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Oxotremorine: acute tolerence to it and its central "cholinolytic" effect in mice

Decsi, Várszegi & Méhes (1961a, b) reported that tremorine lost much of its analgesic, tremorigenic and narcosis-potentiating properties when given to mice. Keranen, Zaratzian & Coleman (1961) observed a progressive decline of the compound's tremorigenic effect after chronic treatment of unstated duration. Oelszner (1965) was unable to corroborate the observation on the analgesic effect of tremorine made by Decsi & others.

Doses of tremorine and oxotremorine prevent albino mice from clinging for more than 3 to 6 s to a rod operated at 7 rotations/min. Activity was regarded as negative in experiments in which the animal held fast to the rotarod for at least 180 s. The doses given are for oxotremorine oxalate, physostigmine salicylate, nicotine hydrogen tartrate, and tremorine dichlorhydrate.

Table 1 shows that a first injection of tremorine reduces the rotarod activity of a second injection given 16 h later, and totally prevents that of oxotremorine. The rotarod activity of oxotremorine (0·5–1·0 mg/kg, i.p.) wears off within 60–90 min.

Table 1. *Rotarod activity of tremorine and oxotremorine*

First i.p. injection at 0 h	Second i.p. injection at 16 h	n	% mice dropped off the rotarod at 16 h 30 min
0·9% NaCl	20 mg/kg tremorine	24	100
25 mg/kg tremorine	20 mg/kg tremorine	20	45
0·9% NaCl	0·5 mg/kg oxotremorine	10	100
25 mg/kg tremorine	0·5 mg/kg oxotremorine	10	0

Table 2. *Rotarod activity of 3 subsequent oxotremorine injections* (given at 0, at 60 or 90 min, and at 120 or 150 min)

Dose and route	n	% mice dropped off the rotarod 30 min after the: 1st injection	2nd injection	3rd injection
0·5 mg/kg all i.p.	56	89	29	5
1·0 mg/kg all i.p.	40	100	50	25
0·5 mg/kg i.p., i.p., i.v.	16	100	19	13
1·0 mg/kg i.p., i.p., i.v.	16	100	40	13

A second injection of the same dose is much less effective, and a third one almost ineffective (Table 2). Acute tolerance is not the result of decreased absorption, as even intravenous oxotremorine possesses negligible activity. No tremor was observed after the third injection.

A single injection of oxotremorine leaves nicotine lethality unaffected, but a second one given 30 min later inhibits it (Table 3). Similarly, a single dose of

Table 3. *The effect of a single and a repeated dose of oxotremorine on nicotine lethality*

Administration i.p. at 0 min	Administration i.p. at 30 min	n	Administration i.v. at 60 min	Lethality (%)
—	0·9% NaCl	12	2 or 2·5 mg/kg nicotine	100
—	1 mg/kg oxotremorine	12		92
0·9% Nacl	0·9% NaCl	26		92
1 mg/kg oxotremorine	1 mg/kg oxotremorine	26		19

Table 4. *LD50 values of physostigmine after oxotremorine and physostigmine*

Administration s.c.	Intervals between injections, min	LD50 values of physostigmine (95% confidence limit) mg/kg	(95% confidence limit) Relative activity
0·9% NaCl, once	30	approx. 1·2	>1·25
1 mg/kg oxotremorine, once ..	30	>1·5	
0·9% NaCl, twice	30	0·91 (0·8–1·04)	1·56 (1·34–1·8)
1 mg/kg oxotremorine, twice ..	30	1·42 (1·28–1·58)	
0·9% NaCl, 3 times	45	1·13 (0·89–1·44)	0·73 (0·52–1·03)
0·4 mg/kg Physostigmine, 3 times	45	0·83 (0·65–1·06)	

oxotremorine reduces physostigmine lethality (Table 4). A second dose applied 30 min later raises the LD50 significantly, by more than 50%. Thus, the development of the acute tolerance by oxotremorine is associated with the development of central anti-nicotine and anti-physostigmine effects.

The present experiments show that tremorine-tremorine, tremorine-oxotremorine, and oxotremorine-oxotremorine tolerances develop rapidly.

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