INFLUENCE OF SUXAMETHONIUM ON THE POTENCY OF ORG NC 45 IN ANAESTHETIZED PATIENTS

N. KRIEG, H. H. L. HENDRICKX AND J. F. CRUL

SUMMARY

The non-depolarizing neuromuscular block produced by Org NC 45 was potentiated by the previous administration of suxamethonium 1 mg kg\(^{-1}\), shown by twitch depression of 91.3 ± 2.4% when the same dose of Org NC 45 was administered after recovery from suxamethonium compared with the control value of 71.9 ± 6.5%. The recovery index was also prolonged from 8.1 ± 0.3 to 10.4 ± 1.0 min after suxamethonium. The dose-response curves for Org NC 45 showed a 1.66 potentiation factor for ED\(_{50}\) and 1.73 for ED\(_{95}\) caused by the previous administration of suxamethonium. This interaction is likely to occur in the plasma.

The influence of depolarizing muscle relaxants on the potency and duration of subsequently injected non-depolarizing neuromuscular blockers has been reported frequently. Foldes and colleagues (1957) observed potentiating effects after suxamethonium infusions on tubocurarine in dogs and cats (Foldes et al., 1957). Katz and others (1969) and Katz (1971) partly confirmed these findings in man. Walts and Dillon (1969) found the opposite for tubocurarine and Walts and Rusin (1977) reported no significant influence for pancuronium. Krieg, Crul and Booij (1980) found such an interaction between suxamethonium and the new non-depolarizing relaxant Org NC 45. We have studied its effect in more detail.

METHODS

Twenty-eight healthy female patients undergoing laparoscopic sterilization (23) or elective abdominal surgery (5) gave informed consent for the study. The body weights ranged from 48 to 84 kg (66 ± 2, mean ± SEM) and the ages from 18 to 58 yr (38 ± 2). Premedication consisted of atropine 0.25 mg, droperidol 5.0 mg and piritramide 0.15 mg kg\(^{-1}\) given i.m. 45 min before induction of anaesthesia.

Induction of anaesthesia was with thiopentone 5–6 mg kg\(^{-1}\) and fentanyl 0.1–0.2 mg i.v. and anaesthesia was maintained with 67% nitrous oxide in oxygen. Small incremental doses of fen-
spray). After a period of at least 5 min of stable thumb twitch response, cumulative doses of Org NC 45 were administered i.v. until 90-95% depression of twitch tension was achieved (priming dose of 15 μg kg⁻¹, incremental doses of 7.5 μg kg⁻¹). Incremental doses were injected when the effect of the preceding dose had stabilized for three consecutive twitches.

By linear regression analysis (least squares method), the cumulative dose-response curve of Org NC 45 was constructed and ED₅₀ was calculated. The mean value of cumulative doses to obtain nearly 95% blockade in the five patients was calculated as "titrated ED₉₅".

Statistics

Student's unpaired t test was applied to compare onset time, duration 90%, recovery index and depth of blockade between groups I and II (with and without preceding suxamethonium administration). Statistical significance was taken as P<0.05.

RESULTS

Bolus injections of Org NC 45 (table I)

A bolus injection of Org NC 45 following administration of suxamethonium caused 19.4% greater twitch depression (group I) than the same dose administered without suxamethonium (group II). In group I the recovery index was 1.28 times longer than in group II (P<0.05). Mean duration 90% was longer after suxamethonium pretreatment, although the difference was not statistically significant (0.05<P<0.1). Onset time was not affected significantly.

Cumulative dose–response curve

The cumulative dose–response curve of Org NC 45 is shown in figure 1. ED₅₀ is 31.6 μg kg⁻¹, as calculated from the regression line. Titrated ED₉₅ amounts to 62.5 ± 3.7 μg kg⁻¹ of Org NC 45. The dotted line in figure 1 is the dose–response curve of Org NC 45 obtained after suxamethonium administration, taken from a previous publication (Krieg, Crul and Booij, 1980).

DISCUSSION

Our results indicate potentiation of a non-depolarizing blocking agent by a depolarizing relaxant: Org NC 45 was potentiated when administered after complete recovery from a preceding bolus injection of suxamethonium 1 mg kg⁻¹. The depth of neuromuscular blockade was greater and the speed of recovery from the block less, the latter being suggested by a greater recovery index in the suxamethonium group.

The interaction of suxamethonium with subsequently administered non-depolarizing relaxants is controversial. Foldes and co-workers (1957) found a potentiation of tubocurarine in dogs and cats if administered after full recovery from a preceding bolus injection of suxamethonium 1 mg kg⁻¹. During prolonged administration of depolarizing agents, the type of block changes and assumes competitive block characteristics. Non-depolarizing agents administered during this so-called Phase-II-block

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Age (yr)</th>
<th>Onset (min)</th>
<th>Duration 90 (min)</th>
<th>Recovery index (min)</th>
<th>% Block</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>With sux.</td>
<td>62 ± 3</td>
<td>36 ± 3</td>
<td>4.2 ± 0.3</td>
<td>26.5 ± 2.5</td>
<td>10.4 ± 1.0*</td>
<td>91.3 ± 2.4*</td>
</tr>
<tr>
<td>Without sux.</td>
<td>66 ± 2</td>
<td>33 ± 2</td>
<td>4.6 ± 0.2</td>
<td>21.5 ± 2.2</td>
<td>8.1 ± 0.3*</td>
<td>71.9 ± 6.5*</td>
</tr>
</tbody>
</table>

TABLE 1. Onset time, duration 90, recovery index, and percentage block (mean values ± SEM) after a bolus injection of Org NC 45 36 μg kg⁻¹ alone and after full recovery from administration of suxamethonium 1 mg kg⁻¹. *Significantly different at P<0.05.
(Churchill-Davidson and Christie, 1959) show a greater potency than usual. This potentiation is likely to be of a different nature from that observed in our study.

Katz and others (1969) found that tubocurarine was potentiated if injected to patients after a bolus administration of suxamethonium, while Walts and Dillon (1969) found the opposite effect. Similar contradictory results were reported on the interactions of suxamethonium with pancuronium in anaesthetized patients; Katz (1971) found a potentiation, while Walts and Rusin (1977) could not show a statistically significant effect. Krieg, Crul and Booij (1980) showed no effect of suxamethonium on pancuronium, alcuronium, and tubocurarine, but there was a suggestion of potentiation in the case of Org NC 45.

To quantify the potentiation of Org NC 45 by suxamethonium, the cumulative dose–response curve of Org NC 45 (this study) was compared with that obtained in another study after administration of suxamethonium (Krieg, Crul and Booij, 1980). There is a potentiation factor of 1.66 for ED$_{50}$, and 1.73 for titrated ED$_{95}$. Caution must be exercised in the interpretation of these figures, since the allocation of the patients was not randomized between the two studies. However, the results are in close agreement with those of Crul and Booij (1980), who found ED$_{50}$ of 28 µg kg$^{-1}$ as a preliminary result, as well as with the findings of Agoston and co-workers (1980), who reported 99.8 ± 0.2% twitch depression following a bolus administration of Org NC 45 70 µg kg$^{-1}$.

In view of the identical slopes of the two dose–response curves of Org NC 45 (fig. 1), and the fact that clear evidence about the potentiation of other non-depolarizing agents is not available (Walts and Dillon, 1969; Walts and Rusin, 1977; Krieg, Crul and Booij, 1980), we conclude that there is an interaction between Org NC 45 and suxamethonium. We suggest that this interaction is the result of a reduction in the rate of degradation of Org NC 45 in the plasma by the previous administration of suxamethonium. Further studies are needed to substantiate this assumption.

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REFERENCES

EINFLUSS VON SUXAMETHONIUM AUF DIE WIRKSAMKEIT VON ORG NC 45 BEI ANÄSTHETISIERTEN PATIENTEN

ZUSAMMENFASSUNG
Die nicht-depolarisierende neuromuskuläre Blockade, die durch Org NC 45 hervorgerufen wurde, wurde durch die vorherige Verabreichung von Suxamethonium (1 mg kg$^{-1}$) potenziert, wie durch Zuckungsunterdrückung von 91,3 ± 2,4% gezeigt wurde, als dieselbe Dosis von Org NC 45 nach Erholung vom Suxamethonium verabreicht wurde. Im Vergleich zum Kontrollwert von 71,9 ± 6,5% der Erholungsindex wurde ebenfalls von 8,1 ± 0,3 auf 10,4 ± 1,0 Min
nach Suxamethonium verlängert. Die Dosiswirkungskurven für Org NC45 zeigten einen Potenzierungsfaktor von 1,66 für $ED_{30}$ und 1,73 für $ED_{95}$, verursacht durch die vorherige Verabreichung von Suxamethonium. Die Wechselwirkung kommt wahrscheinlich im Plasma vor.

INFLUENCIA DEL SUXAMETONIOM EN LA POTENCIA DEL ORG NC 45 EN PACIENTES ANESTESIADOS

SUMARIO
El bloqueo muscular no despolarizante producido por el Org NC 45 fue potenciado por la administración anterior de 1 mg kg$^{-1}$ de suxamethonium, lo que se mostró por la crispatura de 91,3 ± 2,4% cuando se administró la misma dosis de Org NC 45 después de la recuperación, en comparación con el valor del control de 71,9 ± 6,5%. El índice de recuperación se prolongó también desde 8,1 ± 0,3 a 10,4 ± 1,0 min después del suxamethonium. Las curvas de relación dosis–respuesta para el Org NC 45 mostraron un factor de potenciación de 1,66 para $ED_{30}$ y de 1,73 para $ED_{95}$, que fueron ocasionados por la administración anterior de suxamethonium. Esta interacción tendrá lugar, seguramente, en el plasma.