CLINICAL EVALUATION OF ORG NC45

R. K. MIRAKHUR, C. J. FERRES, R. S. J. CLARKE, I. M. BALI AND J. W. DUNDEE

SUMMARY
Org NC45, a new non-depolarizing neuromuscular blocking drug, was evaluated in 200 adult patients. The drug was administered in doses of 0.1, 0.15 or 0.2 mg kg\(^{-1}\). Intubation could be satisfactorily carried out at around 90 s in 90% of patients. The duration of clinical relaxation varied from 23 min with 0.1 mg kg\(^{-1}\) and neuroleptanaesthesia to 71 min with 0.2 mg kg\(^{-1}\) and anaesthesia with halothane or enflurane. The duration of clinical relaxation following repeated administration of 2 - 3 mg was remarkably constant (between 17 and 20 min) thus showing lack of cumulation. The antagonism of residual block was prompt and easy following administration of neostigmine, and the drug lacked any significant cardiovascular effects as seen by routine monitoring.

Currently available neuromuscular blocking drugs, whether depolarizing or non-depolarizing, suffer from certain disadvantages. Although suxamethonium has the assets of a rapid onset and a short duration of action, it suffers from well-documented disadvantages such as muscle pains, hyperkalaemia in susceptible individuals, and increases in intraocular and intragastric pressures (Churchill-Davidson, 1954; Anderson, 1962; La Cour, 1969; Pandey, Badola and Kumar, 1972; Gronert and Theye, 1975).

Non-depolarizing drugs not only have a longer time to the onset of action, but have other side-effects such as histamine release, ganglion blockade and myocardial depression (tubocurarine (Johnstone, Mahmoud and Mrozinski, 1978; Booij, Kreig and Crul, 1980; Moss et al., 1980)) and tachycardia and, occasionally, hypertension with gallamine, pancuronium, alcuronium and fazzadinium (Smith and Whitcher, 1967; Brown and Crout, 1970; Kennedy and Kelman, 1970; Saxena and Bonta, 1970; Kelman and Kennedy, 1971; Savege et al., 1973; Domenech et al., 1976; Iwatsuki et al., 1980).

The side-effects of suxamethonium contraindicate its use in certain situations and most anaesthetists would welcome a competitive agent with a rapid onset and a relatively short duration of action (Norman and Bowman, 1980).

Org NC45 (vecuronium bromide) has been developed as a more rapidly acting non-depolarizing neuromuscular blocking agent (Durant et al., 1979; Savage, Sleigh and Carlyle, 1980), which is a monovalent analogue of pancuronium. The results from initial studies on the drug were reported at a Symposium in Lucerne (Supplement, 1980). This paper describes the results obtained in a more extensive clinical study. Since the drug is not freely available in the United Kingdom, exemption from a Clinical Trials Certificate was obtained by the authors from the Committee on Safety of Medicines.

PATIENTS AND METHODS
The drug was administered to 200 fit adult patients (table I) presenting for elective surgery. All gave informed consent and the study was approved by the Regional Ethics Committee.

Premedication consisted of diazepam 10 - 15 mg given orally 1 h before anaesthesia which was induced with thiopentone 5 mg kg\(^{-1}\). Org NC45, which is available in a freeze-dried cake form, was dissolved immediately before use and administered in a dose of either 0.1 mg kg\(^{-1}\) (80 patients),

<table>
<thead>
<tr>
<th>Dose of Org NC45 (mg kg(^{-1}))</th>
<th>n</th>
<th>Average age (yr) (range)</th>
<th>Average weight (kg) (range)</th>
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<tbody>
<tr>
<td>0.1 mg kg(^{-1})</td>
<td>80</td>
<td>38 (15 - 80)</td>
<td>64 (40 - 98)</td>
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<tr>
<td>0.15 mg kg(^{-1})</td>
<td>60</td>
<td>42 (16 - 72)</td>
<td>62 (40 - 89)</td>
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<tr>
<td>0.2 mg kg(^{-1})</td>
<td>60</td>
<td>47 (19 - 75)</td>
<td>66 (50 - 90)</td>
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0.15 mg kg$^{-1}$ (60 patients) or 0.2 mg kg$^{-1}$ (60 patients). Anaesthesia was maintained with nitrous oxide plus an inhalation agent (0.5–1.0% halothane or 1.0–2.0% enflurane), or fentanyl 100–400 µg plus droperidol 5–10 mg i.v.

Org NC 45 was evaluated with regard to conditions on intubation of the trachea, time to onset of maximum block, durations of action of the initial dose and any supplementary doses, and the quality of reversal of blockade following the administration of an anticholinesterase drug. Heart rate and arterial pressure were recorded.

Relaxation of the jaw, relaxation of the vocal cords and any straining or coughing on the endotracheal tube were taken into consideration in the assessment of intubating conditions. The detailed assessment of intubation has been previously described (Clarke et al., 1981) and only the overall assessment, based on a four-point scale (Lund and Stovner, 1962; Young, Clarke and Dundee, 1975), is presented here. All assessments were carried out by the first three authors at 30, 60, 90 or 120 s following 0.1 mg kg$^{-1}$ and at 30, 60 or 90 s following 0.15 mg kg$^{-1}$ and 0.2 mg kg$^{-1}$. The time at which intubation was attempted was randomized within each dose group. Twenty patients were assessed in each of these groups (fig. 1) and each patient was assessed only once. Intubating conditions were graded as excellent, satisfactory, fair or poor, the first two being taken as clinically acceptable.

The time to the onset of complete block (table II) averaged 245 s following a dose of 0.1 mg kg$^{-1}$ and 162 s following 0.15 mg kg$^{-1}$. The difference between these was significant ($P<0.005$). However, no further decrease in the time to the onset of complete blockade was achieved

<table>
<thead>
<tr>
<th>Dose of Org NC 45</th>
<th>Time (s) (mean ± SEM)</th>
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<tr>
<td>0.1 mg kg$^{-1}$</td>
<td>245 ± 11</td>
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<tr>
<td>0.15 mg kg$^{-1}$</td>
<td>162 ± 10</td>
</tr>
<tr>
<td>0.2 mg kg$^{-1}$</td>
<td>177 ± 11</td>
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RESULTS
The overall assessment of conditions at intubation is shown in figure 1. Irrespective of the dose, very few acceptable intubations could be carried out at 30 s. However, in each dose group the intubating conditions improved as time elapsed. Intubating conditions at 60 s improved as the dose was increased from 0.1 to 0.15 mg kg$^{-1}$. No further improvement was observed with 0.2 mg kg$^{-1}$. The intubating conditions were acceptable in almost 90% of patients at 90 s with all doses, the quality of intubation being slightly better with the two larger doses.

The time taken to the onset of complete blockade (table II) averaged 245 s following a dose of 0.1 mg kg$^{-1}$ and 162 s following 0.15 mg kg$^{-1}$. The difference between these was significant ($P<0.005$). However, no further decrease in the time to the onset of complete blockade was achieved
FIG. 1. Intubating conditions with the three doses of Org NC 45 at the times shown. Excellent and satisfactory are taken as clinically acceptable. (Data based on 20 patients in each group).

by increasing the dose to 0.2 mg kg$^{-1}$.

The average duration of clinical relaxation (fig. 2) increased significantly from 23 to 36 and 55 min respectively when the initial dose was increased from 0.1 to 0.15 and 0.2 mg kg$^{-1}$ when i.v. agents were used in the maintenance of anaesthesia. The use of inhalation anaesthetics for maintenance significantly increased the duration of action at each dose, to 34, 49 and 71 min respectively.

The average duration of clinical relaxation of subsequent increments (2–3 mg) was remarkably constant (table III) and varied between 17 and 20 min. This was true for all the dose groups.

Cardiovascular stability was a prominent feature, with no evidence of systemic hypotension or tachycardia related to the administration of the neuromuscular blocking drug. However, 10 patients, spread throughout the whole series, showed heart rates of 40–50 beat min$^{-1}$ about 20 min following the administration of the drug. All these patients had received fentanyl. This did not appear to be related to surgery and responded to the administration of anticholinergic drugs i.v.

The quality of the antagonism of the neuromuscular blockade following anticholinesterase administration was excellent or good in 94% of patients, satisfactory antagonism being achieved in less than 5 min. Most patients demonstrated three, or all four, responses to train-of-four stimulation before reversal, indicating a recovery of at least 20% of twitch height. Reversal was, however, classified as difficult in 12 patients (6%) because it took 8–10 min to attain reversal and a second smaller dose of neostigmine (20 μg kg$^{-1}$) was administered. These patients showed complete neuromuscular block when antagonism was attempted and six of these did not demonstrate any post-tetanic facilitation, the so-called “period of no response” (Viby-Mogensen, 1982).

**DISCUSSION**

The ideal neuromuscular blocking drug has been described as being non-depolarizing in nature, rapidly acting and with a short duration of action. In addition lack of cumulation and absence of side-effects would be beneficial (Savarese and Kitz, 1975). It appears that Org NC 45 could fill many of these criteria. Although Org NC 45 could not be called a rapidly acting drug in terms of the time

<table>
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<th>No. of increment</th>
<th>Duration (min)</th>
<th>No. of patients</th>
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<tr>
<td>1</td>
<td>20</td>
<td>38</td>
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<tr>
<td>2</td>
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<td>3</td>
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<td>18</td>
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<td>7</td>
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<td>8</td>
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taken to attain complete blockade, Agoston and his colleagues (1977; 1980) observed this to be quicker with 0.05 mg kg$^{-1}$ Org NC 45 than with a comparable dose of pancuronium. However, in their experience the difference in these times was negligible when larger (0.1 mg kg$^{-1}$) doses of the two drugs were compared. In the present study the time taken to attain complete blockade (about 4 min with 0.1 mg kg$^{-1}$) decreased to less than 3 min with 0.15 mg kg$^{-1}$, although there was no further decrease with 0.2 mg kg$^{-1}$. The intubating conditions similarly improved when the dose was increased to 0.15 mg kg$^{-1}$. Little further improvement was noted following 0.2 mg kg$^{-1}$. The method used to assess the onset of complete blockade in the present study was not that used by all workers, but it was one that was feasible for use routinely in the operating theatre and was not dependent on elaborate equipment.

It appears that intubation can be performed more readily with 0.1 mg kg$^{-1}$ after 90 s than by increasing the dose and attempting intubation earlier. It was also clear that intubation could be carried out before the onset of complete neuromuscular block. Norman, Read and Du Boulay (1980) showed that apnoea occurred well before onset of complete block in the adductor pollicis. Agoston and his colleagues (1980) found the intubating conditions to be ideal with a dose of 0.08 mg kg$^{-1}$ at 90–100 s with a blockade of only 40–60% of the twitch response of the adductor pollicis. Harrison and Feldman (1981), on the other hand, found the intubating conditions to be unsatisfactory with a dose of 0.1 mg kg$^{-1}$ at 90 s in five of 10 patients. Although the results of the present study were better than those obtained by Harrison and Feldman (1981), 10–15% of the intubations were unacceptable, in contrast to the uniformly good results obtained by Agoston and his colleagues (1980). Comparative studies of intubating conditions by Clarke and colleagues (1981, 1982) using Org NC 45 0.1 mg kg$^{-1}$ and conventional doses of pancuronium and suxamethonium (0.1 and 1.0 mg kg$^{-1}$ respectively) showed conditions to be most acceptable with suxamethonium. Of the two non-depolarizing drugs, Org NC 45 was the better.

The short duration of action of Org NC 45, when compared with pancuronium, has been described as a consistent feature of this drug. Krieg, Crul and Booij (1980) found the duration of clinical relaxation with Org NC 45 0.036 mg kg$^{-1}$ to be 11.6 min in contrast to 34.4 min with pancuronium 0.062 mg kg$^{-1}$, these doses being considered equipotent. This was confirmed by Crul and Booij (1980) and Agoston and co-workers (1980). However, if the drug has to be used for intubation in place of suxamethonium, a dose of 0.1 mg kg$^{-1}$ would be routinely used and a duration of clinical relaxation of approximately 20 min would result, rather than the duration of approximately 11 min shown by Krieg, Crul and Booij (1980) after 0.036 mg kg$^{-1}$. Whereas this dose may produce 90–95% depression of twitch height of the adductor pollicis, it would be insufficient for tracheal intubation.

The term clinical relaxation, signifying the time from the end of injection to the recovery of 25% twitch height, is more appropriate in the operating theatre than the recovery of 90% often used in pharmacological studies. The duration of clinical relaxation in this study varied with the dose and the maintenance agent used. Thus the drug is versatile enough for use in operations lasting from 20 min to those lasting much longer.

Another desirable feature is the lack of cumulation as shown by similar durations of clinical relaxation following the repeated administration of similar doses. After the first few patients one could almost predict the duration of action of 2–3 mg supplements (between 15 and 20 min). This lack of cumulation was also observed in clinical studies by Krieg, Crul and Booij (1980) and Agoston and colleagues (1980).

The short duration of action of the drug may need greater vigilance on the part of the anaesthetist, especially in operations where sudden movement of the patient would be undesirable and the use of a peripheral nerve stimulator may be required routinely (Norman, 1982). The drug may be suitable for use by constant infusion and the authors are carrying out a study to assess this.

Antagonism of neuromuscular block was usually prompt following the administration of neostigmine. The majority of patients had attained a twitch height of at least 20%, as shown by the presence of at least three twitches in response to a train-of-four stimulation, before administration of the anticholinesterase drug. Antagonism was difficult or prolonged when reversal was attempted at complete block. Baraka (1967) has demonstrated similar results with other non-depolarizing neuromuscular blocking drugs. Thus, some recovery of neuromuscular transmission should be permitted before the residual block is antagonized.

Although the present study was not designed to assess cardiovascular effects in great detail, lack of
significant cardiovascular change was apparent, as has been observed by other workers in man and animals (Krieg, Crul and Booij, 1980; Booij et al., 1980; Marshall et al., 1980). Bradycardia was observed in a small number of patients to whom fentanyl was given. This has not been reported previously and further investigation seems indicated. However, the bradycardia responded promptly to atropine i.v.

One drawback might be the supply of the drug in a freeze-dried cake form which necessitates reconstitution. However, we are all used to dissolving thiopentone, and Org NC45 dissolves readily in less than 10 s.

In conclusion, Org NC45 appears to be a drug permitting relatively early intubation of the trachea with a short dose-related duration of action and without cumulation on repeated administration. It would appear that the drug has sufficient versatility for use in routine clinical anaesthesia.

ACKNOWLEDGEMENTS

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REFERENCES


Savage, D. S., Sleigh, T., and Carlyle, I. (1980). The emergence of Org NC45, 1 (2β, 3α, 5α, 16β, 17β) – 3, 17 – bis(acetyloxy)-
2-(l-piperidinyl) – Androsten – 16-yl-1-methylpiperidinium bromide, from the pancuronium series. Br. J. Anaesth., 52, 3S.


Supplement (1980). Br. J. Anaesth., 52, 1S.


KLINISCHE BEURTEILUNG VON ORG NC 45

ZUSAMMENFASSUNG

Org NC 45, ein neuer nicht-depolarisierender neuromuskulärer Blocker, wurde bei 200 erwachsenen Patienten erprobt. Das Präparat wurde in Dosen von 0,1, 0,15 und 0,2 mg kg⁻¹ verabreicht. Die Intubation konnte bei 90% der Patienten nach 90 s zufriedenstellend ausgeführt werden. Die Dauer der klinischen Relaxation reichte von 23 min bei 0,1 mg kg⁻¹ und Neuroleptanalgesie bis 71 min bei 0,2 mg kg⁻¹ und Halothan- oder Enfluran-Anästhesie. Die Dauer der klinischen Relaxation nach wiederholter Gabe von 2–3 mg war bemerkenswert konstant (zwischen 17 und 20 min) und zeigte somit fehlende Kumulation. Nach Gabe von Neostigmin wurde der restliche Block sofort und leicht antagonisiert. Bei der routinemäßigen EKG-Überwachung zeigte sich keinerlei signifikante kardiovaskulärer Effekt des Präparates.

ETUDE CLINIQUE DE L’ORG NC 45

RESUME

L’Org NC 45, un nouvel agent du bloc neuromusculaire non dépolarisant, a été étudié chez 200 patients adultes. Le produit a été administré à des doses de 0,1, 0,15 ou 0,2 mg kg⁻¹. L’intubation a pu être faite de façon satisfaisante à 90 s environ chez 90% des patients. La durée du relâchement clinique variait de 23 min avec 0,1 mg kg⁻¹ et une neuroleptanesthesie à 71 min avec 0,2 mg kg⁻¹ et une anesthésie à l’halothane ou l’enflurane. La durée du relâchement clinique après l’administration répétée de 2–3 mg était remarquablement constante (entre 17 et 20 min), ce qui objective l’absence d’accumulation. L’antagonisme du bloc résiduel était rapide et facile après administration de neostigmine et le produit n’avait aucun effet cardiovasculaire significatif décelable par la surveillance de routine.

EVALUACIÓN CLÍNICA DEL ORG NC 45

SUMARIO

Se llevó a cabo la evaluación del Org NC 45, una droga bloqueadora neuromuscular no-depolarizante, en 200 pacientes adultos. Se administró la substancia en dosis de 0,1, 0,15 o 0,2 mg kg⁻¹. Se pudo proceder con éxito a la intubación a los 90 s aproximadamente en un 90% de los pacientes. La duración del reposo varió desde 23 min con 0,1 mg kg⁻¹ y neuroleptanestesia hasta 71 min con 0,2 mg kg⁻¹ y anestesia con halotano o enfurana. La duración del reposo después de la administración repetida de 2–3 mg fue marcadamente constante (entre 17 y 20 min), demostrando así la falta de acumulación. El antagonismo del bloqueo residuo fue rápido y fácil después de la administración de neostigmina, y la substancia no tuvo efecto cardiovascular tal como lo comprobó el control de rutina.