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Some anticholinergic activities of BRL 1288—a new anti-Parkinson drug

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Although anticholinergic drugs give symptomatic relief in the treatment of Parkinsonism, their use is limited by the onset of peripheral activity which causes dryness of the mouth and mydriasis. BRL 1288 (2(ethyl-n-propylamino)ethyl-α,α-diphenylglycollate hydrochloride) at a dose of 3·8 mg/kg subcutaneously was found to antagonize the pronounced tremor induced in mice after intraperitoneal injection of oxotremorine (2 mg/kg), whereas mydriasis did not occur until after 19 mg/kg subcutaneously. The tremor was measured on a subjective basis 10 min after injection of oxotremorine.

In a comparative study of BRL 1288 with other anti-cholinergic drugs it has been found that no other drug would inhibit oxotremorine-induced tremor in mice at a dose which did not cause peripheral effects. Benzhexol, the best of the standard compounds tested, had mydriatic activity at one-sixth of the dose required to inhibit tremor.

Peripheral anti-acetylcholine activity was determined by three measures: mydriatic activity in mice, the antagonism of pilocarpine-induced salivation in mice, and *in vitro* action on the guinea-pig ileum.

TABLE 1. *Anti-oxotremorine and peripheral anticholinergic activity of BRL* 1288 *and standard anti-Parkinson agents relative to atropine sulphate*

	Anti-oxotremorine activity		Mydriatic activity		Inhibition of pilocarpine-induced salivation		Anti-acetylcholine activity
Compound	p.o.	s.c.	p.o.	s.c.	p.o.	s.c.	(*in vitro*)
BRL 1288	26	45	2·1	0·32	1·2	0·31	0·60
Benzhexol (Artane)	33	45	13	8·5	8·6	12	34
Atropine sulphate	100	100	100	100	100	100	100
Benztropine (Cogentin)	50	67	111	48	43	19	35
Orphenadrine (Disipal)	—	5·9	2·9	0·67	1·4	0·49	1·9

The results summarized in Table 1 are expressed as activity relative to atropine sulphate. All compounds were administered as their salts.

The pronounced central activity of BRL 1288 relative to its peripheral anticholinergic activity indicates that the compound has great potential in the treatment of Parkinsonism.

The effect of chronic barbitone administration and withdrawal on the sensitivity of the central nervous system to barbiturate

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We have previously reported the effect of chronic barbitone administration and withdrawal on hexobarbitone sleeping time and hepatic drug-metabolizing enzyme activity. During barbitone treatment, rats were found to be tolerant to hexobarbitone and the ability of liver microsomal preparations to oxidize hexobarbitone *in vitro* was increased. Three weeks after withdrawal a hypersensitivity to hexobarbitone, associated with decreased activity of drug-metabolizing enzymes, was found (Stevenson & Turnbull, 1968). These experiments, however, provided no indication as to whether brain sensitivity to barbiturates had altered during barbitone administration and withdrawal. Information on this has now been obtained from studies in which the tissue barbiturate concentration on awakening from a hypnotic dose of labelled barbiturate has been determined.

Female Wistar rats were made dependent on barbiturate by the administration of barbitone sodium in the drinking water (Stevenson & Turnbull, 1968). Barbitone-treated, withdrawn and control animals were killed on awakening following intraperitoneal administration of [^{3}H]-hexobarbitone sodium (150 mg/kg), [^{14}C]-pentobarbitone sodium (40 mg/kg) or [^{14}C]-barbitone sodium (225 mg/kg) and the brain, liver and serum level of labelled barbiturate and metabolites was measured. In addition, the total barbiturate concentration was determined spectrophotometrically, thus enabling the tissue level of unlabelled barbitone (i.e. that taken in the drinking water) to be calculated.

Animals chronically treated with barbitone awoke with a lower tissue concentration of [^{3}H]-hexobarbitone or [^{14}C]-pentobarbitone, but when tissue barbitone was taken into account, the total barbiturate concentration was higher than that found in control rats, indicating a central nervous tolerance. Furthermore, the total brain barbiturate concentration on awakening was found to be higher in rats which had been given barbitone for five weeks than in animals which had received barbitone for only a few days, indicating a gradual development of tolerance throughout the period of barbitone administration. The tissue concentration of labelled barbiturate metabolites, with the exception of the brain level of pentobarbitone metabolites, was higher than that found in control rats. The tissue levels of [^{14}C]-barbitone were found to be the same in barbitone-dependent as in control animals, showing that prolonged treatment with barbitone does not significantly affect the metabolism of this drug.

Our results show that after withdrawal, central nervous tolerance is gradually lost until three weeks after withdrawal animals awoke with the same brain barbiturate level as control rats.