

Induced Tolerance to D-Tubocurarine Chloride in the Cat

In the course of experimental work we found it necessary to administer a standard dose of D-tubocurarine chloride to the same cat on several occasions over a period of months. We observed that in the fifteen animals studied the duration of paralysis of respiratory and other muscle groups became steadily shorter. The work was all done on the intact animal in a warm room. Nitrous oxide in 3 : 1 mixture with oxygen was the sole anaesthetic agent used—thus, in the preliminary stages no drug was involved which was likely to influence the duration of neuromuscular block. D-tubocurarine was administered intravenously in doses of 0.6 mgm./kgm., and during the period of respiratory paralysis artificial respiration was maintained through an endotracheal tube at a rate of 20–25 per min., a soda lime canister being included in the circuit for the absorption of carbon dioxide. In this way adequate oxygenation was maintained throughout all experiments.

So as to investigate further the apparent change in tolerance to D-tubocurarine we compared the duration of paralysis in the anterior tibialis muscle in a group of six animals which were receiving the drug for the first time with four others which had been rendered tolerant by its repeated administration. The painful stimuli involved in setting up a nerve-muscle preparation are such that deeper anaesthesia rather than that provided by nitrous oxide is required. Thiopentone sodium was selected as an extra agent on the grounds that the level of dosage is readily controlled and it is rapidly eliminated from the blood stream. This drug was administered both to experimental and control animals. Anaesthetic induction was therefore carried out with thiopentone sodium, the initial dose of which was 20–50 mgm. Further doses were given as required during the preparatory phase; but a total of 200 mgm. was never exceeded. Endotracheal intubation was performed, and an interval of at least 30 min. allowed to elapse between the last administration of thiopentone sodium and the

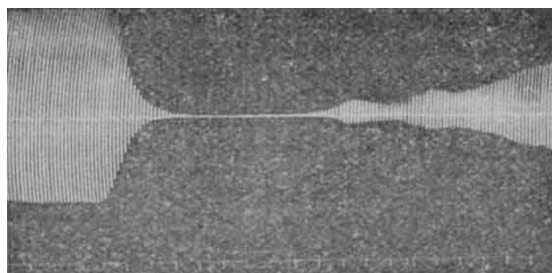


Fig. 2. Myograph of cat No. 14, in which 'tolerance' had been induced. A again indicates the injection of D-tubocurarine (0.6 mgm./kgm. body-weight); note that muscle contractions never disappear completely

intravenous injection of D-tubocurarine in a dose of 0.6 mgm./kgm. body-weight. From this time until the end of the experiment, anaesthesia was maintained with a mixture of nitrous oxide and oxygen (3 : 1).

A Brown-Schuster myograph was used to record the contractions of the anterior tibialis muscle. In order to minimize temperature drop the limb was mounted horizontally¹, the skin was sutured over all incisions, and the laboratory was maintained at a temperature of 68° F. The general environmental conditions were therefore identical to within a few degrees in both groups. Maximal contractions were induced at 4-sec. intervals, through a platinum electrode, and stimulation was continued throughout. The periods elapsing between the administration of D-tubocurarine and the return of muscle contractions, in the four cats in which an altered response to the drug had been induced, are compared with similar periods elapsing in the six cats which had never previously received the drug. The difference between the mean duration of paralysis (20 min.) in the two groups is significant at the 2 per cent level (Table 1).

Thus we feel that our original observation has been confirmed, and that this is a genuine example of induced drug tolerance. Myograph tracings taken from 'normal' and 'intolerant' animals are shown in Figs. 1 and 2.

The mechanism of this altered response is obscure and is being further examined.

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Bigland, B., and Zaimis, E., *J. Physiol.*, **141**, 420 (1958).

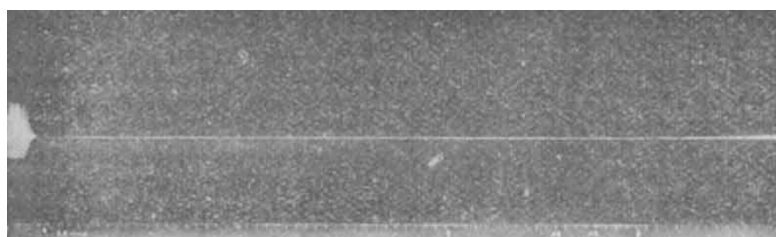


Fig. 1. Myograph of a 'normal' cat, No. 18. A indicates intravenous injection of D-tubocurarine (0.6 mgm./kgm. body-weight), and B the first perceptible muscle contraction. Time marker, 30-sec. intervals

Table 1. DURATION OF PARALYSIS OF ANTERIOR TIBIALIS MUSCLE IN THE CAT DUE TO D-TUBOCURARINE CHLORIDE (0.6 MG./KG. BODY-WEIGHT)

Animals receiving the drug for the first time			Animals rendered tolerant by repeated administration of the drug				
No. of animal	Body-weight (kgm.)	Duration of paralysis (min.)	No. of animal	Body-weight (kgm.)	Duration of paralysis (min.)	No. of previous injections	Period over which drug previously give (weeks)
C 18	3.2	30	E 5	2.7	4	23	74
C 19	2.7	44	E 12	2.3	11	10	6
C 20	2.3	31	E 13	2.7	11	9	18
C 21	2.6	11	E 14	1.5	0	10	13
C 22	2.4	18					
C 23	1.7	25					
Mean		26.5000			6.50000		
Variance		108.9167			22.2500		

t, 3.2161. n, 8. P < 0.02