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Dose-response studies with pancuronium, vecuronium and their combination

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1 Pancuronium, vecuronium and a combination of these were administered in an incremental fashion to study any potentiation of effect with the combination of the two relaxants.

2 The ED_{95} (dose producing a 95% block) of the combination was 29 $\mu g\ kg^{-1}$ for each component in comparison to 57 $\mu g\ kg^{-1}$ for vecuronium and 59 $\mu g\ kg^{-1}$ for pancuronium.

3 The dose-response curves for the three groups did not differ from each other and no potentiation was demonstrated.

Keywords neuromuscular blocking agents vecuronium pancuronium drug interactions

Introduction

Administration of a combination of pancuronium and the chemically unrelated tubocurarine has been demonstrated to result in a greater than additive neuromuscular blocking effect (Lebowitz *et al.*, 1980).

Vecuronium (Org NC 45), a recently introduced competitively acting muscle relaxant (Savage *et al.*, 1980; Agoston *et al.*, 1980), is chemically related to pancuronium and it was therefore of interest to test whether any potentiation occurs when these two related drugs are administered in combination. This has been investigated clinically in the present study.

Methods

Thirty adult, ASA grade I patients, divided into three groups of 10 each, scheduled for elective surgery and requiring the use of non-depolarising neuromuscular blocking drugs were investigated. The study was approved by the Regional Ethical Committee and informed consent was obtained from each patient. Premedication consisted of diazepam 10–15 mg administered orally 60 to 90 min preoperatively. An intravenous infusion of lactated Ringer solution was put up on arrival in the anaesthetic room. Heart rate (ECG) and blood pressure (automatic non-invasive blood pressure monitor with a recorder—Dinamap, Critikon Limited) were monitored throughout. Anaesthesia was induced with thiopentone (4–5 mg kg^{-1}) and fentanyl (3 $\mu g\ kg^{-1}$) and maintained with 70% nitrous oxide in oxygen. Further increments of fentanyl (50 μg) and/or additional thiopentone (50–100 mg) were administered as required. Ventilation was assisted when necessary. No surgical intervention occurred during the study period.

Supramaximal square-wave stimuli (0.1 Hz; duration 0.2 ms) from a peripheral nerve stimulator (Myotest) were applied to the ulnar nerve at the wrist using surface electrodes. The resulting force of contraction of the adductor

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pollicis muscle was recorded using a force displacement transducer and a neuromuscular function analyser (Myograph 2000, Biometer Limited). Control twitch height was allowed to stabilise for at least 10 min, after which the patients received increments of vecuronium 10 $\mu g\ kg^{-1}$, pancuronium 10 $\mu g\ kg^{-1}$ or a mixture of 5 $\mu g\ kg^{-1}$ each, in a randomised fashion, given into the fast flowing intravenous infusion. Stability studies with freshly mixed pancuronium and vecuronium showed no loss of potency of either drug (Savage, personal communication). Following initial pilot studies, the size of increments chosen was such that roughly equal numbers of increments of each relaxant would produce a 95% block. Subsequent increments of the same drug or the combination were administered to each patient when three consecutive twitches of the same height were evoked, until 95% depression of twitch height was obtained (Figure 1). Tracheal intubation was carried out at this point. The time for the twitch height to recover to 25% of control was measured. The study was terminated at this point, and further anaesthesia and relaxation were maintained as required for surgery. The percentage depression of twitch height obtained by each increment of drug in each group was recorded.

An arc-sine transformation of the data relating to the twitch height was carried out according to Armitage (1971), for responses involving the two extreme (0 and 100%) points on the dose response curves. This was used to plot the cumulative dose-response curves using the method of least squares and linear regression. The number of increments of each drug or the combination required to obtain at least 95% depression of twitch height were recorded as also was the time to 25% recovery of the block.

Results

Analysis of the physical characteristics of the patients in each group is given in Table 1. These are broadly similar, and are not significantly different with regard to age, sex or weight.

The cumulative dose-response curves plotted from the percentage depression of twitch height obtained by each increment are shown in Figure 2. The curves for each group do not differ significantly in slope or parallelism, and are virtually superimposed upon each other, thus indicating a lack of potentiation with the combination in comparison with the individual drugs given alone. This is confirmed by the similar number of increments required in each group to achieve either a 50% (ED_{50}) or a 95% (ED_{95}) depression of twitch height as shown in the table, no significant differences being observed between the groups.

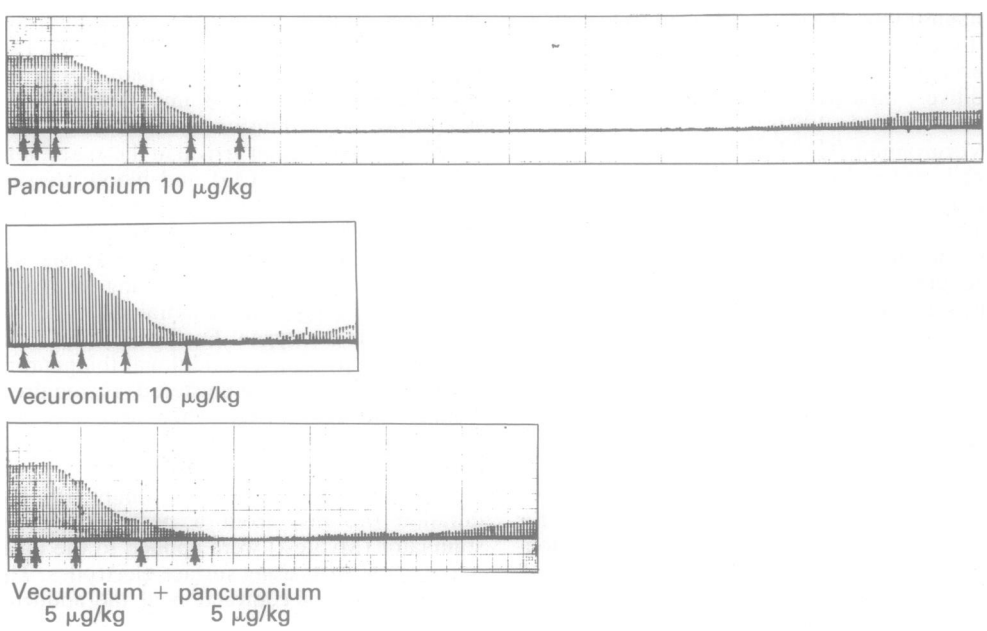

Figure 1 A representative tracing of the study. Arrows represent time of administration of increments and the end of each trace coincides with 25% recovery of twitch height.

Table 1 Physical characteristics, number of increments required for 50 and 95% block and the time to 25% recovery

Muscle relaxant	*Age (years) ± s.e. mean*	*Weight (kg) ± s.e. mean*	*Average number of increments (95% confidence limits)* ED_{50}	ED_{95}	*Time to 25% recovery of twitch height (min) (± s.e. mean)*
Pancuronium	38.7 ± 4.22	72.2 ± 4.20	3.17 (2.74–3.60)	5.91 (4.81–7.00)	34.2 ± 6.26*
Vecuronium	32.9 ± 5.28	58.6 ± 4.01	3.05 (2.44–3.67)	5.67 (4.10–7.25)	9.8 ± 0.78*
Pancuronium + vecuronium	45.6 ±5.04	70.8 ± 3.69	3.05 (2.59–3.52)	5.86 (4.81–6.92)	18.4 ± 2.09*

ED_{50} and ED_{95} represent 50 and 95% block.
*Significantly different from each other.

When the number of increments required to produce a 95% block is converted into the doses of each drug or combination, the ED_{95s} are 59 μg kg^{-1} for pancuronium, 57 μg kg^{-1} for vecuronium and 29 μg kg^{-1} of each for the combination.

The mean time taken for 25% recovery of twitch height is shown in Table 1. It denotes the time from the point of attaining a 95% block to its recovery to 25%. It was shortest (9.8 min) with vecuronium and longest (34.2 min) with pancuronium, that for the combination being in between (18.4 min). These were significantly different from each other.

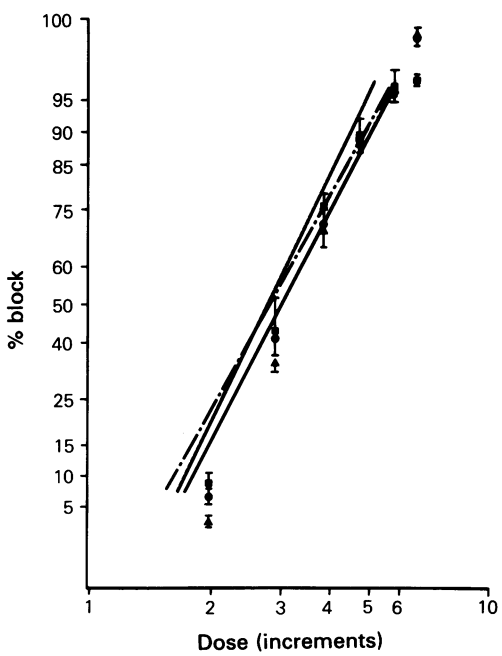

Figure 2 Cumulative dose-response curves for vecuronium (■), pancuronium (▲) and their combination (●). Each point represents mean ± s.e. mean.

Discussion

Potentiation of effect using combinations of nondepolarising neuromuscular blocking drugs has been reported between gallamine and tubocurarine (Wong & Jones, 1971; Ghoneim *et al.*, 1972) as well as between pancuronium on the one hand and tubocurarine or metocurine on the other (Lebowitz *et al.*, 1980; 1981). The possible mechanisms causing this effect include: (i) alteration of the pharmacokinetic behaviour of one drug by the other, (ii) the involvement of augmented conformational attachment of the drugs to pre- and post-junctional cholinergic receptors, and (iii) simultaneous pre- and post-junctional receptor inhibition. Although altered protein binding could be a part of the altered pharmacokinetic behaviour, this has been shown not to occur in combinations of neuromuscular blocking drugs which result in potentiation of effect (Martyn *et al.*, 1983).

Whatever the explanation for the potentiation that occurs between pairs of chemically unrelated drugs, it seems that it does not apply to chemically related drugs such as pancuronium and vecuronium studied here, and tubocurarine and metocurine studied by Lebowitz *et al.* (1980).

In the absence of any potentiation, the duration to 25% recovery after injection of the combination of vecuronium and pancuronium was observed to lie between that of the individual drugs. The duration to 25% recovery is

usually taken from the time of drug administration when single boluses are administered. This is not meaningful when cumulative administration is used as in the present study. Instead we measured the time from attaining a 95% block to 25% recovery which gives an indication of the duration. The shorter times to 25% recovery observed using combinations that are associated with potentiation, e.g. pancuronium with metocurine (Lebowitz *et al.*, 1981) or pancuronium with tubocurarine (Mirakhur *et al.*, 1984) in comparison to individual drugs may be explained on the grounds that smaller amounts of each drug are used in these combinations.

In conclusion, the present study shows that a combination of vecuronium and pancuronium exerts no greater effect than that seen with either agent administered alone.

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References

Agoston, S., Salt, P., Newton, D., Bencini, A., Boomsma, P. & Erdmann, W. (1980). The neuromuscular blocking action of Org NC 45, a new pancuronium derivative, in anaesthetised patients. *Br. J. Anaesth.*, **52**, 53S–59S.

Armitage, P. (1971). *Statistical Methods in Medical Research.*. Oxford: Blackwell Scientific Publications.

Ghoneim, M. M., Urgena, R. B., Dretchen, K. & Long, J. P. (1972). The interaction between d-tubocurarine and gallamine during halothane anaesthesia. *Can. Anaesth. Soc. J.*, **19**, 66–74.

Lebowitz, P. W., Ramsey, F. M., Savarese, J. J. & Ali, H. H. (1980). Potentiation of neuromuscular blockade in man produced by combinations of pancuronium and metocurine or pancuronium and d-tubocurarine. *Anesth. Analg. (Cleve).*, **59**, 604–609.

Lebowitz, P. W., Ramsey, F. M., Savarese, J. J., Ali, H. H. & DeBros, F. M. (1981). Combination of pancuronium and metocurine: neuromuscular and hemodynamic advantages over pancuronium alone. *Anesth. Analg. (Cleve).*, **60**, 12–17.

Martyn, J. A. J., Leibel, W. S. & Matteo, R. S. (1983). Competitive nonspecific binding does not explain the potentiating effects of muscle relaxant combinations. *Anesth. Analg. (Cleve).*, **62**, 160–163.

Mirakhur, R. K., Pandit, S. K., Ferres, C. J. & Gibson, F. M. (1984). Time course of muscle relaxation with a combination of pancuronium and tubocurarine. *Anesth. Analg. (Cleve).*, **63**, 437–440.

Savage, D. S., Sleigh, T. & Carlyle, I. (1980). The emergence of Org NC 45, 1-[(2B, 3, 5, 16B, 17B)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1 methylpiperidinium bromide, from the pancuronium series. *Br. J. Anaesth.*, **52**, 3S–9S.

Wong, K. C. & Jones, J. R. (1971). Some synergistic effects of d-tubocurarine and gallamine. *Anesth. Analg. (Cleve).*, **50**, 285–290.

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