

Early and Late Relative Potencies of Pancuronium and d-Tubocurarine in Man

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In ten patients anesthetized with halothane and nitrous oxide, *d*-tubocurarine or pancuronium was infused continuously for 80 minutes to produce a constant 90 per cent depression of twitch tension. For the first 30-minute period, 8.2 ± 0.32 and 1.09 ± 0.06 (mean \pm SE) mg/m² of *d*-tubocurarine or pancuronium, respectively, were required, and for the last 30-minute period (50 to 80 minutes of infusion) 2.1 ± 10.10 and 0.41 ± 0.02 mg/m² were required, giving potency ratios of $8.2/1.1$, i.e., 7.4, and $2.1/0.41$, i.e., 5.1. The difference in potency ratios in the first and last 30-minute periods implies that potency values determined by single-injection techniques inadequately describe the relative requirements for sustained paralysis. The mean ratios between that amount of relaxant representing tissue uptake and that amount representing metabolism and renal excretion during the first 30 minutes were 3.06 ± 0.28 for *d*-tubocurarine and 1.63 ± 0.19 for pancuronium. The significantly higher ratio for *d*-tubocurarine implies that its tissue uptake relative to metabolism and renal excretion is greater than that for pancuronium. The higher ratio for *d*-tubocurarine may be partly explained by its greater binding to plasma and tissue proteins. (Key words: Neuromuscular relaxants, *d*-tubocurarine; Neuromuscular relaxants, pancuronium; Potency, neuromuscular relaxant.)

THE RELATIVE potencies of muscle relaxants *in vivo* commonly are determined as a function of paralysis produced by a bolus injection or a series of bolus injections.^{1,2} We suggest that this method may not indicate the relative amounts of relaxants required to

sustain paralysis. Our thesis is that the relative potencies of two relaxants *in vivo* may change with the duration of their administration. The relative potencies would change because the relaxants differ in tissue uptakes and rates of elimination.

Proof of this thesis requires that a constant relaxant level in blood produce both a constant level of paralysis and a constant rate of elimination by the kidney and liver. Further, we assume that the rate of intravenous relaxant infusion required to sustain a constant level of paralysis varies with the two forces that remove relaxant from blood: 1) renal and hepatic elimination and 2) uptake by tissue depots. Early in the course of paralysis, both forces would determine the rate of infusion, but with the passage of time the tissues would become saturated with relaxant, leaving elimination the sole determinant of the infusion rate. Given these assumptions, the relationship between uptake and rate of elimination determines early versus late demands for relaxant. Thus, if two relaxants differed in this relationship, their relative potencies would differ with the passage of time. Our report provides evidence for such a difference.

Method

Ten unpremedicated patients (ASA Classes I and II), 38 to 62 years of age, from whom informed consent had been obtained, were anesthetized with halothane and nitrous oxide, 60 per cent in oxygen. The trachea was intubated without the use of other drugs. End-tidal halothane concentrations were maintained between 0.45 and 0.75 per cent. Anesthesia had been given for at least 30 minutes before the first injection of muscle relaxant was made. Controlled ventilation kept P_{aCO_2} at 34.3 ± 3.6 (mean \pm SE) torr. Mean esophageal or nasal temperature was 36.6 ± 0.8 C.

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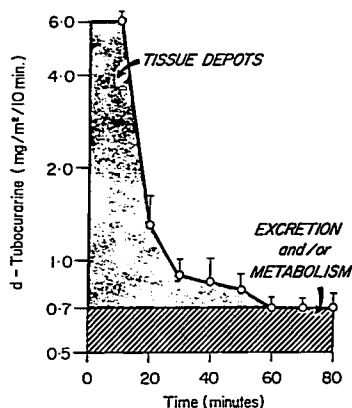


FIG. 1. Correlation between dose (mean \pm SE) of *d*-tubocurarine (mg/m^2) required every 10 minutes for constant 90 per cent depression of twitch height and time of infusion ($n = 5$).

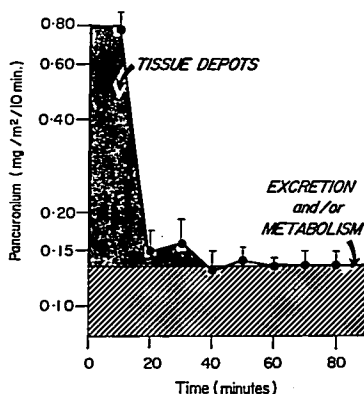


FIG. 2. Correlation between dose (mean \pm SE) of pancuronium (mg/m^2) required every 10 minutes for constant 90 per cent depression of twitch height and time of infusion ($n = 5$).

A Grass S-44 stimulator delivered 0.1 msec supramaximal square-wave bipolar pulses to the ulnar nerve at the wrist through 27-gauge thinwall needle electrodes at 0.3 Hz.

The resultant force of thumb adduction was quantitated with a force-displacement transducer and recorded on a polygraph.

After a bolus intravenous injection of *d*-tubocurarine, 5 mg/m^2 , or pancuronium, 1 mg/m^2 , 1.0 mg/ml of *d*-tubocurarine or 0.2 mg/ml of pancuronium was infused continuously from a Harvard pump to produce a constant 90 per cent depression of twitch tension. The amount of *d*-tubocurarine or pancuronium required every 5 minutes was recorded. We also determined whether the tissue uptakes of *d*-tubocurarine and pancuronium differed when 90 per cent reduction of twitch tension was constant by a method described previously.^{3,4} Briefly, we measured the amount of *d*-tubocurarine or pancuronium infused prior to the time the required infusion rate became constant. From this we subtracted the amount that would have been infused had the constant infusion rate been used. The difference was assumed to equal tissue uptake (figs. 1 and 2). A ratio between that amount of *d*-tubocurarine or pancuronium required to saturate tissue deposits and that required for metabolism and excretion was calculated for each patient. An unpaired *t* test was used for statistical analyses.⁵

Results

The mean amounts of *d*-tubocurarine and pancuronium required for the first 30-minute period were 8.2 ± 0.32 and 1.09 ± 0.06 mg/m^2 , respectively, and for the last 30 minutes (50–80 minutes) 2.10 ± 0.10 and 0.41 ± 0.02 mg/m^2 , respectively (figs. 1 and 2). Thus, the potency ratios between *d*-tubocurarine and pancuronium were 8.2/1.1, or 7.4, for the first 30 minutes and 2.1/0.41, or 5.1, for the last 30 minutes (table 1). The mean ratios between the amount of relaxant representing tissue uptake and the amount representing metabolism and renal excretion were 3.06 \pm 0.28 and 1.63 \pm 0.19 for *d*-tubocurarine and pancuronium, respectively ($P < 0.01$). Mean total tissue uptake of *d*-tubocurarine was 6.1 ± 0.36 mg/m^2 and that of pancuronium was 0.70 ± 0.05 mg/m^2 .

Discussion

Total tissue (including blood) uptake of *d*-tubocurarine was nine times larger than pan-

TABLE 1. *d*-Tubocurarine and Pancuronium Requirements (mg/m² infused) during First and Last 30-minute Periods

	<i>d</i> -Tubocurarine		Pancuronium	
	Total mg/m ² Infused per 10 Min	Tissue Uptake	Total mg/m ² Infused per 10 Min	Tissue Uptake
First 30 minutes				
0-10 min	6.0 ± 0.14†	5.30 ± 0.15	0.78 ± 0.06	0.65 ± 0.12
10-20 min	1.3 ± 0.11	0.60 ± 0.12	0.15 ± 0.02	0.02 ± 0.01
20-30 min	0.9 ± 0.07	0.24 ± 0.07	0.16 ± 0.01	0.03 ± 0.02
TOTAL	8.2 ± 0.32	6.1 ± 0.36	1.09 ± 0.06	0.70 ± 0.05
Last 30 minutes				
50-60 min	0.70 ± 0.04	*	0.140 ± 0.01	*
60-70 min	0.70 ± 0.04	*	0.135 ± 0.01	*
70-80 min	0.70 ± 0.04	*	0.135 ± 0.01	*
TOTAL	2.10 ± 0.10		0.410 ± 0.02	

* Mean ± 1 SE; n = 5.

† Less than 0.01 mg/m².

curonium uptake. Our data indicate that the major saturation of human tissue depots occurs in the first 10 to 30 minutes of infusion (figs. 1 and 2), with uptake becoming unmeasurable after 40-60 minutes. The data also indicate that *d*-tubocurarine has a larger tissue uptake relative to metabolic and renal excretion than does pancuronium.

Protein binding may explain this difference. Approximately 30 per cent of an injected dose of *d*-tubocurarine is bound to plasma and tissue protein,⁶ and a direct correlation between initial *d*-tubocurarine requirements for a given neuromuscular blockade and gamma-globulin levels has been shown.⁷ Apparently pancuronium is not bound to plasma or tissue proteins to any significant extent.⁸ If this relationship also applies to their respective affinities for tissue proteins, the relative depot size for *d*-tubocurarine would be further increased. Our data actually suggest that the affinity of *d*-tubocurarine for tissue proteins exceeds that for plasma. The basis for this conclusion is found in the relative times to complete saturation: equilibration takes longer with *d*-tubocurarine than with pancuronium (figs. 1 and 2). If we presume that blood flow to tissue depots is the same for both relaxants and that diffusion into the tissue depots is not hindered (or is the same for both relaxants), then this difference in time to saturation can be ex-

plained only by a larger tissue-blood equilibrium-relationship for *d*-tubocurarine.

The difference in protein binding may be of some clinical relevance, since it suggests that *d*-tubocurarine may be released from depot sites for a longer period than pancuronium. Thus we might speculate that the danger of "recurarization" may be greater with *d*-tubocurarine. In fact, we recently reported three patients who suffered respiratory insufficiency in the recovery room following renal transplantation during which a *d*-tubocurarine block was antagonized⁹; this had not been reported for transplantations facilitated with pancuronium. Of course, an alternate explanation might be that *d*-tubocurarine depends more on renal excretion for its elimination than does pancuronium.^{10,11}

Last, the larger potency ratio between *d*-tubocurarine and pancuronium in the first 30 minutes as compared with the last 30 minutes (table 1) implies that potency values determined by single-injection techniques may inadequately describe the relative potencies required to sustain paralysis. Our data suggest that doses of *d*-tubocurarine should be reduced proportionately more with time than doses of pancuronium.

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Arrhythmias

CARDIAC ARRHYTHMIAS AND SUC-CINYLCHOLINE The authors studied 120 adult patients undergoing elective surgery. Each received 8-15 mg morphine sulfate 60-90 minutes prior to anesthesia. Forty received 0.3-0.5 mg atropine intramuscularly at the time of administration of morphine. Forty received the same dose of atropine im 15-20 minutes prior to induction. The remaining forty received no atropine. All patients breathed 100 per cent oxygen 4 minutes before induction, which was accomplished with intravenous administration of 4 mg/kg thiamylal. Immediately thereafter followed the intravenous injection of succinylcholine, 1 mg/kg. Laryngoscopy was performed 1 minute later, at which time topical anesthesia was achieved with 4 per cent lidocaine, 2 mg/kg. During the period of observation, anesthesia was maintained with 60 per cent N_2O . Five minutes after induction, an additional 1 mg/kg succinylcholine was given. The electrocardiogram was observed continuously

for 4 minutes before and 6 minutes after induction. Decreases in cardiac rate of more than 15 per cent were uncommon after the first injection of succinylcholine (occurred in 1-3 patients in each group), as was the development of junctional rhythm (0-1 in each group). However, after the second injection of succinylcholine, cardiac slowing occurred in 15-17 patients in each group and junctional rhythm in 4-7 patients. There was no difference in incidence of either slowing or junctional rhythm among the three groups studied. The authors conclude that the addition of atropine to morphine in premedication will not affect the incidence of cardiac slowing or junctional rhythm after either the first or second dose of succinylcholine. (Stoelting RK, Peterson C: *Heart-rate slowing and junctional rhythm following intravenous succinylcholine with and without intramuscular atropine preanesthetic medication*. *Anesth Analg* (Cleve) 54: 705-709, 1975.)