

Date

Title : EFFECT OF AGE ON THE ACTION OF COMPETITIVE RELAXANTS

Authors : R.A. Gertler, M.D., Ph.D., N. Robbins, M.D., Ph.D., and H.F. Cascorbi, M.D., Ph.D.

Affiliation: Departments of Anesthesiology and Anatomy, Case Western Reserve University, School of Medicine, Cleveland, Ohio 44106

**Introduction:** Little is known regarding the comparative effects of competitive relaxants on the neuromuscular junctions of young and old animals. These experiments were designed to study the direct effects of d-tubocurarine (dTC) and pancuronium on neuromuscular transmission in red, white, and diaphragmatic muscles of young and old animals, while eliminating indirect effects of these drugs such as metabolism, excretion and circulatory changes. For this reason, all experiments were done using *in vitro* nerve muscle preparations.

**Methods:** Fully mature (8-12 months old) and senescent (29-36 months old) male mice of the CBF-1 mouse strain were used. Red (soleus), predominantly white (extensor digitorum longus), and diaphragmatic muscles were removed along with their accompanying nerves under methoxyflurane anesthesia and placed in a chamber containing modified Krebs' solution (NaCl, 135 mM; KCl, 5 mM; MgSO<sub>4</sub>, 1 mM; glucose, 11 mM; Na<sub>2</sub>HPO<sub>4</sub>, 1 mM; NaHCO<sub>3</sub>, 23 mM; calcium gluconate, 2.5 mM; and choline, 35 mM) oxygenated at 25 ± 1°C. Proximal and distal tendons were fastened to the chamber and to isometric strain gauges; amplified muscle twitches were recorded on a pen writer and magnetic tape. Indirect twitches were elicited via a suction electrode which delivered current regulated 50 μsec. duration pulses with a current strength twice that which gave a maximal twitch. Muscle length was adjusted to give maximal twitch strength. Muscle twitches in response to train-of-four stimuli at 2Hz were recorded before and after increments in concentration of the relaxants used. Dose-response curves of the first twitch in the train as well as the train-of-four rundown were constructed from these data. Dose-response curves for the first twitch were displayed as percentage of the initial twitch strength prior to exposure to relaxants. Train-of-four rundown was quantified as the ratio of the fourth to the first twitches at any drug concentration. Statistical testing was done by linear regression with confidence interval estimation of the linear region of the dose-response curves.<sup>1</sup>

#### Results:

1. In both young and old mice, the sequence of increasing sensitivity of the first twitch as well as the train-of-four rundown to dTC and pancuronium was invariably diaphragm, soleus, and finally extensor digitorum longus (P < .05).

2. Soleus and diaphragm muscles of old mice were significantly more resistant to dTC and pancuronium than were the same muscles of young mice (P < .10).

There was not a significant difference between old and young extensor digitorum longus muscles.

**Discussion:** The results of the sequential sensitivity of *in vitro* murine red, white, and diaphragm nerve-muscle preparation are consistent with results obtained from *in vivo* human muscles,<sup>2,3,4</sup> suggesting that this *in vitro* model adequately represents human pharmacology. The resistance of elderly muscles to curariform drugs demonstrated in this work has not been previously reported in the literature. This difference may be due in part to the increase in muscle fiber input impedance seen with aging.<sup>5</sup>

#### References:

1. Campbell, RC: Statistics for Biologists, Cambridge University Press, London, 1974.
2. Johansen, SH, Jorgensen, M, and Molbech, S: Effects of tubocurarine on respiratory and non-respiratory muscle power in man. J. Appl. Physiol. 19:990-994, 1964.
3. Unna, KR, et al: Evaluation of curarizing drugs in man. J. Pharmacol. 98:318-329, 1950.
4. Wyman, ML and Eisele, JH: Differential effects of d-tubocurarine on inspiratory and two peripheral muscle groups in anesthetized man. Anesthesiology 48:360-362, 1978.
5. Kelly, SS: Personal communication.