USE OF ATRACURIUM DURING GENERAL SURGERY MONITORED BY THE TRAIN-OF-FOUR STIMULI

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SUMMARY

The use of atracurium in 25 patients undergoing general surgical procedures is described, neuromuscular function being monitored by the "train-of-four" stimuli. An initial dose of atracurium 0.5 mg kg⁻¹ proved to be clinically acceptable, giving good conditions for endotracheal intubation and adequate muscle relaxation for about 40 min. Comparison of the results with those from 15 patients given suxamethonium 50 mg showed that atracurium in this dosage took longer to produce complete ablation of the twitch responses but that it lasted longer (about 40 min). Incremental doses of atracurium (of 0.2 mg kg⁻¹) gave relaxation for about 30 min and there was no evidence of a cumulative effect. Reversal of the neuromuscular block with neostigmine was prompt and adequate. Using simple clinical means no evidence of an important change in heart rate or arterial pressure was found. There were no adverse reactions to the drug.

Atracurium dibesylate is one of a new series of neuromuscular blocking agents developed by Stenlake (1979). The basic pharmacology of the drug has been described by Hughes and Chappie (1981) and an evaluation of its use in anaesthetized patients has also been published (Payne and Hughes, 1981).

Atracurium is a non-depolarizing agent which breaks down mainly by the so-called Hofmann elimination to give metabolic products which have no neuromuscular blocking effects (Hughes and Chappie, 1981). In addition, in vivo, there is some enzymatic hydrolysis, but this does not seem to be an important route of elimination in practice.

Present information indicates that atracurium is stable in solution for at least 18 months at pH 3.5 and temperature 5 °C. However, if the pH is increased to about 7.4 and the temperature to 37 °C, as it is in vivo, more than half of an injected dose of the drug is broken down in 30 min.

A non-depolarizing muscle relaxant which breaks down in this way without requiring the kidney or the liver for the termination of its effect might have a conspicuous advantage, especially in such situations as, for example, hypovolaemic shock. It certainly warrants further investigation, especially as it appears to have little or no effect on the cardiovascular system in clinically useful doses.

One of the commonest techniques in present-day anaesthesia is based on the use of a non-depolarizing muscle relaxant with controlled pulmonary ventilation, anaesthesia being maintained with nitrous oxide in oxygen, supplemented with analgesic drugs. At the end of the procedure the residual action of the relaxant is antagonized with neostigmine.

Examination of previous work showed that there was a place for the study of atracurium based on this type of anaesthetic routine. An investigation was undertaken, therefore, the basic technique being modified only to facilitate monitoring of neuromuscular function. In addition, the speed and duration of action of the initial dose of atracurium were compared with those of a dose of suxamethonium 50 mg.

METHODS

Atracurium was administered to 25 general surgical patients and suxamethonium to 15. In the latter group, who were anaesthetized in precisely the same way as the former, only the results of monitoring neuromuscular function of an initial dose (50 mg regardless of weight) are presented.

Preliminary work with atracurium suggested that an initial dose of 0.5 mg kg⁻¹ with incremental doses of 0.2 mg kg⁻¹ would be suitable for study. This, it was thought, would give adequate conditions for endotracheal intubation and adequate muscle relaxation for surgical procedures of moderate duration.

Patients

Of the 25 patients receiving atracurium 18 were...
males. Ages ranged from 21 to 77 yr (mean 48 yr) and weights from 42 kg to 76 kg (mean 61.5 kg). All were physically fit. The operations were intra-abdominal (10) (vagotomy and pyloroplasty, cholecystectomy, etc.), mastectomy or biopsy of breast (eight), hernia (four), partial thyroidectomy (one), varicose veins (one), and haemorrhoidectomy (one). The duration of operation varied from 60 to 324 min (mean 109 min).

Of the 15 patients receiving suxamethonium, seven were males. Ages ranged from 26 to 76 yr (mean 51 yr) and weights from 57 kg to 100 kg (mean 72 kg). All were physically fit. The operations were similar to those in the group receiving atracurium, but are not listed here since the investigations were completed before surgery was commenced.

Informed consent was obtained from all those patients who received atracurium. Approval for the project was obtained from the hospital ethics committee and a clinical trial certificate was obtained.

**Anaesthesia**

Premedication was with diazepam 10 mg given orally 2 h before operation. Induction of anaesthesia was with fentanyl and droperidol up to 150 μg and 10 mg respectively). This was followed by a small dose of thiopentone (up to 300 mg). Anaesthesia was continued using a mask (with or without an airway), being maintained with a mixture of nitrous oxide in oxygen (5 litre and 2 litre respectively) without any volatile adjuvant, using a Magill attachment. At this stage spontaneous ventilation usually continued, although sometimes assistance was required or ventilation had to be fully controlled, using manual pressure on the reservoir bag.

During this time the equipment for monitoring neuromuscular function was set up. When this had been completed and control measurements taken (in 10–15 min), atracurium 0.5 mg kg⁻¹ was administered into a fast running i.v. infusion set up in the arm which was not being used for the monitoring of neuromuscular function. Controlled ventilation (using an anaesthetic mask) was established as soon as practicable and endotracheal intubation was effected, the laryngoscope being inserted 90 s after the drug had been administered. No topical analgesic was applied to the larynx.

The anaesthetist performing endotracheal intubation gave a simple assessment of the conditions for this manoeuvre: thus conditions were to be classified as “good” if the vocal cords were abducted and there was no response (such as cough) in response to the passage of the tube, “adequate” if the only reaction was a slight cough, and “poor” if there was considerable coughing or other movement when the tube was passed. (In those patients who received suxamethonium the procedure was identical except that suxamethonium 50 mg was given instead of atracurium and the investigation was discontinued when the twitch height had returned to 50% of control.)

Controlled ventilation was continued using a mixture of nitrous oxide 70% in oxygen, again without a volatile adjuvant; the patient was taken into the operating theatre and surgery commenced. A circle circuit was used without an absorber, the fresh gas flow and tidal volume being adjusted to give an arterial blood carbon dioxide tension of about 5.3 kPa (Snowdon et al., 1975). To facilitate this an infra-red carbon dioxide analyser (Datex Normocap) calibrated with a mass spectrometer, was used to determine end-tidal carbon dioxide tension.

Increments of fentanyl 25 μg were given if the arterial pressure or heart rate increased during surgery. Increments of atracurium 0.2 mg kg⁻¹ were given when indicated by 20% return of the height of the initial twitch response (see below) or, on one occasion, when there was a complaint of poor relaxation.

At the end of surgery atropine 0.6 mg was administered, followed by neostigmine 2.5 mg 1 min later. If the height of the first twitch had not returned to about 75% of control 4 min after the neostigmine was given, atropine 0.6 mg was again administered, followed by neostigmine 2.5 mg after a further 1 min; thus in those patients receiving two doses of neostigmine the time interval between the two was 5 min.

When neuromuscular function had returned to the level which was considered acceptable and there was adequate spontaneous ventilation anaesthesia was discontinued in the usual way and monitoring of neuromuscular function was stopped before the patient became conscious. Consciousness returned rapidly after withdrawal of anaesthesia. When the ability to obey simple commands had returned, the adequacy of muscle power was assessed by asking the patient to lift his head and cough.

Shortly afterwards the patient was sent to the recovery ward and was left there for at least 1 h. The patient was interviewed in the ward the next day and questioned about subjective experiences.

**Monitoring of cardiovascular function**

Heart rate and arterial systolic pressure (determined by palpation) were recorded at 1-min inter-
vals during induction until the response to train-of-four had disappeared. Later both variables were recorded at intervals of 5 min.

Blood-gases
At least two "spot" arterial samples of blood were taken during surgery and blood-gases measured using a blood-gas analyser (Instrumentation Laboratories: IL ABL2C), calibrated in the usual way. A total of 48 samples was taken. These were used to supplement data from end-tidal sampling and confirm that acid–base status was at least near normal limits.

Monitoring of neuromuscular function
The train-of-four stimuli was used to monitor neuromuscular function (Ali, Utting and Gray, 1971a,b; Ali and Savarese, 1976). The stimulator was a Grass type S 48. Supramaximal stimuli were applied to the ulnar nerve at the wrist by needle electrodes inserted subcutaneously. The frequency was 2 Hz, the duration of the stimulus 0.3 s (that is there were four stimuli in each train) and the interval between each train was 10 s. The force of thumb adduction was measured using a force-displacement transducer (Grass type, FTO3 C).

It is convenient to designate the heights of the control twitch response to the train-of-four, A, B, C and D before a non-depolarizing muscle relaxant is administered and A', B', C' and D' thereafter. A, B, C and D are equal, or nearly so, but in states of partial block produced by this type of relaxant "fade" is found, and A', B', C' and D' each decrease, but in such a way that height A' > B' > C' > D'. If the degree of block is increased D' disappears first, followed by C' then B' and finally A', recovery taking place in the reverse order. The ratio A'/A and D'/A' are convenient indications of the degree of block, as is the presence of each individual response; thus if A' only is present the degree of block is greater than if A' and B' are present, and so on.

The initial dose of atracurium completely ablated the response to the stimuli. The time to the first appearance of a degree of block and to the complete disappearance of any mechanical response and the time to recovery of the initial response to 10% of its height before the muscle relaxant was administered (A'/A) was also recorded: at this later stage only two of the mechanical responses of the train-of-four were usually visible. The effect of incremental doses (which again ablated all the twitch responses) was also monitored.

At the end of surgery after neostigmine had been administered monitoring was continued until the initial response of the train-of-four had reached at least 75% of control values (the ratio A'/A was 75%), this being the value at which vital capacity should have returned to normal (Ali et al., 1975); at this time the ratio D'/A' was also in the order of 70%.

In those patients who received suxamethonium the method of monitoring was identical to that used with atracurium, but it was only the initial dose from which the results of monitoring were recorded.

RESULTS
Response of the train-of-four
The response to the train-of-four stimuli when atracurium was given showed the characteristic "fade" of the non-depolarizing muscle relaxant and eventually all responses disappeared. This is shown in figure 1.

During recovery the initial "twitch" response (A') re-appeared first, to be followed by B', C' and D', in that order. When an incremental dose was given the twitch responses again disappeared. Figure 2 shows the re-appearance of the responses to the train-of-four and their disappearance when an incremental dose of atracurium had been given.

The mean times (s) to the onset of action of atracurium and suxamethonium and the time to complete disappearance of any response to the train-of-four are shown in table I, as is the mean time (min) to the first reappearance of any response and the time to recovery of the initial response to 10% of its control value. It can be seen that the mean time to disappearance of the train-of-four is shorter with suxamethonium than it is with atracurium; this difference is significant at the usual confidence level (P < 0.001; unpaired Student's t test). It can also be seen that the mean time to re-appearance is long with atracurium, and this disappearance is again
TABLE I. Mean times (SD) to first depression of twitch and its disappearance, reappearance and recovery of the initial response to 10% of its control value. The time to the administration of an incremental dose of atracurium is also shown.

<table>
<thead>
<tr>
<th></th>
<th>Atracurium 0.5 mg kg⁻¹</th>
<th>Suxamethonium 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Time to first depression of response (s)</td>
<td>32 (13.6)</td>
<td>34 (10.9)</td>
</tr>
<tr>
<td>Time to disappearance of response (s)</td>
<td>110 (27.8)</td>
<td>59 (12.1)</td>
</tr>
<tr>
<td>Time to reappearance of response (min)</td>
<td>35 (7.6)</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Time to 10% recovery of initial twitch height (min)</td>
<td>39 (9.7)</td>
<td>7 (2.8)</td>
</tr>
<tr>
<td>Time to first increment (min)</td>
<td>43 (11.2)</td>
<td>—</td>
</tr>
</tbody>
</table>

The conditions provided by the initial dose were as good as (or somewhat better than) the conditions provided by the other commonly used non-depolarizing muscle relaxants. In all but one of the patients receiving suxamethonium conditions were described as “good”; the other was described as “adequate”.

**Incremental doses**

The mean times from the initial dose of atracurium to each increment are shown in Table II. In all but two cases an increment was given when the initial twitch response had reached 20% of its height before the atracurium had been administered. At this time the ratio of the fourth response to the first response was also about 20%.

Incremental doses had to be administered every 10–30 min after the preceding dose had been given. There was no obvious evidence of accumulation with the number of incremental doses used, which ranged up to five (up to a total dose which was three times as large as the dose used for endotracheal intubation).

**Antagonism of neuromuscular block**

Neostigmine effectively antagonized the neuromuscular block (Fig. 3). One or two doses of neostigmine (2.5 mg) was given according to the degree of recovery (see methods). An initial dose was given and 4 min later a decision was made as to whether or not a second dose should be given.

In 11 of the patients the ratio of the height of the first twitch response the control (A'/A) was 75% or
The times (SD) from the administration of the initial dose of atracurium to the incremental doses (0.2 mg kg\(^{-1}\)). An indication of the degree of block remaining when the increments were administered is given by the ratios \(A'/A\) and \(D'/A'\).

<table>
<thead>
<tr>
<th>Increment No.</th>
<th>No. receiving</th>
<th>Mean time (min)</th>
<th>Range (min)</th>
<th>Mean (A'/A) (%)</th>
<th>Mean (A'/D') (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>43 (11)</td>
<td>21–65</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>71 (20)</td>
<td>35–100</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>89 (21)</td>
<td>50–108</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>99 (40)</td>
<td>63–142</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>129 (73)</td>
<td>78–180.5</td>
<td>30</td>
<td>23</td>
</tr>
</tbody>
</table>

FIG 3. Reversal of block with neostigmine. The top panel shows the accelerating recovery after neostigmine; after 2 min, recovery is almost complete (lower panel).

more (range 100–75%) at a time of 4 min after a first dose of neostigmine had been given: at the same time the ratio of the fourth twitch height to the first (D'/A') was within the range 100–47%. No further neostigmine was given.

In the other (14) patients the ratio \(A'/A\) was less than 75% (72–27%) 4 min after the first dose of neostigmine, the ratio D'/A' at this time being in the range 40–2%. These patients received a further dose of neostigmine 2.5 mg (preceded, as before, by atropine 0.6 mg) 1 min later—that is 5 min after the first dose of neostigmine.

The increase in twitch height with time in the group of patients receiving only one dose of neostigmine is shown in figure 4. It can be seen that the administration of neostigmine is followed by a greatly increasing rate of recovery of both ratio \(A'/A\) and \(D'/A'\).

The corresponding results from the group of patients receiving two doses of neostigmine are shown in figure 5. Here the ratios \(A'/A\) and \(D'/A'\) were lower than in previous group before neostigmine was administered and the rate of recovery at the time was also slower. It can be seen that, although the rate of recovery accelerated greatly after the first dose of neostigmine, it is not possible adequately to assess the effect of the second dose.

**Blood-gases**

In all 48 “spot” arterial blood samples were taken from the patients. The mean pH was 7.34 (range 7.27–7.48) and mean \(P_{aCO_2}\) was 5.0 kPa (range 3.6–6.0 kPa). There was thus no evidence of gross alkalaemia (or acidaemia) in the series.

**Cardiovascular variables**

No clinically significant changes in arterial pressure or heart rate which could be attributed to atracurium were observed after either the initial or incremental doses of the drug. For example, the mean heart rate and systolic pressure just before the atracurium was administered were 76 beat min\(^{-1}\) and 127 mm Hg respectively. After the large initial dose had been administered (just before endotracheal intubation was performed) the corresponding figures were 77 beat min\(^{-1}\) and 117 mm Hg respectively.
FIG. 4. The effect of neostigmine in those patients to whom only one dose (of 2.5 mg) was administered. The top line (•) shows the mean of the ratio $A'/A$ (as percentage) and SEM. The lower line (O) shows the mean of the ratio $D'/A'$ (as percentage); the SEM is not delineated (to avoid confusion). The increased rate in recovery from block is clearly seen.

FIG. 5. The effect of neostigmine in those patients to whom two doses (each 2.5 mg) were administered. As in figure 4 the upper line (■) represents $A'/A$ (with SEM) and the lower (O) $D'/A'$. There is rapid antagonism of neuromuscular block. It is difficult, however, to assess the effect of the second dose of neostigmine.
The investigators sought, but did not find, clinical evidence of histamine release. In three of the patients (all female) a transient flush was seen over the face and shoulders after the administration of the first dose of atracurium, which cleared within 2–3 min. This was not accompanied by any change in arterial pressure.

Postoperative interviews

No subjective accounts suggesting postoperative muscle weakness were obtained. There were no complaints of diplopia, either volunteered spontaneously or elicited by questioning.

DISCUSSION

Atracurium is not as rapid in action as suxamethonium; this is shown by the fact that the time to complete disappearance of the response to the train-of-four stimuli is longer with atracurium using doses which might be considered as clinically acceptable in both cases. Atracurium will not replace suxamethonium in those circumstances in which speed of tracheal intubation is important. Similarly, the duration of action of suxamethonium is shorter than that of atracurium.

The incremental doses of atracurium used in this study were large in comparison with the dose for endotracheal intubation: thus, for example, if it be conceded that the initial dose of atracurium is equivalent, in terms of conditions provided for endotracheal intubation, with tubocurarine in a dose in the order of 45 mg given to a patient of 70 kg body weight, then the incremental doses of atracurium would be equivalent to about 18 mg of the older drug. Despite this, recovery from each and every incremental dose of atracurium was rapid, even when up to five incremental doses had been administered. There was prompt reversal of the block by neostigmine and no diplopia after operation. However, the ultimate evidence that atracurium is non-cumulative will come from pharmacokinetic studies, although clinical studies of atracurium in renal failure (Hunter, Jones and Utting, 1982—accompanying paper) indicate that atracurium is non-cumulative.

Antagonism of the neuromuscular block with neostigmine was satisfactory. Inspection of the graphical results shows that, in those to whom one dose was administered (fig. 4), there was prompt reversal of the block: this is not surprising since, in this group, the block was wearing off rapidly. In the other group, to whom two doses were administered, antagonism also appeared satisfactory, although here the degree of block present was greater before the neostigmine was given (fig. 5).

Close inspection of figure 5 reveals that the second dose of neostigmine may, indeed, have been associated with the development of a further degree of "fade". Payne, Hughes and Al Azawi (1980) described such a phenomenon and as it could, in some circumstances, be antagonized with gallamine and potentiated by suxamethonium, they suggested that the neostigmine was producing an acetylcholine-induced block. It may be that the use of neostigmine 5 mg in the current series represented an overdosage relative to the residual block and that one dose of 2.5 mg would have been sufficient.

Cardiovascular monitoring in this series was recognizably crude. Nevertheless, there can be little doubt that there is little gross upset when the drug is used as it was here. There was no observable change in arterial pressure or in heart rate attributable to the drug.

Atracurium thus seemed to be a suitable non-depolarizing muscle relaxant for use in general surgical procedures. If, as pharmacological studies suggest, it is non-cumulative, it proves to be a useful agent both in general use and, more especially, in such situations as renal failure and shock.

ACKNOWLEDGEMENTS

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REFERENCES


UTILISATION DE L’ATRACURIUM EN CHIRURGIE GENERALE, CONTROLEE PAR LE STIMULUS DU TRAIN DE QUATRE

RESUME

Cet article décrit l’utilisation de l’atracurium chez 25 patients subissant un acte de chirurgie générale, la jonction neuromusculaire étant surveillée par le stimulus du “train de quatre”. Une dose initiale de 0,5 mg kg\(^{-1}\) s’est révélée cliniquement acceptable, fournissant de bonnes conditions d’intubation endotrachéale et un relâchement musculaire satisfaisant pendant environ 40 min. Si on compare les résultats à ceux de 15 patients ayant reçu 50 mg de suxaméthonium, on voit qu’à cette posologie l’atracurium met plus longtemps à induire une suppression complète des réponses au twitch mais que sa durée d’action est plus longue (environ 40 min). Des doses successives d’atracurium (de 0,2 mg kg\(^{-1}\)) ont entraîné un relâchement pendant environ 30 min sans qu’il y ait de signe d’effet cumulatif. L’annulation du bloc musculaire par la prostigmine était rapide et complète. L’utilisation de contrôles cliniques simples n’a pas montré de modifications importantes de fréquence cardiaque ou de pression artérielle. Le produit n’a pas entraîné d’effets secondaires néfastes.

VERWENDUNG VON ATRAKURIUM BEI ALLGEMEINNARKOSE UND ÜBERWACHUNG MIT HILFE VON “TRAIN-OF-FOUR” REIZEN

ZUSAMMENFASSUNG

Es wird die Verwendung von Atrakurium bei 25 Patienten, die sich einer Operation in Allgemeinarkose unterziehen mußten, beschrieben, wobei die neuromuskuläre Funktion durch “train-of-four” Reize überwacht wurde. Eine Anfangsdosis von Atrakurium 0,5 mg kg\(^{-1}\) erwies sich als klinisch brauchbar, da sie gute Bedingungen für die endotracheale Intubation und adäquate Muskelrelaxierung für ungefähr 40 min ergab. Ein Vergleich der Ergebnisse mit denen von 15 Patienten, die Suxamethonium 50 mg erhalten hatten, zeigte, daß es bei Atrakurium in dieser Dosierung länger dauerte, bis die Zuckungsexkursionen vollständig aufhörten, daß aber die Wirkung länger andauerte (ungefähr 40 min). Zusätzliche Dosen von Atrakurium (0,2 mg kg\(^{-1}\)) ergaben eine Relaxierung für ungefähr 30 min ohne Anzeichen für eine Akkumulation. Die Antagonisierung mit Neostigmin erfolgte schnell und adäquat. Bei Benutzung der einfachen klinischen Mittel waren keine Anzeichen für eine wichtige Veränderung der Herzfrequenz oder des arteriellen Blutdruckes zu finden. Es traten keine unerwünschten Wirkungen auf.

USO DEL ATRACURIO DURANTE CIRUGÍA GENERAL CONTROLADA POR LOS ESTIMULOS EN SERIE DE CUATRO

SUMARIO

Se da una descripción del uso del atracurio en 25 pacientes sometidos a operaciones quirúrgicas generales, la función neuromuscular encontrándose controlada por los estímulos en serie de cuatro. Se comprobó que una dosis inicial de atracurio de 0,5 mg kg\(^{-1}\) era clínicamente aceptable y que daba buenas condiciones para la intubación endotraqueal así como un relajamiento muscular adecuado durante 40 min aproximadamente. Al comparar los resultados con los obtenidos en 15 pacientes a los cuales se administró 50 mg de suxametionio, se demostró que el atracurio en esa dosis exigía un periodo mayor para producir una ablación total de las respuestas de contracción, pero que su efecto duraba más tiempo (alrededor de 40 min). Dosis crecientes de atracurio (de 0,2 mg kg\(^{-1}\)) produjeron un relajamiento de cerca de 30 min y no hubo prueba de un efecto cumulativo. La inversión del bloqueo neuromuscular con neostigmina fue rápido y adecuado. Al usar medios clínicos simples, no se halló ningún a prueba de cambio importante del ritmo cardíaco o de la presión arterial. No hubo reacciones adversas a dicha substancia.