Title: LOWER MOTOR NEURON INJURY INDUCES RESISTANCE TO d-TUBOCURARINE

Authors: Charles W. Hogue Jr. M.D.,J.A. Jeevendra Martyn, M.D.

Affiliation: Department of Anaesthesiology, Harvard Medical School and the Clinical Pharmacology Laboratory, Anesthesia Services of Massachusetts General Hospital and Shriners Burn Institute, Boston, MA 02114

INTRODUCTION: Lower motor neuron denervation of skeletal muscle results in an increase in acetylcholine receptors (AchR) that peaks at two to three weeks post-denervation.[1] In the cat model the proliferation of AChR after denervation occurs in both the denervated leg and the contralateral nondenervated leg.[2] The increase in AChR results in hypersensitivity to agonist or depolarizing muscle relaxants like succinylcholine.[3] Resistance to antagonist or nondepolarizing neuromuscular relaxants has been documented with upper motor neuron lesions[4] and other pathological states[5]. However, the response to antagonist neuromuscular relaxants in lower motor neuron lesions is unknown. This study in rats tested the hypothesis that the proliferation of AChR following lower motor neuron denervation induces hyposensitivity to antagonist neuromuscular relaxants like d-tubocurarine (dTc). A completely transected nerve fails to conduct nerve impulses within 36 hours. Therefore, the dose-response curves to dTc were studied, in vivo, in the partially transected sciatic nerve-gastrconemius preparation.

METHODS: All experimental procedures adhered to National Institutes of Health and institutional animal-care guidelines. Sprague-Dawley rats were anethetized with 50 mg/kg of pentobarbital I.P. and later with incremental doses given as needed. The experimental group of six animals had the left sciatic nerve partially transected through an incision in the posterior thigh. An approximate 75-80% transection of the nerve was performed while leaving some continuity of the nerve pathway. Six control rats were subjected to a sham procedure with a similar incision and dissection in the left leg to expose the sciatic nerve but no transection was made. The skin was then closed with 2-0 silk and an antibiotic ointment was applied. Dose-response and plasma concentration-response to dTC were studied under anesthesia at 6-17 days post sham or post denervation procedure. A tracheotomy was performed and rats were ventilated with room air via a Harvard respirator. Venous access was obtained via the internal jugular vein and ventilation adjusted to maintain physiologic venous blood gases. Rectal temperature was monitored and a heat lamp was used to maintain temperature at 35-38°C.

The right and left gastrconemius muscles and sciatic nerves were isolated and the tendons connected to a Grass FT03 force transducer. The right gastrocnemius baseline tension in both experimental and control groups was set at 50 gms. The left gastrocnemius muscle in the denervated limb would not contract with 50 gms of tension. Therefore, in both experimental and control animals the baseline tension in the left limb was set at 10 gms. Supramaximal pulses of 0.15 Hz and 0.2ms duration were applied to the sciatic nerve. Twitch responses were recorded on a Western Graphtec WR7500. After a period of stabilization incremental doses of d-tubocurarine were given until 95-99% twitch suppression occurred. Blood samples were obtained during recovery of twitch to correlate plasma dTc concentrations with twitch recovery. Plasma dTc concentrations were analyzed by HPLC method.

Dose response curves were constructed on log probit coordinates. Effective dose (ED) which produces 50 and 95 percent twitch suppression were calculated using least squares regression techniques. Significance between and within groups were tested using analysis of variance with values of $p<0.05$ being considered significant.

RESULTS: The ED_{50} and ED_{95} for control and experimental groups are indicated in Table 1. There were no differences in the ED between right and left legs in the control group despite differences in baseline tension. Likewise, there were no differences in the ED between control and the contralateral undenervated leg. The relationship between plasma dTc levels and twitch recovery for the left leg is shown in figure 1.

Table 1. Effective Dose (ED) for dTc (Mean ± SE)

	Tension	ED_{50} (mg/kg)	ED_{95} (mg/kg)
Control (R) leg	50 gm	0.08 ±.01	0.15 ±.05
Control (L) LEG	10 GM	0.08 ±.02	0.13 ±.03
Contralateral(R) Leg	50 gm	0.097 ±.02	0.16 ±.04
Denervated (L) Leg	10 gm	0.125 ±.03+	0.26 ±.07+*

*P<0.05, denervated vs. contralateral
+P<0.05, denervated vs. control left leg.

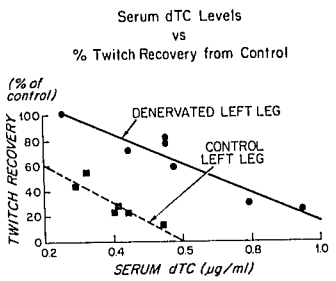

Figure 1. The Denervated left leg recovered at higher plasma dTc levels compared to left leg in controls.

DISCUSSION: Our study confirms that lower motor neuron lesions also induce a resistance to dTc in the denervated leg but not in the undenervated contralateral leg. There were no differences in the ED between the contralateral undenervated leg and control legs despite previous findings of prolifertion of AChR on the contralateral leg of denervated cat.[2] The magnitude of AChR change in the contralateral leg muscle may not have been sufficient to alter the sensitivity to dTc. The twitch recovery at higher plasma dTc concentrations in the denervated compared to control animal left leg confirms that the changes in ED are related to changes in target organ sensitivity.

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