RELATIVE POTENCY OF ORG NC 45, PANCURONIUM, ALCURONIUM AND TUBOCURARINE IN ANAESTHETIZED MAN

N. KRIEG, J. F. CRUL AND L. H. D. J. BOOIJ

SUMMARY

The relative potency, time-course of action and cardiovascular effects of Org NC 45, a new non-depolarizing neuromuscular blocking agent, have been compared with those of pancuronium, alcuronium and tubocurarine in 64 anaesthetized patients. The relative potency (ED$_{60}$) to Org NC 45 was 1.74, 3.69 and 8.57 respectively. In doses which caused useful surgical relaxation, duration of action of Org NC 45 was 34%, 39% and 26% that of pancuronium, alcuronium and tubocurarine. After administration of repeated doses no cumulation was seen for Org NC 45. The new drug was free from any effect on arterial pressure and heart rate.

Org NC 45, the monoquaternary homologue of pancuronium, is a non-depolarizing neuromuscular blocking agent. It was shown to be a short-acting drug with fast onset of action. The absence of the acetylcholine-like fragment in the A-ring of the molecule made it devoid of vagolytic action while the preservation of the D-ring configuration contributed to the maintenance of strong curariform potency (Buckett, Hewett and Savage, 1973; Savage, Sleight and Carlyle, 1980). In animal experiments its neuromuscular blocking properties have been characterized by a short time to peak effect, a short duration of action and a fast recovery of the neuromuscular block (Durant et al., 1979). A comparative study with other non-depolarizing agents in dogs (Booij et al., 1980) indicated that Org NC 45 was almost free from cardiovascular side-effects. First clinical trials (Crul and Booij, 1980) were very promising and confirmed the impression that most of the properties of Org NC 45 found in animals were valid in man.

We have compared neuromuscular blocking and cardiovascular effects of Org NC 45 with those of pancuronium, alcuronium and tubocurarine, the most commonly used relaxants. We investigated relative potency by means of cumulative dose-response curves and by titrated 95% neuromuscular blocking doses. In the second part of the study effects and side-effects of equipotent bolus injections of the four drugs were studied.

METHODS

Healthy patients undergoing elective lower limb or abdominal surgery, and who had given consent to the study, were premedicated with atropine 0.25 mg, droperidol 5 mg and piritramide 0.15 mg kg$^{-1}$ i.m., 45 min before anaesthesia. Induction was with thiopentone 5 mg kg$^{-1}$ i.v. and anaesthesia was maintained with 67% nitrous oxide in oxygen and incremental doses of fentanyl as needed. A Grass S 88 nerve stimulator delivered supramaximal stimuli at a rate of 0.1 Hz and of 0.2 ms duration, via thin-wall needle electrodes placed subcutaneously over the ulnar nerve near the wrist. Adduction force of the thumb was quantified with a Statham UC 3 force displacement transducer and recorded on a polygraph together with heart rate taken from e.c.g.

Part A

Twenty patients (mean age 46 ± 3 yr; body weight 66 ± 2 kg) were randomly allocated to four groups. After induction of anaesthesia and the injection of suxamethonium 1 mg kg$^{-1}$ i.v., the trachea was intubated. When the depression of twitch tension had recovered completely for at least 5 min, cumulative doses of constant amounts of Org NC 45, pancuronium, alcuronium or tubocurarine i.v. were given till nearly 95% depression of twitch tension was obtained. Incremental doses were administered when the twitch height remained constant for three consecutive twitches. When about 95% depression was reached the neuromuscular blockade

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was allowed to recover spontaneously. At 25% of control twitch tension one-quarter of the total cumulative dose was administered i.v. as a maintenance dose (individual maintenance dose). The maintenance dose was repeated, whenever 25% of control twitch height returned, until the end of the surgical procedure. The mean of total cumulative doses of each relaxant tested was calculated as the mean dose resulting in a 95% depression (titrated ED<sub>95</sub>).

**Part B**

Forty-four patients (mean age 37 ± 2 yr; body weight 66 ± 1 kg) were randomly divided into four groups. In half the number in each group the trachea was intubated as described in part A. After recovery from suxamethonium, which took between 9 and 14 min, and stable twitch response over 5 min, the titrated ED<sub>95</sub> dose (part A) of Org NC 45, pancuronium, alcuronium or tubocurarine was administered i.v. as a bolus. In the remaining patients of each group the trachea was intubated after administration of the “titrated ED<sub>95</sub>” doses, without prior suxamethonium administration, when thumb twitch depression had reached its maximum—between 4 and 12 min.

Arterial pressure was monitored carefully immediately before and 2, 5, 15 and 30 min after the bolus injection of neuromuscular blockers. Patients in this group showing large changes in arterial pressure or heart rate (being obviously a result of intubation) were excluded from the study.

Cumulative dose–response curves were constructed by means of linear regression analysis and compared statistically by an analysis of covariance (Neter and Wasserman, 1974). Student’s t test was applied to compare time from the end of the injection of the neuromuscular blocker to maximal effect (onset), time from end of injection until recovery of the twitch height to 25% and 90% of control (duration 25, duration 90), time elapsed from 25% to 75%, twitch response (recovery index) and changes in heart rate and arterial pressure. Statistically significant differences were assumed at P<0.05.

**RESULTS**

**Part A**

The cumulative dose–response curves of the four relaxants differed from each other, but were parallel (fig. 1). Taken from ED<sub>60</sub> calculated by linear regression, the ratio of potency Org NC 45 : pancuronium : alcuronium : tubocurarine was 1 : 1.74 : 3.69 : 8.57. Mean titrated ED<sub>95</sub> of the four drugs are given in table I. The potency ratio of these 95% blocking doses was 1 : 1.72 : 3.9 : 9.43. The individual

![Figure 1](image.png)

**TABLE I. Mean cumulative doses of relaxants to produce a 90-95% depression of twitch height (mean ± SEM)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (μg kg⁻¹)</th>
<th>% Block</th>
<th>Duration 25 (min)</th>
<th>Duration 25 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>62.2 ± 4.9</td>
<td>95.1 ± 0.8</td>
<td>25.9 ± 6.8</td>
<td>34.4 ± 6.7</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>140.8 ± 12.4</td>
<td>93.4 ± 2.0</td>
<td>27.5 ± 2.8</td>
<td>33.2 ± 4.5</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>340.6 ± 36.9</td>
<td>95.3 ± 0.6</td>
<td>38.3 ± 7.5</td>
<td>42.3 ± 8.6</td>
</tr>
<tr>
<td>Org NC 45</td>
<td>36.1 ± 5.7</td>
<td>92.4 ± 0.9</td>
<td>8.0 ± 0.7</td>
<td>8.5 ± 0.8</td>
</tr>
</tbody>
</table>

**TABLE II. Time-course of maintenance of neuromuscular blockade. Doses amounted to one-quarter of individual 95%, blocking dose. Duration 25 was significantly prolonged after the third injection of pancuronium, alcuronium and tubocurarine. It remained constant for Org NC 45 (P<0.05; mean ± SEM).**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (μg kg⁻¹)</th>
<th>First repeat</th>
<th>Second repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Block</td>
<td>Duration 25</td>
<td>% Block</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>15.6 ± 1.2</td>
<td>89.7 ± 2.0</td>
<td>25.9 ± 6.8</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>35.2 ± 3.1</td>
<td>94.6 ± 1.5</td>
<td>27.6 ± 3.1</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>38.2 ± 9.2</td>
<td>92.1 ± 0.9</td>
<td>38.3 ± 7.5</td>
</tr>
<tr>
<td>Org NC 45</td>
<td>9.0 ± 1.4</td>
<td>87.9 ± 2.0</td>
<td>8.0 ± 0.7</td>
</tr>
</tbody>
</table>
maintenance dose caused statistically identical reductions of thumb twitch response in all groups (table II). The recovery time to 25% of control twitch tension (duration 25) was significantly longer after the second maintenance dose of pancuronium, alcuronium and tubocurarine compared with the first dose (table II). For Org NC 45 duration 25 did not change significantly over a series of four injections: 8.1 ± 1.0 and 9.0 ± 0.8 after the third and fourth repeat dose respectively.

Part B

Mean neuromuscular blockade achieved by bolus injection of the titrated ED₉₅ was smaller than that of the cumulative administration. The difference was not statistically significant. The blocking effect of the bolus injections was identical comparing the patients within groups (with and without prior suxamethonium) and between groups (table III). Onset, duration and recovery index of neuromuscular blockade are shown in table IV. Onset was equal in the Org NC 45 and pancuronium groups. All other time-courses of action were significantly shorter for Org NC 45.

Pancuronium, alcuronium and tubocurarine increased heart rate significantly in the first 5 min after administration, whereas heart rate in the Org NC 45 group remained unchanged. Arterial pressure decreased significantly after alcuronium and tubocurarine and increased after pancuronium; however, the last effect was not statistically significant. Patients who received Org NC 45 showed no significant change in arterial pressure (fig. 2).

**DISCUSSION**

The relative potency of pancuronium, alcuronium and tubocurarine found in this study is in accord with previous animal studies (Cass et al., 1976; Booij et al., 1980) and human studies (Lund and Stovner, 1970; Donlon, Ali and Savarase, 1974) and with clinical experience (Baird and Reid, 1967; Baird, 1968; Crul, 1970; Levin and Dillon, 1971). Somogyi, Shanks and Triggs (1978) calculated the amount of a bolus injection of pancuronium producing an almost complete block to be 62.5 μg kg⁻¹ body weight. This is almost identical with our finding (62.2 ± 4.9 μg kg⁻¹).

The relative potency of Org NC 45 to pancuronium (1.7) in this study differs from that reported by Agoston and others (1980), who found the drugs to be equipotent. The difference may be explained by differences in method. We facilitated intubation of the trachea with suxamethonium 1.0 mg kg⁻¹ before titration of the 95% blocking dose by steps, whereas Agoston’s group administered bolus injections of Org NC 45 without prior suxamethonium. The influence of suxamethonium on the potency of subsequently given non-depolarizing neuromuscular blocking agents is contested (Walts and Dillon, 1969; Katz, 1971; Walts and Rustin, 1977). We did not observe a significant influence on pancuronium, alcuronium and tubocurarine (Walts and Rustin, 1977), but prior administration of suxamethonium seems to enhance the neuromuscular blocking effect of Org NC 45 (table III).

**Table III. Percent neuromuscular blockade after bolus injection of non-depolarizing relaxant, with and without previous suxamethonium 1 mg kg⁻¹ and between groups combined (mean ± SEM)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (μg kg⁻¹)</th>
<th>Without % Block</th>
<th>With sux. % Block</th>
<th>All % Block</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>62</td>
<td>92.9 ± 3.5</td>
<td>84.6 ± 6.9</td>
<td>88.7 ± 3.9</td>
<td>12</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>141</td>
<td>84.4 ± 4.9</td>
<td>79.9 ± 11.9</td>
<td>82.1 ± 6.1</td>
<td>10</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>341</td>
<td>84.4 ± 3.8</td>
<td>83.2 ± 5.1</td>
<td>83.8 ± 3.0</td>
<td>10</td>
</tr>
<tr>
<td>Org NC 45</td>
<td>36</td>
<td>78.8 ± 6.5</td>
<td>90.7 ± 4.1</td>
<td>83.8 ± 4.1</td>
<td>12</td>
</tr>
</tbody>
</table>

**Table IV. Time-course of neuromuscular blockade in patients after a bolus injection of relaxant (mean ± SEM)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (μg kg⁻¹)</th>
<th>Onset (min)</th>
<th>Duration 25 (min)</th>
<th>Duration 90 (min)</th>
<th>Recovery index (min)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>62</td>
<td>4.9 ± 0.7</td>
<td>34.4 ± 5.8</td>
<td>73.2 ± 11.4</td>
<td>31.9 ± 4.5</td>
<td>12</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>141</td>
<td>5.9 ± 0.4</td>
<td>29.3 ± 1.6</td>
<td>62.6 ± 7.5</td>
<td>29.0 ± 2.3</td>
<td>10</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>341</td>
<td>9.9 ± 1.1</td>
<td>33.8 ± 4.3</td>
<td>96.4 ± 16.1</td>
<td>59.3 ± 8.1</td>
<td>10</td>
</tr>
<tr>
<td>Org NC 45</td>
<td>36</td>
<td>4.5 ± 0.2</td>
<td>11.6 ± 1.2</td>
<td>24.9 ± 2.4</td>
<td>9.7 ± 0.8</td>
<td>12</td>
</tr>
</tbody>
</table>
The short time-course of action of Org NC 45 seen in animals (Durant et al., 1979) and in man (Agoston et al., 1980; Crul, Krieg and Booij, 1980), is confirmed by our results. Katz (1971) reported a recovery time to 90% of control twitch tension of 58 min after a bolus of pancuronium 40 \( \mu \text{g} \text{kg}^{-1} \), which is in agreement with our results (62 \( \mu \text{g} \text{kg}^{-1} \), 73 min). Allowing for the different doses used, the duration of action of a bolus injection of Org NC 45 (degree of block averaging 83.8%) is only one-third that of an equipotent dose of pancuronium. The same is true for the duration of useful surgical relaxation (duration 25). After a bolus of pancuronium 40 \( \mu \text{g} \text{kg}^{-1} \) (Katz, 1971) or 62 \( \mu \text{g} \text{kg}^{-1} \) (this study) duration 25 was 26 or 34 min respectively. Again, pancuronium acted three times longer than Org NC 45. Thus the time course of action of Org NC 45 almost meets the demands of an “ideal short acting” non-depolarizing muscle relaxant (Savarese, and Kitz, 1975).

During maintenance of neuromuscular blockade (repeated administration of constant doses of relaxant at 25% recovery of twitch tension) pancuronium, alcuronium and tubocurarine showed clear evidence of cumulation; duration 25 was significantly prolonged after the second maintenance dose. In the case of Org NC 45 both duration 25 and % block were virtually unchanged until the fourth repeat injection (duration 25 ranging from 8.0 to 9.0 min and % block ranging from 87.1% to 90.2%). Agoston and others (1980) reported that maintenance doses during long-lasting operations were “required at a remarkably regular rate”.

The absence of chronotropic or pressor effects after the administration of Org NC 45 is notable. In spite of the relatively inaccurate method of arterial pressure monitoring, the time course of changes in arterial pressure and heart rate are similar to those reported by other investigators (Kennedy and Kelman, 1970; Loh, 1970; Kelman and Kennedy, 1971; Coleman et al., 1972). Differences between these and our results are doubtless because of the greater accuracy of their methods or the different doses of relaxants used in some cases. Changes in heart rate and arterial pressure following intubation of the trachea are of minor importance in this study because in half of the patients suxamethonium had

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**Fig. 2. Time-course of percent change in heart rate (HR) and mean arterial pressure (MAP) after bolus injections of relaxants (doses as in table III). ◊ = value before induction of anaesthesia; ○ = value immediately before injection of relaxant. ∗ Significantly different changes are marked in line with * at the different times ($P < 0.05$).**
been given and the tracheal tube inserted 14–19 min before administration of the non-depolarizing relaxants, whereas in the others the tracheal tube was inserted not earlier than 4–12 min after injection of the non-depolarizing relaxant when the maximum twitch depression was reached. Moreover, there was no difference in heart rate and arterial pressure changes between these two groups. Any influence of premedication upon heart rate and arterial pressure was probably negligible because of the low dosage of these drugs and the time interval of at least 1 h between premedication and the administration of the relaxant. We conclude that Org NC 45, in the doses used, is free from vagolytic and cardio-depressive side-effects. It is a powerful neuromuscular blocking agent with a short duration of action and minimal cumulation of action. Further studies to determine its role in routine clinical anaesthesia are needed.

ACKNOWLEDGEMENT
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REFERENCES


