TITLE: A Marked Potentiating Effect in Man of Combined Pancuronium and Metocurine or Pancuronium and d-Tubocurarine Neuromuscular Blockade

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It is generally assumed that the neuromuscular blocking properties of nondepolarizing agents are additive. If so, summated equipotent doses of all nondepolarizers should elicit the same degree of neuromuscular blockade, alone or in combination. The present study was intended to test this assumption

Methods: Twenty-seven consenting ASA Class I-II patients of either sex undergoing elective surgical procedures were studied. No patient had neuromuscular, renal, or hepatic disease, nor was any patient receiving medication known to have effects on myoneural transmission.

Patients were premedicated with diazepam 0.15 mg/kg p.o. After thiopental 4-5 mg/kg for induction, anesthesia was maintained with 60% nitrous oxide in oxygen, meperidine 1.5-3 mg/kg, and additional thiopental as needed. Ulnar nerve stimulation was performed at the wrist via 23 ga steel needle electrodes at 0.15 Hz with square wave pulses 0.2 msec in duration. The stimuli were delivered at supramaximal voltage by a Grass S88 stimulator through an SIU5 isolation unit. Evoked force of thumb adduction was measured with a Grass FT10 force-displacement transducer.

Pancuronium was assumed to be four times as potent as metocurine and six times as potent as d-tubocurarine (dTc). Patients were randomly divided into three groups of nine. Each group received incremental doses of one of the following relaxant combinations: dTc and pancuronium (.03 mg/kg plus .005 mg/kg), metocurine and pancuronium (.02 mg/kg plus .005 mg/kg), or dTc and metocurine (.03 mg/kg plus .02 mg/kg).

Dose-response curves for neuromuscular blockade were plotted on log-probit coordinates. The best-fit straight lines were determined by probit regression and compared with data obtained under identical conditions for metocurine, pancuronium, and dTc individually[1].

Results: Comparison of ED95 values (see Table 1) may be made in terms of relaxant-equivalents, i.e., 1 relaxant-equivalent = .005 mg/kg of pancuronium = .02 mg/kg of metocurine = .03 mg/kg of dTc. Isobolograms constructed from this data indicate that pancuronium-metocurine and pancuronium-dTc both displayed greater than additive neuromuscular blocking potency. This marked potentiation was not seen with the metocurine-dTc combination.

Table 1

Drug(s)	ED95 (mg/kg)	Relaxant-Equivalents
Panc-Meto	.018 + .072	3.6 + 3.6 = 7.2
Panc-dTc	.024 + .144	4.8 + 4.8 = 9.6
Meto-dTc	.172 + .258	8.6 + 8.6 = 17.2
dTc alone	.51	17.0
Panc alone	.07	14.0
Meto alone	.28	14.0

Discussion: Little is known about the interaction between pairs of nondepolarizing muscle relaxants. Wong[2] using mice and rabbits and Ghoneim et al[3] in halothane-anesthetized human subjects both demonstrated potentiation between dTc and gallamine. In the present study we found marked potentiation with pancuronium-dTc and with pancuronium-metocurine, but not with dTc-metocurine.

We can only speculate about the underlying mechanism. In addition to the well recognized postjunctional activity (ACh receptor blockade) of nondepolarizing muscle relaxants, prejunctional effects (decreased ACh mobilization and release) have been established for dTc[4] and pancuronium[5]. Galindo[6] and others have indicated a relative preponderance of prejunctional effects for dTc and of postjunctional effects for pancuronium. Facilitated occurrence of both these actions simultaneously might be possible with both drugs used in combination, but not with either drug alone. Presumably, metocurine behaves similarly to dTc in this regard because of its chemical similarity. In addition, the drugs in combination may promote improved distribution kinetics, i.e., decreased uptake of relaxant by non-specific binding sites such as plasma and tissue proteins. Alternatively, pancuronium and dTc (or metocurine) may bind to different types of cholinergic receptors at the neuromuscular junction.

Nonetheless, regardless of mechanism, combining pancuronium with dTc or with metocurine can provide profound surgical relaxation, as well as ideal intubating conditions, at such low doses of each drug that cardiovascular side effects are likely to be minimized

References

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