COMPARISON OF LARGE DOSE OF VECURONIUM WITH PANCURONIUM FOR PROLONGED NEUROMUSCULAR BLOCKADE

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Vecuronium has been reported to be without adverse cardiovascular effects, even after the administration of doses as large as 0.3 mg kg\(^{-1}\) [1]. Thus by using different doses of this intermediate acting drug, flexibility in its clinical use might be achieved. The purpose of this study was to determine the dose of vecuronium which was necessary to produce a duration of action similar to that of a standard dose of pancuronium (0.1 mg kg\(^{-1}\)). Subsequently, these doses of vecuronium and pancuronium were compared with regard to onset time, duration of action, rate of recovery and cardiovascular effects.

PATIENTS AND METHODS

Patients (ASA class I, age 18–60 yr) undergoing elective surgery under general anaesthesia were studied. Signed informed consent was obtained and the study was approved by the hospital Ethics Committee. Haemoglobin concentration, hematocrit and serum concentrations of ASAT, ALAT, ALP, creatinine, calcium and magnesium were determined. Only patients with normal biochemical indices were included in the study. Exclusion criteria were pregnancy, puerperium, medication interfering with neuromuscular function, neuromuscular disorders and body weight deviating by more than 20% from normal.

All patients received diazepam 10 mg by mouth about 1 h before the induction of anaesthesia. In the operating theatre a catheter was inserted into a vein on the back of one hand and connected to a continuous infusion of Ringer's lactate solution. Atropine 0.6 mg, diazepam 10 mg and fentanyl 0.2 mg were given i.v. before needle electrodes were placed s.c. near the ulnar nerve at the wrist, using the arm without the i.v. cannula. Supramaximal stimuli of 0.2 ms duration at a frequency of 0.1 Hz were delivered from a Myotest nerve stimulator (Biometer, Denmark). The force of adduction of the thumb was measured by using a TD-100 transducer (Biometer, Denmark) and

SUMMARY

Dose-duration relationships for vecuronium were determined and the duration of action produced by vecuronium 0.3 mg kg\(^{-1}\) shown to equal that of pancuronium 0.1 mg kg\(^{-1}\). Using these doses, the neuromuscular blocking properties and cardiovascular effects of the two drugs were compared. With large dose administration of vecuronium (0.3 mg kg\(^{-1}\)), both the onset time (mean 81 s) and the 25–75% recovery index (mean 13.9 min) were about one-half those associated with pancuronium (means 168.5 s and 29.3 min, respectively). The duration of action until 25% recovery was similar with both drugs. There was no evidence of cardiovascular instability with the large dose of vecuronium. Heart rate, however, was significantly slower (range 89.7–94.2% of control) 2–20 min after the injection of vecuronium. Vecuronium 0.3 mg kg\(^{-1}\) may have more favourable neuromuscular blocking effects than pancuronium 0.1 mg kg\(^{-1}\) and may be preferable to pancuronium when prolonged neuromuscular blockade is required.
recorded by a Myograph 2000 (Biometer, Denmark). The resting thumb tension was maintained between 200 and 300 g during recordings. Heart rate, systolic, diastolic and mean arterial pressure were recorded with an oscillotonometer (Criticon Dinamap Adult/Pediatric vital signs monitor, Criticon Inc., Florida, U.S.A.). Once a stable twitch response had been obtained, anaesthesia was induced with thiopentone 5 mg kg\(^{-1}\) and fentanyl 0.2 mg. Ventilation was assisted via a face mask: 70% nitrous oxide in oxygen was used. Increments of fentanyl were given, as required, during the procedure.

Three minutes after induction of anaesthesia with thiopentone the neuromuscular blocking agent was injected as a single dose over 2–3 s into a fast running infusion of Ringer's lactate solution. Five minutes later the trachea was intubated and mechanical ventilation was instituted (end-tidal carbon dioxide concentration between 4 and 5 vol% (Datex Normocap, Datex, Sweden)). Heart rate and arterial pressure were recorded 3, 2 and 1 min before the injection of the neuromuscular blocking drug.

Onset time was defined as the period from the end of the injection of the neuromuscular blocking drug until the single twitch was depressed to 5% of the control value. Duration of action was defined as the period from the end of the injection until the single twitch response had recovered to 25% of the control value. Recovery index was the time interval from 25 to 75% recovery of single twitch. Neuromuscular function was allowed to recover spontaneously.

The study consisted of two consecutive parts. In part I, 56 patients were selected randomly for study. Sixteen patients received pancuronium 0.1 mg kg\(^{-1}\). Forty patients were divided into five groups receiving vecuronium 0.10, 0.15, 0.20, 0.25 or 0.30 mg kg\(^{-1}\). Onset time and duration of neuromuscular blockade were recorded. Dose–duration curves were constructed and used to estimate the dose of vecuronium producing a duration of action equal to that of pancuronium 0.1 mg kg\(^{-1}\). In part II, 20 patients were allocated to receive, on a random basis, either pancuronium 0.1 mg kg\(^{-1}\) or vecuronium 0.3 mg kg\(^{-1}\). The onset time, duration of action and the 25–75% recovery index were recorded. Heart rate and arterial pressure were measured before and 2, 4, 10, 15 and 20 min after the injection of the neuromuscular blocking agent. This part of the study was double-blind.

![FIG. 1. Effect of increasing doses of vecuronium on the onset of neuromuscular blockade. Experimental conditions as described in the Patients and Methods section.](image)

### Table I. Onset time and duration of neuromuscular blocking actions of pancuronium and vecuronium (mean ± SEM)

<table>
<thead>
<tr>
<th>Dose (mg kg(^{-1}))</th>
<th>n</th>
<th>Onset time (s)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium 0.1</td>
<td>16</td>
<td>214.4 ± 21.1</td>
<td>87.4 ± 5.3</td>
</tr>
<tr>
<td>Vecuronium 0.10</td>
<td>8</td>
<td>168.8 ± 11.9</td>
<td>27.6 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>146.3 ± 8.1</td>
<td>41.4 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>110.0 ± 6.3</td>
<td>55.2 ± 3.1</td>
</tr>
<tr>
<td>0.25</td>
<td>8</td>
<td>92.1 ± 5.6</td>
<td>70.4 ± 4.7</td>
</tr>
<tr>
<td>0.30</td>
<td>8</td>
<td>76.9 ± 4.5</td>
<td>86.1 ± 3.1</td>
</tr>
</tbody>
</table>

### Statistical analysis

A linear regression line was used to estimate the vecuronium dose which produced a duration of action equal to that of pancuronium 0.1 mg kg\(^{-1}\). Student's \(t\) test was used for two-group comparison of neuromuscular blocking effects. Multivariate analysis of variance, including repeated measures, was used to compare the effects on heart rate and arterial pressure. Differences were considered statistically significant if \(P \leq 0.05\).
RESULTS

Part I

The increases in the dose of vecuronium from 0.1 to 0.3 mg kg⁻¹ were associated with decrease in onset time (fig. 1, table I). By increasing the dose of vecuronium (as described in the methods section) significant decreases in onset time were observed with all doses greater than 0.15 mg kg⁻¹. The duration of neuromuscular blockade after the administration of vecuronium increased in a dose-dependent manner (fig. 2, table I). Despite applying different regression models to these data, a non-linear term could not be demonstrated. A linear regression line was subsequently determined by the method of least squares. The dose of vecuronium giving a mean duration of action equal to that of pancuronium 0.1 mg kg⁻¹ was calculated to be 0.307 mg kg⁻¹. A dose of 0.288 mg kg⁻¹ was found to produce a duration of neuromuscular blocking action equal to the median duration produced by pancuronium 0.1 mg kg⁻¹. In part II of the study, vecuronium 0.3 mg kg⁻¹ was considered as being equivalent to pancuronium 0.1 mg kg⁻¹.

Part II

The groups receiving vecuronium 0.3 mg kg⁻¹ (n = 10) or pancuronium 0.1 mg kg⁻¹ (n = 10) were comparable with regard to age, weight and body surface area (table II). As shown in figure 3 and table III, the onset time of vecuronium 0.3 mg kg⁻¹ was significantly shorter than that of pancuronium 0.1 mg kg⁻¹ (P < 0.05). The duration of neuromuscular blockade was the same for both drugs (fig. 3). The recovery index was
significantly shorter after vecuronium ($P < 0.001$). A decrease in heart rate ($P < 0.01$), which lasted for 20 min, was seen after the injection of vecuronium ($P < 0.01$) (fig. 4, table IV). When comparing the changes in heart rate following pancuronium or vecuronium there was a significant difference between the two drugs ($P < 0.01$). No significant differences in systolic and mean arterial pressures were seen within or between the vecuronium or pancuronium groups (table IV).

![Graph](image)

**Fig. 4.** Effect of vecuronium $0.3 \text{ mg kg}^{-1}$ (●) or pancuronium $0.1 \text{ mg kg}^{-1}$ (△) on the heart rate: mean ($±\text{ SEM}$) changes from values before neuromuscular blockade. Experimental conditions as described in the Patients and Methods section.

**DISCUSSION**

Vecuronium $0.3 \text{ mg kg}^{-1}$ induced neuromuscular blockade which had a duration of action equal to that of pancuronium $0.1 \text{ mg kg}^{-1}$. Using these doses, however, the speed of onset and rate of recovery were about twice as rapid with vecuronium compared with pancuronium. Cardiovascular instability was not seen with either drug.

The relative potency for initial blockade with pancuronium and vecuronium is about 1:1.25 [2]; the dose of vecuronium used in this study ($0.3 \text{ mg kg}^{-1}$) was nearly four times as potent as pancuronium $0.1 \text{ mg kg}^{-1}$.

A dose-dependent speed of onset was observed after vecuronium throughout the dose range $0.1–0.3 \text{ mg kg}^{-1}$. Other investigators have reported an apparent ceiling effect when using increasing doses to increase the speed of onset. After the injection of vecuronium $0.1$, $0.15$ or $0.20 \text{ mg kg}^{-1}$, Mirakhur and co-workers [3] found no difference in onset time between the two larger doses (162 and 177 s, respectively). Similar findings were reported by Casson and Jones [4]. They found decreasing onset times with vecuronium in doses ranging from $0.05$ to $0.15 \text{ mg kg}^{-1}$. The differences were negligible with doses of $0.15$, $0.2$ and $0.4 \text{ mg kg}^{-1}$ ($99$, $95$ and $87$ s, respectively). A dose-related decrease in onset time after large doses has been observed by Fahey and co-workers [5], who found onset times of $3.8$, $2.8$ and $2.1$ min after $0.07$, $0.14$ and $0.28 \text{ mg kg}^{-1}$, respectively. Because the speed of onset after vecuronium $0.3 \text{ mg kg}^{-1}$ (81 s) is about twice that of pancuronium $0.1 \text{ mg kg}^{-1}$ (168 s), the large dose of vecuronium may be useful for rapid tracheal intubation when

| Table IV. Heart rate (HR), systolic arterial pressure (SAP) and mean arterial pressure (MAP) after injection of either vecuronium $0.3 \text{ mg kg}^{-1}$ ($n = 10$) or pancuronium $0.1 \text{ mg kg}^{-1}$ ($n = 10$). Results ($\text{mean} ± \text{ SEM}$) are expressed as percentage of values before injection |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Time after injection (min)** | 2 | 4 | 10 | 15 | 20 |
| **Vecuronium** | | | | | |
| HR | 90.4 ± 1.7 | 89.7 ± 2.1 | 94.2 ± 2.2 | 92.4 ± 2.3 | 91.6 ± 2.1 |
| SAP | 98.3 ± 1.1 | 98.1 ± 1.6 | 97.5 ± 2.2 | 97.6 ± 1.6 | 97.6 ± 1.5 |
| MAP | 102.3 ± 3.2 | 97.0 ± 3.5 | 103.4 ± 3.9 | 101.1 ± 3.7 | 99.4 ± 2.4 |
| **Pancuronium** | | | | | |
| HR | 99.6 ± 2.6 | 100.3 ± 2.7 | 107.7 ± 2.2 | 103.6 ± 2.6 | 99.8 ± 2.1 |
| SAP | 104.2 ± 2.8 | 103.9 ± 3.5 | 104.3 ± 2.5 | 99.6 ± 2.5 | 102.0 ± 3.1 |
| MAP | 104.7 ± 3.3 | 102.6 ± 3.8 | 106.3 ± 3.2 | 104.7 ± 2.5 | 102.5 ± 3.4 |
suxamethonium is contraindicated. Rapid onset of neuromuscular blockade with vecuronium may also be achieved using the priming principle, which allows complete blockade after 84 s [6], 75.5 s [7] or 102 s [8]. However, because the priming dose may produce partial muscle weakness [9, 10], a large single dose may be preferable to facilitate rapid tracheal intubation.

The mean duration of action after the large dose of vecuronium was somewhat less than after pancuronium in the second part of the study. However, this difference was not significant (P = 0.35). The data on duration of effect in part II are thereby consistent with the results of the initial dose-finding study. The duration of blockade until 25% recovery after pancuronium 0.1 mg kg\(^{-1}\) was comparable to the findings of Savarese, Ali and Antonio [11] and Buzello and Nøldge [12]. Using vecuronium 0.2 mg kg\(^{-1}\), Mirakhur and co-workers [3] determined the duration of action to be 55 min. To our knowledge, the effect of larger doses of vecuronium given without inhalation anaesthetics has not been previously studied.

The large dose of vecuronium did not appear to produce a slower rate of recovery. The mean recovery index in our study (13.9 min) was comparable to findings reported after smaller single doses of vecuronium, 11.6 min and 15.5 min after 0.1 and 0.12 mg kg\(^{-1}\), respectively [13].

There was no evidence of cardiovascular instability after pancuronium or the large dose of vecuronium. Absence of cardiovascular side effects from vecuronium has been shown after small doses (0.036 mg kg\(^{-1}\)) [14] and after large doses (0.3 mg kg\(^{-1}\)) [1]. In our study, heart rate decreased about 10% after vecuronium, which was significantly different from the pancuronium group, in which the values were virtually unchanged. Since atropine was given before induction, all patients had a tachycardia initially and, consequently, the reasons for these changes in heart rate may be complex. The arterial pressure was slightly greater after pancuronium than after vecuronium. This difference, however, was not significant. These observations indicate a greater rate–pressure product after pancuronium 0.1 mg kg\(^{-1}\) than after vecuronium 0.3 mg kg\(^{-1}\) and may indicate a lower myocardial oxygen consumption in the latter group. Thomson and Putnins [15] demonstrated, in patients undergoing coronary bypass grafting, that myocardial ischaemia was significantly correlated to the value of the rate–pressure product. A large dose of vecuronium may thereby be more beneficial than a standard dose of pancuronium in patients with ischaemic heart disease.

In conclusion, a large dose of vecuronium will have favourable neuromuscular blocking properties by producing a rapid onset of action and a rapid recovery, as well as cardiovascular stability. A large dose of vecuronium may thus provide a safer alternative than a standard dose of pancuronium when long-lasting neuromuscular blockade is desired.

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REFERENCES