ANTAGONISM OF ORG NC45 (VECURONIUM) AND PANCURONIUM NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE

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SUMMARY

The antagonism, by neostigmine, of neuromuscular blockade produced by either Org NC45 or pancuronium was studied in 29 anaesthetized patients during a continuous infusion of the myoneural blocker. The ED₅₀ of neostigmine (dose which produced a 50% antagonism) when antagonizing Org NC45 and pancuronium was 0.011 mg kg⁻¹ and 0.010 mg kg⁻¹ respectively. The dose-response relationships for the antagonism of Org NC45 and pancuronium neuromuscular blockades were not significantly different. The duration of the effect of neostigmine was not different when antagonizing an Org NC45- or pancuronium-induced blockade. We concluded that Org NC45 and pancuronium are effectively and equally (independent of their pharmacokinetics) antagonized by neostigmine in man.

Org NC45 (new generic name, vecuronium), a homologue of pancuronium, is a new, short acting, non-depolarizing neuromuscular blocking agent. In animal studies, neuromuscular blockade induced by Org NC45 was antagonized easily by acetylcholinesterase inhibitors and amino-pyridines (Marshall et al., 1980). A comparative study in rats showed no difference in the amount of neostigmine required to antagonize the neuromuscular blockade produced by either pancuronium or Org NC45 (Booij et al., 1980) yet, in man, Fahey and others (1981b) found that less neostigmine was required to antagonize an Org NC45 neuromuscular blockade as compared with that required to antagonize blockade from pancuronium. However, as this analysis was made during a changing neuromuscular blockade we have re-evaluated the ability of neostigmine to antagonize an Org NC45- or pancuronium-induced neuromuscular blockade using a steady-state infusion technique.

PATIENTS AND METHODS

Twenty-nine adult patients were studied. Their mean age (±1 SD) and body weight were 41 ± 15 yr and 70.2 ± 15.8 kg respectively. Informed consent was granted by each patient for participation in the study according to the guidelines of the University of California, San Francisco's Committee on Human Research. One hour after receiving diazepam 10–20 mg by mouth, anaesthesia was induced with thiopentone 1–3 mg kg⁻¹ i.v., halothane and 60% nitrous oxide in oxygen and maintained with halothane 0.4–1.2% end-tidal concentration (as determined by mass spectrometry) and 60% nitrous oxide in oxygen. Endotracheal intubation was accomplished without the use of neuromuscular blockade. Ventilation was controlled to maintain an end-tidal Pco₂ of 3.99–5.32 kPa. Oesophageal temperature was maintained between 34.5 and 36.0°C with a warming blanket.

A Grass S-44 stimulator was used to apply supramaximal square-wave bipolar pulses of 0.15 ms duration and 0.15 Hz to thin-wall 27-gauge steel needle electrodes placed 2–3 cm apart near the ulnar nerve on the wrist. The resultant adduction of the thumb was measured by a force displacement transducer (Grass FT-10) and recorded continuously on a polygraph.

After at least 30 min of anaesthesia, either pancuronium (n = 14) or Org NC45 (n = 15) was infused continuously from a Harvard Apparatus Infusion pump to maintain a constant 90% depression of twitch tension. When the required infusion rate and depression of twitch tension were constant for at least 15 min, a randomly selected dose of neostigmine was given as an i.v. bolus during the continuous infusion. The required infusion rates for pancuronium and Org NC45 were 0.41 ± 0.18 µg min⁻¹ (mean ± SD) and 1.08 ± 0.67 µg min⁻¹ respectively. The doses of neostigmine administered to the patients receiving Org NC45 were 0.005 mg kg⁻¹ (n = 3), 0.010 mg kg⁻¹ (n = 3), and 0.015 mg kg⁻¹ (n = 1).
0.01 mg kg\(^{-1}\) (n = 5), 0.02 mg kg\(^{-1}\) (n = 4) and 0.03 mg kg\(^{-1}\) (n = 3). The doses of neostigmine for the patients receiving pancuronium were 0.005 mg kg\(^{-1}\), (n = 5), 0.01 mg kg\(^{-1}\) (n = 5) and 0.03 mg kg\(^{-1}\) (n = 4). The 0.02 mg kg\(^{-1}\) dose of neostigmine was omitted in the pancuronium group because it was not required to define the neostigmine dose–response curve. Each patient was studied only once and received only one dose of neostigmine. The resultant maximum antagonism of twitch depression was noted (here presented as a percentage of the pre-existing value of twitch depression). Times from the injection of neostigmine to 50 and 100\% of peak effect and 75 and 50\% return to relaxant depressed twitch tension were calculated. This technique has been described in more detail by Miller and colleagues (1974).

The dose–response curves for neostigmine when antagonizing either pancuronium or Org NC45 were calculated by analysis of linear regression on a semi-logarithmic scale. The dose–response and duration–effect data were compared by analysis of covariance (Snedecor and Cochran, 1967). Statistically significant differences were assumed at P<0.05.

RESULTS

The ED\textsubscript{50} of neostigmine (the doses of neostigmine which produced a 50\% antagonism) when antagonizing Org NC45 and pancuronium were 0.011 mg kg\(^{-1}\) and 0.010 mg kg\(^{-1}\) respectively (fig. 1). The regression coefficients of the neostigmine dose–response linear regressions for Org NC45 and pancuronium on the semi-logarithmic plot were 76.4 and 72.9; the common regression coefficient of the data was 74.05. The neostigmine dose–response curves for the antagonism of neuromuscular blockade produced by Org NC45 and pancuronium were not significantly different.

The duration of the effect of neostigmine was not different when antagonizing an Org NC45 or pancuronium neuromuscular blockade (fig. 2).

![Graph 1](image1.png)

**Fig. 1** Relationship between dose of neostigmine and percentage of either the Org NC45- or pancuronium-depressed twitch antagonized in patients (mean ± SEM). The lines represent linear regression analyses. •••• = Org NC45; o---o = pancuronium.

![Graph 2](image2.png)

**Fig. 2** Plot of time and percentage of either the Org NC45- or pancuronium-depressed twitch antagonized by neostigmine 0.01 mg kg\(^{-1}\) or 0.03 mg kg\(^{-1}\) (mean ± SEM). Org NC45: △--△ = neostigmine 0.03 mg kg\(^{-1}\), ▲—▲ = neostigmine 0.01 mg kg\(^{-1}\). Pancuronium: o---o = neostigmine 0.03 mg kg\(^{-1}\), —— = neostigmine 0.01 mg kg\(^{-1}\).

The time from injection to peak effect of neostigmine 0.01 mg kg\(^{-1}\) was shorter when antagonizing Org NC45 (5.3 min) than pancuronium (10.7 min). However, the times to peak effect were not different with neostigmine 0.03 mg kg\(^{-1}\).

DISCUSSION

The similarity of neostigmine dose and effect on the neuromuscular blockades produced by Org NC45 and pancuronium in animals (Booij et al., 1980; Durant, Houwertjes and Crul, 1980) is in accord with our results. Yet in man, Fahey and colleagues (1981b) found that less neostigmine was required to antagonize an Org NC45- as compared with a pancuronium-induced neuromuscular blockade. This apparent discrepancy
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May be explained by differences in experimental methods and the dissimilarity of the pharmacokinetics of Org NC45 and pancuronium. The neuromuscular block of Org NC45 has a shorter duration of action and faster rate of recovery than the blockade from pancuronium (Van der Veen and Bencini, 1980) probably because Org NC45 has a shorter elimination half-life (Fahey et al., 1981a). Moreover, Fahey and co-workers (1981b) administered intermittent boluses of neostigmine with an initial 95% twitch depression from Org NC45 without compensation for the different pharmacokinetics and durations of action of Org NC45 and pancuronium. Under such circumstances, neuromuscular blockade from Org NC45 would decrease more quickly than blockade from pancuronium and hence contribute to the apparently enhanced effect. However, in our study, the differences in Org NC45 and pancuronium pharmacokinetics and the durations of neuromuscular blockade were obviated by the use of a continuous infusion of the neuromuscular blockers which was adjusted to achieve equal and unchanging depression of twitch tension. We conclude that Org NC45 and pancuronium are effectively and equally (independent of their different pharmacokinetics and durations of effect) antagonized by neostigmine in man.

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REFERENCES


ANTAGONISME DE L'ORG NC45 (NORCURON) ET DU PANCURONIUM DANS LE BLOCAGE NEUROMUSCULAIRE PAR LA NEOSTIGMINE

RESUME

Chez 29 patients anesthésiés au cours d’une infusion continue d’agent de blocage myoneural, on a étudié l’antagonisme de la neostigmine vis-à-vis du blocage neuromusculaire produit soit par l’Org NC45 soit par le pancuronium. L’ED50 de la neostigmine (dose qui produisait un antagonisme de 50%) pour antagoniser l’Org NC45 et le pancuronium était de 0,011 mgkg⁻¹ et de 0,010 mgkg⁻¹, respectivement. Les rapports dose-réponse pour l’antagonisme des blocages neuromusculaires de l’Org NC45 et du pancuronium n’étaient pas sensiblement différents. La durée de l’effet de la neostigmine n’était pas différente lorsque cette substance antagonisait le blocage obtenu par l’Org NC45 ou par le pancuronium.

Nous en concluons que l’Org NC45 et le pancuronium sont effectivement et également antagonisés par la neostigmine chez l’homme (indépendamment de leur pharmacocinétique).

GEGENWIRKUNG AUF ORG NC45 (NORCURON) UND PANCURONIUM ALS NEUROMUSKULARE BLOCKIERUNG DURCH NEOSTIGMIN

ZUSAMMENFASSUNG

Die Neostigmin-Gegenwirkung auf neuromuskuläre Blockierung entweder durch Org NC45 oder Pancuronium wurde bei 29 narkotisierten Patienten während kontinuierlicher Infusion des Blockierungsmittels untersucht. Das ED50 von Neostigmin (die Dosis, die einen 50%igen Antagonismus bewirkte) war bei der Gegenwirkung auf Org NC45 und Pancuronium 0,011 mgkg⁻¹ und 0,010 mgkg⁻¹. Das Dosis-Reaktionsverhältnis für die Aufhebung neuromuskulärer Blockierungen bei Org NC45 und bei Pancuronium zeigt keinen signifikanten Unterschied bei den beiden Drogen nicht besonders unterschiedlich. Die Wirkungsduer von Neostigmin war ebenfalls bei beiden Narkosemitteln nicht unterschiedlich. Wir schlussfolgern daraus, dass diese beiden Narkosemittel wirksam und gleichermaßen (unabhängig von ihrer Pharmakokinetik) durch Neostigmin antagonisiert werden.
ANTAGONISMO DEL ORG NC45 (NORCURON) Y DEL PANCURONIO EN EL BLOQUEO NEUROMUSCULAR POR NEOESTIGMINA

SUMARIO
Se estudió en 29 pacientes anestesiados durante la infusión continua del bloqueador mioneural, el antagonismo por la neoestigmina en el bloqueo neuromuscular producido tanto por el Org NC45 como por el pancuronio. El ED$_{30}$ de neoestigmina (dosis que produce un antagonismo del 50%) al antagonizar el Org NC45 y el pancuronio era de 0,011 mg kg$^{-1}$ y de 0,010 mg kg$^{-1}$, respectivamente. Las relaciones dosis-respuesta para el antagonismo del bloqueo neuromuscular por Org NC45 y pancuronio no variaban de manera significante. La duración del efecto de la neoestigmina no era distinta cuando antagonizaba un bloqueo inducido por Org NC45 o por pancuronio. Sacamos la conclusión de que la neoestigmina antagoniza igual y efectivamente tanto el Org NC45 como el pancuronio en el hombre (independientemente de su farmacocinética).