Antagonism by amantadine of prochlorpemazine-induced catalepsy

Amantadine (1-adamantanamine hydrochloride), an antiviral agent (Davies, Grunert & others, 1964) was given by Schwab, England & others (1969) to prevent influenza in a patient with Parkinson's disease with a remarkable effect on the parkinsonian symptoms. These authors confirmed on 163 patients with Parkinson's disease the efficacy of amantadine "usually consisting of a reduction of akinesia and rigidity and some lessening of tremor". These results were recently confirmed by a controlled trial of Parkes, Zilkha & others (1970).

The toxicological and pharmacological properties of amantadine were examined by Vernier, Harmon & others (1969) who observed, at high doses, a moderate increase of spontaneous motor activity in mice, an antagonism of tetrabenazine-induced sedation in mice and some convulsions at toxic doses.

We studied some effects of amantadine in rats and mice (after intraperitoneal administration, doses are expressed in weight of amantadine). The excitation was moderate between 4 and 64 mg/kg; at these doses, hypothermia and mydriasis were noticed. At doses between 1 and 64 mg/kg, we did not observe any antagonism against oxotremorine-induced hypothermia and tremors or against reserpine-induced hypothermia and ptosis in mice. Amantadine, at doses higher than 16 mg/kg, antagonized the loss of righting-reflex induced by pentobarbitone or barbitone in mice. When administered 30 min before (+)-amphetamine sulphate (3 mg/kg, i.p. in rats), amantadine (at doses higher than 4 mg/kg) significantly increased the intensity of stereotypicities (licking, gnawing . . .); this effect was less marked if amantadine was injected 1 h before (+)-amphetamine and non-existent if the interval was 2 h.

Considering the important therapeutic effect of amantadine on akinesia and rigidity, we examined the effect of this drug on the prochlorpemazine-induced catalepsy in rats.

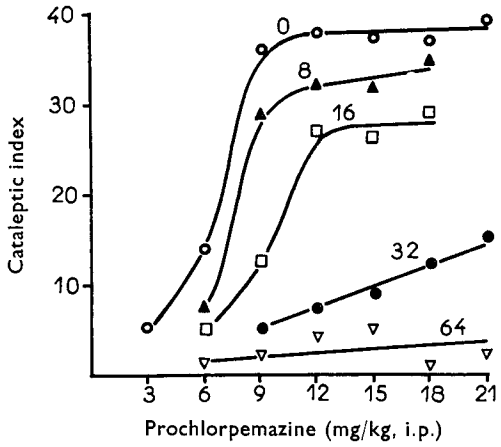

FIG. 1. Homolateral legs crossing test. The "cataleptic index" was calculated by adding the number of cataleptic rats, the homolateral legs crossing test being performed every hour during 7 h (6 animals per group, maximal cataleptic index = 42). The numbers on the curves indicate the dose of amantadine previously administered.

Table 1. *Anticataleptic effect of amantadine.* The CD50 (cataleptic dose) of prochlorpemazine is an arbitrary measurement calculated graphically. It represents the dose of prochlorpemazine inducing catalepsy in 50% of the rats during the 7 h of the test (catalepsy was estimated every hour and the results obtained at each hour were added)

Pretreatment	CD 50 prochlorpemazine mg/kg., i.p. 3 cm-high cork	9 cm-high cork	Hom. legs crossing	Parallel bars	Grid
—	5	6·5	7	7	7
Amantadine 8 mg/kg	6·5	8	8	9	8
" 16 "	9	13	11	17	14
" 32 "	13	21	>21	>21	17
" 64 "	>21	>21	>21	>21	>21

We used four tests (3 cm high-cork, 9 cm high-cork, crossing of homolateral legs, parallel bars) previously detailed by Simon, Langwinski & Boissier (1969) and the grid test. The rat was placed gently on a vertical grid; it was considered as cataleptic if it did not move its paws during 20 s. These five tests were made every hour during 7 h after prochlorpemazine treatment (3, 6, 9, 12, 15, 18 or 21 mg/kg, i.p.); amantadine (0, 8, 16, 32 or 64 mg/kg, i.p.) was injected 15 min before prochlorpemazine (groups of 6 rats). The results obtained with the homolateral legs crossing tests are in Fig. 1. The catalepsy-inducing doses (CD 50) of prochlorpemazine on the five different tests after administration of various doses of amantadine are in Table 1.

The clear antagonism of amantadine towards prochlorpemazine-induced catalepsy could have allowed one to predict the efficiency of this drug in patients with Parkinson's disease (Boissier & Simon, 1964). Besides, the stimulating effects of amantadine, as shown by the observation of the behaviour of animals, by the potentiation of (+)-amphetamine and by the antagonism to barbiturates, corroborate some of the side-effects (jitteriness, insomnia, dizziness) described in patients by Schwab & others (1969).

The authors thank Rhone Poulenc Laboratories for their generous supply of amantadine.

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March 20, 1970

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