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TITLE: HYPOTENSIVE ACTION OF d-TUBOCURARINE IN MAN:HISTAMINE PREDOMINANCE.

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Introduction. The administration of d-Tubocurarine (dTC) to animals and man has been reported to produce hypotension. Experiments in animals suggest that the hypotension is a result of both ganglionic blockade and histamine release. In man, administration of normal paralyzing doses of dTC may cause hypotension, but the mechanism for this hypotension has not been demonstrated. Using a novel radioenzymatic assay for plasma histamine we measured plasma histamine following the administration of dTC to twenty one elective orthopedic surgery patients during their course of anesthetic. Our data suggest that the administration of dTC to man can cause significant elevations in the plasma histamine concentration which correlated with decreases in blood pressure.

Methods. All patients were ASA 1 or 2 undergoing peripheral orthopaedic procedures. Following institutionally approved informed consent, all patients were premedicated with pentobarbital (3 mg/kg i.m.) two hours prior to induction of anesthesia. Following the placement of an intravenous cannula in one arm and an additional cannula in the opposite forearm for sample collection, a control sample was drawn. Fentanyl (3 mcg/kg) was administered intravenously over thirty seconds and two minutes later a second sample was drawn. Thiopental 6 mg/kg was then administered over a thirty second period and four minutes later a third sample of plasma was drawn. Then dTC in doses of 0.25 -0.75 mg/kg was administered as a bolus. Samples were drawn two and five minutes following curare administration. Heart rate and blood pressure were monitored and recorded at each sampling. Samples were immediately placed on ice and the plasma was separated and frozen. Histamine was measured using a modification of the single isotope radioenzymatic assay described by Beaven. The biogenic amine was converted to a tritiated methylated derivative using tritiated s-adenosylmethionine as a methyl donor and rat kidney histamine -N-methyl transferase as the catalyst. Following enzymatic conversion and separation with solvent extraction, the tritiated methylhistamine was evaporated, separated by TLC, scraped and counted. This assay shows normal values in the 600-1000pg/ml range with a sensitivity of 100 pg/ml. Linearity is preserved at levels of $r > 0.99$. Specificity is conferred by the enzyme and subsequent extraction techniques.

Results. The data are presented in Table 1. Plasma histamine did not change significantly following the administration of pentothal and fentanyl. Following the bolus administration of dTC, plasma histamine showed a dose-dependent increase. While administration of 0.25 mg/kg of dTC only increased plasma histamine to 137 $\pm$ 106 percent of control levels, A dose of 0.5 mg/kg, which appeared to be above the threshold dose, caused a fourfold increase in plasma histamine. Five minutes following the administration of dTC, plasma histamine had returned to baseline levels. Although there was a considerable variability in the extent of histamine release between subjects in the same group, plasma histamine concentration following the administration of dTC was significantly related to the change in systolic blood pressures.One of the two patients receiving 0.75 mg/kg dTC developed a 1300% increase in plasma histamine. A relationship between blood pressure change and plasma histamine could be derived as follows:

$$\frac{\text{BP post dTC}}{\text{BP pre dTC}} = -0.2 \log (\text{plasma histamine}) - 1.5$$

$$r = 0.61 \quad (p < .005)$$

Table 1.

CHANGES IN HISTAMINE FOLLOWING dTC ADMINISTRATION
PLASMA HISTAMINE (% CONTROL)

		0.25 mg/kg	0.5 mg/kg
preanesthesia control		100	100
post-thiopental		118±41	100±40
post-fentanyl		104±49	109±31
post-dTC	2'	137±106	406±210
	5'	129±56	126±45
	10'	146±90	106±28
		N = 8	N = 6

Discussion. While both ganglionic blockade and the release of histamine have been cited as possible mechanisms in the hypotensive action of dTC administration in man, neither effect has been demonstrated directly. Our data show that there is a significant increase in plasma histamine following the administration of curare. This increase in plasma histamine is dose-dependent and is significantly related to the decrease in systolic blood pressure. A ganglionic effect cannot be excluded but our data suggest that in man histamine release alone is sufficient to explain the fall in blood pressure that occurs.