Indian J Physiol Pharmacol 1996; 40(3): 241-244

EFFECT OF ORAL LITHIUM ON THE ACTION OF VARIOUS C.N.S. ACTIVE DRUGS

P. K. AWASTHI, H. K. GARG, V. K. SRIVASTAVA*, K. C. SINGHAL, TAPAS CHATTARAJ AND MAHDI HASAN**

*Departments of Pharmacology, *Neurosurgery and **Anatomy,*
J. N. Medical College,
A.M.U., Aligarh - 202 002

(Received on March 22, 1995)

Abstract : Effect of prolonged lithium administration was seen on the action of various psychoactive drugs in animals. Apomorphine induced pecking in pigeons increased significantly by lithium treatment for 14 days, from 1445.3 ± 202.5 in control to 2785.8 ± 205.8 in Gp. B.

Haloperidol-induced catalepsy score in albino rats increased significantly following chronic lithium treatment compared to control.

Chlorpromazine-induced hypothermia in rabbits was immediate but transient, while in lithium treated rabbits induction of hypothermia was delayed, sustained and of greater magnitude. This action of lithium may be mediated by increasing the permeability of blood-brain barrier, or enhancing the sensitivity of alpha-adrenoceptors in brain.

Key words : lithium, apomorphine, haloperidol, chlorpromazine

INTRODUCTION

Lithium is often prescribed along with psychoactive drugs (1). Since lithium is known to alter the behaviour in mania and manic depressive psychosis (MDP) (2), the interactions of lithium and some psychoactive drugs were studied, taking apomorphine induced pecking, haloperidol-induced catalepsy and chlorpromazine-induced hypothermia as the recognized paradigms.

METHODS

Apomorphine induced pecking in pigeons: Adult pigeons of either sex weighing 180 to 300 g were divided into lithium treated (Gp A) and control (Gp B) groups of six birds each. Gp A pigeons were administered apomorphine hydrochloride 400 μg/kg, im, 5 min before the onset of experiment. Gp B pigeons were administered lithium carbonate 1 meq/kg, per day, orally for 14 days. Apomorphine was administered on day 15 as in Gp A. Each bird was placed in a separate cage for observation. The experiment was carried out at an ambient temperature of 18 to 25°C. Pecking was considered positive only if the bird pecked more than 10 times following apomorphine injection (3). The severity of pecking was assessed by the total number of pecks counted for each bird. Effects such as preening and restlessness were observed whenever present. The differences in the mean number of pecks were compared and analysed statistically by Student's 't' test.

Haloperidol-induced catalepsy in rats: Albino rats of either sex weighing 100 to 150 g were divided into two Gps of 6 rats each. One Gp of rats was administered haloperidol (25 mg/kg, ip), 2 hrs before the onset of experiment and

*Corresponding Author

served as control (Gp A). The other group (Gp B) was administered lithium carbonate (1 meq/kg per day, orally) for 14 days, Gp B were administered haloperidol as in Gp A.

Catalepsy was scored as follows (4) :

Stage I : The rat has no desire to make any movements, it sits quitely where it has been placed.

Stage II : The rat shows movements only after gentle push.

Stage III : The rat maintains its posture when its forelimbs are placed on a cork 3 cm high.

Stage IV : The rat maintains its fixed posture, sitting on its hind limbs, one of its forelimbs is placed on a cork 9 cm high and the other forelimb is allowed to hang free.

The cataleptic score is considered positive if the animal maintains the same posture for 10 sec. Each stage is tested on both right and left sides. For a positive response on each side of the body, 0.5 point is reckoned for Stage III and 1 point for Stage IV. Maximum cataleptic response is allotted 3 points.

Cataleptic activity was scored in both the groups at an interval of 2 hrs, 4 hrs, 6 hrs, and 22 hrs after haloperidol administration. The result of the two groups were compared and analysed statistically with the help of Student's 't' test.

Chlorpromazine-induced hypothermia in rabbits: Four male albino rabbits weighing 1.5 to 2.0 kg were selected for the study. Each rabbit was injected chlorpromazine 5 mg/kg, iv, and hypothermic effect was observed for 3 hrs. Ten days later, the same rabbits were administered lithium carbonate, 1 meq/kg, orally, for 14 days. Twentyfour hrs after the last dose of lithium carbonate, chlorpromazine was administered to these rabbits, as done earlier. The study was conducted at an ambient temperature of 24 ± 4°C. A few hours before the experiment, a thermistor was inserted about 10 cm into the rectum and taped to tail of each rabbit. The other end of the probe was connected to a multichannel Aplab thermometer. The rabbit was placed in a 140x16x10 cm open tin box and was restrained as little as possible. Rectal temperature was noted every 15 min. The data were analysed and compared by Student's 't' test.

Observations

Apomorphine (400 μg/kg, · im) induced pecking in pigeons: Pecking increased significantly in lithium treated Gps. The mean number of pecks was 1445.3 ± 202.5 in Gp A and 2785.8 ± 205.8 in Gp B ($P < 0.001$).

Haloperidol-induced catalepsy in albino rats: The cataleptic scores at 2 hrs in Gp A and B were 0.25 ± 0.12 and 0.83 ± 0.11 respectively ($P < 0.05$). At 4 hrs, the difference was highly significant ($P < 0.001$), the scores being 0.66 ± 0.11 and 1.58 ± 0.16. At 76 hrs the scores were 0.66 ± 0.18 and 1.75 ± 0.12 ($P < 0.01$). At 22 hrs, Gp A (control) rats had completely stopped exhibiting any catalepsy, whereas the Gp B rats showed a score of 0.58 ± 0.09 ($P < 0.001$).

Chlorpromazine-induced hypothermia in rabbits: In the control group chlorpromazine in a dose of 5 mg/kg administered intravenously caused immediate lowering of body temperature. The fall in body temperature became significant after 45 min ($P < 0.05$). The fall continued upto next 90 min when it attained minimum level ($P < 0.001$). Thereafter, the body temperature started rising and attained predrug administration level after about another 60 min.

In lithium pretreated rabbits (1 meq/kg, oral, 14 days), following administration of chlorpromazine (5 mg/kg, iv) the onset of hypothermia was delayed and was manifest 120 min after the drug administration ($P < 0.05$). The fall continued till next 75 min ($P < 0.001$, Table I).

TABLE I : Effect of prolonged administration of lithium carbonate (1 meq/kg, orally) for 14 days on chlorpromazine (5 mg/kg, iv) - induced hypothermia in rabbits (n = 4).

(Date are mean ± S.E.M.)

Time interval (min)	*Rectal temperature (°C)*		*P value*
	Chlorpromazine	*Chlorpromazine + lithium carbonate*	
0	39.0 ± 0.08	39.5 ± 0.18	–
15	39.9 ± 0.06	39.8 ± 0.14	–
30	40.0 ± 0.06	39.8 ± 0.14	–
45	39.5 ± 0.28	40.0 ± 0.11	–
60	39.4 ± 0.20	39.9 ± 0.20	–
75	39.0 ± 0.14	40.0 ± 0.11	0.001
90	39.0 ± 0.14	39.7 ± 0.20	0.01
105	39.0 ± 0.16	39.5 ± 0.18	0.05
120	38.9 ± 0.11*	39.2 ± 0.15	–
135	39.1 ± 0.08	39.1 ± 0.08	–
150	39.4 ± 0.15	38.6 ± 0.21*	0.05
165	39.5 ± 0.17	38.3 ± 0.22*	0.001
180	39.6 ± 0.23	38.2 ± 0.14*	0.001
195	39.8 ± 0.14	38.0 ± 0.18*	0.001

*P < 0.001 vs corresponding values at time 0 min.

It is interesting to note that after 120 mts. of chlorpromazine administration the effect of chlorpromazine on temperature was over and it started increasing till it attained predrug level whereas in lithium pretreated rabbits the chlorpromazine hypothermia was persistent and sustained. The temperature continued to show downward trend till the observation period of 165 min (Fig.1).

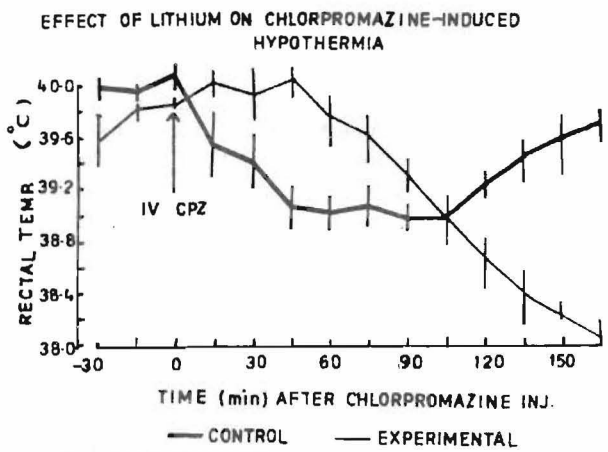

Fig. 1 : Effect of prolonged administration of Lithium carbonate (1 meq/kg orally for 14 days) on Chlorpromazine (5 mg/kg, iv)-induced hypothermia in rabbits.

DISCUSSION

It has been noted clinically that the beneficial effects of lithium therapy are obtained not with a single dose within 24 hours but a number of doses and requires a couple of weeks. The animals included in this study were administered lithium in a dose of 1 meq/kg, once daily for 14 days, so that we might simulate experimentally the conditions prevailing in patients under lithium therapy. It has been suggested that lithium exerts its therapeutic effect by altering levels of excitatory and/or inhibitory neurotransmitters (5).

Marley (6) reported that immature birds (1 to 3 wks old) differed from older birds (more than 3 months old) in the response to biogenic amines. For example, peripherally administered noradrenaline has been shown to produce sedation in 1 to 3 weeks old chicken, but not in the older ones (7). It has been suggested that immature birds do not possess an effective blood brain barrier (B.B.B.). The administered drug, therefore, reaches the brain and produces effects in immature birds and not in mature birds. In earlier experiments conducted by us, we have also observed that non-adrenaline (24 mg/kg,

sc) produced sedation in 2 weeks old chicken but failed to do so in 4 months old chicken, which kept behaving normally.

It has been shown that chronic lithium treatment can enhance the development of presynaptic supersensitivity (8). In our study, apomorphine (400 mg/kg, im) in lithium treated pigeons evoked significant increase in pecking response.

Cohen and Cohen (9) were the first to question the compatibility of lithium with neuroleptics. Stahorn and Nash (10) have reported several cases of neurotoxicity resulting from lithium and neuroleptics. We have observed that chronically lithium treated rats exhibited significant increase in cataleptic score by haloperidol, as compared to control rats. The increased cataleptic score could be due to decreased dopamine level in the brain, or higher levels of drugs reaching the brain. Khan and Hasan (5) have shown that chronic lithium treatment reduced the level of dopamine, but the possibility of higher levels of drugs due to altered permeability of B.B.B. cannot be excluded.

In the central nervous sytem, adrenoceptors play an important role in the adjustment of body temperature. Chlorpromazine can act as alpha-adrenoceptor antagonist. In our study, chronically lithium treated rats showed significantly greater hypothermia as compared to controls. This may be due to greater permeability across BBB or due to hypersensitivity of alpha adrenoceptors by lithium carbonate.

The results may have clinical significance. The effects of apomorphine, haloperidol, and chlorpromazine were potentiated following prolonged administration of lithium carbonate. Therefore, the requirement of CNS-active drugs appears to be reduced in patients undergoing lithium therapy. Special attention is required for phenothiazines, since catalepsy may be precipitated by small doses in patients getting lithium, as compared to patients receiving phenothiazines alone.

REFERENCES

1. Gershon S. Use of lithium salts in psychiatric disorders. *Dis Nerv Syst* 1968; 29 : 31-35.
2. Malitz S. Lithium in the treatment of manic-depressive illness. *Bull NY Acad Med* 1972; 45 : 767-778.
3. Dhawan BN, Saxena PN. Apomorphine induced pecking in the pigeons. *Brit J Pharmacol* 1960b; 15 : 285-289.
4. Wirth W, Goswald R, Hordein U, Risse KLH, und icreioskott Zur. Pharmakologic acylierter phenothiazine derivative. *Arch Int Pharmacodyn Ther* 1958; 115 : 1-3.
5. Khan SA, Hasan M. Effect of various doses of lithium on the level of biogenic amines in discrete areas of rat brain. *Indian J Med Res* 1979; 69 : 489-494.
6. Marley E. In : Advances in Pharmacology. The adrenergic system and sympathomimetic amines. 3rd Ed. Garattni and PA Shore Eds. (Academic Press, New York), 1965; p. 167.
7. Spooner CE, Winters WD. Evidence for a direct action of monoamines in chick C.N.S. *Experientia* 1965; 21 : 256-259.
8. Gallager DW, Part A, Bunney WE. Haloperidol-induced presynaptic dopamine hypersensitivity is blocked by chronic lithium. *Nature (Lond)* 1978; 273 : 309-311.
9. Cohen WJ, Cohen NH. Lithium carbonate, haloperidol, and irreversible brain damage. *JAMA* 1975; 230(9) : 1284-1287.
10. Stahorn JM, Nash JL. Severe neurotoxicity despite 'therapeutic' serum lithium levels. *Dis Nerv Sys* 1977; 38 : 107-109.