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Comparative Effects of Pancuronium and *d*-Tubocurarine on Blood Histamine and Sympathetic Activity (38340)

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Pancuronium bromide (Pavulon) is a new long-acting, nondepolarizing type muscle relaxant (1–3). Any drug chosen to clinically replace *d*-tubocurarine, must be devoid of its untoward effects. Hypotension is one of these. It has been demonstrated in cats that hypotension from *d*-tubocararine is associated with a decrease in spontaneous postganglionic sympathetic activity in low doses and with the added dimension of histamine release at higher doses (4). The present study was conducted to comparatively evaluate pancuronium and *d*-tubocurarine on those same functions that are responsible for the hypotensive action of the latter agent.

Methods and Materials. Unpremedicated cats (2.1–3.2 kg) were lightly anesthetized with 20 mg/kg iv pentobarbital sodium (Nembutal) and maintained at this level with intermittent doses of 2.5–5 mg/kg as necessary. Mean arterial pressure (MAP) and heart rate were recorded from a catheter in the femoral artery. Drug injections and fluid replacement (Lactated Ringers solution, 10 ml/kg/hr) were made through a femoral venous catheter. Blood histamine was determined according to a modified method of Anton and Sayre (4, 5) on samples obtained from the right atrium via a jugular venous catheter. The trachea was cannulated and pulmonary ventilation was controlled by a Palmer pump with room air adequate to maintain arterial blood gases at Pa_{O_2} 98 ± 10 Torr and Pa_{CO_2} 36 ± 4 Torr. Rectal temperature was maintained at 37 ± 0.5° with a warming–cooling blanket.

The tibialis anterior muscle tendon was divided and attached to a FT03B force displacement transducer under 20 g tension while the sciatic nerve was sectioned and the common peroneal nerve placed on a bipolar electrode. Stimulations were at supramaximal voltage, 0.1 msec duration and 0.2 Hz from a Grass S4 stimulator and recordings made with a Grass 5B polygraph.

A postganglionic nerve from the celiac ganglion, exposed by a left flank retroperitoneal approach, was isolated and placed on a bipolar platinum electrode. Action potentials were displayed on a Tektronix 565 oscilloscope photographed with a Grass Kymographic camera at a film speed of 5 mm/sec. For quantitation the spontaneous postganglionic sympathetic activity (SPGSA) was simultaneously transmitted to a Grass 5P3 EMG integrator preamplifier with a 0.2 sec time constant and recorded on a Grass 5B polygraph at 5 mm/sec. The area under the integrated activity for 10 sec was measured with a planimeter. Injections of 0.75 mg/kg trimethaphan (Arfonad) at the conclusion of the experiment were used to prove the postganglionic nature of the activity.

Results. The dose-response curve constructed for pancuronium bromide indicated that the minimum fully effective dose was between 0.02 and 0.04 mg/kg. Therefore, each of the seven cats used herein were given an initial dose of 0.04 mg/kg of pancuronium, which produced complete paralysis in all cats. Two and one-half times this dose (0.1 mg/kg) of pancuronium then was chosen for comparison with 1 mg/kg of *d*-tubocurarine chloride, determined in an identical manner.

Neither dose of pancuronium had a significant effect on mean arterial blood pressure, heart rate, blood histamine titers and spontaneous postganglionic sympathetic activity (Figs. 1 and 2).

d-Tubocurarine, in a neuromuscular blocking

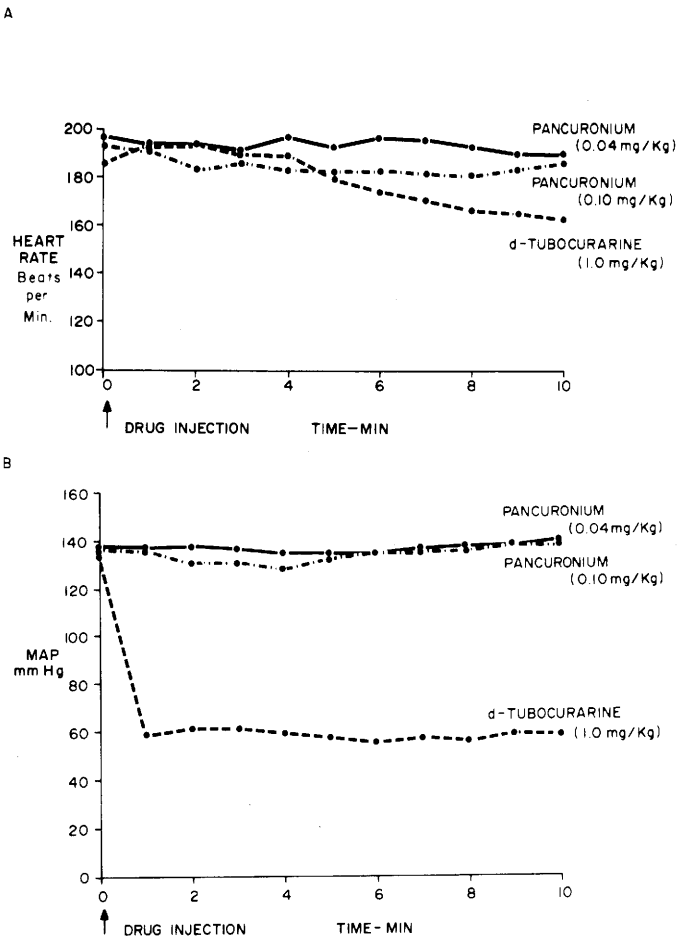

FIG. 1. Mean heart rate (A) and blood pressure (B) responses to the iv administration of indicated skeletal muscle relaxants.

dose proportional to the higher dose of pancuronium produced an initial slight increase in heart rate followed by a significant decrease ($P < 0.05$) at 5 min post injection in confirmation of previous studies (Fig. 1A). Moreover, *d*-tubocurarine effected a significant ($P < 0.001$) fall in mean arterial blood pressure (Fig. 1B) coincident with an approximate threefold increase in blood histamine (Fig. 2A) ($P < 0.001$) at 1 min, subsiding to a twofold elevation at 3 min postinjection ($P < 0.01$). Additionally, *d*-tubocurarine reduced SPGSA ($P < 0.001$) at 1 (Fig. 2B) and 3 min following drug administration. These changes with *d*-tubocurarine are identical with a previous study reported by our laboratory showing the effect of a muscle paralyzing dose (0.4 mg/kg) and a 2.5 times the muscle paralyzing dose (1.0 mg/kg) of *d*-tubocurarine on heart rate, MAP, SPGSA and histamine (4).

Discussion. *d*-Tubocurarine has been accepted as the standard nondepolarizing muscle relaxant since Griffith introduced it in 1942 (6). We have shown in our laboratory that curare induced hypotension is associated with a decrease in SPGSA and with histamine release (4). Critical to our explanation of this hypotension and contrary to earlier studies (7) was the evidence that ganglionic blockade could be demonstrated under conditions of intrinsic (spontaneous) nerve activity at a dose of curare that had no effect on ganglionic transmission under the contrived conditions of electrical stimulation of a preganglionic sympathetic trunk. At a higher

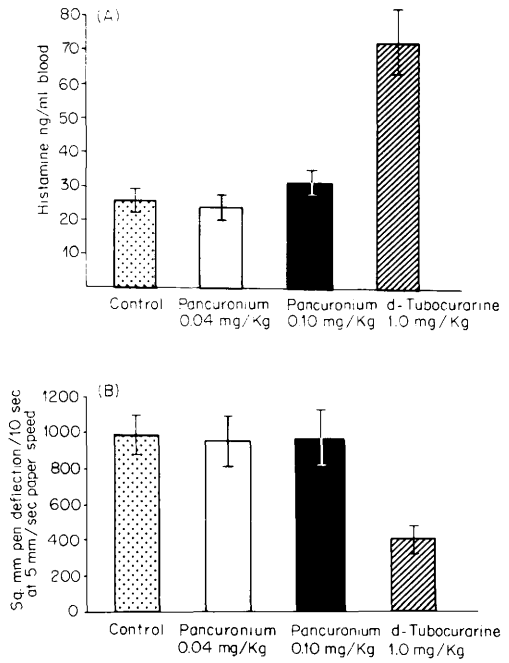

FIG. 2. Blood histamine titers (A) and quantitated sympathetic activity (B) 1 min following the iv administration of indicated skeletal muscle relaxants. Standard errors are indicated.

dose of *d*-tubocurarine, ganglionic blockade to electrical stimulation as well as a marked elevation in blood histamine could be demonstrated (4). It was thereby concluded that drug effects on SPGSA allowed a more valid interpretation of the mechanism of hypotension than the classical experiments dependent on electrically induced activity. For this reason, we retained this approach in evaluation of the pharmacological effects of pancuronium.

Other authors have presented indirect evidence to show that the absence of ganglionic blockade and histamine release is responsible for the circulatory stability with pancuronium (1–3). Our demonstration in the cat that pancuronium at 2.5 times the minimal muscle paralyzing dose has no significant effect on SPGSA nor stimulates histamine release provides direct confirmation of the prior findings. Subsequent treatment of the cat with *d*-tubocurarine indicates that the mechanisms of the potential untoward response to pancuronium were intact and responsive.

Summary. Pancuronium does not cause any change in heart rate, mean arterial pressure, blood histamine or spontaneous postganglionic sympathetic activity, at a neuromuscular blocking dose equivalent to a demonstrably adverse dose of *d*-tubocurarine.

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