PROBABLE HISTAMINE LIBERATION WITH ATRACURIUM
A Case Report

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Atracurium, a neuromuscular blocking drug with an intermediate duration of action, has been introduced recently to clinical practice (Payne and Hughes, 1981; Basta et al., 1982). Although cutaneous erythema is relatively common with this agent (Mirakhur et al., 1983) it is rarely associated with other histaminoid responses. While carrying out a study of the effects of dosage of atracurium on its neuromuscular blocking and side effects, we encountered a generalized histaminoid reaction after thiopentone and atracurium 1.0 mg kg$^{-1}$. The clinical features, management and subsequent investigation of this patient are described.

CASE REPORT

The patient, a 16-year-old, 60-kg female, was scheduled for surgical repair of a retinal detachment. She was otherwise well, had no previous anaesthetic history and no known allergies or atopic tendencies. Her only medication was a tetracycline preparation prescribed for her ophthalmic condition.

Premedication consisted of diazepam 10 mg orally 60 min before arrival in the anaesthetic room, where an infusion of Hartmann’s solution was commenced, and appropriate monitoring (electrocardiogram, arterial pressure (Dinamap, Critikon Ltd) and myoneural blockade (Myotest, Biometer Ltd)) initiated. Anaesthesia was induced with thiopentone 325 mg (over 20 s). One minute later atracurium 60 mg was given over 10 s into the running infusion. Respiration was assisted manually using 60 % nitrous oxide in oxygen.

Within 1 min of the administration of the atracurium, a generalized erythematous macular rash appeared; it started on the chest and upper arms and extended over the trunk. The rash became more florid and confluent without any weal ing over the next 5 min and was present for 15 min before any fading. Over this same period severe bronchospasm occurred and caused difficulty in manual inflation of the chest. The patient’s arterial pressure decreased from a preinduction value of 115/65 mm Hg to 104/60 mm Hg after the thiopentone and then to 80/48 mm Hg 3 min after the administration of the atracurium, and remained around this value for a further 7 min. During this period there was a concurrent increase in heart rate which reached 147 beat min$^{-1}$, 60 s after the administration of the atracurium (fig. 1).

Management of the patient consisted of manual ventilation with 100 % oxygen, early intubation of the trachea, head-down tilt and the rapid infusion of 500 ml of lactated Ringer’s solution. The patient’s condition improved with these measures and, 25 min after induction, her condition having stabilized, surgery was commenced. Seventy minutes after induction, when additional muscle relaxation was required, a further dose of atracurium 0.125 mg kg$^{-1}$ was given without any ill effect. Subsequent anaesthesia, using fentanyl, nitrous oxide, oxygen and halothane, was unremarkable as was the recovery and the period after operation. The patient was discharged on the 6th day after the operation.

SUMMARY

An histaminoid reaction after the administration of thiopentone and atracurium is described. Serial blood sampling showed no evidence of complement activation. Intradermal testing 6 weeks later yielded a positive result with atracurium (1 in 1000), but not with thiopentone. The clinical course of the reaction and the subsequent investigations suggest a direct pharmacological liberation of histamine.

bottles) were taken during the early stages of the reaction (time 0) and at 1, 3 and 24 h for measurement of haemoglobin concentration, and differential white cell and platelet counts. Samples were also taken at time 0 and at 1, 3, 6 and 24 h, and 5 days (8 ml in heparinized bottles); these were centrifuged shortly after collection and the serum stored at —20 °C until serial complement studies were performed.

Six weeks later, intradermal testing was carried out using the method described by Fisher (1979). The challenging agents were 0.9 % saline, thiopentone (2.5 % solution diluted with saline 1 in 100) and atracurium solution (10 mg ml⁻¹ diluted with saline to 1 in 1000 and 1 in 10000). The skin responses were read 30 min after intradermal injection of 0.1 ml of each solution using a 27-s.w.g. needle.

The potential to trigger histamine liberation has been ascribed to many neuromuscular blocking drugs (Bowman, 1982). Despite early claims of absence of any histamine release with doses of 0.2–0.4 mg kg⁻¹ (Payne and Hughes, 1981; Sokoll et al., 1983), atracurium in a commonly used dose of 0.6 mg kg⁻¹ was shown by Basta and his colleagues (1983) to cause significant histamine release, the plasma histamine concentrations approximating one-sixth of those obtained after an equipotent dose of tubocurarine. Skin histamine release after intradermal injection has also been reported (Robertson et al., 1983). The relatively short duration of bronchospasm and hypotension, as seen in this patient, point to pharmacological histamine liberation; the remarkably constant haematological indices, complement values and lack of any previous exposure make an immunolo-

### RESULTS

Haemoglobin concentration, platelet count and differential white cell count showed no changes from the values at time zero over the period of sampling (table I). Complement assay showed no decrease in C3 and C4 fractions over the entire period. IgE concentrations remained in the low-normal range throughout.

Intradermal testing produced no local response with thiopentone, saline or atracurium (1 in 10000 dilution). Atracurium (1 in 1000 dilution) triggered a positive skin reaction—a circular area of erythema 2.9 cm in diameter with a central weal 1.1 cm in diameter.

Plasma histamine concentration was not measured, because of lack of facilities.

### DISCUSSION

The potential to trigger histamine liberation has been ascribed to many neuromuscular blocking drugs (Bowman, 1982). Despite early claims of absence of any histamine release with doses of 0.2–0.4 mg kg⁻¹ (Payne and Hughes, 1981; Sokoll et al., 1983), atracurium in a commonly used dose of 0.6 mg kg⁻¹ was shown by Basta and his colleagues (1983) to cause significant histamine release, the plasma histamine concentrations approximating one-sixth of those obtained after an equipotent dose of tubocurarine. Skin histamine release after intradermal injection has also been reported (Robertson et al., 1983). The relatively short duration of bronchospasm and hypotension, as seen in this patient, point to pharmacological histamine liberation; the remarkably constant haematological indices, complement values and lack of any previous exposure make an immunolo-

### TABLE I. Haematological and immunological indices. N = Neutrophils; E = eosinophils; M = monocytes; L = lymphocytes

<table>
<thead>
<tr>
<th>Time</th>
<th>Hb (g dl⁻¹)</th>
<th>Platelets (x 10⁹ ul⁻¹)</th>
<th>C3 (g litre⁻¹)</th>
<th>C4 (g litre⁻¹)</th>
<th>IgE (i.u.ml⁻¹)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>E</td>
<td>M</td>
</tr>
<tr>
<td>0</td>
<td>13.8</td>
<td>175</td>
<td>59</td>
<td>1</td>
<td>10</td>
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<td>1 h</td>
<td>14.2</td>
<td>175</td>
<td>63</td>
<td>0</td>
<td>3</td>
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<td>3 h</td>
<td>13.6</td>
<td>175</td>
<td>54</td>
<td>1</td>
<td>9</td>
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<td>6 h</td>
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<td>—</td>
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<tr>
<td>24 h</td>
<td>13.9</td>
<td>175</td>
<td>55</td>
<td>1</td>
<td>10</td>
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<td>5 days</td>
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<td>—</td>
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</table>

- **Hb** (haemoglobin) (g dl⁻¹)
- **Platelets** (x 10⁹ ul⁻¹)
- **C3** and **C4** complement fractions (g litre⁻¹)
- **IgE** (i.u.ml⁻¹)
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The dose of atracurium administered (1.0 mg kg\(^{-1}\)) was large compared with the usual intubating dose and thus might be more likely to trigger histamine release pharmacologically. However, this dose may be indicated in situations where a rapid onset of block without an unduly prolonged action is desired. Indeed, bronchospasm has been reported after 0.5 mg kg\(^{-1}\) of the drug (Sale, 1983). With doses ranging from 0.4 mg kg\(^{-1}\) to 1.0 mg kg\(^{-1}\), we have found the occurrence of skin reactions to be dose-related (unpublished observations). Lack of any signs of further significant histamine release in this patient after a smaller dose (0.125 mg kg\(^{-1}\)) of atracurium would support this view.

Intradermal testing yielded a positive result only to the lower dilution of atracurium; immunological sensitivity should have produced a response to both dilutions. Fisher (1979) has advocated such intradermal testing after an anaphylactoid reaction, to identify the responsible agent. This case, at first glance, seems to bear this out. However, from our intradermal testing studies we have found that, of 60 patients tested before operation with atracurium (1 in 1000 dilution), 40 (67%) produced an area of erythema at least 1.0 cm in diameter, and six (10%) produced skin responses equal in magnitude to that described above. None of these patients had any previous exposure to atracurium, and so the validity of such testing after an histaminoid reaction with this drug is open to question.

ACKNOWLEDGEMENTS

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REFERENCES


