 60 bpm.

Elevation of blood pressure was greatest following

TABLE I Demographic data (mean ± SD)

	Atracurium *n = 16*	*d-Tubocurarine* *n = 16*	*Pancuronium* *n = 18*	*Vecuronium* *n = 17*
Age (years)	4.0 ± 1.3	4.1 ± 1.7	3.4 ± 1.1	3.9 ± 1.5
Height (cm)	101.0 ± 11.0	109.2 ± 16.8	101.4 ± 11.0	103.1 ± 11.0
Weight (kg)	16.3 ± 2.6	18.2 ± 4.7	15.8 ± 2.4	16.4 ± 3.0

p = N.S.

TABLE II Initial hemodynamic data under halothane anaesthesia (mean ± SD)

	Atracurium	*d-Tubocurarine*	*Pancuronium*	*Vecuronium*
SBP (mmHg)	93.4 ± 6.3	93.3 ± 8.0	91.8 ± 8.8	89.1 ± 7.2
HR (BPM)	91.4 ± 10.9	89.3 ± 11.6	93.0 ± 11.9	89.6 ± 14.1

p = N.S.

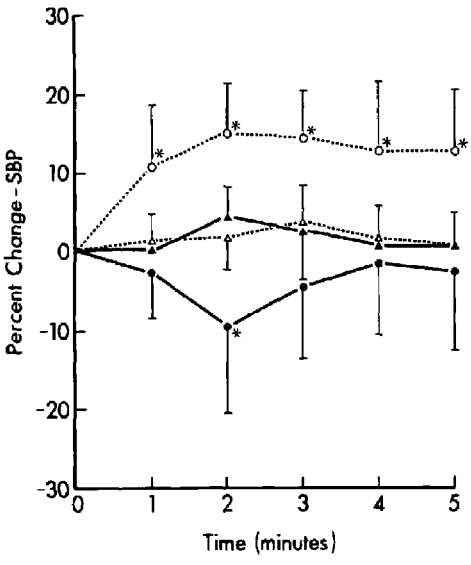

FIGURE 2 Change in systolic blood pressure (SBP) expressed as per cent change from control: atracurium Δ--Δ; d-tubocurarine ●—●; pancuronium ○--○; and vecuronium ▲—▲; *significantly different from control (mean value ± SD).

pancuronium (+10.8 to 14.8 per cent) and significantly different at all study intervals ($p < 0.05$). Blood pressure was least changed following atracurium (+0.7 to +3.7 per cent), but this was not significantly different from vecuronium (0.0 to +4.4 per cent) or d-tubocurarine except for the second minute reading (−9.3 per cent) (Figure 2).

Because of technical difficulties with the EMG recorder and subsequent use of the uncalibrated mode, onset times were recorded in only 47 of the 67 subjects. Recovery times were frequently not recorded for d-tubocurarine and pancuronium due to the longer duration of action and necessity for reversal, and thus are only shown as greater than 60 minutes. One atracurium and three vecuronium recovery times were not included because of recording problems. The mean time to maximum twitch depression was not different between groups. They ranged from 2.1 (±0.6) minutes for pancuronium to 2.5 (±0.9) minutes for atracurium. The recovery time to T1/Tc 25 per cent following vecuronium (25.5 ± 6.3 minutes) was significantly shorter than after atracurium (37.5 ± 7.0 minutes) (Table III).

Intubating conditions were excellent in all but three patients. In two of the vecuronium group, slight cord movement was noted and in one of the atracurium group, cough and diaphragmatic movement were observed. There was no significant difference between muscle relaxants.

Flushing of any degree was only noted in the d-tubocurarine group. This occurred in ten of the 16 cases (63 per cent) and was mild in four and severe in six of these. In one case with severe flushing, bronchospasm was also recorded. No hypotension requiring treatment (SBP < 70 mmHg) occurred with the flushing.

Discussion

No previous studies have compared the haemodynamic effects in children of the four commonly used muscle relaxants under identical anaesthetic conditions. Several recent studies[1,2,4] comment on the relative haemodynamic stability of atracurium and vecuronium, but the observations may have been affected by the concurrent haemodynamic response to intubation. This could have masked a hypotensive or vagotonic effect of the muscle relaxants. For these reasons, all measurements were made after an equilibration period with 1.5 per cent halothane in 60 per cent nitrous oxide and prior to intubation or any other surgical stimulation.

The greatest haemodynamic changes followed pancuronium which resulted in marked hypertension and tachycardia. This has previously been reported to be more prominent in younger infants and children.[5] Pancuronium is known to exert its vagolytic effect at clinical doses by blocking postjunctional muscarinic receptors. More recent-

TABLE III Onset and recovery times (mean ± SD)

	Atracurium	*d-Tubocurarine*	*Pancuronium*	*Vecuronium*
Time to maximum twitch depression: (minutes)	2.5 ± 0.9 (n = 12)	2.1 ± 1.2 (n = 9)	2.1 ± 0.6 (n = 12)	2.5 ± 0.6 (n = 14) NS
Time of recovery of T1/Tc 25%: (minutes)	37.5 ± 7.0 (n = 11)	60 (n = 8)	60 (n = 9)	25.5 ± 6.3 (n = 11)

$p < 0.05$.

ly sympathetic effects have been postulated: increased release of norepinephrine and also a blockage of reuptake. This may be due to a block of acetylcholine mediated inhibition of the sympathetic nervous system.[6]

The results following d-tubocurarine were more variable between patients and more delayed (the maximum change occurred at the second minute). The degree of tachycardia was similar to that seen with pancuronium but followed a fall in blood pressure of as much as −37.2 per cent. These changes are similar to those described in adults during nitrous oxide anaesthesia.[7]

Cutaneous changes indicative of histamine release (which were not observed in any other group) occurred in 63 per cent of cases. Local flushing was not observed with any of the other drugs and this is contrary to other studies.[8,9] This may be due to the slow injection rate of 60 seconds into a rapidly running intravenous line and the use of an injection site remote from the thiopentone injection.

d-Tubocurarine is known to release histamine in clinical doses. Increases greater than 200 per cent of control are associated with hypotension due to decreased systemic vascular resistance. The pronounced tachycardia observed may also be based on the known autonomic ganglionic blocking action of d-tubocurarine in clinical doses. There may be a greater effect on parasympathetic than sympathetic ganglia, thus a predominantly vagolytic effect is seen.[6] In addition, the stimulation of cardiac histamine receptors (H_2) and resulting positive ionotropy and chronotropy may be contributory.

The observed haemodynamic stability following atracurium or vecuronium is in agreement with previous investigators.[4,9–11] If vagolytic drugs are not given, clinically important bradycardia has been described in adults after vecuronium during halothane anaesthesia as a result of vagotonic stimulation.[12] This may be expected to occur more frequently in children with their vagal predominance, although only one case in this study required atropine prior to intubation.

The onset times of the muscle relaxants were not significantly different at the doses studied; however, the recovery times were different. The time to recovery of T1/Tc 25 per cent was shorter with vecuronium than atracurium. This has also recently been reported for higher doses of these drugs.[9] The shorter duration of vecuronium may also reflect the use of a less than equipotent dose of the drug. The ED_{95} of 35 $\mu g \cdot kg^{-1}$ adopted for this study has also been reported as high as 64 $\mu g \cdot kg^{-1}$ using a single dose technique[10] and also, using a cumulative method, 56 $\mu g \cdot kg^{-1}$.[2] The recovery time to T1/Tc 25 per cent for atracurium 0.4 $mg \cdot kg^{-1}$, under similar anaesthetic conditions, using EMG monitoring has been reported as 23 minutes[13,14] but, in other studies, as long as 37.6 minutes[2] which is similar to our finding of 37.5 minutes. Clinically, both atracurium and vecuronium are excellent, haemodynamically stable, intermediate-acting agents which are easily reversible in under thirty minutes at intubating doses, contrary to d-tubocurarine and pancuronium which only occasionally demonstrated 25 per cent recovery at 90 minutes.

In summary, the haemodynamic effects of intubating doses of atracurium, d-tubocurarine, vecuronium, and pancuronium are described in healthy children. No effects of any of the drugs were clinically detrimental but results may provide a basis for the rational choice of muscle relaxant when a specific haemodynamic effect is required. Recovery times suggest that vecuronium may result in a faster recovery than atracurium.

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Résumé

Afin de déterminer le début d'action et le temp de récupération ainsi que les effets hémodynamiques des doses d'intubation d'atracurium (0.4 mg·kg^{-1}), d-tubocurarine (0.8 mg·kg^{-1}), pancuronium (0.12 mg·kg^{-1}) et vécuronium 0.07 mg·kg^{-1}), 67 enfants âgés de un à huit ans ont été étudiés sous anesthésie à l'halothane et protoxyde d'azote. Le temps pris pour la dépression maximale du twitch et le temps de récupération de T1/Tc à 25 pour cent était enregistré avec un enregistreur EMG évoqué intégré. La fréquence cardiaque et la pression artérielle systolique étaient enregistrées pour cinq minutes après l'administration du médicament et avant l'intubation. Il n'y avait aucune différence dans les temps du début d'action entre les médicaments. Le temps de récupération de T1/Tc à 25 pour cent après vécuronium (25.5 ± 6.3 minutes) était plus court qu'après atracurium (37.5 ± 7.0 minutes). Les temps de récupération pour la d-tubocurarine et le pancuronium étaient supérieurs à 60 minutes. L'augmentation de la fréquence cardiaque est survenue après l'administration de pancuronium (+29.8 à +38.6 pour cent) et d-tubocurarine (+31 à +34.9 pour cent), mais aucun changement n'a été observé après atracurium ou vécuronium. L'élévation de la pression artérielle était supérieure après pancuronium (+10.8 à +14.8 pour cent). Aucun changement significatif n'a été observé après atracurium ou vécuronium. Une diminution transitoire de la pression artérielle (−9.3 pour cent) est survenue après d-tubocurarine.