HARMLESS CUTANEOUS REACTIONS ASSOCIATED WITH THE USE OF ATRACURIUM

A Report of 1200 Anaesthetics

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In view of reports of the histamine-releasing potential of atracurium (Basta et al., 1983; Scott et al., 1985), and of cutaneous reactions associated with its use (Coleman, Hunter and Hunt, 1983; Nightingale and Bush, 1983; Lavery and Mirakhur, 1984; Mirakhur et al., 1985), the anaesthetic records of 1200 patients to whom atracurium had been given were examined in an attempt to assess the clinical significance of these findings.

PATIENTS AND METHODS

Atracurium was given by the author on 1200 occasions to 1123 patients, aged between 4 and 91 yr, undergoing elective or emergency operations requiring the use of a neuromuscular blocking drug as part of the anaesthetic regimen. The study began 21 months before the issue of a product licence in the U.K. (Rowlands, 1983).

Three hundred and twelve patients received no premedication, 722 were given diazepam 5—10 mg by mouth, 78 received lorazepam 2.5—5 mg by mouth; the remainder received other premedicants. Anaesthesia was induced with methohexitone 1.1—1.7 mg kg$^{-1}$ i.v. (to which lignocaine had been added to reduce the frequency of pain during the injection (Rowlands, 1969)) given over 20—85 s. Atracurium 0.3—0.6 mg kg$^{-1}$ was then given through the same 27-gauge (12 x 0.4-mm) needle over 5—10 s.

The drugs were injected to a vein on the dorsum of the hand in approximately three-quarters of the patients, and to a vein in the antecubital fossa in most of the remainder.

In 62 patients droperidol 5—10 mg and fentanyl 0.1—0.2 mg were administered i.v. before the methohexitone and atracurium. On 150 occasions a priming dose of atracurium 2.5 or 5.0 mg was given to the patient 2—3 min before the induction of anaesthesia (Foldes, 1984).

Arterial pressure was recorded by sphygmomanometry immediately before the induction of anaesthesia, between 3 and 7 min later and then at regular 7.5-min intervals. A 10% decrease (or greater) in systolic arterial pressure from the pre-anaesthetic value was regarded as evidence of "hypotension".

Initially, cutaneous reactions were noted when they occurred (group 1; $n = 400$ administrations of atracurium). Following reports of reactions they were sought more actively (group 2; $n = 800$).

RESULTS

Details of the doses of atracurium, the sexes and mean ages of the 151 patients in whom a transient cutaneous reaction occurred are given in table I, and the distribution between groups 1 and 2 in table II.

Twenty-five of the 106 who gave a previous history of allergy showed a cutaneous reaction. No reactions developed in the 17 patients with history of asthma. The reactions occurred within
0.5–6 min after the initial dose of atracurium. One patient developed four weals on the trunk at 6 min, the largest being 1.7 x 1.2 cm, one of which (1.0 x 0.5 cm) was still present at the end of the operation 50 min later. The remainder of the reactions varied from a slight redness to generalized flushing of the chest or neck, and occasionally of the face, abdomen and limbs. On 22 occasions there was redness or a solitary weal (twice) at the injection site or for a small distance along the injection vein in addition to the truncal rash, and on seven occasions the injection site or vein alone were affected. No generalized urticaria occurred. Two of the rashes lasted for 30 min, one for 17 min; the remainder were fading or had cleared within 5 min.

The incidence of reactions was not reduced by the administration of a priming dose, and one occurred after atracurium 5 mg (0.08 mg kg\(^{-1}\)) before the methohexitone had been given. No reactions occurred with incremental doses.

Three patients with cutaneous reactions developed hypotension. In one patient, the systolic pressure decreased from 115 to 60 mm Hg at 3 min and returned to the pre-anaesthetic value within 1 min. In two other patients there were transient decreases of between 10 and 15% of the pre-anaesthetic value. There was no cause for anxiety in any of the patients who developed cutaneous reactions, nor was any treatment given.

Blood samples from the first of these patients were sent to the National Adverse Anaesthetic Reaction Advisory Service at Sheffield for investigation (Watkins, Thornton and Clarke, 1976). The report suggested that this was a “harmless reaction involving some anxiety of the patient and perhaps an underlying immunopathology following a viral infection”.

Three patients developed a cutaneous reaction on their first anaesthetic with atracurium but not on their second, and two patients developed a reaction during their second anaesthetic, having shown no reaction during their first anaesthetic.

Two cases of bronchospasm occurred in asthmatic patients in whom intubation was attempted prematurely before the atracurium had taken full effect; there were no problems with incremental doses in these patients.

**DISCUSSION**

The lower incidence of reactions in group 1 (table II) may be because some minor or transient rashes were not detected. Table I suggests that the
incidence in the dose range 0.3–0.6 mg kg\(^{-1}\) was not dose-related, and both tables show that cutaneous reactions occurred mainly in female patients younger than 70 yr.

Nightingale and Bush (1983) reported a local histamine-like response around the injection vein after atracurium in most of 154 children in whom anaesthesia was induced with thiopentone and who were given atracurium into a different vein in the palmar surface of the wrist. Lavery and Mirakhur (1984) reported a higher incidence of reactions in children who were given thiopentone–atracurium (13 in 33) than in those given atracurium without thiopentone (three in 17) (the i.v. details were not given).

Coleman, Hunter and Hunt (1983) reported a 25 % incidence of skin reactions (including 8 % urticaria) in 64 patients using thiopentone and atracurium through the same needle, with two examples of bronchospasm (one of questionable clinical significance).

Mirakhur and his colleagues (1985) found a dose-dependent cutaneous flushing in five groups of 40 patients: 17 % when using 0.4 mg kg\(^{-1}\), 32.5 % with 0.5 and 0.6 mg kg\(^{-1}\), reaching 55 % at 0.75 mg kg\(^{-1}\) and 72.5 % at 1.0 mg kg\(^{-1}\), with one example of bronchospasm and hypotension at the highest dose. The latter two doses are considerably greater than those used normally in clinical practice, and it is not stated how the drugs were given.

From these reports and from the one patient in this series who developed a rash after atracurium 5 mg, it appears that atracurium alone can cause a cutaneous reaction, but that this is much more likely when the drug is given through the same needle as thiopentone.

The data in group 2 may give a more accurate indication of the incidence of cutaneous reactions than those of the whole series. The 16 % incidence in 800 anaesthetics is decreased by the presence of 32 % of elderly patients who have few reactions, while the 23 % incidence in the 546 patients younger than 70 years is increased by the presence of 62 % female patients, who have many. Direct comparison with other studies is difficult as the sex of their patients with reactions is not given, but it is probable that the incidence of reactions in this series is lower than in those mentioned above.

The occurrence of transient hypotension in three patients with rashes may have been attributable to methohexitone.

Hughes (1985) suggested that local reactions could be minimized if the induction agents and atracurium were injected to the vein through a fast flowing infusion, and if their administration was separated by an interval of about 30 s. Watkins (1986) suggested that the mixing and precipitation which occurs between the thiopentone and atracurium injected through the same indwelling cannula may initiate systemic aggregate anaphylaxis and potentially life-threatening bronchospasm. Sale (1983) reported a patient with bronchospasm as well as erythema and weal along the line of the vein into which thiopentone and atracurium had been given through a 21-gauge Butterfly needle.

Methohexitone is generally regarded as causing fewer allergic responses than thiopentone; furthermore, a random test indicated that the 1 % methohexitone–lignocaine solution used for induction in this series was less alkaline (pH 12.8) than 2.5 % thiopentone (pH 14). However, the lower onset of cutaneous reactions and the absence of urticaria, bronchospasm and serious hypotension in this series could be the result of the smaller interface available between the two drugs for reactions to occur when they are given through a small (12 x 0.4-mm) needle rather than through a large needle or Butterfly needle, where mixing can take place more readily.

Slow (75 s) injection of atracurium may reduce histamine release (Scott et al., 1985), and the incidence of cutaneous reactions could possibly be reduced by an injection time slower than the 5–10 s taken in the present study. The incidence of cutaneous reactions in this series was not decreased by a priming dose as suggested by Foldes (1984). A cutaneous reaction was not regarded as a contraindication to the further use of atracurium in view of the blood samples of the patient in whom the first reaction occurred and the fact that no reactions occurred with incremental doses in any patient.

Galletly and Treuren (1985) have found the female sex to be a predisposing factor to sensitivity to neuromuscular blockers—cutaneous reactions occurred mainly in females younger than 70 yr in this series.

An allergic reaction to atracurium has been reported by Aldrete (1985) who gave 0.6 mg kg\(^{-1}\) rapidly followed by thiopentone 4 mg kg\(^{-1}\). A severe cutaneous reaction occurred as well as a slight increased resistance to ventilation. Skin testing 24 h later gave a positive reaction to
atracurium. However, the findings of my series support the statement by Watkins (1986) that, in clinical terms, atracurium emerges as a safe drug with useful neuromuscular blocking properties, but with an irritating tendency to produce predominantly harmless cutaneous manifestations. Provided due care is taken to avoid mixing of drugs, atracurium may be used in patients with a history of asthma or allergic reactions.

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REFERENCES