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BRIEF COMMUNICATION

Effect of Antipsychotic and Other Classes of Drugs on Spontaneous Locomotor Activity and Neurotoxicity in Mice[1]

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MCLEAN, J. R., R. B. PARKER AND L. L. COUGHENOUR. *Effect of antipsychotic and other classes of drugs on spontaneous locomotor activity and neurotoxicity in mice.* PHARMAC. BIOCHEM. BEHAV. 8(1) 97–99, 1978. – Quantitative estimates were made of the effects of several classes of drugs on spontaneous activity and neurotoxicity in mice. Clinically effective antipsychotic agents had a more selective action on spontaneous activity than other classes of drugs with the exception of clonidine and a related compound.

Antipsychotics Locomotor activity Neurotoxicity

IN ORDER to predict that a compound has potential antipsychotic activity, a variety of laboratory test procedures in which there is some degree of correlation between activity in the laboratory test and clinical efficacy are used. These tests include assessment of the ability of compounds to inhibit apomorphine-induced emesis, aggressive behavior in monkeys, and the locomotor stimulant and lethal effects of d-amphetamine, and inhibition of the conditioned avoidance response [4,5]. In addition to these behavioral tests, biochemical tests are used to measure the postsynaptic binding of dopamine and haloperidol [3,11].

The complexity of these tests, most of which require trained animals or specialized techniques, limits the number of compounds that can be tested. Antagonism of the locomotor stimulant effect of d-amphetamine is a useful test for the selection of potential antipsychotic agents for further study. However, in such a test, there is the possibility of effects on the metabolism or brain levels of d-amphetamine by the test compound, and the neurotoxicity of the test compound must be determined on separate groups of animals. We wished to develop a rapid primary test method that could be used to select compounds for further study. It appeared to us that a comparison of the ED_{50} values for drugs that decrease spontaneous locomotor activity and cause neurotoxicity might provide the basis of such a test.

When mice are treated with a range of doses of antipsychotic agents such as chlorpromazine and haloperidol, subjective observation indicates that the mice are quiet at doses below those causing neurotoxicity and loss of reflexes. On the basis of inspection of dose-response curves for locomotor activity measured in photocell cages and neurotoxicity measured using the rotorod, Kinnard and Carr [6] reported that in mice chlorpromazine had a relatively greater effect on locomotor activity than amobarbital and secobarbital. In the experiments reported here, quantitative assessments were made of the effects in mice of drugs from several different therapeutic and pharmacological categories on locomotor activity and performance on a horizontal screen. The horizontal screen test is a simple procedure which uses untrained mice and gives a measure of neurotoxicity or motor impairment [2].

Male Swiss-Webster mice weighing 25–30 g were fasted approximately 18 hr before being given oral doses of the test compounds dissolved or suspended in 0.05% methocel. One hour later the number of mice failing to cling to the bottom of a horizontal screen for 60 sec was recorded. The mice were than placed in actophotometer boxes which are

[1] This research was carried out with animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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TABLE 1

THE EFFECT OF DRUGS ON THE SPONTANEOUS ACTIVITY OF MICE AND ON THEIR ABILITY TO CLING TO THE BOTTOM OF A HORIZONTAL SCREEN

	A	B	
COMPOUND	ED_{50} FOR FALLING OFF SCREEN*	ED_{50} FOR INHIBITION OF SPONTANEOUS ACTIVITY*	ACTIVITY RATIO (A/B)
CHLORPROMAZINE	23.5 ± 0.47	3.48 ± 0.04	6.8
CLOZAPINE	30.8 ± 1.55	4.84 ± 0.07	6.4
HALOPERIDOL	77.4 ± 1.83	0.31 ± 0.01	250.
THIORIDAZINE	119. ± 2.82	5.75 ± 0.09	21.
CHLORDIAZEPOXIDE	47.1 ± 1.44	58.9 ± 2.19	0.8
DIAZEPAM	4.72 ± 0.11	11.5 ± 0.47	0.4
PENTOBARBITAL	≅ 50.**	≅ 60.**	≅ 1.
PHENOBARBITAL	27.7 ± 0.69	≅ 90.**	< 1.
PHENOXYBENZAMINE	> 400.£	50.9 ± 5.33	> 8.
PHENTOLAMINE	> 400.£	170. ± 18.0	> 2.
PROPRANOLOL	173. ± 3.27£	97.5 ± 12.7	1.8
CLONIDINE	72.3 ± 15.8£	0.36 ± 0.06	201.
LON-798	389. ± 176.	1.30 ± 0.04	299.

*ED_{50} of oral doses in mg/kg ± SEM. **Due to the steepness of the dose-response curves and variability of the data the computer program failed to give a definitive ED_{50}. The values given were obtained by visual inspection of the dose-response curves. £There were one or more deaths per group in the following groups: phenoxybenzamine 50, 100, 200, and 400 mg/kg; propranolol 200 and 400 mg/kg; clonidine 80 and 160 mg/kg.

connected to a computer for automatic storage and analysis of the data [9], and locomotor activity was recorded during the following hour. Each drug was tested at four or more doses. At each dose, 12–24 mice were used for the screen test, and 6–8 actophotometer boxes containing three mice each were used for the measurement of locomotor activity.

ED_{50} values for performance on the horizontal screen were determined using the non-linear regression technique for quantal data developed by Waud [13]. ED_{50} values for inhibition of locomotor activity were determined by fitting the data to a modified form of the logistic function as described by Waud [14]. The ratio obtained by dividing the ED_{50} for falling from the screen by the ED_{50} for the inhibition of spontaneous activity is referred to as the activity ratio; a high ratio indicates a selective action.

The values obtained are shown in Table 1. The antipsychotics tested (chlorpromazine, clozapine, haloperidol, and thioridazine) showed considerable selectivity in inhibiting spontaneous activity, having activity ratios of 6.4 to 250. The two antianxiety agents, chlordiazepoxide and diazepam, and the two hypnotic agents, pentobarbital and phenobarbital, decreased performance on the horizontal screen at doses similar to or below the doses decreasing spontaneous activity.

Large doses of the β-adrenergic blocking agent propanolol have been reported to have antipsychotic activity [15]. In the horizontal screen and spontaneous activity tests, propanolol had an activity ratio of 1.8, much lower than the ratios seen with the established antipsychotic agents. The α-adrenergic blocking agents phenoxybenzamine and phentolamine caused death at doses near the ED_{50} for inhibition of spontaneous activity even though the surviving mice retained their ability to cling to the horizontal screen.

The results obtained with phenoxybenzamine and phentolamine indicate that with certain classes of drugs, motor discoordination as measured by the horizontal screen test may not occur until lethal doses are reached. In such cases, comparison of the doses having a lethal effect with the doses inhibiting spontaneous motor activity could be used to determine whether or not to select a compound for further study. Both phenoxybenzamine and phentolamine would be excluded from further study on the basis that death occurred at doses equal to or below the ED_{50} for inhibition of motor activity.

Clonidine is a centrally acting antihypertensive drug that stimulates norepinephrine receptors [1]. Although clonidine causes marked sympathomimetic signs, it decreases locomotor activity in mice [8]. Clonidine also inhibits the conditioned avoidance response in rats [7]. LON–798 is a compound related to clonidine and reported to have a higher selectivity of action in stimulating norepinephrine receptors [10]. In a study on chronic schizophrenic patients, Simpson *et al.* [12] reported that clonidine did not have an antipsychotic action. Both clonidine and LON–798 showed a high selectivity in inhibiting spontaneous activity in mice. These results indicate that, unless clonidine has antipsychotic activity not yet detected, inhibition of the conditioned avoidance response and spontaneous activity may not predict antipsychotic activity with this class of compounds.

The correlation between selective inhibition of spontaneous activity and antipsychotic activity is not absolute. However, the degree of correlation appears to be sufficiently high to make this rapid simple test useful in selecting compounds for further study as potential antipsychotic agents.

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