Release of histamine is one of the side effects associated with the administration of non-depolarizing neuromuscular blocking drugs. It is seen frequently with tubocurarine, less with metocurine and rarely with atracurium (Basta et al., 1983); pancuronium and vecuronium seem to be free of histaminergic properties. Clinical manifestations of histamine release (confirmed by the measurement of plasma histamine concentration (Scott et al., 1985)) include a skin rash and, occasionally, mild systemic arterial hypotension (Mirakhur et al., 1983; Rowlands 1983). With the refinement of the plasma histamine assay at a sensitivity in the range of pg ml$^{-1}$, more sensitive evaluations can be performed.

There is a general feeling among paediatric anaesthetists that children differ from adults in regard to the side effects commonly associated with the release of histamine. Hypotension, for instance, seems to be rare in children, and skin rashes, although observed occasionally in adolescents (Goudsouzian, Liu and Savarese, 1978; Goudsouzian et al., 1983), are infrequent in the young, especially in those younger than 10 years of age. In fact, most of the observed histaminomimetic reactions in children have been observed locally along the tract of the injected vein (Nightingale and Bush, 1973, 1983). It is unknown whether this difference is attributable to a lesser release of histamine than in the adult, or whether the child’s end organs are simply less responsive.

The recent introduction of atracurium and vecuronium to clinical practice has led to a close evaluation of their side effects. While the implications of histamine release have been well defined in adults (Scott et al., 1985), no study in children has yet addressed this problem.

**SUMMARY**

The histamine releasing potential of equivalent bolus doses of atracurium 0.6 mg kg$^{-1}$ or vecuronium 0.12 mg kg$^{-1}$ was evaluated in 20 children anaesthetized with halothane. Blood samples were obtained before, and at 2 and 5 min after the administration of the neuromuscular blocker. The twitch response to 0.15 Hz was also evaluated. None of the 10 patients receiving vecuronium had a significant increase in plasma histamine concentration. In two of the 10 children receiving atracurium, the plasma histamine concentration increased markedly, but without any apparent clinical manifestations. Recovery of neuromuscular function (to 95% twitch height) after vecuronium 0.12 mg kg$^{-1}$ was faster than after atracurium 0.6 mg kg$^{-1}$ ($P < 0.02$).

**PATIENTS AND METHODS**

Twenty healthy children (ASA I) aged 1–10 yr were studied. The design of the study was approved by the Subcommittee on Human Studies, Committee on Research, of the Massachusetts General Hospital, and written parental consent was obtained.

Premedication in children younger than 7 yr consisted of methohexitone 25 mg kg$^{-1}$ per rectum; older children were not premedicated. Anaesthesia was induced with nitrous oxide and halothane in oxygen via a face mask, the inspired halothane concentration being maintained at 1–1.5%. Heart rate, arterial pressure (by auscult-
Table I. Age and weight of the patients and cardiovascular variables before and after the administration of atracurium or vecuronium (mean values ± SEM)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Systolic arterial pressure</th>
<th>Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Change (%)</td>
<td>Before</td>
</tr>
<tr>
<td>Atracurium</td>
<td>4.6±0.9</td>
<td>19.3±2.4</td>
<td>87.4±5.5</td>
<td>85.3±5.2</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>5.4±0.8</td>
<td>21.1±1.9</td>
<td>88.8±3.2</td>
<td>92.3±3.7</td>
</tr>
</tbody>
</table>

Table II. Histamine concentrations (mean ± SEM and range) before and after the administration of atracurium and vecuronium in children

<table>
<thead>
<tr>
<th>Histamine concn (pg ml⁻¹)</th>
<th>Control</th>
<th>2 min</th>
<th>5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium 0.6 mg kg⁻¹</td>
<td>794±126</td>
<td>1780±56</td>
<td>981±255</td>
</tr>
<tr>
<td></td>
<td>424–1834</td>
<td>411–10250</td>
<td>471–2755</td>
</tr>
<tr>
<td>Vecuronium 0.12 mg kg⁻¹</td>
<td>567±62</td>
<td>570±105</td>
<td>557±91</td>
</tr>
<tr>
<td></td>
<td>148–832</td>
<td>110–1187</td>
<td>185–1302</td>
</tr>
</tbody>
</table>

Results

The children studied were aged 1–10 yr and their weights varied between 9 and 32 kg. There were no significant differences in the ages and the weights of the two groups of patients studied (table I), nor were there significant differences in the cardiovascular variables before and after the administration of the neuromuscular blocking drug (table I).

The mean control plasma histamine concentration from all the children studied during halothane anaesthesia was 681±73 pg ml⁻¹ (mean ± SEM). The inter- and intra-assay variations were 8% in our laboratory. The samples were assayed in duplicate with duplicate internal standards.

Statistical analysis was performed by non-correlated Student’s t test. Data were considered significant at P < 0.05.
values within 5 min (fig. 1). Her systolic arterial pressure decreased slightly from 80 mm Hg to 70 mm Hg with no change in heart rate. She did not develop any rash. Retrospectively, close inquiry of the mother revealed that this child had frequent symptoms of rhinorrhea. However, she did not need any special treatment and was not receiving any medication. She did not have any other allergic symptoms.

In the second, a 7-yr-old boy whose histamine concentration was within the normal control range (567 pg ml\(^{-1}\)), the histamine concentration quadrupled after atracurium, and remained increased at 2755 pg ml\(^{-1}\) for at least 5 min. There were no haemodynamic changes. In the remaining eight patients there was little change in the plasma histamine concentrations (control 693 ± 60; 2 min 668 ± 75; 5 min 606 ± 41 pg ml\(^{-1}\)).

In the vecuronium group, two patients also merited some attention. In the first the plasma histamine concentration increased from 685 to 1187 pg ml\(^{-1}\) at 2 min, and then to 1302 pg ml\(^{-1}\) at 5 min. In the second, the concentration increased by the same magnitude at 2 min but had returned to the control value at 5 min (fig. 1). These changes were less pronounced than those in the atracurium patients and were not accompanied by changes in heart rate or arterial pressure. None of the patients in either group developed a skin rash.

The onset of action of the equipotent doses of the two drugs was comparable: 1.9 min for atracurium, 2.2 min for vecuronium (table III). Although the recovery index (25–75% recovery) was comparable in the two groups, time to full recovery was somewhat longer in the atracurium group. The recovery of the twitch to 5% and from 5% to 25% was significantly longer (\(P < 0.001\) and \(P < 0.05\)) after atracurium than after vecuronium and, hence, the total recovery time to 95% twitch height was also significantly longer (\(P < 0.02\)).

**DISCUSSION**

**Histamine**

One important observation of this study was the infrequent increase in plasma histamine concentration in the atracurium group, a result different from that obtained in studies in adults conducted similarly. For example, Scott and colleagues (1985) studied a group of nine adults who also received a bolus of atracurium 0.6 mg kg\(^{-1}\). Plasma histamine concentrations were measured using the same technique. The mean control value was 715 ± 94 pg ml\(^{-1}\), a value comparable to that obtained in the children. However, after this dose the plasma histamine concentration increased, on average, in most of the adults, to about twice the control value, the mean concentration being 1415 ± 203 pg ml\(^{-1}\) before decreasing to

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inject. to D(_{\text{max}})</th>
<th>D(_{\text{max}})-5%</th>
<th>5–25%</th>
<th>25–75%</th>
<th>5–95%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6 mg kg(^{-1})</td>
<td>1.9 ± 0.2</td>
<td>38.8 ± 2.7</td>
<td>9.7 ± 1.5</td>
<td>11 ± 1.6</td>
<td>24.3 ± 3.0</td>
<td>58.7 ± 4.2</td>
</tr>
<tr>
<td>Vecuronium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.12 mg kg(^{-1})</td>
<td>2.2 ± 0.3</td>
<td>21.4 ± 1.2</td>
<td>5.8 ± 0.6</td>
<td>10.5 ± 1.2</td>
<td>22.9 ± 2.5</td>
<td>44.6 ± 2.7</td>
</tr>
</tbody>
</table>

\(P < 0.001\) \(< 0.05\) \(< 0.02\)
1086 ± 238 pg ml⁻¹ at 5 min. In our sample of 10 children, the change in the mean plasma histamine concentration was similar in direction, but insignificant statistically. More important, however, were the changes in certain individuals. Most of the adults showed moderate changes in plasma histamine concentration, each contributing to the mean increase. In contrast, the mean change in the children was attributable to results in two patients: the one with a high control value had a five-fold increase at 2 min which returned to control within 5 min (fig. 1). To exclude the possibility of laboratory error, this patient’s samples were re-assessed against known controls and the results found to be accurate. Interestingly, the measured increase in histamine concentration in this subject was comparable to that previously reported in a child who had a cutaneous reaction, bronchospasm, and hypotension following the rectal administration of methohexitone. That child’s plasma histamine concentration was 6270 pg ml⁻¹ after ephedrine and diphenhydramine (Liu, Liu and Moss, 1984).

In further contrast to the findings in the adult studies was the fact that, in our sample, both clinical and cardiovascular changes were minimal, even when the plasma histamine concentrations were increased. Again, in the child with the five-fold increase in plasma histamine concentration, systolic arterial pressure decreased by only 10 mm Hg. We did not measure arterial pressure directly in this patient, or in any of the others, because we could not justify the insertion of an intra-arterial cannula in healthy children; we could easily, however, have detected significant cardiovascular changes with the precordial stethoscope, minute by minute auscultation of arterial pressure, and by electrocardiography with a digital readout.

These data confirm our clinical impression that histamine release after atracurium is less of a problem in children than in adults. In our earlier clinical studies with atracurium 0.4 mg kg⁻¹, no rashes were detected in children; mild rashes have, however, been seen in adolescents (Goudsouzian et al., 1983). An isolated case of generalized rash with minimal hypotension and, possibly, bronchospasm in an 11-yr-old boy has been reported (Aldrete, 1985). Furthermore, when atracurium is given following thiopentone in a small vein at a dose of 0.6 mg kg⁻¹ a local histamine-like response or reddening of the vein proximal to the injection site has been noted. This effect is more pronounced in adolescents than in children 5–10 yr, and is seen least of all in children younger than 5 yr (Nightingale and Bush, 1983).

There are no data in the literature on the incidence of histamine release (in vivo) after the administration of other drugs in children. It is our impression that this is the first study of this problem. Marone and coworkers (1983) have, however, addressed the effect of age with respect to histamine release from basophils in vitro. They found that, with increasing age, more histamine was released at any concentration of anti-IgE. They also found an increase with age in the maximum percent histamine release induced by an optimal anti-IgE concentration. In their study the youngest children (0–9 yr) exhibited the least response, with the older age group (up to 60 yr) showing a progressively greater increase. In our study of children 1–10 yr we did not find any special tendency; neither the control histamine concentration nor the percent increase was related to specific age.

Pharmacodynamics

The times to onset of action (interval to maximum depression of the twitch) of atracurium and vecuronium were comparable—approximately 2 min. At the equipotent doses of 0.6 mg kg⁻¹ and 0.12 mg kg⁻¹, respectively, these drugs provided excellent conditions for intubation at approximately 2.5 min after administration. The duration of complete paralysis (absent twitch response) proved longer (P < 0.001) with atracurium (38.8 ± 2.7 min) than with vecuronium (21.4 ± 1.2 min), indicating that a single dose of vecuronium will generally be shorter-acting than atracurium. Hence, at these doses vecuronium is probably a better choice for relatively short procedures. It remains true, however, that the recovery index was comparable for the two drugs, and that once recovery had started the rates of recovery were practically the same.

In a previous study conducted in the same manner with a similar rate of frequency of stimulation, we found that a dose of atracurium 0.4 mg kg⁻¹ produced maximum twitch depression in 3.7 ± 0.4 min, with the duration of complete paralysis lasting 19.4 ± 1.6 min (Goudsouzian et al., 1986). In the present study the larger dose (0.6 mg kg⁻¹) markedly improved the onset time (1.9 ± 0.2 min), but increased the duration of complete paralysis to 38.8 ± 2.7 min. With the larger dose, conditions for intubation were rated
excellent in all patients. When evaluated after 0.4 mg kg⁻¹, conditions were considered excellent in only 80% of the cases (Goudsouzian et al., 1983).

CONCLUSION

It remains difficult to ascertain whether the release of histamine is of concern in children. Neither of the two children cited above in whom the concentration of histamine increased following atracurium showed any significant cardiovascular changes or clinical signs such as a rash. However, we may conclude that, as a general rule, a large bolus dose of atracurium should best be avoided in an asthmatic patient, since such a dose may possibly trigger an attack. Vecuronium may be a better choice. If atracurium is for some reason indicated, it may be safely administered at a slow rate, as this technique has been shown to decrease markedly histamine release in adults (Scott et al., 1985). For short procedures where suxamethonium has to be avoided, vecuronium might be a better choice than atracurium on account of its shorter duration of action.

REFERENCES


