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Enhancement of *d*-Tubocurarine Neuromuscular Blockade by Diuretics in Man

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Renal failure may prolong neuromuscular blockade by *d*-tubocurarine because of retarded excretion and/or interaction with antibiotics.[1-3] The following case reports additionally suggest that mannitol or furosemide augments *d*-tubocurarine-induced neuromuscular blockade in patients undergoing renal transplantation.

REPORT OF THREE CASES

Force of thumb adduction (measured with a Grass FT-10 force-displacement transducer) induced by stimulation of the ulnar nerve at the wrist was monitored in all patients. A Grass S-44 stimulator administered single stimuli of 0.1 msec duration with a voltage at least 1.5 times that necessary to evoke a maximal twitch response.

Patient 1. A 33-year-old man who had had chronic glomerulonephritis since 1972 had been maintained on hemodialysis since 1973. He was receiving prednisone, 25 mg, *b.i.d.*, azathioprine, 75 mg per day, and alpha-methyldopa, 250 mg, *b.i.d.*, orally. Blood pressure was 140/110 torr. Hemoglobin, potassium, and creatinine were 8.8 g/100 ml, 4.6 mEq/l, and 15.0 mg/100 ml, respectively. The patient received no preoperative medication prior to anesthesia for renal transplantation.

After administration of thiopental, 150 mg, iv, anesthesia was maintained with halothane and nitrous oxide, 60 per cent. The trachea was intubated after spray with 2 ml 4 per cent lidocaine. No other drug was administered.

Approximately 60 minutes after induction of anesthesia, *d*-tubocurarine, 0.3 mg/kg (16.5 mg total), given iv, depressed twitch tension 96 per cent. Forty-three minutes later twitch height was depressed 62 per cent. Mannitol, 12.5 g, and furosemide, 80 mg, were given iv, and 10 minutes later twitch height gradually decreased to 72 per cent depression. Forty minutes later, twitch height returned to the level obtained before administration of mannitol and furosemide.

Patient 2. A 38-year-old man who had a six-month history of end-stage renal disease was scheduled for renal transplantation. He was hypertensive and was receiving chronic treatment with apresoline, 25 mg, *q.i.d.*, and propranolol, 20 mg, *b.i.d.*, orally. Blood pressure the day before operation was 190/100 torr. The patient also received prednisone, 120 mg, and azathioprine, 300 mg, before operation. Hemoglobin, potassium, and creatinine were 12.7 g/100 ml, 4.0 mEl/l, and 15.0 mg/100 ml, respectively. The patient received no preanesthetic medication.

Anesthesia was induced and maintained with halothane and nitrous oxide. After spraying the trachea with 2 ml 4 per cent lidocaine, endotracheal intubation was accomplished without the use of other drugs. Forty-two minutes later, *d*-tubocurarine, 0.3 mg/kg (total 24 mg), given iv, abolished twitch tension (fig. 1). Eighty-seven minutes later an additional 3 mg *d*-tubocurarine were administered. After an additional 58 minutes twitch tension was nearly half the control valve. Mannitol, 12.5 g, and furosemide, 80 mg, then were administered iv. Twitch tension immediately decreased, and over the course of an hour and a half was reduced to less than one quarter of the control value (fig. 1).

Patient 3. A 15-year-old boy who had end-stage renal disease was scheduled for renal transplantation. Blood pressure was 160/100 torr. Hemoglobin, potassium, and creatinine were 7.7 g/100 ml, 4.9 mEq/l, and 8.9 mg/100 ml, respectively. The patient received prednisone, 100 mg, azathioprine, 300 mg, and alpha-methyldopa, 250 mg, *b.i.d.*, orally before operation. He received no preanesthetic medication.

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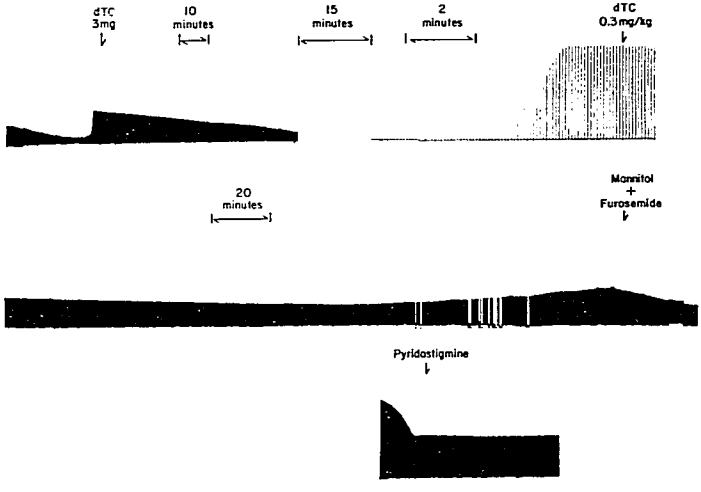

FIG. 1. (The panel reads from right to left.) A decrease in twitch tension following intravenous administration of mannitol, 12.5 g, and furosemide, 80 mg.

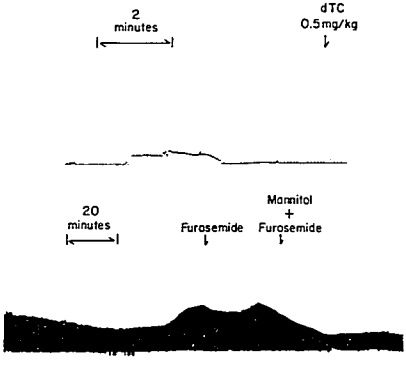

FIG. 2. In this recording from Patient 3, mannitol, 12.5 g, and furosemide, 40 mg, given together caused a decrease in twitch tension. An additional 40 mg furosemide caused a further and even greater reduction.

Forty minutes after induction of halothane anesthesia, *d*-tubocurarine, 0.5 mg/kg (29.5 mg total), was administered iv. One hundred per cent depression of twitch height followed (fig. 2). About 2.5 hours later, mannitol, 12.5 g, and furosemide, 40 mg, were given iv. Twitch height decreased from 46 to 36 per cent of control. An additional 40 mg furosemide given 25 minutes later was followed by twitch height decrease to 22 per cent of control (fig. 2). The plasma concentration of *d*-tubocurarine, measured by immunoassay,[4] concomitantly increased from 0.74 μg/ml immediately prior to diuretic administration to 0.82 μg/ml at the time of the 22 per cent reading despite no

TABLE 1. Percentage Depression of Twitch Tension and Plasma *d*-Tubocurarine Concentrations

	Time*	Percentage Depression of Twitch Tension	*d*-Tubocurarine (μg/ml)
	3	100	6.61
	15	100	3.39
	30	100	2.24
	60	92	1.96
	90	84	1.04
	150	54	0.74
Mannitol and furosemide	180	78	0.82
	230	66	0.71

* Minutes after administration of *d*-tubocurarine, 0.5 mg/kg.

additional administration of *d*-tubocurarine (table 1). Furthermore, a lower plasma concentration of *d*-tubocurarine produced greater neuromuscular blockade following diuretic administration. Before giving mannitol or furosemide, 0.74 μg/ml *d*-tubocurarine was associated with 54 per cent depression of twitch height. After mannitol and furosemide, 0.71 μg/ml *d*-tubocurarine was associated with 66 per cent depression.

In all three cases, the residual neuromuscular blockade was antagonized easily with pyridostigmine, 14 mg, or neostigmine, 3.0 mg with 1.2 mg of atropine.

DISCUSSION

Our results indicate the diuretics furosemide and mannitol enhance the neuromuscular blockade produced by *d*-tubocurarine. That furosemide alone augmented the *d*-tubocurarine-induced blockade in Patient 3 as much as the combination of mannitol and furosemide suggests that mannitol has little effect on neuromuscular blockade. Indirect support for this supposition was provided by Matteo *et al.*,‡ who found that mannitol does not alter the rate of renal excretion of *d*-tubocurarine. However, they did not monitor the effect of mannitol on neuromuscular blockade, and hence their study alone would not rule out a direct effect on the myoneural junction.

‡ Matteo RS, Pua EK, Horowitz PE, et al: Urinary excretion of *d*-tubocurarine in man—effect of osmotic diuretic. ASA Abstracts of Scientific Presentations, 1975, pp 211–212.

Furosemide (and mannitol) may augment a *d*-tubocurarine-induced neuromuscular blockade by: 1) a direct depressant effect on the neuromuscular junction; 2) a change in extracellular electrolyte concentration; 3) redistribution of *d*-tubocurarine from inactive to active depot sites; and/or 4) decrease in intravascular and extracellular fluid volumes, resulting in concentration of or increase in the plasma concentration of *d*-tubocurarine.

The effect of mannitol or furosemide on the neuromuscular junction has not been studied. However, ordinary doses of chlorothiazide, chlorthalidone, and acetazolamide enhance neuromuscular blockade by *d*-tubocurarine in rabbits.[5] In contrast, much larger doses of chlorothiazide antagonize *d*-tubocurarine-induced blockade both *in vivo* and *in vitro*. Obviously the *in-vitro* results suggest that redistribution of *d*-tubocurarine or changes in extracellular fluid volume or electrolytes need not be invoked to explain the effect seen.

Decreases in extracellular calcium and potassium concentrations may augment *d*-tubocurarine-induced neuromuscular blockade.[6] However, although urinary excretion of calcium and potassium is enhanced by administration of furosemide and mannitol,[7,8] plasma concentrations are not acutely altered, and therefore these agents are unlikely to affect muscle contraction by this mechanism. It is not known whether neuromuscular junction membrane potentials are altered. This is a possibility, however, since ionic flux across other membranes such as isolated erythrocytes and the inner ear is altered by diuretics.[9,10] Since we did not measure plasma electrolyte concentrations intraoperatively, the above discussion is speculative.

The increases in plasma *d*-tubocurarine concentrations following furosemide and mannitol suggest redistribution or concentration of *d*-tubocurarine. Although the increase is small, it is within the limits of accuracy of the radioimmunoassay technique, which measures as little as 5 ng/ml *d*-tubocurarine with confidence limits of 5 per cent.[4] The decrease in extracellular fluid volume that begins to occur immediately after administration of these diuretics[7] would potentially concentrate the residual *d*-tubocurarine. Pos-

sibly *d*-tubocurarine may be redistributed from inactive to active sites. Furosemide may have a stronger affinity for plasma and tissue proteins than does *d*-tubocurarine.[11]

In summary, these case reports suggest that furosemide and possibly mannitol augment *d*-tubocurarine-induced neuromuscular blockade. This is of particular significance to patients undergoing renal transplantation, since such patients already are at risk of prolonged neuromuscular blockade. We speculate that redistribution of *d*-tubocurarine and/or a direct depressant effect on the neuromuscular junction is the mechanism by which these diuretics augment the effect of *d*-tubocurarine.

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Another Hazard of Free-standing Vaporizers, Increased Anesthetic Concentration with Reversed Flow of Vaporizing Gas

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Although Munson[1] has pointed out that free-standing flow-through vaporizers present a hazard through the possibility of tipping, several of these units remain in use in our department for reasons of economy and convenience. We have recently recognized another hazard of these non-attached vaporizers, that of flowing the vaporizing gases through backwards.

Three times over the past five months, attending anesthesiologists have discovered these vaporizers set up in a reverse manner by residents and student nurse-anesthetists. Twice it was discovered prior to use of the equipment, and once during use. The Cyprane* vaporizers that we use can easily be set up by mistake to allow vaporizing gases to flow through them in a reverse direction. All that is required is to connect the delivery tube from the common gas outlet of the anesthesia machine to the outlet side of the vaporizer, and to connect the delivery tube to the patient's breathing circuit to the inlet side of the vaporizer. Although the inlet and outlet sides of the vaporizer are labeled, the labeling is not conspicuous. The same size of tubing fits either side.

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