Potentiation by amantadine hydrochloride of L-dopa-induced effects in mice

Recently a therapeutic effect of the antiviral agent amantadine in Parkinsonism has been reported (Schwab, Poskanzer & others, 1969; Millac, Hasan & others, 1970). Since it is generally recognized that L-dopa is effective in Parkinsonism, it is of interest that administration of amantadine to Parkinsonian patients receiving L-dopa lowers the dose of L-dopa required to maintain the effect (Schwab, 1969). Therefore we have investigated the effect of amantadine hydrochloride on L-dopa-induced effects on motor activity and gross behaviour in mice.

Female NMRI mice, about 20 g, were injected intraperitoneally with L-dopa in doses ranging from 75–1000 mg/kg. Some of the animals received amantadine hydrochloride 100 mg/kg 95 min before L-dopa. Control mice were treated with saline 0·6 ml or amantadine hydrochloride, 100 mg/kg, and 95 min later saline 0·6 ml all intraperitoneally. Measurements of motor activity were made on groups of three mice by means of two sets of Animex activity meters, (Svensson & Thieme, 1969). Recordings were made for 10 min beginning 25 min after the injection of L-dopa or saline and 20 min after placing the animals in the test cages.

Amantadine 100 mg/kg did not exert any influence of its own on motor activity. Vernier, Harmon & others, (1969), also found that only high doses of amantadine caused a moderate increase in motor activity. Neither did we find any change in the general appearance of the animals. Pretreatment with amantadine did cause a potentiation of the L-dopa effects on motility (Fig. 1). The dose curve of L-dopa after amantadine pretreatment parallels that of L-dopa alone. There was no significant difference between the slopes of the corresponding linear parts of the curves. After amantadine about half the amount of L-dopa was required to obtain the same effects as those of L-dopa alone.The potentiation is of the same magnitude as that caused by MK 485, a peripheral dopa decarboxylase inhibitor [α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl) propionic acid] (Strömberg, 1970). However, in contrast to MK 485, amantadine also appeared to potentiate the peripheral effects of L-dopa.

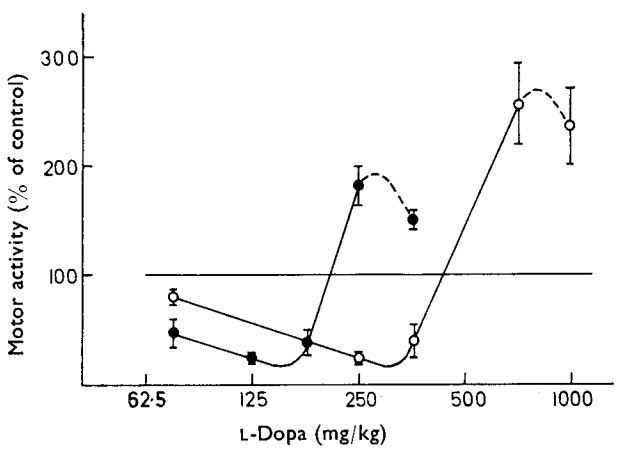

FIG. 1. Potentiating effect of amantadine hydrochloride on L-dopa induced changes in motor activity in mice. Shown are the means ± s.e. expressed as % of the respective control values. These were 534 ± 106 and 647 ± 93 for saline (0·6 ml) and amantadine hydrochloride (100 mg/kg) respectively. Each point represents the mean activity of four groups consisting of three mice. Recordings were made during 10 min beginning 25 min after the injection of L-dopa or saline and 120 min after amantadine. All injections were given i.p. ●—● Amantidine HCl 100 mg/kg + L-dopa. ○—○ L-Dopa.

Thus it is unlikely that amantadine acts by inhibiting dopa decarboxylase in the peripheral sympathetic system.

Animals receiving amantadine and L-dopa, 250 mg/kg, were less jerky than those given L-dopa 700 mg/kg and showed a general appearance similar to that seen after treatment with apomorphine and clonidine by Andén, Corrodi & others, (1970).

Some of the animals receiving L-dopa, 350 mg/kg, after amantadine died in convulsions within 2 h. Similar convulsions, although less pronounced, were also seen in a few mice given L-dopa alone at 1000 mg/kg. This probably explains the reduction in motor activity found in the animals at these doses.

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Intestinal blood flow and absorption of non-dissociable substances

Experiments concerning the influence of intestinal blood flow on absorption of drugs are rare. Ochsenfahrt & Winne (1969) have shown that the appearance of aniline, amidopyrine, antipyrine, benzoic and salicylic acid in the intestinal venous blood of rats is dependent on blood flow. These findings are now complemented by data of the following non-dissociable substances: tritiated water, methanol, ethanol, urea, ethylene glycol, glycerol, erythritol, and ribitol. Jejunal loops (6–10 cm) of urethane-anaesthetized and heparinized rats were perfused by an isotonic phosphate buffer (pH 7), or by Ringer solution containing the substances. The jejunal vein of the loop was punctured and the outflowing blood collected and weighed (= blood flow). The lost blood was substituted by an infusion of heparinized rat blood into the jugular vein. The intestinal blood flow was changed from high to low and from low to high values by varying the blood infusion. A drop recorder in the venous outflow provided a control record. The concentrations of the [^{14}C]-labelled substances and of tritiated water were measured in the collected blood. Appearance rate and blood flow are referred to wet tissue weight (Ochsenfahrt & Winne, 1969).

The results are summarized in Fig. 1. The figures are corrected to a concentration of 50 nmol/ml in the perfusion solution. Tritiated water showed the highest appearance rate which was almost strictly dependent on blood flow. The absorption rate and its dependence on blood flow decreased in the order ethanol, methanol, glycerol, ethylene glycol, urea, erythritol, and ribitol. The absorption of ribitol is independent of blood flow.