CLINICAL AND PHARMACOLOGICAL ACTIONS OF A BOLUS INJECTION OF SUXAMETHONIUM: TWO PHENOMENA OF DISTINCT DURATION

A. A. D’HOLLANDER, S. AGOSTON, A. DE VlLLE AND F. CUVELIER

SUMMARY

Twenty-five healthy adult patients undergoing general anaesthesia for elective surgery were randomly allocated to five groups (n = 5) and their mechanical isometric adductor pollicis activity (twitch height (TH)) was monitored. The patients in groups I, II and III received suxamethonium 1 mg kg⁻¹ followed by Org NC45 40 μg kg⁻¹ 5 min (group I), 15 min (group II) or 30 min (group III) after complete recovery from muscle paralysis. The patients in groups IV and V received only Org NC45 40 and 80 μg kg⁻¹, respectively. Mean maximum TH depression (about 42% of initial value in group IV and 5% in group V) decreased to less than 4% in groups I, II and III regardless of the time interval between the injections of suxamethonium and Org NC45. Mean duration to 90% recovery of Org NC45-induced blockade was prolonged in patients in groups I, II and III when compared with the patients in group IV (28 min v. 12 min).

The electrophysiological properties of depolarizing neuromuscular blockade in man are characterized by the absence of, or minimal, fade after train-of-four or tetanic stimulation (Churchill-Davidson, Christie and Wise, 1960; Katz, Wolff and Papper, 1963; Ali and Savarese, 1976; Lee, 1975; Ramsey et al., 1980). Thus, once the twitch height has returned to its control value after neuromuscular blockade induced by a single dose of suxamethonium, one may assume that the transmission process has been restored completely. Several reports have described the interaction between suxamethonium and non-depolarizing neuromuscular blocking agents. These studies have shown considerable potentiation of the effect of the non-depolarizing drugs when given after suxamethonium (Katz, 1971; Krieg, Crul and Booij, 1980; Krieg, Hendrickx and Crul, 1981). In this study, this interaction has been investigated in an attempt to define the total duration of the pharmacological action of a single dose of suxamethonium. The non-depolarizing agent, Org NC45, was administered at various time intervals after full recovery from neuromuscular blockade produced by suxamethonium. Org NC45 was chosen because recent work (Krieg, Crul and Booij, 1980; Krieg, Hendrickx and Crul, 1981) has indicated that potentiation following the prior administration of suxamethonium was particularly obvious with this new monouquaternary derivative of pancuronium.

PATIENTS AND METHODS

Twenty-five healthy adult patients, of either sex, undergoing general anaesthesia for elective surgery gave informed consent and were included in the study. All were free from renal, hepatic and neuromuscular disease. Mean body weight (± SEM) was 68.1 (± 4.9) kg and mean age was 32.0 (± 3.9) yr. Premedication consisted of diazepam 0.2 mg kg⁻¹ by mouth 1 h before the induction of anaesthesia. The patient’s forearm and hand were secured firmly to an arm board and a force displacement transducer (Statham UC3 - UL4/20) placed in the patient’s hand. The ulnar nerve was stimulated at the wrist by needle electrodes with square-wave, supra-maximal stimuli of 0.2 ms duration at a frequency of 0.1 Hz (Grass stimulator 88). The isometric twitch tension of the indirectly stimulated adductor pollicis muscle was recorded on a polygraph. Anaesthesia was induced with methohexitone 1 mg kg⁻¹ and fentanyl 5 μg kg⁻¹ i.v.; a face-mask was applied and the patient’s ventilation assisted or controlled (oxygen 5 litre min⁻¹; nitrous oxide 5 litre min⁻¹). After a consistent and stable twitch height was obtained, the patients were randomly allocated to five subgroups. Fifteen patients received suxamethonium 1 mg kg⁻¹ i.v. followed by Org NC45 0.04 mg kg⁻¹ 5 min (group I; n = 5), 15 min (group II; n = 5) or 30 min (group III; n = 5).
after full recovery from the neuromuscular blockade produced by the suxamethonium. The patients of group IV \((n = 5)\) and group V \((n = 5)\) received Org NC 45 0.04 mg kg\(^{-1}\) and 0.08 mg kg\(^{-1}\) respectively, without any previous administration of suxamethonium. The indices studied were: peak twitch height depression (suxamethonium or Org NC 45, or both); onset time (the time from the end of the injection of Org NC 45 until the maximum effect was reached); the duration to 25% recovery; the time required from 25% to 75% recovery of the twitch height; and the duration (the time between the end of the injection of Org NC 45 until recovery of the twitch height to 90% of control). Endotracheal intubation was performed in groups I, II, III and V at the point of maximum twitch height depression following the administration of suxamethonium or Org NC 45 0.08 mg kg\(^{-1}\) and the lungs were ventilated mechanically with a gas mixture of nitrous oxide in oxygen (2:1 v/v). The patients of group IV were ventilated artificially with nitrous oxide in oxygen (4:2 v/v) via a face-mask. Blood-gas analyses were performed regularly and the volume of ventilation adjusted to achieve normocapnia \((\text{PaCO}_2 \text{ 4.99–5.59 kPa})\).

Statistical analysis of the data was performed using an unpaired bilateral Wilcoxon test. Statistical significance was assumed when \(2P\) was less than 0.05.

**RESULTS**

In all the patients receiving suxamethonium, the duration of complete neuromuscular block was 13 min (range 10–21 min). During recovery from the suxamethonium blockade, train-of-four (2-Hz) stimulations, given at random, never showed a fade phenomenon (by definition: \(T_4/T_1\) ratio less than 0.7 (Durant and Katz, 1982)).

The neuromuscular blockade induced by the administration of Org NC 45 0.04 mg kg\(^{-1}\) given at different intervals (5, 15 and 30 min after full recovery from suxamethonium blockade) was similar in the various

<table>
<thead>
<tr>
<th>Suxamethonium (1 mg kg(^{-1}) i.v. bolus)</th>
<th>Competitive neuromuscular blocking agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal twitch height depression (% IV)</td>
<td>Duration to full and stable recovery (min)</td>
</tr>
<tr>
<td>---------------------------------</td>
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</tr>
<tr>
<td>Group I</td>
<td></td>
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<tr>
<td>Sx + Org NC 45 0.04 mg kg(^{-1}) after 5 min of full recovery</td>
<td>2.2 b</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
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<tr>
<td>Sx + Org NC 45 0.04 mg kg(^{-1}) after 15 min of full recovery</td>
<td>4.6 b</td>
</tr>
<tr>
<td>Group III</td>
<td></td>
</tr>
<tr>
<td>Sx + Org NC 45 0.04 mg kg(^{-1}) after 30 min of full recovery</td>
<td>5.0 b</td>
</tr>
<tr>
<td>Group IV</td>
<td></td>
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<tr>
<td>Org NC 45 0.04 mg kg(^{-1})</td>
<td>42.0</td>
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<tr>
<td>Group V</td>
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<td>Org NC 45 0.08 mg kg(^{-1})</td>
<td>3.0 c</td>
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**Table I. Effects of Org NC 45 0.04 mg kg\(^{-1}\) and 0.08 mg kg\(^{-1}\) given alone or at various time intervals following complete recovery of paralysis of the adductor pollicis muscle, induced by suxamethonium 1 mg kg\(^{-1}\), in man (mean ± SEM; range in parentheses). IV = initial value; Sx = suxamethonium. a = group V v. group I, or group II, or group III: \(P < 0.01\); b = group IV v. group I, or group II, or group III: \(P < 0.01\); A = group V v. group IV, or group II, or group III: \(P < 0.05\); c = group V v. group IV: \(P < 0.01\).**
groups (table I), and no significant differences could be detected in the indices under consideration. The mean values obtained in groups I, II and III were: peak TH depression = 4% of initial value (range 0–25); onset time = 3.8 min (range 2.5–6); duration to 25% of recovery = 15.3 min (range 12–31); recovery rate = 10.7 min (range 12–31). When compared with group IV, in which OrgNC45 0.04 mg kg$^{-1}$ was used without the previous administration of suxamethonium, the patients in groups I, II and III showed more pronounced maximal TH depression ($P<0.01$) and a longer total duration to 90% recovery ($P<0.01$). Since the administration of OrgNC45 0.08 mg kg$^{-1}$ alone produced neuromuscular blockade comparable to that produced by OrgNC45 0.04 mg kg$^{-1}$ following suxamethonium, this group of patients (group V) served as a control group for the comparison with groups I, II and III as their maximal TH depressions were identical: 3% of initial value (range 0–8) against 4% (range 0–25). Although the onset time of group V (6.9 min, range 5–9.5) was longer than that in groups I, II and III (3.8 min, range 2.5–6; $P<0.01$) no significant differences were observed for the duration to 25% of recovery and the TH$_{25}$ recovery rate.

In groups II and III, the duration to 90% recovery was shorter ($P<0.05$) than for group V (26.6 and 26.2 min v. 38.3 min).

**DISCUSSION**

After full recovery from a single dose of suxamethonium i.v., the subsequent administration of OrgNC45 in the dose which, when given alone, produced approximately a 50% depression in twitch height (Krieg, Hendrickx and Crul, 1981: see also results of group IV patients) was followed by almost complete neuromuscular blockade. This potentiation of the neuromuscular blocking action of OrgNC45 by the previous administration of suxamethonium is unlikely to be a transitory event. The degree of TH depression produced by OrgNC45 following suxamethonium was not modified by increasing time (5 min to 30 min) after full recovery from the depolarizing blockade. As compared with the patients receiving either OrgNC45 0.04 or 0.08 mg kg$^{-1}$ alone, the previous administration of suxamethonium not only markedly shortened the onset time, but also prolonged the duration of action of OrgNC45. Once again, these alterations of the neuromuscular effects of OrgNC45 were not changed significantly by the time between the administration of suxamethonium and that of OrgNC45.

The reasons for the prolonged abnormal function of the neuromuscular junction after the administration of suxamethonium in man under the conditions of this investigation are not easy to delineate because of the absence of relevant data concerning the plasma and the junctional concentrations of suxamethonium and its metabolite (succinylmonocholine) in relation to the neuromuscular blocking effect of suxamethonium in animals and in man. Additionally, any changes in the electrophysiological properties of the motor-end plate following the administration in sequence of suxamethonium and non-depolarizing neuromuscular blocking drugs are not known.

Nevertheless, one possibility is that once the blockade induced by suxamethonium, and recorded by monitoring the twitch height has worn off, numerous end-plate receptors either remain occupied by suxamethonium, or are free from suxamethonium but have developed an abnormality of function which results in an increased affinity for antagonists. In non-mammalian neuromuscular preparations Rang and Ritter (1969) observed enhanced antagonist binding after pretreatment with agonists. Such an alteration in the function of end-plate receptors in the mammal remains to be confirmed experimentally, but could explain the potentiation of non-depolarizing neuromuscular blocking activity, the decrease in onset time and the delayed recovery observed after the administration of depolarizing and non-depolarizing drugs in sequence in man.

In conclusion, the present results confirm that the dose of OrgNC45, and probably other non-depolarizing blockers, can be decreased following the administration of suxamethonium. Moreover, the present observations indicate that this decrease in dose could be applicable for at least 30 min after total clinical recovery from the neuromuscular blockade induced by suxamethonium.

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References


Actions Cliniques et Pharmacologiques d'une Injection Flash de Suxamethonium: Deux Phénomènes de Durée Distincte

Résumé

Vingt cinq patients adultes en bonne santé subissant une anesthésie générale pour une chirurgie réglée ont été répartis au hasard en cinq groupes (*n* = 5) et l'activité mécanique isométrique de leur adducteur du pouce (hauteur du twitch (TH)) a été surveillée. Les patients du groupe I, II et III ont reçu du suxamethonium 1 mg kg⁻¹, suivi d'Org NC 45 40 μg kg⁻¹ 5 min (groupe I), 15 min (groupe II) ou 30 min (groupe III) après récupération complète de la paralysie musculaire. Les patients des groupes IV et V n'ont reçu que de l'Org NC 45, 40 et 80 μg kg⁻¹ respectivement. La dépression moyenne maximum de la HT (environ 42% de la valeur initiale dans le groupe IV et 5% dans le groupe V) s'est abaissee à moins de 4% dans les groupes I, II et III, quelque soit l'intervalle de temps entre les injections de suxamethonium et d'Org NC 45. La durée moyenne de récupération à 90% du bloc induit par l'Org NC 45 était prolongée chez les patients des groupes I, II, III, par rapport aux patients du groupe IV (28 min par rapport à 12 min).

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Klinische und Pharmacologische Wirkungen einer Bolusinjektion von Suxamethonium: Zwei Phänomene von Bestimmter Dauer

Zusammenfassung

25 erwachsene, erwachsene Patienten unter Vollnarkose für elective chirurgische Eingriffe wurden willkürlich in 5 Gruppen eingeteilt (*n* = 5), und die mechanisch isometrische Aktivität des adducteur pollicis (Zuckhöhe (TH)) wurde gemessen. Die Patienten in den Gruppen 1–3 erhielten Suxamethonium 1 mg kg⁻¹, gefolgt von Org NC 45 40 μg kg⁻¹, 5 min (Gruppe 1), 15 min (Gruppe 2) oder 30 min (Gruppe 3) nach der völligen Erholung von Muskelläähmung. Die Patienten in den Gruppen 4 und 5 erhielten nur Org NC 45, jeweils 40 und 80 μg kg⁻¹. Die mittlere maximale TH-Dämpfung (etwa 42% des Ausgangswerts in Gruppe 4, und 5% in Gruppe 5) sank auf weniger als 4% in Gruppen 1–3, ungeschehen des Zeitintervalls zwischen den Injektionen der beiden Drogen. Die mittlere Dauer bis zur 90%igen Erholung der Org NC 45-Blockierung war länger in den Gruppen 1–3 als bei den Patienten in Gruppe 4 (28 min anstatt 12 min).

Acciones Clínicas y Farmacológicas De Una Inyección de Bo lo de Suxametoni o: Dos Fenómenos de Distinta Duración

Sumario

Se distribuyeron al azar a veinticinco pacientes adultos sanos a quienes se administró una anestesia general con midazolam e isometamid a una cirugía electiva en cinco grupos (*n* = 5) y se controló la actividad isométrica mecánica de su aductor del pulgar (altura de contracción— *twitch height*) Los pacientes de los grupos I, II y III recibieron 1 mg kg⁻¹ de suxamethonium seguido por 40 μg kg⁻¹ de Org NC 45 a los 5 min (Grupo I), a los 15 min (Grupo II) o a los 30 min (Grupo III) después de la completa recuperación de la parálisis muscular. Los pacientes de los grupos IV y V recibieron solamente 40 y 80 μg kg⁻¹ de Org NC 45, respectivamente. La depresión máxima promedio de la TH (alrededor del 42% del valor inicial en el Grupo IV y del 5% en el Grupo V) bajó por debajo del 4% en los Grupos I, II y III, independientemente del intervalo de tiempo entre las inyecciones de suxamethonium y de Org NC 45. Se prolongó la duración promedio hasta el 90% de recuperación del bloqueo inducido por el Org NC 45 en los pacientes de los Grupos I, II y III en comparación con los pacientes del Grupo IV (28 min contra 12 min).