Atracurium and vecuronium are recently introduced non-depolarizing neuromuscular blocking drugs with intermediate durations of action. Cumulation seems to be negligible, and recovery is relatively rapid with both drugs (Agoston et al., 1980; Payne and Hughes, 1981). Since comparative clinical evaluations of these drugs require a knowledge of the relative dose requirements associated with different techniques of administration, we estimated previously the dose–response relationship during initial neuromuscular blockade with these drugs using a cumulative dose regimen (Gramstad and Lilleaasen, 1982). In the present investigation we have evaluated these dose–effect relationships following a single bolus. In addition, the dose requirements for sustained neuromuscular blockade were estimated by the administration of continuous i.v. infusions of the drugs and the corresponding plasma concentrations were determined for vecuronium and pancuronium.

PATIENTS AND METHODS

Thirty patients (ASA class I) undergoing surgery on the ear, nose or parotid gland, with an expected duration of anaesthesia of more than 2.5 h, were investigated. Informed consent was obtained before the patients were randomly allocated to receive atracurium, vecuronium or pancuronium. Stratified sampling was used to obtain an even sex distribution. Exclusion criteria were: pregnancy, medication for infectious or other diseases, more than 20% deviation from normal weight, age less than 18 or greater than 60 yr.

Patients were premedicated with pethidine 50–100 mg and atropine 0.6 mg i.m. about 1 h before the induction of anaesthesia. After arrival in the operating theatre, sedation and analgesia were achieved with diazepam 5–10 mg and fentanyl 0.1–0.2 mg i.v. Subcutaneous needle electrodes were placed at the wrist, and supramaximal stimuli at 0.1 Hz were delivered from a nerve stimulator (Myotest). The evoked addition force of the thumb was measured with a Statham UC3 transducer (with UL4-20 load cell) connected to a Hewlett-Packard 7702B recorder equipped with 8805C amplifier. Resting thumb tension was maintained between 200 and 300 mg throughout the study. When the evoked twitch
response was stable, anaesthesia was induced with diazepam 5–10 mg, fentanyl 0.1 mg, and thiopentone 100–300 mg until the eyelash reflex disappeared. 

ED₉₅ doses of the neuromuscular blocking drugs (which had been estimated previously by the cumulative technique (Gramstad and Lilleaasen, 1982)), were given as a single bolus injection. The doses were: atracurium 279 µg kg⁻¹, vecuronium 56 µg kg⁻¹ and pancuronium 64 µg kg⁻¹. Once the maximum effect had been obtained, the trachea was intubated, and ventilation was controlled using a Servo 900B ventilator equipped with a Siemens-Elema CO₂ Analyzer 930. Anaesthesia was maintained with 65 % nitrous oxide in oxygen, and increments of fentanyl were given as required. Ventilation was adjusted to maintain the end-tidal carbon dioxide concentration between 4 and 5 vol %. Rectal temperature was monitored with a Digimed H10 thermometer and was maintained between 35.0 and 37.0 °C in all patients.

Once the maximal effect of the initial dose had been achieved, the neuromuscular blocker was administered by a continuous infusion (Hoechst PP50 infusion pump). The drug solutions were prepared with physiological saline at 4 °C immediately before the induction of anaesthesia. The concentrations of the solutions were chosen such that the 50-ml infusion syringe should not normally have to be replaced during the investigation. The concentrations were: atracurium 1.8 mg ml⁻¹, vecuronium 0.4 mg ml⁻¹ and pancuronium 0.16 mg ml⁻¹.

At first the rate of infusion was titrated to produce a constant 90% twitch depression. After 60 min the rate of the infusion was held constant and the drug requirement and the twitch response were noted. After a subsequent 15-min period of constant-rate infusion, the twitch response was re-assessed, and the individual change in response during the 15-min time interval recorded. The infusion pump was then stopped and was restarted about 4 min before the twitch height was expected to reach 50%. The rate of infusion was then titrated to produce a constant 50% depression of the control twitch force. After 30 min the infusion rate was held constant; the drug requirement was noted and the twitch response was measured at the start and end of a subsequent 15-min period, as undertaken previously.

An additional dose of neuromuscular blocker equal to one-third of the initial bolus dose, was then given as a single injection. After the maximal effect had been achieved, the infusion was discontinued, and the recovery time from 25% to 75% twitch height recorded.

Blood samples were obtained from the patients in the vecuronium and pancuronium groups at the end of the 15-min constant infusion–response intervals at 90% and 50% twitch depression, for determination of plasma concentrations of the drugs. For the vecuronium assay, 5-ml samples of whole blood were placed in test tubes containing 1 ml of KH₂PO₄ 1 mol litre⁻¹. The blood was mixed thoroughly with the buffer, and kept at 4 °C until it was centrifuged (within 2 h). The plasma was separated and stored at −70 °C until analysis. The concentrations of vecuronium were determined by a fluorimetric technique. The method has a sensitivity of 5 ng ml⁻¹, showing a 3–10% variation in precision in the range 5–1000 ng ml⁻¹ (U. W. Kersten, in preparation). For the pancuronium assay, blood samples were collected in heparin-containing tubes (Vacutainer) and kept at 4 °C until centrifuged within 3 h. The plasma was separated and stored at −70 °C until analysis. The drug concentrations were determined by the fluorimetric method described by Kersten, Meijer and Agoston (1973).

Plasma clearance was calculated conventionally, where the rate of input by a zero-order infusion was divided by the plasma concentration at assumed steady-state.

Ringer's acetate solution was the only fluid administered during the operation. Bleeding was minimal. Lignocaine 5 mg ml⁻¹ with adrenaline 5 µg ml⁻¹ was injected to the operative field no later than 15 min before the constant infusion–response intervals.

Depression of twitch height was analysed statistically in probit values (Finney, 1952), and log transformation was used in the statistical analyses of dose requirements and plasma concentrations of the drugs. In the analyses of the twitch responses, the Kruskal–Wallis test or the Wilcoxon test was used, unless another method was indicated. Other statistical analyses were by Student's t test. Differences were considered statistically significant at P < 0.05.

RESULTS

The three groups of patients were comparable with respect to age, weight and body surface area (table I).

Figure 1 demonstrates that there were no
TABLE I. Characteristics of the three groups of patients (mean values ± SD)

<table>
<thead>
<tr>
<th>Drug group</th>
<th>n</th>
<th>M/F</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Body surface area (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>10</td>
<td>1</td>
<td>33.9 ± 12.8</td>
<td>68.2 ± 13.3</td>
<td>1.80 ± 0.21</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>10</td>
<td>1</td>
<td>37.8 ± 12.9</td>
<td>66.9 ± 9.5</td>
<td>1.80 ± 0.16</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>10</td>
<td>1</td>
<td>29.0 ± 12.1</td>
<td>70.5 ± 6.1</td>
<td>1.85 ± 0.13</td>
</tr>
</tbody>
</table>

Fig. 1. Individual responses to bolus injections of estimated ED₉₅ doses. V = vecuronium 56 µg kg⁻¹, P = pancuronium 64 µg kg⁻¹ and A = atracurium 279 µg kg⁻¹.

Differences in sensitivity to the three neuromuscular blocking drugs between men and women (P > 0.4 in either drug group). To test the overall sex difference, we calculated Wilcoxon test statistic for each drug group, assuming a normal approximation with continuity correction (Lehmann, 1975). By addition of χ²-statistics (Armitage, 1980), the estimated P = 0.56. Because there was no indication of a sex difference in the sensitivity to the neuromuscular blockers, the stratification factor was ignored in the subsequent statistical analysis.

Single bolus injections of the previously calculated mean ED₉₅ doses produced neuromuscular blockade which did not differ significantly between groups (table II). The equivalent median responses of the mean ED₉₅ doses were estimated from the data of the previous cumulative dose–response study (Gramstad and Lilleaasen 1982), and quoted in table II. The cumulative dose–response technique gave a slightly more marked response for pancuronium and slightly less marked response for vecuronium, compared with equivalent single bolus injections; however, the differences were not significant. Neither were the differences significant if only female patients were compared with each other. Median bolus effects (%) with total ranges in these patients were: atracurium 97.3 (83.6-100), vecuronium 96.5 (87.5-98.9), and pancuronium 93.3 (83.7-97.7).

If we assume that the bolus dose–response relationships have slopes similar to the cumulative dose–response curves (Gramstad and Lilleaasen, 1982), the potency ratio for bolus doses producing about 95 % twitch depression was 1:4.1:5.1 for atracurium, pancuronium and vecuronium, respectively.

Practically stable infusion–response conditions were obtained in all patients before we tested the change in response at fixed-rate infusion for the 15-min period. Figure 2 shows the distribution of the responses at each end of these time intervals. The individual changes in response from start to end of the constant-rate infusion are given in table III. One per cent change of control twitch height equals 0.057 probits at 90 % response and 0.025 probits at 50 % response. One patient in the vecuronium group was excluded from the 90 % constant effect interval because of leakage from the infusion line.

The drug requirements during the 15-min intervals at 90 % and 50 % twitch depression are presented in table IV. Figure 3 gives a graphic presentation of the dose–response relationships.

TABLE II. Median bolus effects of mean cumulative ED₉₅ doses. Equivalent median effects of the latter doses are quoted. 98 % confidence intervals are given in parentheses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean ED₉₅ (µg kg⁻¹)</th>
<th>Equivalent median effect (%)</th>
<th>Median bolus effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>279</td>
<td>95.7 (80.2-98.6)</td>
<td>95.8 (83.6-98.6)</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>56</td>
<td>93.7 (85.8-98.9)</td>
<td>96.5 (90.5-98.9)</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>64</td>
<td>96.3 (88.9-97.5)</td>
<td>94.7 (86.6-97.7)</td>
</tr>
</tbody>
</table>
for the three drugs at the two levels of neuromuscular blockade. The relative dose-requirements for 90% and 50% continuous blockade were: atracurium 1.62, vecuronium 1.63 and pancuronium 1.86.

The concentrations of vecuronium and pancuronium in plasma at the end of the constant dose-response intervals (EC₉₀ and EC₅₀), as well as the calculated plasma clearances of the drugs, are presented in table V. Two patients in the vecuronium group were excluded from the EC₉₀ determination, because of leakage from the

TABLE III. Changes in response during the 15-min constant-rate infusions. Values are probit medians with total and interquartile ranges (0.28–0.72 fractile when n = 9)

<table>
<thead>
<tr>
<th>Drug</th>
<th>90%-interval (10⁻⁴ probits)</th>
<th>50%-interval (10⁻⁴ probits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>3 (2.2–10.19)</td>
<td>3 (1.2–4.10)</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>2 (n = 9)</td>
<td>6 (0.1–12.15)</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>3 (1.2–7.14)</td>
<td>1 (0.1–2.3)</td>
</tr>
</tbody>
</table>

TABLE IV. Dose requirements for the maintenance of constant responses. These values are mean drug infusion rates with 95% confidence limits. The corresponding responses at the end of the constant-rate infusion periods are mean values with total ranges

<table>
<thead>
<tr>
<th>Drug</th>
<th>90% response level</th>
<th>50% response level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (μg kg⁻¹ h⁻¹)</td>
<td>Block (%)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>382.8 (331.0–452.7)</td>
<td>89.2 (86.4–90.8)</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>101.9 (n = 9)</td>
<td>88.6 (n = 9)</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>36.9 (31.1–43.7)</td>
<td>90.0 (87.5–91.7)</td>
</tr>
</tbody>
</table>

TABLE V. Plasma concentrations and estimated plasma clearances at the end of the constant-rate infusion periods. Values are means with 95% confidence intervals. †Clearance was 5.4 ml min⁻¹ kg⁻¹ (4.4–6.4) for n = 8 (paired values with those measured at 90% response). *Values significantly different from each other (P < 0.001) (paired t test)

<table>
<thead>
<tr>
<th>Drug</th>
<th>90% response level</th>
<th>50% response level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concen (mg litre⁻¹)</td>
<td>Clearance (ml min⁻¹ kg⁻¹)</td>
</tr>
<tr>
<td>VECURONIUM</td>
<td>0.29 (n = 8)</td>
<td>5.9 (n = 8)</td>
</tr>
<tr>
<td></td>
<td>(0.25–0.33)</td>
<td>(4.9–7.0)</td>
</tr>
<tr>
<td>PANCRONIUM</td>
<td>0.32</td>
<td>2.0*</td>
</tr>
<tr>
<td></td>
<td>(0.29–0.35)</td>
<td>(1.6–2.4)</td>
</tr>
</tbody>
</table>
infusion line, and an unsuccessful collection of the plasma sample. The relative potencies of vecuronium and pancuronium in plasma were 1.1:1 both for 50% and 90% twitch depression.

The 25—75% recovery time was only estimated for atracurium and vecuronium, since surgery was completed in three patients in the pancuronium group before the completion of the recordings. The median neuromuscular blockade from which the drug effects declined were 94.3% and 95.1%, respectively. The mean 25-75% recovery index with standard error was significantly longer (P < 0.05) for atracurium (10.3 min±0.59) than for vecuronium (8.5 min±0.51).

**DISCUSSION**

The mean cumulative ED95 dose of each drug, which was calculated in a previous study (Gramstad and Lilleaasen, 1982), produced similar median responses in the three drug groups when injected as a single bolus. Median values were used for this estimation, since the bolus effect in two patients approximated 100%, for which the probit is not defined. Cumulative median responses of the mean ED95 doses were, therefore, also calculated from our previous study to permit relevant comparisons. The present findings confirm the previous estimation of the relative potencies of atracurium, vecuronium and pancuronium to be approximately 1:5:4. Robertson and co-workers (1983) estimated vecuronium to be 4.4 times more potent than atracurium using the cumulative technique; however, atracurium appeared slightly less potent after the bolus injection of these relative doses.

Even though the bolus responses corresponded well with those observed with the cumulative technique, the latter method tended to slightly over-estimate the potency of pancuronium and slightly under-estimate the potency of the shortest-acting drug, vecuronium.

Fisher and colleagues (1982) and Katz and co-workers (1982) found a wider discrepancy between the two techniques for the potency of vecuronium and atracurium, respectively. In our previous study, we restricted the cumulative injections to four doses. The limited time might explain the better agreement with our bolus responses. The cumulative technique might be further improved by the use of three cumulative doses for the intermediate-acting neuromuscular blockers.

An initial loading dose was given so that steady-state conditions at 90% response, during the continuous infusion, would be achieved rapidly. The optimal size of this initial bolus should not be larger than the product of the desired steady-state concentration and the apparent distribution volume (Hull, 1979). By using the data of Shanks and colleagues (1980) we estimated this maximal dose of pancuronium to be 75.4 μg kg⁻¹, which made it reasonable to select the ED95 (64 μg kg⁻¹) as the loading dose. Because our EC50 value (0.32 mg litre⁻¹) was larger than the value estimated from the data of Shanks and colleagues (1980) (0.246 mg litre⁻¹), the possibility of initially overloading the peripheral tissues was even less likely. Assuming a distribution volume for vecuronium of 252 ml kg⁻¹ (Bencini et al., 1983) and EC50 = 0.29 mg litre⁻¹ (present finding), the maximal suitable loading dose in our study would be 73 μg kg⁻¹, which provided a proper margin to the selected ED95 (56 μg kg⁻¹).

In all patients, stable 90% twitch responses were obtained before 60 min of blockade had elapsed, after which the change in response to the constant-rate infusion was minimal. During infusions producing a constant response, equilibrium with peripheral compartments approaches 95% of steady-state after four to five distribution half-lives. By evaluating the distribution kinetics of the drugs in the literature, we chose 60 min as the time after which the assumed constant infusion—response conditions were continued for a further interval. Atracurium has been shown to distribute rapidly with a half-life of 2 min (Ward et al., 1983). The distribution of vecuronium has been estimated to be slower: half-life 3.9 min (Van der Veen and Bencini, 1980), 8.5 min (Fahey et al., 1981), and 13 min (Cronnelly et al., 1983). The distribution half-life of pancuronium is reported
INFUSION OF ATRACURIUM, VECURONIUM AND PANCURONIUM

pancuronium could not be detected in urine for at least 2 h following administration (Shanks, Somogyi and Triggs, 1979), making it probable that the breakdown products appear in low concentration in the plasma during the first few hours of an administration.

The mean plasma concentrations of vecuronium during 90% and 50% sustained blockade measured in our study (0.29 and 0.21 mg litre⁻¹, respectively) are greater than previously reported. Van der Veen and Bencini (1980) estimated EC₉₀ and EC₅₀ to be 0.206 and 0.137 mg litre⁻¹, respectively; and Cronnelly and co-workers (1983) estimated EC₉₀ to be 0.094 mg litre⁻¹ during 0.5–0.7% halothane anaesthesia. Both these groups used integrated pharmacokinetic–pharmacodynamic modelling for their estimations.

The plasma clearance of vecuronium at 90% sustained block (5.9 ml kg⁻¹ min⁻¹) was significantly larger than was estimated at 50% block (5.2 (5.4) ml kg⁻¹ min⁻¹). These values are consistent with the findings of Bencini and colleagues (1983) and Cronnelly and co-workers (1983), which were 4.93 and 5.2 ml kg⁻¹ min⁻¹, respectively, but are greater than those reported by Fahey and colleagues (1981) (3.0 ml kg⁻¹ min⁻¹). Assuming linear pharmacokinetics for vecuronium and equal distribution volumes at the two constant-effect intervals, the insignificant difference in the plasma clearances at 90% and 50% sustained blockade, indicates that the dose requirements for the maintenance of 50% response were also closely related to the steady-state conditions.

The mean plasma concentration of pancuronium measured at 50% sustained blockade (0.23 mg litre⁻¹) is similar to previous findings by Shanks, Somogyi and Triggs (1979) (0.20 mg litre⁻¹), Hull, English and Sibbald (1980) (0.296 mg litre⁻¹), and Evans and co-workers (1984) (0.21 mg litre⁻¹). Calculated mean estimates of EC₉₀ from the reported results of those papers range from 0.25 to 0.42 mg litre⁻¹, and are in agreement with our mean value (0.32 mg litre⁻¹).

Plasma clearance of pancuronium at 90% blockade was estimated to be 1.99 ml kg⁻¹ min⁻¹, which is in agreement with previous findings of 2.11 ml kg⁻¹ min⁻¹ (Somogyi, Shanks and Triggs, 1978), 1.76 ml kg⁻¹ min⁻¹ (Miller et al., 1978), and 1.84 ml kg⁻¹ min⁻¹ (Duvaldestin, Demetriou and d'Hollander, 1982).

At the later 50% blockade the estimated plasma clearance was significantly smaller. The pharmacokinetics of pancuronium have been shown to be linear (Duvaldestin, Demetriou and
d'Hollander, 1982) and, when assuming that the volume of distribution remained constant, this reduction in the estimated plasma clearance can be explained by a continuous transfer of drug from peripheral tissues to plasma, even at 45 min infusion time with 50 % sustained blockade. This invalidates our estimation of the dose requirement of pancuronium for the maintenance of 50 % response.

The plasma concentrations of atracurium were not measured, as an assay technique was not readily available, and prolonged sample storage was not attempted because of possible in vitro degradation. The major route of inactivation of atracurium is by "Hofmann elimination", and degradation will also take place in peripheral tissues (Ward et al., 1983). This makes it unlikely that significant transfer of drug from peripheral tissues to plasma would occur when establishing the 50 % response. Moreover, the short distribution half-life makes it reasonable to assume that steady-state conditions will be attained rapidly during the constant response infusion. The drug requirements of both atracurium and vecuronium at 90 % and 50 % sustained blockade can thereby be adequately compared.

The relative maintenance doses for 90 % and 50 % sustained blockade were found to be: atracurium 1.62 and vecuronium 1.63. From the results in the previous cumulative dose–response study we found the relative dose requirements for the initial blockade to be 1.64 and 1.62, respectively, for the same response interval. This implies that the same relative increase in dose is required from 50 % to 90 % blockade for the induction as well as the maintenance of neuromuscular blockade with atracurium and vecuronium.

The recovery rate from 25 % to 75 % twitch height was significantly shorter for vecuronium than for atracurium, when recovering from about 95 % twitch depression. Robertson and co-workers (1983) observed significantly shorter recovery after vecuronium than atracurium after giving ED90 doses, but no difference after 3 × ED90 doses. They suggested that the prolonged recovery might be the result of saturation of the distribution volume at the higher dose. Estimations of the 25–75 % recovery index for atracurium have given consistently similar results in different studies and with different doses (Basta et al., 1982; Robertson et al., 1983).

In conclusion, our study confirms that the relative potencies for initial blockade with atracurium, vecuronium and pancuronium are approximately 1:5:4. The relative dose requirements for sustained neuromuscular blockade were 10.4:3.8:1, respectively, for 90 % neuromuscular blockade. The same dose ratio also applied to sustained 50 % blockade for atracurium and vecuronium. The relative potency of vecuronium and pancuronium in plasma was 1.1:1.

REFERENCES

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INFUSION OF ATRACURIUM, VECURONIUM AND PANCURONIUM


