VECURONIUM AND ATRACURIUM IN PATIENTS WITH END-STAGE RENAL FAILURE

A Comparative Study

J. Y. LEPAGE, M. MALINGE, A. COZIAN, M. PINAUD, Y. BLANLOEIL AND R. SOURON

Vecuronium bromide and atracurium besylate are intermediate-acting competitive neuromuscular blocking agents the elimination of which is, most probably, independent of renal excretion. Previous kinetic and dynamic studies of both drugs, using either a single dose (Fahey et al., 1981a, b; Meistelman et al., 1983; Lebrault et al., 1984) or repetitive administration (Hunter, Jones and Utting, 1982, 1984; Bevan et al., 1984), have highlighted the similarity of responses between patients with end-stage renal failure and patients with normal renal function. Therefore, vecuronium or atracurium have been recommended for patients with altered renal function.

However, the dose–response relationship of atracurium in patients with end-stage renal failure has not yet been reported. Furthermore, the possible differences between the two drugs have not been investigated fully; the sole comparative study in end-stage renal failure (Hunter, Jones and Utting, 1984) failed to find evidence of cumulation of atracurium or vecuronium. However, this study involved non-synchronous groups and neither estimated their potency ratio nor compared the recovery times after repeated administration—aspects which are of great clinical concern during prolonged surgery. The present study was undertaken to assess these points.

SUMMARY

Twenty patients with end-stage renal failure, undergoing kidney transplantation, were assigned randomly to receive either vecuronium or atracurium under evoked twitch tension control. The cumulative-dose technique was used to obtain 95% twitch depression (vecuronium: initial bolus 15 μg kg\(^{-1}\), increments 6 μg kg\(^{-1}\); atracurium: initial bolus 100 μg kg\(^{-1}\), increments 40 μg kg\(^{-1}\)). Using \(ED_{95}\) values derived from the log–probit dose–response curves, vecuronium was 4.6 times more potent than atracurium. The durations of action of the initial cumulative-doses (from end of injection of the last increment to 25% recovery) were 11.1 ± 3.3 min for vecuronium and 16.2 ± 3.9 min for atracurium (\(P < 0.05\)). In terms of duration of action of the maintenance doses (vecuronium one-quarter of the total incremental dose; atracurium one-third) some cumulation was observed with vecuronium (interaction time \(\times\) treatment; cumulation ratio 1.46 ± 0.31 v. 0.98 ± 0.10 for atracurium, \(P < 0.001\)). After 2 h of surgery, the mean recovery times (25% to 75% twitch height) did not differ (18.5 ± 2.8 min and 16.7 ± 4.4 min). It is concluded that vecuronium might be less safe than atracurium in patients with end-stage renal failure undergoing prolonged operations.

PATIENTS AND METHODS

The investigation was approved by the local Ethics committee and informed consent was given by all patients.

Patients

Twenty patients of either sex, aged between 23–42 yr and undergoing cadaver kidney trans-
Table I. Demographic and biochemical data (mean±SEM). No difference between vecuronium and atracurium is significant.

<table>
<thead>
<tr>
<th></th>
<th>Vecuronium (n = 7)</th>
<th>Atracurium (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>32.2±3.9</td>
<td>33.1±8</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>58.4±8.4</td>
<td>49.7±5.9</td>
</tr>
<tr>
<td><strong>Duration of procedure (min)</strong></td>
<td>141.85±21.48</td>
<td>118.03±16.12</td>
</tr>
<tr>
<td><strong>Blood urea (mmol litre^&quot;1)</strong></td>
<td>16.0±6.2</td>
<td>14.3±6.2</td>
</tr>
<tr>
<td><strong>Creatinine clearance (ml min^&quot;1)</strong></td>
<td>9.7±11.6</td>
<td>3.11±2.1</td>
</tr>
<tr>
<td><strong>Sodium (mmol litre^-1)</strong></td>
<td>136.88±3.71</td>
<td>137.78±1.26</td>
</tr>
<tr>
<td><strong>Potassium (mmol litre^-1)</strong></td>
<td>4.0±0.71</td>
<td>4.20±0.54</td>
</tr>
<tr>
<td><strong>Calcium (mmol litre^-1)</strong></td>
<td>2.43±0.20</td>
<td>2.56±0.13</td>
</tr>
<tr>
<td><strong>Magnesium (mmol litre^-1)</strong></td>
<td>1.02±0.04</td>
<td>0.99±0.02</td>
</tr>
<tr>
<td><strong>Haemoglobin (g litre^-1)</strong></td>
<td>9.6±1.6</td>
<td>9.7±1.9</td>
</tr>
<tr>
<td><strong>Albumin (g litre^-1)</strong></td>
<td>41.23±1.12</td>
<td>40.21±0.98</td>
</tr>
<tr>
<td><strong>Total protein (g litre^-1)</strong></td>
<td>68.43±0.94</td>
<td>69.55±1.02</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.37±0.04</td>
<td>7.37±0.02</td>
</tr>
<tr>
<td><strong>Bicarbonate (mmol litre^-1)</strong></td>
<td>20.75±1.73</td>
<td>20.73±1.63</td>
</tr>
<tr>
<td><strong>Pco2 (kPa)</strong></td>
<td>4.40±0.31</td>
<td>4.67±0.44</td>
</tr>
</tbody>
</table>

planned, were randomly assigned (computer random number program) to two groups of 10 to receive either vecuronium or atracurium. All had been dialysed within 8 h of surgery and were free from cardiac and hepatic dysfunction. There was no previous allergic history. No patient was being treated with calcium or magnesium salts, or enzyme inhibiting or inducing drugs. Four in each group were receiving beta-adrenoceptor blocking agents. No peri-operative antibiotics were given. Table I summarizes the preoperative status of the patients.

**Anaesthesia**

Premedication was with diazepam 10 mg orally 60 min before the induction of anaesthesia and atropine sulphate 10 μg kg^-1 i.v. 10 min before anaesthesia was induced with flunitrazepam 20 μg kg^-1 and fentanyl 10 μg kg^-1. Tracheal intubation was performed after spraying the pharynx, larynx and trachea with topical 5% lignocaine. Balanced anaesthesia was maintained with 60% nitrous oxide in oxygen, increments of fentanyl 1 μg kg^-1 and vecuronium or atracurium as indicated below. Ventilation was controlled throughout so that the end-tidal carbon dioxide concentration was maintained at 5±0.30% (47210 A capnometer, Hewlett-Packard). Oesophageal temperature was kept within the normal range (36.4±0.8 °C).

**Assessment of neuromuscular function**

The ulnar nerve was stimulated at the wrist using surface electrodes. Ten percent supramaximal pulses were delivered by a 750 Bard Biomedical stimulator at a rate of 0.1 Hz with a duration of 0.2 ms.

The resultant force of adduction of the thumb, as quantified by a force displacement transducer (Statham UC 3 gold cell), was recorded on a polygraph (Monitor V Roche Dassault) (Ali and Savarese, 1976; Stanec, Stanec and Ing, 1983). The sensitivity of the recording system was adjusted to give reliable measurements of 95% twitch depression. The study was divided into two sections.

**Section A.** The cumulative-dose method was used to determine the potencies of the two neuromuscular blockers. When the twitch height had been stable for at least 10 min, repeated small doses of vecuronium (initial bolus 15 μg kg^-1, additional doses 6 μg kg^-1), or atracurium (initial bolus 100 μg kg^-1, additional doses 40 μg kg^-1) were administered i.v. After the injection of each dose the resulting twitch depression was observed until it was maximum,—that is three consecutive twitches of equal height were recorded; the next incremental dose was then given (Donlon, Savarese and Ali, 1974) in order to achieve 95% suppression of the evoked twitch response with careful titration. Patients whose response exceeded this fixed end-point were excluded. The total incremental dose was calculated for each remaining patient. The dose-response curves of each patient and each drug-group were constructed using the log-probit method (Lichtfield, Wilcoxon and Wilcoxon, 1949). Slopes, ED_{50}, ED_{90} and ED_{45} values were derived.
Section B. The maintenance doses were one-third of the total incremental dose of atracurium and one-quarter that of vecuronium. They were administered when the twitch had recovered to 25% of control. The variables of time course of neuromuscular blockade were measured: clinical duration of the initial cumulative-dose, from the end of injection of the last incremental dose to 25% twitch recovery (Dur_{25}); durations of maintenance doses, from end of the injection of each maintenance dose to 25% recovery (Dur_{rep25}); recovery time from 25% to 75% recovery after the last maintenance dose (RI). A cumulation ratio for each drug was estimated (duration of the last maintenance dose/duration of the first maintenance dose).

All variables were calculated as mean ± SEM.

Statistical analysis

The patient groups and the slopes of the dose–response curves were compared using Student's t tests. The cumulative effect in each drug group was assessed by comparison of the Dur_{rep 25} (two-way analysis of variance followed by a multiple protected t test). Statistical differences were considered significant when P < 0.05 (two-tailed tests).

RESULTS

The demographic and biochemical data of the patients are summarized in table I. There were no significant differences between the two groups.

Section A

The twitch response was completely suppressed in four patients (three vecuronium, one atracurium); they were excluded from further analysis. Between two and eight incremental doses were required over 6.2 ± 3.1 min to obtain 95% twitch depression in all the patients in the study.

The log–probit dose–response curves are shown in figure 1. Their slopes did not differ and the figures for ED_{50}, ED_{90} and ED_{95} obtained from the curves (table II) were 23.1 μg kg⁻¹, 37.9 μg kg⁻¹ and 43.8 μg kg⁻¹, respectively, for vecuronium and 123 μg kg⁻¹, 181 μg kg⁻¹ and 202 μg kg⁻¹, respectively, for atracurium. If it is assumed that the ED_{95} dose will provide suitable muscle relaxation, vecuronium was 4.6 times as potent as atracurium.

Section B

The largest doses required to maintain at least 75% blockade in procedures lasting about 2 h (table I) were 0.18 mg kg⁻¹ of vecuronium and 1.8 mg kg⁻¹ of atracurium.

| Table II. ED_{50}, ED_{90} and ED_{95} for vecuronium and atracurium (mean ± SEM) |
|-------------------------------|-------------------|-------------------|
|                               | Vecuronium (n = 7) | Atracurium (n = 9) |
| ED_{50} (μg kg⁻¹)             | 23.1 ± 6.9         | 123 ± 27          |
| ED_{90} (μg kg⁻¹)             | 37.9 ± 9.9         | 181 ± 47          |
| ED_{95} (μg kg⁻¹)             | 43.8 ± 11.1        | 202 ± 55          |
Table III shows the $D_{50}$, RI and cumulation ratios. When the first equipotent repeat doses were given, vecuronium appeared to be shorter-acting than atracurium ($P < 0.05$), but after further administration its cumulation ratio was significantly greater ($P < 0.001$), while the mean RI in the two groups did not differ.

The crossing of the $D_{rep 75}$ curves (fig. 2) emphasizes a time × treatment interaction. Although there was a progressive decrease in the numbers of patients concerned with the reinjections, the variabilities of the responses in the two groups were quite similar. However, it is noticeable that the change in the $D_{rep 75}$ in the atracurium group was not statistically significant, although it was so in the vecuronium group. The duration of the seventh dose was one and a half times that of the first one.

**DISCUSSION**

A number of aspects of the methodology of this study require comment. Flunitrazepam (a long acting benzodiazepine, extensively degraded by the liver) was used in order to avoid halogenated inhalation agents, which have been shown to enhance the effects of vecuronium and atracurium (Rupp, Miller and Gencarelli, 1984; Rupp, McChristian and Miller, 1984). All benzodiazepines, by an action on spinal neurones, have a muscle relaxant effect, that of diazepam being considered to be maximum and that of flunitrazepam to be intermediate (Dantlo et al., 1984). Diazepam has been shown not to interact with competitive neuromuscular blocking drugs (Asbury et al., 1981; McIndewar and Marshall,
1981; Chapple, Clarke and Hughes, 1983), but flunitrazepam has not been investigated in this respect.

The cumulative-dose technique overestimates the ED$_{50}$ of the intermediate-acting non-depolarizing agents (Fisher et al., 1982; Miller et al., 1984). This has been explained on the basis of the relatively short action of vecuronium and atracurium, particularly in small doses, in relation to the time it takes to administer further increments in a cumulative-dose technique. We used this method because it requires fewer patients than the single bolus method and relatively few patients with no renal function undergo prolonged operations.

The elimination of four patients whose twitch response exceeded the fixed 95% end-point of the cumulative-dose method described by Donlon, Savarese and Ali (1974), might have introduced some bias and produced artificially high values for ED$_{50}$, ED$_{90}$ and ED$_{95}$. It is, however, clear that these four patients could not be included in the main part of the study. The aim was to compare the effect of repeated doses of atracurium and vecuronium in patients with end-stage renal failure using maintenance doses calculated from the total initial dose for each patient. Those patients who were eliminated did not lose the twitch response after the initial dose of neuromuscular blocking drug, but after the third incremental dose (three patients) and after the fifth (one). When the dose–response curves were constructed with all the recorded points, the calculated ED$_{95}$ were 204.5 ± 45 μg kg$^{-1}$ for atracurium and 44.1 ± 13.5 μg kg$^{-1}$ for vecuronium. These figures do not differ significantly from the results as presented.

There were two other possible sources of bias in the present study. First, there was no peroperative control of acid–base balance, so that a mild metabolic acidosis cannot be excluded, although all patients had been recently dialysed. This bias could have affected both groups, but in unpredictable ways, since variations in pH have been shown to alter the dynamics of vecuronium in man (Gencarelli et al., 1983), but those of atracurium only experimentally (Hughes and Chapple, 1981).

Second, the release of the vascular clamps on the transplanted kidney was not taken into account in the evaluation of the Dur$_{rep}$ 5s. Early excretion of tubocurarine in this situation has been established by Miller and colleagues (1977). The renal excretion of atracurium is assumed to be nil or negligible, but 10–25% of a dose of vecuronium may be excreted in the urine, most of it apparently unchanged (Fahey et al., 1981a; Upton et al., 1982).

In spite of these points, the results of this study were in accord with other published data, and certain aspects may be emphasized. The ED$_{50}$, ED$_{95}$ and potency ratio of vecuronium and atracurium in patients with end-stage renal failure were comparable to those reported in normal patients when the cumulative-dose technique was used (Gramstad, Lilleasen and Minsaas, 1983; Robertson et al., 1983). The finding that vecuronium was initially shorter-acting than atracurium—as in normal patients (Hunter, Jones and Utting, 1982, 1984; Foldes et al., 1983; Meistelman et al., 1983; Lebrault et al., 1984)—is in agreement with the work of Bevan and colleagues (1984). Hunter, Jones and Utting (1984) noted a greater variability in response in end-stage renal failure, especially to vecuronium, but this point was not directly investigated in our study.

The lack of cumulation of atracurium has been demonstrated also by kinetic studies in patients with end-stage renal failure (Fahey et al., 1984) and in normal patients (Weatherley, Williams and Neill, 1983) for a geometric progression of doses; its effects depend heavily upon elimination (Miller et al., 1984) as a result of its peculiar spontaneous non-enzymic degradation by the Hoffman route (Stenlake et al., 1981). However, the surprising decrease in the Dur$_{rep}$ 5s observed in this series deserves confirmation and elucidation. Although cumulation of vecuronium could be expected from its kinetic properties (Miller et al., 1984), most dynamic studies in normal patients (Krieg, Crul and Booij, 1980; Fahey et al., 1981b; Buzello and Noldge, 1982; Bevan et al., 1984) and one in patients with end-stage renal failure (Hunter, Jones and Utting, 1984) have failed to find evidence of it. However, two comparative studies with atracurium in normal patients (Ali et al., 1983; Michel et al., 1984) and that of Bevan and colleagues (1984) in patients with end-stage renal failure suggested a tendency to cumulation. Kinetic studies comparing patients with and without renal failure (Fahey et al., 1981a; Bencini et al., 1983; Meistelman et al., 1983) did not find significant clinical differences, but all were based on single, relatively small doses (0.14 mg kg$^{-1}$, 0.10 mg kg$^{-1}$, and 0.05 mg kg$^{-1}$ of vecuronium, respectively). The data from the present dynamic trial (interaction time × treatment, increased dura-
tion of maintenance doses along with reinjections, cumulation ratio) indicated a cumulation of vecuronium in end-stage renal failure that reached statistical significance after the fourth maintenance dose, although the largest dose administered in the series (1.8 mg kg\(^{-1}\)) was relatively small. Whether this cumulation of vecuronium in end-stage renal failure was a result of decreased degradation or elimination, or of redistribution, cannot be elucidated on a dynamic basis. Vecuronium does not seem to be converted in large amounts into active metabolites. Renal excretion by itself does not influence its duration of action, since Fahey and colleagues (1981a) found similar plasma clearances in patients with and without renal failure. An increase in the biliary route in end-stage renal failure has been suggested (Upton et al., 1982; Bencini et al., 1983) and this could become saturated. Nevertheless, in this study the RI of atracurium, which did not cumulate, did not differ from that of vecuronium, which did. This was reported in normal patients by Miller and colleagues (1984) in a review article, but Roberton and colleagues (1983) observed a prolonged RI when three times the ED\(_{50}\) was given. Since the RI is assumed to be the best index of the effect of the elimination mechanisms on the overall duration of action of competitive neuromuscular blockers, elimination would not be involved in this dose range in the cumulative effect of vecuronium. Hence saturation of the distribution volume in end-stage renal failure is suggested.

It is concluded that, in patients with end-stage renal failure, vecuronium exhibits a slight, but documented cumulative effect which might make it less safe than atracurium in prolonged surgical procedures. The kinetics and lack of cumulation of atracurium point to the value of an infusion technique in this group of patients.

**ACKNOWLEDGEMENTS**

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**REFERENCES**


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