CLINICAL STUDIES ON ORG NC45: COMPARISON WITH PANCURONIUM

W. J. KERR AND W. L. M. BAIRD

SUMMARY

Some actions of OrgNC45 have been compared with those of pancuronium in a study on 50 patients anaesthetized with nitrous oxide and narcotic supplements. The train-of-four technique was used to assess the recovery of neuromuscular blockade and its antagonism. Org NC45 was shown to have a duration of action from injection of the intubating dose (0.1 mg kg\(^{-1}\)) to the reappearance of the first twitch response of 23.5 ± 1.1 min; the corresponding time for pancuronium 0.1 mg kg\(^{-1}\) was 50.5 ± 3.6 min. Recovery time from the initial incremental dose to the reappearance of the first train-of-four response was 11.6 ± 0.8 min with Org NC45 and 31 ± 4.7 min with pancuronium. No evidence of cumulation was seen following several incremental doses of Org NC45. The rate of onset of paralysis of adductor pollicis was faster with Org NC45 than with pancuronium, but the difference did not reach statistical significance. Satisfactory spontaneous recovery from Org NC45 blockade could be achieved without undue delay. Org NC45 was shown to produce significantly less tachycardia.

The animal pharmacology of OrgNC45 was described by Durant and his co-workers (Durant et al., 1979; Durant, Houwertjes and Crul, 1980). Further animal studies, and the preliminary clinical reports were the subject of a symposium, the proceedings of which were edited by Bowman and Norman (1980).

In man Org NC45 has a potency slightly greater than, and a duration of action one-half to one-third that of pancuronium. There is a rapid offset of action and little or no cumulation following multiple doses. The neuromuscular blockade is easily antagonized by neostigmine. There is no evidence of cardiovascular side-effects even at doses in excess of those required to ensure good muscle relaxation during surgery.

These clinical characteristics have been confirmed by Fahey and others (1981), who concluded that Org NC45 warrants further investigation since it appears to offer advantages over the currently available neuromuscular blocking drugs.

The present study compares aspects of the pharmacological profile of Org NC45 with that of pancuronium when used in approximately equipotent doses for tracheal intubation and for muscle relaxation.

METHODS

Fifty healthy patients undergoing elective surgery requiring muscle relaxation were studied. Written consent for the study was obtained from each patient.

Each patient was randomly assigned to one of two groups to receive Org NC45 0.1 mg kg\(^{-1}\) or pancuronium 0.1 mg kg\(^{-1}\). These doses were selected because Agoston and others (1980) considered that the potency of Org NC45 approximated to that of pancuronium in anaesthetized patients. The anaesthetic technique was otherwise identical for each group. I.m. premedication was either morphine 10 mg and atropine 0.6 mg, or papaveretum 15-20 mg and hyoscine 0.3-0.4 mg, given approximately 1 h before induction of anaesthesia. An i.v. infusion of Ringer's lactate solution was commenced. Anaesthesia was induced with droperidol 5–10 mg and fentanyl 0.1–0.15 mg given into the infusion, followed 5 min later by a dose of thiopentone sufficient to induce sleep (200–400 mg). Injection of the neuromuscular blocker followed immediately and tracheal intubation was performed 90 s later. Anaesthesia was maintained with 66% nitrous oxide in oxygen and increments of fentanyl were given as required. The lungs were ventilated artificially. Heart rate and arterial systolic pressure were measured throughout using a Roche 105 E.C.G. monitor and a sphygmomanometer respectively. Neuromuscular transmission was monitored.
using a Myotest peripheral nerve stimulator (Viby-Mogensen, Hansen et al., 1980) surface electrodes being placed over the ulnar nerve at the right wrist. A train-of-four stimulus (Ali, Utting and Gray, 1971) was given with tactile evaluation of the evoked response of adductor pollicis, the same investigator (W.B.) making the assessment on every occasion.

The elapsed time between the return of each successive response to train-of-four stimulation was noted. Increments of relaxant drug (25% of the initial dose) were given when the third response to the train-of-four stimulation was detectable, or sooner if clinically indicated. On completion of the surgery, anaesthesia was maintained until the train-of-four stimulation produced at least one twitch response. Thereafter, neostigmine 0.02 mg kg⁻¹ with atropine was administered; if required, further increments of neostigmine 0.004 mg kg⁻¹ were given at 2-min intervals (with additional atropine) until the fourth response to train-of-four stimulation was judged to be essentially of the same magnitude as that of the first response. This was taken as being equivalent to a train-of-four ratio (fourth twitch expressed as a percentage of the first) of 75% or better and therefore indicating adequate antagonism of the neuromuscular blockade for clinical purposes (Ali and Katz, 1973). Anaesthesia was then discontinued. As a further assessment, the patient was asked to open his eyes, protrude the tongue, and raise his head off the pillow after recovery of consciousness.

RESULTS

Table I shows the duration of action of and spontaneous recovery from the initial dose of Org NC 45 and pancuronium as judged by the return of the train-of-four response, and the corresponding data for the first incremental dose. Two patients were excluded from the Org NC 45 group and three from the pancuronium group; following the intubating dose of relaxant, a diminished first twitch response persisted and thus it was impossible to record the time interval from injection to the re-appearance of the first twitch. This marked variation in response to the relaxants is well recognized.

With the intubating dose (table I), the mean time from injection of Org NC 45 until re-appearance of the first twitch response was 23.5 ± 1.1 min, whereas with pancuronium the corresponding time was 50.5 ± 3.6 min. Thereafter recovery to the third response required a further 8.9 and 23.5 min for Org NC 45 and pancuronium respectively. Similarly, the mean time for recovery from the first incremental dose to the re-appearance of the first response to the train-of-four (table I) was 11.6 ± 0.8 min with Org NC 45 and 31 ± 4.4 min with pancuronium, following which a further 8.7 and 18.3 min respectively were required to achieve a third train-of-four response. It is generally accepted that, in an “adequately” anaesthetized patient, satisfactory muscle relaxation for abdominal surgery exists when two of the train-of-four responses are eliminated (Miller, 1981). These recovery times indicate that Org NC 45 has a significantly shorter duration of action than that of pancuronium (P < 0.01).

In figure 1 the return of the train-of-four responses following intubation, and first incremental

<table>
<thead>
<tr>
<th>Time interval between re-appearance of successive twitches of train-of-four</th>
<th>Mean SEM</th>
<th>n</th>
<th>Mean SEM</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection to 1st twitch (min)</td>
<td>23.5 ± 1.1</td>
<td>23</td>
<td>50.5 ± 3.6</td>
<td>22</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>1st to 2nd twitch (min)</td>
<td>5.2 ± 0.7</td>
<td>23</td>
<td>15.0 ± 2.3</td>
<td>12</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>2nd to 3rd twitch (min)</td>
<td>3.7 ± 0.6</td>
<td>7</td>
<td>8.5 ± 2.5</td>
<td>2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>First incremental dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection to 1st twitch (min)</td>
<td>11.6 ± 0.8</td>
<td>16</td>
<td>31.0 ± 4.4</td>
<td>7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>1st to 2nd twitch (min)</td>
<td>5.1 ± 0.7</td>
<td>16</td>
<td>10.8 ± 1.6</td>
<td>5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>2nd to 3rd twitch (min)</td>
<td>3.6 ± 0.4</td>
<td>13</td>
<td>7.5 ± 1.0</td>
<td>4</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
ORG NC45 AND PANCURONIUM

FIG. 1. Recovery of train-of-four response following the intubation doses and first incremental doses of Org NC45 and pancuronium. Each value represents the mean of the time intervals between the re-appearance of successive twitches of the train-of-four. ■ = Org NC45, intubation dose (0.1 mg kg\(^{-1}\)); ◆ = pancuronium, intubation dose (0.1 mg kg\(^{-1}\)); ○ = Org NC45, first incremental dose (0.025 mg kg\(^{-1}\)); □ = pancuronium, first incremental dose (0.025 mg kg\(^{-1}\)).

Doses of both Org NC45 and pancuronium, are plotted against the mean time (min). The steeper slope of the lines joining the points for Org NC45 compared with those for pancuronium reflects the more rapid rate of recovery from the former drug.

Although limitation of operating time precluded the administration of multiple incremental doses to patients in the pancuronium group, the significantly shorter duration of action of Org NC45 frequently allowed several doses to be given within the operating time. Table II shows the data for these patients who received multiple doses of Org NC45.

Satisfactory spontaneous recovery from the blockade produced by Org NC45 (train-of-four ratio greater than 75%) occurred in four patients: in the first patient, 50 min after the initial dose, and in the remaining three, in times ranging from 31 to 40 min following incremental doses (table II).

When the return of the train-of-four response following the initial and each subsequent incremental dose is plotted against time (min) (fig. 2), it can

FIG. 2. Recovery of train-of-four response following repeated doses of Org NC45. Each value represents the mean of the time intervals between the re-appearance of successive twitches of the train-of-four. ■ = intubation dose (0.1 mg kg\(^{-1}\)); ◆ = second dose (0.025 mg kg\(^{-1}\)); □ = third dose (0.025 mg kg\(^{-1}\)); ○ = fourth dose (0.025 mg kg\(^{-1}\)).

Table II

<table>
<thead>
<tr>
<th>Time interval between re-appearance of successive twitches of train-of-four</th>
<th>1st dose (0.1 mg kg(^{-1}))</th>
<th>2nd dose (0.025 mg kg(^{-1}))</th>
<th>3rd dose (0.025 mg kg(^{-1}))</th>
<th>4th dose (0.025 mg kg(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SEM n</td>
<td>Mean SEM n</td>
<td>Mean SEM n</td>
<td>Mean SEM n</td>
<td></td>
</tr>
<tr>
<td>Injection to 1st twitch (min)</td>
<td>23.5±1.1 23</td>
<td>11.6±0.8 16</td>
<td>10.9±1.3 7</td>
<td>8.8±1.4 5</td>
</tr>
<tr>
<td>1st to 2nd twitch (min)</td>
<td>5.2±0.7 23</td>
<td>5.1±0.7 16</td>
<td>5.9±1.3 6</td>
<td>3.6±0.6 5</td>
</tr>
<tr>
<td>2nd to 3rd twitch (min)</td>
<td>3.7±0.6 7</td>
<td>3.6±0.4 13</td>
<td>5.0±1.0 4</td>
<td>3.0±0.5 5</td>
</tr>
<tr>
<td>3rd to 4th twitch (min)</td>
<td>2.6±0.4 5</td>
<td>2.6±1.3 10</td>
<td>3.7±0.4 4</td>
<td>2.6±0.6 5</td>
</tr>
<tr>
<td>Total time from injection to full recovery (min) (four patients)</td>
<td>50 1</td>
<td>33 1</td>
<td>40 1</td>
<td>31 1</td>
</tr>
</tbody>
</table>
be seen that for each dose the recovery rate, as represented by the slope, is similar; each incremental dose completely abolished the train-of-four response for approximately 9–11 min. These results suggest absence of drug cumulation.

The mean total dose of neostigmine required to achieve satisfactory reversal of blockade (train-of-four ratio greater than 75%) in the two groups of patients was compared (table III), the four patients in the Org NC45 group who did not require anticholinesterase having been excluded. Overall, the Org NC45 group required significantly less neostigmine ($P<0.05$) than those in the pancuronium group. When the two groups were matched for degree of residual neuromuscular block at the time of administration of the antagonist, however, the neostigmine requirement was less in the Org NC45 group than in the pancuronium group, but the difference was not statistically significant.

The mean onset time as measured from injection until there was no response evoked by the train-of-four stimulation (table IV) was 2.81 ± 0.5 min and 3.47 ± 1.6 min for Org NC45 and pancuronium respectively. These results are not statistically different. As in table I, the five patients in whom blockade was incomplete were excluded.

Figures 3 and 4 display the heart rate and arterial systolic pressure changes for the first 30 min following injection of the intubating dose of each drug. Fifteen minutes after injection of the relaxant, when the effects of endotracheal intubation could probably be discounted, the mean heart rate in those patients who had received Org NC45 was approximately 30 beat min$^{-1}$ less than in those receiving pancuronium. At this time surgery was either about to commence or had merely reached the stage of skin incision. In contrast, the corresponding arterial systolic pressure recordings were not markedly differ-

**Table III. Doses of neostigmine (mg kg$^{-1}$) required for complete antagonism of neuromuscular blockade. Four Org NC45 patients did not require neostigmine and are excluded from the overall comparison. Student's t test has been applied**

<table>
<thead>
<tr>
<th>Neostigmine requirement (mg kg$^{-1}$)</th>
<th>Org NC45 group</th>
<th>Pancuronium group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Train-of-four response at time of neostigmine injection</td>
<td>Mean</td>
<td>SEM</td>
</tr>
<tr>
<td>1 twitch present</td>
<td>0.030</td>
<td>1</td>
</tr>
<tr>
<td>2 twitches present</td>
<td>0.022 ± 0.002</td>
<td>6</td>
</tr>
<tr>
<td>3 twitches present</td>
<td>0.020 ± 0.001</td>
<td>10</td>
</tr>
<tr>
<td>4 twitches present</td>
<td>0.020 ± 0.0</td>
<td>4</td>
</tr>
<tr>
<td>Overall</td>
<td>0.021 ± 0.001</td>
<td>21</td>
</tr>
</tbody>
</table>

**Table IV. Time (min) from injection of intubation dose of Org NC45 and pancuronium to complete abolition of the train-of-four response. (Student's t test applied; difference is not significant) Five patients were excluded because of incomplete blockade (see text)**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>n</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Org NC45</td>
<td>2.81 ± 0.5</td>
<td></td>
<td>23</td>
<td>$&gt;0.05$</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>3.47 ± 1.6</td>
<td></td>
<td>22</td>
<td>$&gt;0.05$</td>
</tr>
</tbody>
</table>

**Fig. 3. Changes in heart rate from pre-induction values following injection of intubating doses (0.1 mg kg$^{-1}$) of Org NC45 and pancuronium. The values are expressed as mean ± SEM ($n=25$ for each group). The heart rate is significantly less in the Org NC45 group from 5 min onwards ($P<0.01$).**
FIG. 4. Changes in arterial systolic pressure from pre-induction values following injection of intubation doses (0.1 mg·kg\(^{-1}\)) of Org NC45 and pancuronium. The values are expressed as mean ± SEM (n = 25 for each group). At no time was there a significant difference between the groups.

DISCUSSION

There is a need for caution when interpreting the data from a clinical study which does not include large numbers of patients. Nonetheless, our results confirm that, with an anaesthetic technique that excludes volatile agents, Org NC45 has a duration of action between one-third and one-half that of pancuronium. The doses used in this study were recognized as being only approximately equipotent since most previous authors had found Org NC45 to be a little more potent than pancuronium (Baird and Herd, 1980; Krieg, Crul and Booj, 1980; Vibu-Mogensen, Jorgensen et al., 1980; Fahey et al., 1981). Consideration of this fact would probably further emphasize the difference in duration of action between the two drugs.

The relative lack of cumulation following repeated doses of Org NC45 has already been described. In this study patients who received several supplementary doses of Org NC45 showed no evidence of prolonged block.

Recently Gencarelli and Miller (1982), using an elegant technique which took account of the different spontaneous recovery rates of Org NC45 and pancuronium, have shown that, in man, the two drugs are effectively and equally antagonized by neostigmine. In our study those who had received Org NC45 required less neostigmine than those in the pancuronium group for recovery from an equivalent neuromuscular block, although the difference was not statistically significant. This difference could be attributed to a more rapid spontaneous recovery from Org NC45 blockade.

The four patients in whom adequate recovery from Org NC45 blockade was achieved without anticholinesterase are of particular interest. It would seem that, after Org NC 45, provided neuromuscular transmission is monitored, neostigmine may be safely omitted and yet satisfactory recovery be obtained without undue delay. This advantage of Org NC 45 was noted by Baird, Bowman and Kerr (1982) with reference to the complications ascribed to neostigmine following ileo-rectal anastomosis (Bell and Lewis, 1968; Wilkins et al., 1970).

In this study the onset time to total block of the evoked response to train-of-four stimulation was slightly shorter with Org NC 45 compared with pancuronium, but the difference was not statistically significant. This finding is in agreement with that of Fahey and colleagues (1981), while Crul and Booj (1980) found Org NC 45 to be shorter in onset “but not dramatically so”, and Agoston and others (1980), when using the same dose (0.1 mg·kg\(^{-1}\)), described the onset time of both drugs as equal. The relationship between onset time and intubating conditions is complex, however, and the extent of central depression of reflex activity plays an important role. Agoston and others (1980) emphasized that tracheal intubation can be effected with Org NC 45 well before there is total block of the evoked response of the adductor pollicis and Norman, Read and Du Boulay (1980) noted that, with this drug, apnoea preceded paralysis of the hand muscles. When comparing Org NC 45 0.1 mg·kg\(^{-1}\) with pancuronium 0.1 mg·kg\(^{-1}\), Harrison and Feldman (1981) described the intubating conditions at 90 s as being not markedly different and our experience in this study would support this.

At 15 min following injection of Org NC 45, and when the surgical stimulus was absent or minimal, there was no evidence of tachycardia; this agrees with the findings from other clinical studies of this drug. Animal experiments have shown that, in contrast to pancuronium and other non-depolarizing agents, Org NC 45, in doses 20 times greater than those required for neuromuscular blockade, has no effect on the heart rate, arterial pressure or the sympathetic nervous system (Marshall et al., 1980).
REFERENCES


ACKNOWLEDGEMENTS

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ETUDES CLINIQUES SUR L'ORG NC 45:
COMPARAISON AVEC LE PANCURONIUM

RESUME

Certaines actions de l'Org NC 45 ont été comparées à celles du pancuronium dans une étude effectuée chez 50 patients anesthésiés au protoxyde d'azote avec des adjuvants morphinominétiques. La technique du train de quatre a été utilisée pour préciser la récupération du bloc neuromusculaire et son antagonisme. L'Org NC 45 s'est révélé avoir une durée d'action à partir de l'injection d'une dose suffisante pour l'intubation (0,1 mg kg\(^{-1}\)) jusqu'à la réapparition de la première réponse du twitch de 23,5±1,1 min; la durée correspondante pour le pavulon (0,1 mg kg\(^{-1}\)) était de 50,5±3,6 min. Le temps de récupération entre la dose initiale et la réapparition de la première réponse au train de quatre était 11,6±0,8 min avec l'Org NC 45 et 31±4,7 min avec le pancuronium. Il n'y a pas eu de signes d'accumulation après plusieurs doses croissantes d'Org NC 45.

La vitesse d'installation d'une paralysie du muscle adducteur pollicis était plus rapide avec l'Org NC 45 qu'avec le pancuronium, mais la différence n'était pas statistiquement significative.

Une récupération spontanée satisfaisante du bloc à l'Org NC 45 a pu être obtenue sans délais excessifs. L'Org NC 45 s'est révélé induire une tachycardie significativement moins importante.

KLINISCHE STUDIEN ÜBER ORG NC 45:
VERGLEICH MIT PANCURONIUM

ZUSAMMENFASSUNG

Einige Wirkungen von Org NC 45 wurden mit denen von Pancuronium in einer Studie an 50 Patienten verglichen. Die Narkose wurde mit Lachgas und weiteren Narkosemitteln durchgeführt. Die train-of-four Technik wurde zur Beurteilung der Erholung der neuromuskulären Blockade und deren Antagonisierung verwendet. Es zeigte sich, daß Org NC 45 eine Wirkungsdauer von der Injektion der Intubationsdosis (0,1 mg kg\(^{-1}\)) bis zum Wiederauftreten der ersten Zuck-Antwort von 23,5±1,1 s besaß. Die entsprechende Zeit für Pancuronium 0,1 mg kg\(^{-1}\) betrug 50,5±3,6 min. Die Erholungszeit von der "initial" ansteigenden Dosis bis zum Wiederauftreten der ersten train-of-four Antwort war 11,6±0,8 min bei Org NC 45 und 31±4,7 bei Pancuronium. Es trat keine Akkumulation nach mehreren größer werdenden Dosen von Org NC 45 auf. Die Rate des Einsetzens der Lähmung des M. adductor pollicis war bei Org NC 45 schneller als bei Pancuronium, der Unterschied war aber nicht statistisch signifikant. Ausreichende spontane Erholung von der Org NC 45-Blockade wurde ohne ungewöhnliche Verzögerung erreicht. Org NC 45 verursachte signifikant weniger Tachykardien.
ESTUDIOS CLÍNICOS DEL ORG NC45:
COMPARACIÓN CON EL PANCURONIO

SUMARIO
Se llevó a cabo la comparación de algunas acciones del Org NC45 con las del pancuronio en el curso de un estudio de unos 50 pacientes anestesiados con óxido nitroso y complementos narcóticos. Se usó la técnica de la serie-de-cuatro para evaluar la recuperación del bloqueo neuromuscular y su antagonismo. El Org NC45 demostró tener una duración de acción entre la inyección de la dosis de intubación (0,1 mg kg\(^{-1}\)) y la reaparición de la primera respuesta de contracción, de 23,5 ± 1,1 min.; el periodo correspondiente del pancuronio (0,1 mg kg\(^{-1}\)) fue de 50,5 ± 3,6 min. El tiempo de recuperación desde la dosis creciente inicial hasta la reaparición de la primera respuesta de serie-de-cuatro fue de 11,6 ± 0,8 min con el Org NC45 y de 31 ± 4,7 min con el pancuronio. No se observó ninguna prueba de acumulación a raíz de las distintas dosis crecientes de Org NC45. El ritmo de acción de la parálisis del abductor del pulgar era mayor con el Org NC45 que con el pancuronio, pero la diferencia no tenía significado desde el punto de vista estadístico. Pudo conseguirse sin demora indebida la recuperación espontánea satisfactoria del bloqueo del Org NC45. Se observó que el Org NC45 produce mucho menos taquicardia.