The effect of amantadine on spontaneous locomotor activity in the rat

Direct observation of mice (Vernier, Harmon & others, 1969) and rats (Abuzzahab, 1971) after injection of the new anti-parkinsonian agent, amantadine, has suggested that this drug increases spontaneous locomotor activity, but more objective measures have failed to confirm this increase in mice treated with 100 mg/kg (Svensson & Stromberg, 1970) or in rats treated with 10 or 100 mg/kg (Abuzzahab, 1971). We have investigated the effect of various doses of this compound on spontaneous locomotor activity and have found a significant increase in activity which is dose and time dependent.

Male Wistar rats (Woodlyn Farms, Ontario, Canada), 275–325 g, were injected subcutaneously with amantadine hydrochloride (25, 50 or 100 mg/kg of the salt in a volume of 1 mg/kg of distilled water), or with distilled water. One half hour after the injection, each animal was placed in a circular cage (14″ in diameter) equipped with two sets of photocells which recorded one count each time a photobeam was broken. Counts were automatically recorded every half hour for 3 h.

Amantadine produced a significant dose-related increase in activity ($F = 7{\cdot}96$, d.f. $= 3, 44$, $P < 0{\cdot}01$). All doses used produced a significant increase in the cumulative 3 h activity (25 mg/kg: $t = 2{\cdot}19$, d.f. $= 22$, $P < 0{\cdot}05$; 50 mg/kg: $t = 4{\cdot}23$, d.f. $= 22$, $P < 0{\cdot}01$; 100 mg/kg: $t = 2{\cdot}94$, d.f. $= 22$, $P < 0{\cdot}01$).

The effect of the various doses of amantadine across time varied (Fig. 1). Amantadine at 25 mg/kg produced a significant increase in activity only in the early part of the 3-h period. The 50 mg/kg dose produced a significant effect throughout the period, while the 100 mg/kg group was consistently more active only during the last hour. The long latency required for the 100 mg/kg dose to elicit locomotor stimulation may have been due to toxic effects and may account for the failure by Abuzzahab (1971) to find a significant increase in activity.

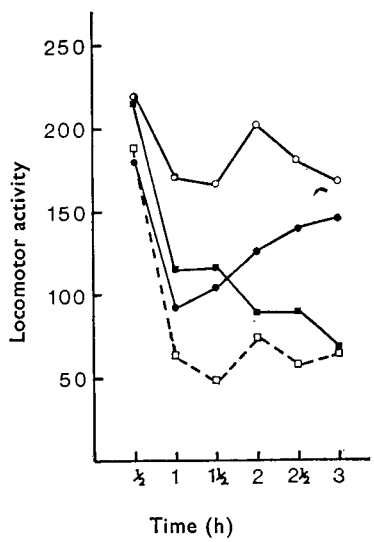

FIG. 1. The effect of amantadine HCl on spontaneous locomotor activity (30 min periods) over 3 h. Each point represents the mean of 12 animals. Control □ - - - □; 25 mg/kg ■——■; 50 mg/kg ○——○; 100 mg/kg ●——●.

These results indicate that amantadine HCl has a significant stimulant effect on locomotor activity in rats. In mice, amantadine appears to increase spontaneous locomotor activity only after reserpine pretreatment (Svensson & Stromberg, 1970; Stromberg, Svensson & Waldeck, 1970). The mechanism by which amantadine exerts this effect is not clearly understood. It is interesting, however, that this drug has recently been shown to resemble (+)-amphetamine in some of its actions on dopamine and noradrenaline metabolism in brain (Scatton, Cheramy & others, 1970; Stromberg & others, 1970). α-Methyl-*p*-tyrosine, a drug which is known to block amphetamine-mediated locomotor stimulation (Weissman, Koe & Tenen, 1966) also appears to antagonize amantadine-mediated excitation in rats (Fibiger, Fox, McGeer and McGeer, unpublished observations) and in reserpine pretreated mice (Stromberg & others, 1970).

We were impressed by the variability of the response to amantadine, a point also discussed by Abuzzahab (1971) both in locomotor activity and in brain dopamine concentrations.

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An automated method for the determination of dissolution rate and urinary concentration of sulphonamides

Several methods of determining dissolution rate have been automated (Schroeter & Wagner, 1962; Niebergall & Goyan, 1963; Michaels, Greely & others, 1965). We have developed a method similar to that described by Barzilay & Hersey (1968) except that our method uses an AutoAnalyzer dialyser.

Determination of sulphonamides in blood by means of automated methods has been described by Falk & Kelly (1965) and Probst, Rehm & others (1965), the sulphonamide being diazotized and coupled according to the procedure of Bratton & Marshall (1939) on which our automated procedure is also based. We have compared manual and automated procedures in the assessment of dissolution rates and urine concentrations of sulphonamides.

Sulphathiazole was dissolved, with heat if necessary, in fresh, protein-free urine to give concentrations of 5, 10, 25, 50, 75 and 100 mg%. Also, the urine collected under normal urine conditions (Goossens & van Oudtshoorn, 1970) from subjects who had ingested 500 mg sulphathiazole (tablet) was analysed both for free and total sulphathiazole by both methods.