PHARMACOLOGY OF ORG NC 45 COMPARED WITH OTHER NON-DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

I. G. MARSHALL, S. AGOSTON, L. H. D. J. BOOIJ, N. N. DURANT AND F. F. FOLDES

SUMMARY

From results of pharmacological tests on the neuromuscular and autonomic blocking actions of a series of pancuronium analogues, Org NC 45, the C16 monoquaternary analogue of pancuronium, was selected for detailed study. Org NC 45 has a non-depolarizing mechanism of action, is more rapid in onset and shorter in duration of action than pancuronium. It shows less cumulation than pancuronium or tubocurarine, and is easily antagonized by anticholinesterases and aminopyridines. Org NC 45 exhibits a low propensity to release histamine. Its ability to inhibit cholinesterases is not likely to be important at neuromuscular blocking doses. Org NC 45 possesses negligible ganglion-blocking activity and is readily antagonized by neostigmine. The block was enhanced when the stimulation frequency was increased from 0.1 Hz to 1 Hz, but no prolonged block of the hemicholinium type occurred. These results indicated that the block was mainly postjunctional in nature and was of a non-depolarizing type (Marshall, 1968). With the knowledge available at the time, no striking advantages of Org NC 45 were realized; furthermore, the compound was unstable in aqueous solution. Further work on it at that time was abandoned.

Since the early studies on the pancuronium series, the importance of cardiovascular side-effects of neuromuscular blocking agents has become apparent. Accordingly, a series of analogues of pancuronium, including Org NC 45, was tested for both neuromuscular and autonomic blocking activities (Durant et al., 1979). Org NC 45 was selected for further study from this series on the grounds that it was the compound most likely to be capable of producing neuromuscular block without concomitant cardiovascular side-effects. Its development and chemical properties and the means of overcoming its instability in aqueous solution are discussed by Savage in this supplement (Savage, Sleigh and Carlyle, 1980).

Neuromuscular blocking action

In the isolated chick biventer cervicis nerve–muscle preparation, Org NC 45 produced a depression of indirectly elicited twitch responses and of responses to added acetylcholine without a concomitant contracture of the multiple innervated fibres (Durant et al., 1979). This observation
The neuromuscular blocking action of Org NC 45 has been tested in largely unpublished experiments on rats, cats, dogs and monkeys by several groups of workers (in Glasgow, Groningen, and Nijmegen) and its actions have been compared where appropriate with those of pancuronium and of other neuromuscular blocking drugs. Table I compares the potency of and time-course of the effects of Org NC 45 with those of pancuronium in the above four species.

The results show that Org NC 45 is of the same order of potency as pancuronium, being somewhat more potent in the dog and somewhat less potent in the other three species. Its onset of action (time from injection to maximum effect) is slightly more rapid than that of pancuronium (e.g. about 1.3 times more rapid in the cat) and its duration of action (time from injection to 90% recovery) and recovery (time of recovery from 25% to 75% control twitch height) are substantially shorter than those of pancuronium. When the same dose of Org NC 45 (0.25 mg kg\(^{-1}\)) was repeatedly injected into anaesthetized rats, the second and subsequent doses being administered at the time of full recovery of the twitches after the preceding dose, there was a small degree of cumulation between the first and second doses, but the effects of subsequent doses were essentially the same. Cumulation was more marked with successive doses of pancuronium and was still more pronounced when tubocurarine was the blocking agent used. The histograms of figure 1 illustrate the depths and durations of successive blocks produced by tubocurarine, pancuronium and Org NC 45.

Similar results were obtained in anaesthetized cats. Thus, when a dose of Org NC 45 (35 μg kg\(^{-1}\)) sufficient to produce 80–90% twitch block of the gastrocnemius muscle was injected repeatedly, each dose being administered at the time of full recovery from the preceding dose, there was little or no cumulation as illustrated in figure 2. In contrast, pancuronium, and especially tubocurarine, were strongly cumulative.

Reversal by anticholinesterases and by amino-pyridines

Reversal of the neuromuscular block produced by Org NC 45 has been assessed by two types of experiment. In one type of experiment the re-

### Table I. Potencies and time-courses of action of Org NC 45 and pancuronium in anaesthetized rats, cats, dogs and monkeys. *Time to 50% recovery with 3 × ED\(_{90}\) dose

<table>
<thead>
<tr>
<th>Species, anaesthetic and muscle</th>
<th>Drug</th>
<th>Dose to produce about 90% twitch block</th>
<th>Mean block (%)</th>
<th>Time from injection to max block (min)</th>
<th>Time from injection to 90% recovery (min)</th>
<th>Recovery time from 25% to 75% control twitch (min)</th>
<th>References other than present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Sodium pentobarbitone</td>
<td>Org NC 45</td>
<td>250 μg kg(^{-1})</td>
<td>88 ± 3.1</td>
<td>1.17 ± 0.15</td>
<td>3.3 ± 0.6</td>
<td>0.9 ± 0.2</td>
<td>I. McIndewar (unpublished)</td>
</tr>
<tr>
<td>Tibialis anterior</td>
<td>Pancuronium</td>
<td>100 μg kg(^{-1})</td>
<td>84.7 ± 11.6</td>
<td>1.4 ± 0.1</td>
<td>9.1 ± 3.8</td>
<td>2.6 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Cat, a-Chloralose Gastrocnemius</td>
<td>Org NC 45</td>
<td>38 μg kg(^{-1})</td>
<td>85.2 ± 2.6</td>
<td>4.72 ± 0.25</td>
<td>8.18 ± 0.58</td>
<td>1.9 ± 0.24</td>
<td>Durant, Houwertjes and Crul (1980)</td>
</tr>
<tr>
<td></td>
<td>Pancuronium</td>
<td>24 μg kg(^{-1})</td>
<td>84.1 ± 2.0</td>
<td>5.93 ± 0.21</td>
<td>12.12 ± 0.93</td>
<td>3.06 ± 0.33</td>
<td>Booij and others (1980)</td>
</tr>
<tr>
<td>Rhesus monkey, Ketamine-sodium pentobarbitone-nitrous oxide Adductor pollicis</td>
<td>Org NC 45</td>
<td>10 μg kg(^{-1})</td>
<td>82.4 ± 5.5</td>
<td>7.8 ± 0.6</td>
<td>20.4 ± 1.6</td>
<td>6.6 ± 0.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancuronium</td>
<td>7 μg kg(^{-1})</td>
<td>79.5 ± 2.5</td>
<td>7.3 ± 1.3</td>
<td>22.4 ± 5.4</td>
<td>8.8 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Dog, Halothane, Hind limb extensors</td>
<td>Org NC 45</td>
<td>14 μg kg(^{-1})</td>
<td></td>
<td>42 ± 2*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancuronium</td>
<td>22 μg kg(^{-1})</td>
<td></td>
<td>108 ± 10*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Similar results were obtained in anaesthetized cats. Thus, when a dose of Org NC 45 (35 μg kg\(^{-1}\)) sufficient to produce 80–90% twitch block of the gastrocnemius muscle was injected repeatedly, each dose being administered at the time of full recovery from the preceding dose, there was little or no cumulation as illustrated in figure 2. In contrast, pancuronium, and especially tubocurarine, were strongly cumulative.

Reversal by anticholinesterases and by amino-pyridines

Reversal of the neuromuscular block produced by Org NC 45 has been assessed by two types of experiment. In one type of experiment the re-
Repeated doses of tubocurarine 0.08 mg kg\(^{-1}\), pancuronium 0.1 mg kg\(^{-1}\) or Org NC 45 0.25 mg kg\(^{-1}\) were administered to rats under sodium pentobarbitone anaesthesia and the depths and durations (time from injection to 90% recovery) of the neuromuscular blocks produced in the tibialis anterior muscle (stimulated through its nerve at 0.1 Hz) were noted. Only one drug was administered to any one rat. Each dose was injected at the time of complete recovery from the preceding dose. Each drug was studied in six rats. **Significant difference from block produced by first dose (\(P < 0.01\)).

![Fig. 1. Repeated doses of tubocurarine 0.08 mg kg\(^{-1}\), pancuronium 0.1 mg kg\(^{-1}\) or Org NC 45 0.25 mg kg\(^{-1}\) were administered to rats under sodium pentobarbitone anaesthesia and the depths and durations (time from injection to 90% recovery) of the neuromuscular blocks produced in the tibialis anterior muscle (stimulated through its nerve at 0.1 Hz) were noted. Only one drug was administered to any one rat. Each dose was injected at the time of complete recovery from the preceding dose. Each drug was studied in six rats. **Significant difference from block produced by first dose (\(P < 0.01\)).

FIG. 2. Tibialis anterior muscle–sciatic nerve preparation of the chloralose-anaesthetized cat; stimulation frequency 0.1 Hz. The effects of the second, third and fourth doses of a series of successive administrations of Org NC 45 40 \(\mu\)g kg\(^{-1}\). Note the lack of cumulative effects with successive doses.

![Fig. 2. Tibialis anterior muscle–sciatic nerve preparation of the chloralose-anaesthetized cat; stimulation frequency 0.1 Hz. The effects of the second, third and fourth doses of a series of successive administrations of Org NC 45 40 \(\mu\)g kg\(^{-1}\). Note the lack of cumulative effects with successive doses.](https://academic.oup.com/bja/article-abstract/52/suppl_1/11S/263338)

Recovery time from 25% to 75% of control twitch height, after an approximately 90% blocking dose of neuromuscular blocking agent, has been assessed before and after the injection of the reversal agent. For example, in four cats, Org NC 45 40 \(\mu\)g kg\(^{-1}\) produced a neuromuscular block in which the time from 25% to 75% recovery was 2.1 ± 0.3 min. Neostigmine 70 \(\mu\)g kg\(^{-1}\) injected at the peak of the neuromuscular block reduced this time to 0.98 ± 0.2 min. Similar results were obtained in rats and dogs.

In another study using this type of analysis Durant, Houwertjes and Crul (1980) have compared the abilities of anticholinesterases and aminopyridines to reverse pancuronium- and Org NC 45-induced neuromuscular blockades in the anaesthetized rhesus monkey (table II).

In the second type of experiment, the neuromuscular blocking drugs were infused i.v. into anaesthetized rats until a steady state 90% block of twitch height was achieved. Reversal agents, either singly or combined, were then injected as an i.v. bolus with the infusion continuing. In this way dose-antagonism plots can be obtained and doses of antagonists producing 50% reversal can be calculated (Miller et al., 1978). By means of this technique it has been shown that neostigmine, pyridostigmine and 4-aminopyridine are effective antagonists of both pancuronium- and Org NC 45-induced neuromuscular block and that the anticholinesterases interact with 4-aminopyridine in a synergistic manner (Miller et al., 1978; Booij et al., 1980) (table III).

**Unwanted effects of non-depolarizing neuromuscular blocking drugs**

The main unwanted effects of various non-depolarizing blocking agents in current clinical use are (i) release of histamine and other autacoids, (ii) anticholinesterase activity, (iii) autonomic ganglion block, (iv) block of cardiac vagus neuro-effector transmission and of muscarinic receptors.

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**Table II. Effects of anticholinesterases and aminopyridines on recovery (from 25 to 75% control twitch height) from pancuronium and Org NC 45-induced neuromuscular blockade in the anaesthetized monkey ulnar nerve-adductor pollicis muscle preparation**

<table>
<thead>
<tr>
<th>Reversal agent</th>
<th>Dose</th>
<th>Pancuronium mean ± SD</th>
<th>Org NC 45 mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>12.3 ± 1.7</td>
<td>7.1 ± 0.5</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>35 (\mu)g kg(^{-1})</td>
<td>3.9 ± 0.9</td>
<td>3.8 ± 0.8</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>105 (\mu)g kg(^{-1})</td>
<td>8.8 ± 2.0</td>
<td>3.9 ± 0.7</td>
</tr>
<tr>
<td>4-Aminopyridine</td>
<td>1 mg kg(^{-1})</td>
<td>4.4 ± 2.1</td>
<td>5.2 ± 0.7</td>
</tr>
<tr>
<td>3,4-Aminopyridine</td>
<td>1 mg kg(^{-1})</td>
<td>3.5 ± 0.2</td>
<td>2.9 ± 1.0</td>
</tr>
</tbody>
</table>

**Table III. Comparison of the doses (\(\mu\)g kg\(^{-1}\)) of neostigmine, pyridostigmine and 4-aminopyridine alone or in combination required to produce 50% antagonism of pancuronium or Org NC 45-induced neuromuscular block in the anaesthetized rat. (From Booij et al., 1980)**

<table>
<thead>
<tr>
<th>Reversal agent</th>
<th>Pancuronium</th>
<th>Org NC 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neostigmine</td>
<td>18</td>
<td>14.5</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>49</td>
<td>75</td>
</tr>
<tr>
<td>4-Aminopyridine</td>
<td>440</td>
<td>466</td>
</tr>
<tr>
<td>Neo + 4-AP</td>
<td>7.4</td>
<td>9.8</td>
</tr>
<tr>
<td>Pyr + 4-AP</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>4-AP + Neo + Pyr</td>
<td>220</td>
<td>215</td>
</tr>
<tr>
<td>4-AP + Pyr</td>
<td>76</td>
<td>130</td>
</tr>
</tbody>
</table>

**Table IV. Comparison of the doses (\(\mu\)g kg\(^{-1}\)) of neostigmine, pyridostigmine and 4-aminopyridine alone or in combination required to produce 50% antagonism of pancuronium or Org NC 45-induced neuromuscular block in the anaesthetized rat. (From Booij et al., 1980)**

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<th>Reversal agent</th>
<th>Pancuronium</th>
<th>Org NC 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neostigmine</td>
<td>35</td>
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</tr>
<tr>
<td>Pyridostigmine</td>
<td>49</td>
<td>75</td>
</tr>
<tr>
<td>4-Aminopyridine</td>
<td>440</td>
<td>466</td>
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<td>130</td>
</tr>
</tbody>
</table>
on noradrenergic nerve endings, (v) inhibition of neuronal noradrenaline re-uptake and possibly stimulation of noradrenaline release.

In addition, potency may be modified by the pH of the extracellular fluids and by body temperature. The drugs are likely to interact with some of the various anaesthetics and adjuvants to anaesthesia used concurrently, and possibly with other medication taken by the patient. Cardiovascular effects of Org NC 45 are the subject of the paper by Marshall and colleagues (1980) in this supplement, and its interactions with other drugs are described by Krieg and colleagues (1980), also in this supplement. Here we confine ourselves to dealing with items (i), (ii) and (iii) listed above, and with the ability of neuromuscular blocking drugs to block the cardiac vagus in the cat.

(i) Histamine release. Tubocurarine provides the main example of a neuromuscular blocking drug that releases histamine. The effect is relatively unimportant with the other drugs in current use. The matter has been reviewed by MacLagan (1976).

Arterial pressure, heart rate, transpulmonary pressure, rate of airflow and tidal volume were recorded simultaneously with maximal twitches of a tibialis anterior muscle (0.1 Hz) in artificially ventilated cats under chloralose anaesthesia (I. W. Rodger, personal communication). Tubocurarine in a dose sufficient to produce about 90% block of the twitches (0.4 mg kg^-1) caused a decrease in arterial pressure, a reflex increase in heart rate, and usually a slowly developing increase in transpulmonary pressure without change in rate of airflow or tidal volume (Gandiha et al., 1975). A similar increase in transpulmonary pressure was produced by a small dose of histamine, and may be attributed to constriction of alveolar ducts and respiratory bronchioles. The effect of histamine and the effect of tubocurarine on transpulmonary pressure were blocked by mepyramine 0.5 mg kg^-1. Part of the decrease in arterial pressure produced by tubocurarine was also blocked by mepyramine. The mepyramine-sensitive effects of tubocurarine on arterial pressure and transpulmonary pressure may be attributed to histamine release.

Neither pancuronium nor Org NC 45 in doses up to three times those necessary to produce 90% twitch block (the maximum doses used) produced any evidence of histamine release in Rodger's experiments. Figure 3 illustrates the absence of effect of Org NC 45 on respiratory parameters.

In human volunteers, the ability of Org NC 45 to release histamine was compared with that of pancuronium, metocurine and tubocurarine (L. H. D. J. Booij, N. Krieg and J. F. Crul, unpublished data). Intradermal injections of equiactive neuromuscular blocking doses of the compounds produced skin redness and induration. Tubocurarine and metocurine produced the largest diameters of redness and induration; pancuronium came next in order. Org NC 45 produced by far the smallest area of redness and induration.

Thus, in both experimental animals and human volunteers Org NC 45 produced less evidence of histamine release than any of the other muscle relaxants tested.

(ii) Cholinesterase inhibition. From the point of view of their inhibitory effect on human red cell acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BuChE), the non-depolarizing neuromuscular blocking agents may be divided into three sub-groups. The members of the first sub-group, tubocurarine, metocurine, alcuronium and gallamine, are relatively weak inhibitors of both AChE and BuChE and there is no great
difference between their inhibitory effect on the two types of enzymes (table IV). The lone member of the second sub-group, benzoquinonium, is a potent inhibitor of AChE and is a 100-times more potent inhibitor of this enzyme than of BuChE.

### Table IV. The inhibitory effect of neuromuscular blocking agents on the hydrolysis of acetylcholine by human red cell acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BuChE).

<table>
<thead>
<tr>
<th>Neuromuscular blocking agent</th>
<th>$I_{50}$ (mol litre$^{-1}$)</th>
<th>$I_{50}$ AChE</th>
<th>$I_{50}$ BuChE</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-Tubocurarine</td>
<td>$7.2 \times 10^{-4}$</td>
<td>$3.0 \times 10^{-4}$</td>
<td>2.4</td>
</tr>
<tr>
<td>Metocurine</td>
<td>$3.2 \times 10^{-3}$</td>
<td>$4.8 \times 10^{-4}$</td>
<td>6.6</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>$6.7 \times 10^{-4}$</td>
<td>$5.4 \times 10^{-5}$</td>
<td>12.4</td>
</tr>
<tr>
<td>Gallamine</td>
<td>$4.5 \times 10^{-4}$</td>
<td>$2.4 \times 10^{-4}$</td>
<td>1.9</td>
</tr>
<tr>
<td>Benzoquinonium</td>
<td>$2.2 \times 10^{-7}$</td>
<td>$2.1 \times 10^{-5}$</td>
<td>0.01</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>$3.0 \times 10^{-4}$</td>
<td>$5.6 \times 10^{-8}$</td>
<td>4838.7</td>
</tr>
<tr>
<td>Org NC 45</td>
<td>$6.6 \times 10^{-5}$</td>
<td>$6.2 \times 10^{-7}$</td>
<td>106.4</td>
</tr>
</tbody>
</table>

The members of the third sub-group, pancuronium and to a lesser extent Org NC 45, are potent inhibitors of BuChE. Pancuronium and Org NC 45 respectively inhibit BuChE at concentrations about 5000 and 100 times less than those required to inhibit AChE.

Because of its high AChE inhibitory potency, the administration of neuromuscular blocking doses of benzoquinonium may be accompanied by severe muscarinic side-effects such as circulatory collapse. For this reason its clinical use has been abandoned.

Inhibition of BuChE by pancuronium has important theoretical considerations, as it would be expected that pancuronium would prolong the action of drugs, such as procaine, that are dependent upon BuChE-mediated hydrolysis for the termination of their action. Since the BuChE-inhibitory potency of Org NC 45 is about 10 times less than that of pancuronium, prolongation of the effects of such drugs is less likely to occur after the preliminary administration of Org NC 45.

(iii) **Ganglion block.** Sympathetic ganglion block produced by tubocurarine and fazadinium contributes to the hypotension seen in man with these agents (McDowell and Clarke, 1969; Blogg et al., 1973; Ungerer and Erasmus, 1974).

Neither pancuronium nor Org NC 45 produces ganglion block at neuromuscular blocking doses as assessed by measuring responses of the anaesthetized cat nictitating membrane preparation to preganglionic cervical sympathetic nerve stimulation (Buckett et al., 1968; Durant et al., 1979). The absence of effect of a neuromuscular blocking dose of Org NC 45 on responses of the nictitating membrane to preganglionic stimulation is illustrated in figure 4.

(iv) **Blockade of cardiac vagus neuroeffector transmission.** Neuromuscular blocking doses of gallamine, pancuronium, alcuronium and fazadinium can cause tachycardia in man (Smith and Whitcher, 1967; Kennedy and Kelman, 1970; Kelman and Kennedy, 1971; Blogg et al., 1973). Gallamine and pancuronium have been studied in detail and have been found to have atropine-like actions that are confined to the cardiac vagus neuroeffector junction (Riker and Wescoe, 1951; Saxena and Bonta, 1970). Thus atropine itself will block both the bradycardia and the vasodilator action of the muscarinic agonist acetyl $\beta$-methylcholine, whereas drugs that selectively block the cardiac receptors block only the bradycardial response, leaving the vasodilator response intact.

The anaesthetized cat has very little spontaneous vagal tone, but blockade of cardiac vagus neuroeffector transmission may be conveniently measured by assessing the antagonism of the
bradycardial responses to stimulation of the right vagus. All the non-depolarizing agents in current use have been tested in this way and table V summarizes the relationship between neuromuscular and vagal blocking doses in the cat. It can be seen from table V that the drugs with low vagal/neuromuscular blocking ratios are the compounds associated with the production of tachycardia in man. Org NC 45 has an extremely high ratio and even doses of the drug many times greater than those required to produce neuromuscular block do not increase heart rate in experimental animals (Booij et al., 1980; Durant, Houwertjes and Crul, 1980). Figure 4 contrasts the effect of a neuromuscular blocking dose of gallamine in blocking the cardiac vagus with the absence of this effect of a neuromuscular blocking dose of Org NC 45.

Effects of Org NC 45 metabolites

As discussed by Savage, Sleigh and Carlyle (1980) in this supplement, it is probable that Org NC 45 is primarily metabolized to its 3-deacetyl derivative, Org 7268. Hydrolysis will also take place to form the 17-deacetyl derivative (Org NC 58) and finally to the 3,17-bis-deacetyl derivative (Org 7402).

In the isolated rat phrenic nerve-hemidiaphragm preparation the concentration of Org NC 45 producing 50% reduction of maximal responses to nerve stimulation is 3.4 μg ml⁻¹. The equiactive doses of the metabolites were: Org 7268 (3-OH) 5.16 μg ml⁻¹; Org NC 58 (17-OH) 34.2 μg ml⁻¹; Org 7402 (3,17-OH) 59.9 μg ml⁻¹.

Thus, Org NC 45 is 1.5 times more potent than the 3-deacetyl metabolite, 10.1 times more potent than the 17-deacetyl derivative and 17.6 times more potent than the 3,17-bisdeacetyl derivative (L. H. D. J. Booij and F. van der Pol, unpublished observations).

The neuromuscular and vagal blocking activities of the three potential metabolites have also been compared in cats anaesthetized with chloralose (I. Marshall, unpublished observations). The results are summarized in table VI. Thus Org NC 45 will probably hydrolyse to a compound which also possesses very low vagal blocking potency. Despite the 3,17-OH analogue possessing considerably greater vagal blocking potency than Org NC 45, it is unlikely that sufficient of the analogue will be formed from neuromuscular blocking doses of Org NC 45 to produce sufficient vagal block to lead to tachycardia.

Effects of pH on Org NC 45 neuromuscular block

The effects of acute changes in acid–base balance on the neuromuscular blocking action of Org
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NC 45 have been studied in the pentobarbitone-anaesthetized cat and in the isolated phrenic nerve–hemidiaphragm preparation (Funk, Crul and van der Pol, 1980). In cats respiratory alkalosis (pH 7.53; $P_{\text{a}CO_2}$ 1.9 kPa) slightly but not significantly antagonized neuromuscular block produced by continuous infusion of Org NC 45 and slightly increased the cumulative dose required to produce 85–95% twitch blockade. Metabolic alkalosis (pH 7.64; $P_{\text{a}CO_2}$ 3.5 kPa) significantly antagonized neuromuscular block produced by infusion, but only slightly and not significantly increased the 85–95% blocking dose.

In contrast, respiratory acidosis (pH 6.98; $P_{\text{a}CO_2}$ 10.3 kPa) and metabolic acidosis (pH 7.13; $P_{\text{a}CO_2}$ 4.9 kPa) both significantly augmented block produced by an infusion of Org NC 45 and reduced the 85–95% blocking dose.

Similar results were obtained in the isolated rat hemidiaphragm in which alkaline conditions (pH 7.68) only slightly antagonized Org NC 45-induced neuromuscular block whereas acid conditions (pH 7.05) significantly augmented the block.

It is likely that these results may in part be attributed to an increased rate of metabolism of Org NC 45 by alkaline hydrolysis and a greater molecular stability during acidosis.

CONCLUSION

In animal experiments Org NC 45 has been shown to be a non-depolarizing neuromuscular blocking agent with a high potency, approximating to that of pancuronium. The onset and duration of action of Org NC 45 were found to be shorter than those of pancuronium. Repeated doses of Org NC 45 exhibited less cumulative effects than seen with tubocurarine or pancuronium. The neuromuscular block produced by Org NC 45 was antagonized by anticholinesterase agents and by aminopyridines. Also, its weak inhibitory actions against acetylcholinesterase and butyrylcholinesterase are unlikely to lead to poor antagonism by anticholinesterases or adverse interactions involving suxamethonium.

Org NC 45 has also been tested for effects at sites other than the skeletal muscle neuromuscular junction. The compound showed less propensity than other commonly used muscle relaxants to release histamine. Org NC 45 exhibited negligible ganglion blocking activity and a wide margin between neuromuscular and vagal blocking doses was seen. Although factors other than vagal block are likely to be involved in the tachycardia produced by many muscle relaxants, vagal block in the cat is a good indication that tachycardia is likely to occur in man. Thus it can be predicted from the above results that Org NC 45, at neuromuscular blocking doses, is unlikely to produce marked cardiovascular side-effects in man.

It can be predicted that Org NC 45 will hydrolyse fairly rapidly to its 3-deacetyl derivative which, like Org NC 45, possesses low vagal blocking activity. The proposed final metabolite, the 3,17-bis-deacetyl derivative, is unlikely to be produced in sufficient quantities to induce neuromuscular or vagal block.

Thus Org NC 45 is a highly potent compound with a high degree of selectivity for the receptors at the neuromuscular junction. It is probable that the compound will produce few cardiovascular side-effects in man and its emergence represents a potentially useful addition to the armamentarium of clinically useful muscle relaxants.

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REFERENCES


PHARMACOLOGIE D'ORG NC 45 COMPARÉE À CELLES D'AUTRES AGENTS DE BLOCAGE NEUROMUSCULAIRE NON DEPOLARISANTS

RESUME

Parmi les résultats des tests pharmalogiques effectuées sur le blocage autonome et neuromusculaire d'une série d'analogues du pancuronium, on a choisi Org NC 45, qui est l'anologue monoquaternaire C16 du pancuronium, pour faire l'objet d'une étude détaillée. Org NC 45 a un mécanisme d'action non dépolarisant; il a un début d'action plus rapide et une plus courte durée d'action que le pancuronium. Il entraîne moins d'accumulation que le pancuronium ou la tubocurarine et il est facile de le neutraliser à l'aide d'anticholinestérases et d'aminopyridines. Org NC 45 n'a qu'une faible tendance au dégagement d'histamine. Sa possibilité de freiner la cholinestérase ne semble pas avoir d'importance aux doses utilisées pour les blocages neuromusculaires. Org NC 45 a la possibilité de bloquer les ganglions, mais celle-ci est négligeable et il y a une grande marge entre les doses de blocage neuromusculaire et celles requises pour le blocage pneumogastrique. De ce fait, il est peu probable qu'il y ait des effets cardiovasculaires secondaires, lorsqu'on utilise Org NC 45. Il s'hydrolyse surtout avec son analogue 3-hydroxyle qui, comme Org NC 45, dispose d'une grande marge entre les doses requises pour le blocage neuromusculaire et celles nécessaires pour le blocage pneumogastrique. Org NC 45 a une haute sélectivité pour le carrefour neuromusculaire et constitue une addition potentiellement utile du point de vue clinique à l'arsenal des relaxants musculaires.

DIE PHARMAKOLOGIE VON ORG NC 45 IM VERGLEICH MIT ANDEREN NICHT-DEPOLARISIERENDEN NEUROMUSKULÄREN BLOCKIERUNGSDROGEN

ZUSAMMENFASSUNG

selbst einen weiten Abstand zwischen neuromuskulärer und vagaler Blockierung zeigt. Org NC 45 zeigt eine hohe Selektivität für neuromuskuläre Verbindungsstellen und stellt eine wertvolle Ergänzung des Bestandes klinisch nützlicher Muskelentspannungsmittel dar.

LA FARMACOLOGIA DEL ORG NC 45 EN COMPARACION CON OTRAS DROGAS DE BLOQUEO NEUROMUSCULAR NO DESPOLARIZANTES

SUMARIO
Como consecuencia de los resultados de las pruebas farmacológicas sobre las acciones de bloqueo neuromuscular y autonómico de una serie de productos análogos al pancuronium, se seleccionó el Org NC 45, que es el producto monocuaternario C16 análogo al pancuronium, para llevar a cabo un estudio detallado. El Org NC 45 posee un mecanismo de acción no despolarizante, su acción es más rápida y el período de ésta es más corto que en el caso del pancuronium. Muestra menos acumulación que el pancuronium o que la tubocuramina, y se contrarresta fácilmente con anticolesteras y aminopiridinas. El Org NC 45 muestra una menor propensión a liberar histamina. Su habilidad para inhibir colinesteras no varía con seguridad, de importancia al nivel de dosis de bloqueo neuromuscular. El Org NC 45 posee una acción de bloqueo de los ganglios que es despreciable y existe un amplio margen entre las dosis de bloqueo neuromuscular y vagal. Es por esto que no es probable que se presenten efectos secundarios de tipo cardiovascular a causa del uso del Org NC 45. Se hidrolizará principalmente hasta su análogo 3-hidroxi el cual, al igual que el Org NC 45, posee un amplio margen entre las dosis de bloqueo neuromuscular y vagal. El Org NC 45 posee una alta selectividad para la confluencia neuromuscular y representa, a nivel potencial, una valiosa incorporación al arsenal de relajantes musculares de utilidad clínica.