PHARMACOKINETICS OF ORG NC45 (NORCURON) IN PATIENTS WITH AND WITHOUT RENAL FAILURE


SUMMARY

To determine the influence of renal failure on the pharmacokinetics and neuromuscular blockade of Org NC45 (Norcuron), a new monoquaternary homologue of pancuronium, 13 patients under halothane and nitrous oxide anaesthesia were studied. Org NC45 was administered by 2-min infusion in doses of 0.28 mg kg⁻¹ (normal renal function group, n = 4) and 0.14 mg kg⁻¹ (renal failure group, n = 5). Four additional patients with normal renal function were given Org NC45 0.14 mg kg⁻¹ to determine the onset, duration and recovery rate of neuromuscular blockade. The serum concentration of Org NC45 was determined by normal-phase high performance liquid chromatography (sensitivity 50 ng ml⁻¹), and a two-compartment open pharmacokinetic model was fitted to resulting data. Estimates of distribution half-life (T₁/₂), elimination half-life (T₁/₂), volume of distribution at steady state (Vss) and clearance of Org NC45 did not differ significantly between patients with normal renal function and those with renal failure. The onset, duration and recovery rate times of the neuromuscular blockade by Org NC45 0.14 mg kg⁻¹ in patients with normal renal function and those with renal failure also did not differ significantly.

Org NC45 (Norcuron) is a monoquaternary homologue of pancuronium developed by Savage, Sleigh and Carlyle (1980) which produces a neuromuscular blockade of shorter duration than pancuronium and which apparently is devoid of any cardiovascular effects in both animals (Booij et al., 1980) and man (Agoston et al., 1980; Marshall et al., 1980). The shorter duration of action of Org NC45 may be a result of its shorter elimination half-life. Van der Veen and Bencini (1980) found the elimination half-life of Org NC45 to be less than that published for pancuronium (31 min v. 133 min) by Somogyi, Shanks and Triggs (1976, 1977). However, in their Org NC45 study, the elimination half-life was determined from plasma concentration values apparently collected over 1 h following administration of Org NC45 compared with at least 6 h for pancuronium.

Durant, Houwertjes and Agoston (1979) found that duration of neuromuscular blockade following Org NC45 was not prolonged by ligation of renal pedicles in cats; the duration of pancuronium block was significantly prolonged. We have compared the pharmacokinetics and neuromuscular blockade of Org NC45 in patients with normal renal function with those with renal failure.

METHODS

Fifteen adult surgical patients (20–55 yr, 50–90 kg) gave signed consent for the study which had local approval of ethics. Eight of the patients had normal renal function and were undergoing elective surgery. In four of these the pharmacokinetics of Org NC45 0.28 mg kg⁻¹ were studied; in the other four neuromuscular blockade by Org NC45 0.14 mg kg⁻¹ was studied. Five patients had renal failure and were to receive cadaver kidney transplants. The pharmacokinetics and neuromuscular blockade of Org NC45 0.14 mg kg⁻¹ were studied. The blood urea and creatinine concentrations in the patients with renal failure were 76.3 ± 23.4 (SD) mg dl⁻¹ and 12.4 ± 2.6 mg dl⁻¹ respectively. All patients with impaired renal function had undergone haemodialysis just before surgery.

After premedication with diazepam 10 mg orally, anaesthesia was induced with thiopentone 1 mg kg⁻¹ i.v. and inhalation of halothane in 60% nitrous oxide in oxygen. The trachea was intubated without giving muscle relaxants. Ventilation of the lungs was controlled and anaesthesia maintained with 0.4–1.0% halothane end-tidal with 60% nitrous oxide, measured continuously with a mass spectrometer. Oesophageal temperature and P_{aco}_2 were maintained within normal limits.
Neuromuscular function was evaluated by measuring the strength of thumb adduction with a force-displacement transducer (Grass FT-10) in response to supramaximal stimuli of 0.15 Hz and 0.2 ms duration (Grass S44 stimulator) delivered through two steel 27-gauge needles inserted subcutaneously over the ulnar nerve at the wrist.

When the desired inhalation anaesthetic concentration had been maintained for at least 20 min, Org NC45 was infused continuously for 2 min, $0.28 \text{mg kg}^{-1}$ in patients with normal renal function ($n = 4$) and $0.14 \text{mg kg}^{-1}$ in patients with renal failure ($n = 5$). Venous blood was sampled 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 min after the start of the infusion. Samples for each were centrifuged and the serum combined with phosphate buffer 150 $\mu$litre for each ml of serum to maintain stability of Org NC45. Samples were then frozen until analysis.

The analytical procedure was a modification of the method of Paanakker and Van de Laar (1980), which uses normal-phase high performance liquid chromatography analysis. After the internal standard, neostigmine, was added, the serum samples were treated with saturated potassium iodide and Org NC45 was extracted into dichloromethane as an ion pair. The dried residue from the organic layer was taken up in methanol 30 $\mu$litre and eluted through a Micropack Si-5 column with methanol containing 0.25% ammonia gas and tetramethylammonium chloride 8.5 mmol litre$^{-1}$.

Because of the basicity of the mobile phase, a precolumn hand-packed with LiChrosorb Si-60 was installed ahead of the injector. The sensitivity of the assay was 50 ng per ml of serum and the day-to-day precision ranged from 15% (coefficient of variation; $n = 5$) at 50 ng ml$^{-1}$ to 0.6% (coefficient of variation; $n = 5$) at 2.5 $\mu$g ml$^{-1}$.

A two-compartment open pharmacokinetic model (equation (1)) was fitted to the serum concentration-time data weighting each point (1/concentration) (equation (2)).

$$ C_r = \frac{D}{\tau} \cdot \frac{(k_{21} - \alpha)}{\alpha(\beta - \alpha)} \cdot (e^{\alpha \tau} - 1) \cdot e^{-\alpha \tau} + \frac{(k_{21} - \beta)}{\beta(\alpha - \beta)} \cdot (e^{\beta \tau} - 1) \cdot e^{-\beta \tau} $$

(1)

where $C_r =$ Org NC45 concentration in plasma; $D =$ dose; $\tau =$ time from commencement of dosing; $t =$ duration of infusion; $\tau' =$ $t$ while $t < \tau$, but $\tau' =$ $\tau$ when $t > \tau$; $V =$ apparent volume of distribution in the sampled compartment; $\tau, \alpha, \beta$ and $k_{21}$ are estimated by least squares fit of the model to experimental $C_r, t$ data; $V^*$ was estimated according to equation (2):

$$ V^* = \frac{V_c(\alpha + \beta - \alpha \beta | k_{21})}{k_{21}} $$

(2)

In the normal patient group, an elimination half-life was determined using the first 90 min of data to obtain an appropriate half-life to compare with that already published for Org NC45 by Van der Veen and Bencini (1980). Statistical comparisons of pharmacokinetic parameters were made by analysis of variance.

The following indices of neuromuscular blockade by Org NC45 0.14 mg kg$^{-1}$ were determined: the onset (time from injection to maximal twitch depression), the duration of action (time from injection to 90% recovery of control twitch), and the recovery rate (time for twitch to spontaneously recover from 25% to 75% of control twitch). These indices were obtained in four of the eight normal patients and four of the five renal failure group (the other renal failure patient required antagonism of neuromuscular blockade before adequate spontaneous recovery) and comparison was made again by analysis of variance.

RESULTS

Figure 1 shows the fit of the two-compartment open pharmacokinetic model to the serum concentrations of Org NC45. Model-derived estimates of

![Figure 1](https://academic.oup.com/bja/article-abstract/53/10/1049/403675/fig.1)

**Fig. 1.** Computer fit to serum concentration of Org NC45 $v$. time data from a patient with normal renal function, given 0.28 mg kg$^{-1}$. Patient no. 1. $T_{1}^\alpha = 5.0$ min; $T_{1}^\beta = 79.1$ min; $V^* = 223.4$ ml kg$^{-1}$; $C_l = 274.8$ ml min$^{-1}$.
**Table I. Comparison of pharmacokinetic parameters of Org NC45 in patients with and without renal failure (mean ± SD)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>n</th>
<th>$T_{\text{d}}$ (min)</th>
<th>$T_{\text{e}}$ (min)</th>
<th>$V^*$ (ml kg$^{-1}$)</th>
<th>Clearance (ml min$^{-1}$)</th>
<th>Clearance (ml kg$^{-1}$ min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Normal (Org NC45)</td>
<td>4</td>
<td>8.5 ± 4.0</td>
<td>79.5 ± 13.6</td>
<td>194.3 ± 41.3</td>
<td>227.5 ± 37.5</td>
<td>3.0 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>Renal failure (Org NC45)</td>
<td>5</td>
<td>10.5 ± 4.8</td>
<td>97.1 ± 37.7</td>
<td>238.7 ± 62.6</td>
<td>176.1 ± 34.2</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>Van der Veen and Bencini (1980)</td>
<td>Normal (Org NC45)</td>
<td>6</td>
<td>3.9 ± 2.8</td>
<td>30.7 ± 18.5</td>
<td>179 ± 69</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Somogyi, Shanks and Triggs (1977)</td>
<td>Normal (pancuronium)</td>
<td>7</td>
<td>12.5 ± 4.2</td>
<td>132.5 ± 24.9</td>
<td>261.1 ± 45.7</td>
<td>122.9 ± 41.4</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Renal failure (pancuronium)</td>
<td>10</td>
<td>12.1 ± 8.6</td>
<td>257.3 ± 128.2</td>
<td>295.9 ± 158.3</td>
<td>53.0 ± 15.7</td>
<td>—</td>
</tr>
</tbody>
</table>

The distribution half-life ($T_{\text{d}}$), the elimination half-life ($T_{\text{e}}$), volume of distribution at steady state ($V^*$) and clearance of Org NC45 were not statistically different when the normal and renal failure patient groups were compared (table I). When only the first 90 min of Org NC45 serum concentration data in the normal patient group were used to estimate $T_{\text{e}}$, the estimate decreased from 79.5 ± 13.6 (SD) min to 35 ± 8 min. In the renal failure group, the average time from the commencement of the Org NC45 infusion until the transplanted kidney was functioning was 116 ± 44 min.

In all cases, administration of Org NC45 caused a 100% depression of twitch tension. No statistically significant difference was observed in duration of neuromuscular blockade of Org NC45 between normal and renal failure patients (table II). There was no statistically significant difference in onset or recovery time between the two groups of patients.

**DISCUSSION**

The shorter duration of neuromuscular blockade of Org NC45, when compared with pancuronium, may be at least partly explained by a shorter elimination half-life for Org NC45 (table I). This elimination half-life of 79.5 ± 13.6 min appears to be shorter than that found for pancuronium by Agoston and others (1973) (108–147 min), McLeod, Watson and Rawlins (1976) (100 min), Somogyi, Shanks and Triggs (1976) (132.5 min) and Miller and others (1978) (110 min). This difference in half-life seems to be the result of a difference in clearance rather than in volume of distribution (table I). The reason for the greater clearance of Org NC45 has not been determined.

**Table II. Indices of neuromuscular blockade by Org NC45 0.14 mg kg$^{-1}$ in patients with and without renal failure (mean ± SD)**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function</td>
<td>4 ± 0.6</td>
<td>103.8 ± 12.9</td>
<td>20.7 ± 2.5</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>4 ± 0.7</td>
<td>104.1 ± 45.7</td>
<td>28.7 ± 22.7</td>
</tr>
</tbody>
</table>

but the pattern of elimination of the two drugs appears to be quite different. For example, in preliminary studies in rats, we found that 45% of an injected dose of Org NC45 was excreted unchanged in the bile in the 1st hour following administration, while less than 4% of unchanged pancuronium was excreted. Whether this preferential biliary excretion of Org NC45 is also present in man remains to be determined.

No significant difference was found between pharmacokinetic parameters for Org NC45 estimated for patients with normal renal function compared with those with renal failure. Certainly with a larger number of patients, a significant difference might have been demonstrated. Our data indicate that such a difference, if found, would be small in comparison with the difference in pancuronium clearance between patients with and without renal function, as found by Somogyi, Shanks and Triggs (1977). Thus Org NC45 appears to be less dependent on renal excretion for its elimination than is pancuronium (table I). A greater degree of hepatic elimination of Org NC45 could explain these findings.

Patients in the renal failure group probably had an improvement in renal function at 116 ± 44 min.
after Org NC45 administration, as their transplanted kidney was perfused. Miller and others (1977) have shown that a newly transplanted kidney is capable of excreting tubocurarine. Obviously, we did not determine the extent to which Org NC45 may have been excreted by the new kidney. Somogyi, Shanks and Triggs (1977) also studied patients receiving newly transplanted kidneys. The markedly prolonged elimination half-life of pancuronium in this study thus allows us to conclude that Org NC45 is less dependent on renal excretion for its elimination than is pancuronium.

Because of the limited sensitivity of our assay, we were able to achieve a longer sampling time (4 h) by administering a larger dose of Org NC45 (0.28 mg kg\(^{-1}\)) to patients with normal renal function. In our renal failure group, however, we hesitated to use Org NC45 0.28 mg kg\(^{-1}\) lest prolonged neuromuscular blockade occur. Thus half the dose was given (0.14 mg kg\(^{-1}\)), which still allowed sampling time of 240 min. The influence of a longer sampling duration can be seen when comparing the “terminal” elimination half-life obtained using the first 90 min of serum concentration data (35 ± 8 min) with that using all 240 min (79.5 ± 13.6 min). The study of Van der Veen and Bencini (1980) on the pharmacokinetics of Org NC45 suffers in this regard since their elimination half-life was 30.7 ± 18.5 min. A more sensitive assay for Org NC45 would give an even more accurate “terminal” elimination half-life than that estimated in this study.

Despite these large doses of Org NC45, the duration of neuromuscular blockade did not differ in patients with normal renal function and those with renal failure (table II). This finding, combined with the similarity in pharmacokinetics, has led us to conclude that renal excretion may not be the main route of elimination of Org NC45. Org NC45 may be a suitable non-depolarizing muscle relaxant for patients with impaired renal function.

ACKNOWLEDGEMENTS
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de pouvoir déterminer le commencement, la durée et le taux de récupération du bloqueage neuromusculaire. La concentration d'Org NC45 dans le sérum a été déterminée par chromatographie en phase liquide normale à haute performance (sensibilité 50 ng ml⁻¹) et on a monté les données obtenues sur un modèle pharmacocinétique ouvert à deux compartiments. Les estimations de la demi-vie de répartition ($T_{1/2}$), de la demi-vie d'élimination ($T_{1/2}$), du volume de répartition à l'équilibre cinétique ($V_{eq}$) et le coefficient d'épuration d'Org NC45 n'ont pas différé beaucoup, que les patients aient des fonctions rénales normales ou pas. Les temps relatifs au commencement, à la durée et au taux de récupération du bloqueage neuromusculaire par l'Org NC45 à raison de 14 mg kg⁻¹ sur le patients ayant des fonctions rénales normales et sur les patients ayant une insuffisance rénale, n'ont pas différé d'une manière significative.

DIE PHARMAKOKINETIK VON ORG NC45 (NORCURON) BEI PATIENTEN MIT UND OHNE NIERENVERSAGEN

ZUSAMMENFASSUNG

Um den Einfluss von Nierenversagen auf die Pharmakokinetik und die neuromuskuläre Blockade von Org NC45 (Norcuron), einem neuen monoquaternären Homolog von Pancuronium, bestimmen zu können, wurden 13 Patienten unter Halothan- und Stickoxydulnarkose studiert. Org NC45 wurde durch 2-minütige Infusion mit Dosen von 0,28 mg kg⁻¹ (Gruppe mit normaler Nierenfunktion, $n = 4$) bzw. 0,14 mg kg⁻¹ (Gruppe mit Nierenversagen, $n = 5$) verabreicht. Zusätzliche Patienten mit normaler Nierenfunktion bekamen auch Org NC45 0,14 mg kg⁻¹ um den Anfang, Dauer und Erholungsgeschwindigkeit von neuromuskulärer Blockade bestimmen zu können. Die Serumkonzentration von Org NC45 wurde durch Normalphase-Hochleistungs-Flüssigkeitschromatographie (Empfindlichkeit 50 ng ml⁻¹) bestimmt, und ein offenes pharmakokinetisches Modell mit zwei Abteilungen wurde an die Ergebnisdaten angepasst. Schätzungen von Verteilungshalbwerten ($T_{1/2}$), Ausscheidungshalbwerten ($T_{1/2}$), Verteilungsvolumen im Gleichgewichtszustand ($V_{eq}$) und Clearance von Org NC45 zeigten keine bedeutende Unterschiede zwischen Patienten mit normaler Nierenfunktion und Patienten mit Nierenversagen. Anfang, Dauer und Erholungsgeschwindigkeit von der neuromuskulären Blockade nach Org NC45 0,14 mg kg⁻¹ bei Patienten mit normaler Nierenfunktion waren nicht bedeutend anders als bei Patienten mit Nierenversagen.

FARMACOCINETICAS DEL ORG NC45 (NORCURON) EN PACIENTES CON FALLO RENAL Y SÉN EL

SUMARIO

Se sometieron a estudio 13 pacientes bajo anestesia efectuada por halotano y óxido nitroso, para determinar la influencia del fallo renal en las farmacocinéticas y en el bloqueo neuromuscular del Org NC45 (Norcuron), que es un homólogo monocuaternario del pancuronio. El Org NC45 se administró por infusión en dosis de 0,28 mg kg⁻¹ (grupo de función renal normal, $n = 4$) y de 0,14 mg kg⁻¹ (grupo de fallo renal, $n = 5$). A otros pacientes que presentaban una función renal normal se les administró Org NC45 0,14 mg kg⁻¹ para determinar el inicio, la duración y el régimen de recuperación del bloqueo neuromuscular. La concentración de Org NC45 en el suero se determinó mediante cromatografía líquida de alta resolución y fase normal (sensibilidad de 50 ng ml⁻¹), y a la información resultante se le ajustó un modelo farmacocinético de dos compartimentos. Las estimaciones de la vida media de la distribución ($T_{1/2}$), la vida media de la eliminación ($T_{1/2}$), el volumen de distribución en el estado de régimen ($V_{eq}$) y la eliminación del Org NC45 no se diferenció de forma significativa entre los pacientes con funciones renales normales y aquellos con fallo renal. Los tiempo correspondientes al inicio, duración y régimen de recuperación del bloqueo neuromuscular por parte del Org NC45 0,14 mg kg⁻¹ en pacientes con función renal normal y en los de fallo renal, no se diferenciaron de forma significativa.