INFLUENCE OF LITHIUM ON THE ANTICONVULSANT ACTIVITY OF CARBAMAZEPINE

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Summary : The present study was undertaken to see whether the recently reported synergism between lithium and carbamazepine (CBZ) in mania also extends against convulsions. The anti-convulsant effect of various doses of CBZ was assessed in albino rats pretreated with vehicle or lithium salt (0.54 mEg/kg/day, p.o. for 9 days). The animals were subjected to 3 tests : maximum electro shock seizures (MES); minimum electro convulsive thresholds (MET) and pentylenetetrazol (PTZ)-induced convulsions: abolition of hind limb extension after electro shock, increases in the MET for appearance of neck jerk and absence of convulsions for one hr after PTZ were taken as parameters of the anticonvulsive effect respectively. In the MES and MET tests lithum did not alter the anticonvulsive effect of CBZ. Lithium, however, potentiated the anticonvulsant effect of CBZ against PTZ-induced convulsions.

Key words : lithium convulsions carbamazepine synergism

INTRODUCTION

Lithium salts have been reported to potentiate the anticonvulsant effect of diphenylhydantoin (22). Recent reports indicate that a combination of lithium and carbamazepine (CBZ) is favourable in mania (6, 11, 13) though the basis of this synergism is not known. The present study was undertaken to see whether this synergism between lithium and CBZ extends also to the anticonvulsant effect of CBZ.

MATERIAL AND METHODS

Albino rats of either sex weighing about 150 g were used as experimental models. Anticonvulsant effect of the drugs was assessed using a battery of 3 tests : The maximum electroshock seizure (MES) ; minimnm electro convulsive threshold (MET) and pentylenetetrazol (PTZ) induced convulsions.

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MES was produced with an alternating current of 150 mA delivered through ear-clip electrodes for 0.2 sec. On day 1, all animals were given MES and only those animals showing hind-limb extensor tone (HLE) were used for subsequent testing, They were divided into groups of 10 each. On day 2, control and test animals were administered CBZ 2.5, 5, 7.5 and 10 *mg/kg*, i.p. MES was given at 0.75, 2, 4, 6 and 24 hrs time interval after CBZ and observed for the occurance of hind-limb extension (HLE). Abolition of HLE was taken as the parameter of anti-convulsant activity. On day 3, test animals were started on lithium therapy for 9 days while controls were given vehicle of lithium. 24 hr after the last dose of lithium, CBZ was given in the dosage mentioned above and MES tested at the specified periods of time. The critical ratio of the difference in proportions of animals protected by various doses of CBZ at each period of the time in the vehicle or lithium pretreated groups was calculated and the significance of the difference ascertained (21),

The METs were determined by giving the animals shock of increasing intensity starting from 0.5 mA with increments of 1 mA, the duration of shocks being 0.2 sec. The apperarance of neck jerk was taken as the end point. On day 1, baseline thresholds were determined for 72 animals, the shock being given at intervals of 30 min. They were then divided into 12 groups of 6 each. METs were ascertained 45 mins after a dose of CBZ 10 *mg/kg* (i p) in test and control animals before and after treatment with lithium or vehicle of lithium. To avoid repetitive shocks, each animal was subjected to only one trial, i.e. shock was given only once to each animal with stepped voltage increments for each group of animals. The median threshold was found out for each group and the significance of the difference tested by student's 't' test.

PTZ convulsions were induced by 60 *mg/kg* of the drug given sc (in preliminary experiments this was found to be the minimum dose required to produce full convulions). Animals were divided into 12 groups of 6-8 each. CBZ in doses of 2.5, 5, 10, 15 and 20 *mg/kg* (ip) were administered to control and test animals which were treated with vehicle or lithium respectively. 45 min after CBZ, PTZ was administered. Absence of convulsions during one hour period after PTZ was considered as the parameter for anti-convulsant effect The percentage of animals protected by various doses of CBZ in control and test groups were compared and significance calculated as for MES.

In all the above tests, there were parallel controls to study the per se effect of lithium, i.e. the lithium treated animals were testsd after the vehicle of CBZ.

Drugs : Lithium carbonate (E. Merck) was suspended in distilled water and converted to lithium chloride by adding 1N hydrochloric acid until pH was neutral. Lithium salt was always administered in the dose of 0.54 mEg/kg/day orally for 9 days.

CBZ was dissolved in a mixture of 60% alcohol and 40% propylene glycol and was administered ip in the volume of 1 *ml/kg*. Dosage schedule of CBZ for each of the tests were determined using the reported ED_{50} of CBZ.

RESULTS

Fig. 1 shows the percentage of animals protected in the vehicle or lithium pretreated groups by the various doses of CBZ at the specified time intervals as tested by MES. The maximum protection by all doses used, viz. 2.5,5,7.5 and 10 *mg/kg* CBZ was seen at 45 min, the effect gradually wearing off to no protection at 24 hr. Lithium treatment alone did not have any anticonvulsant effect, nor did it alter the intensity or duration of anticonvulsant action of CBZ as tested by MES.

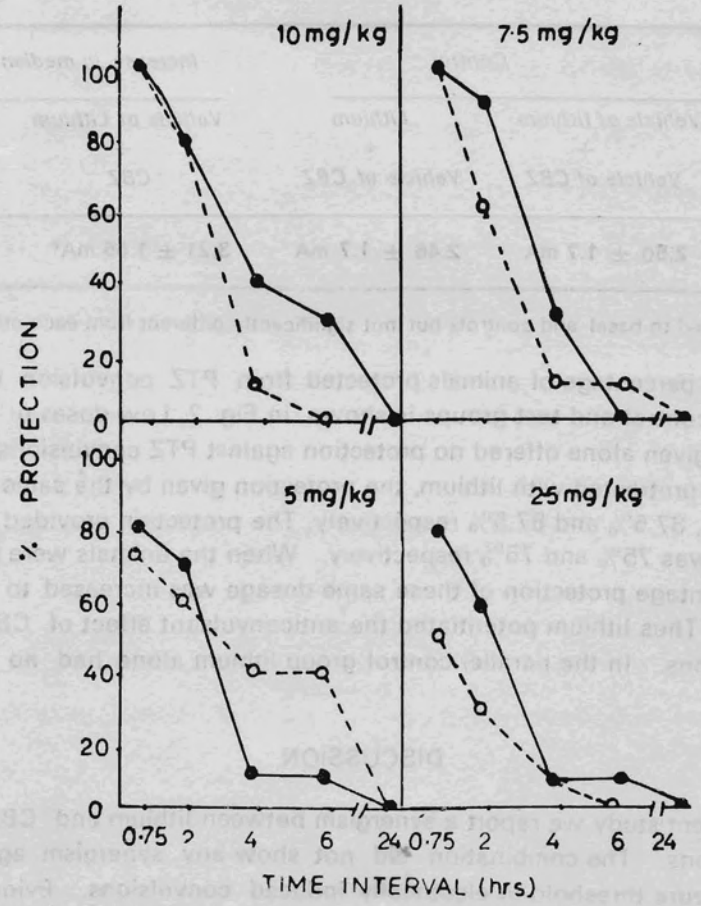

Fig. 1 ; Effect of various doses of carbamazepine in control (●—●) and lithium pretreated (○—○) animals against maximum electroshock seizures. % protection, n=10.

MET : The effect of CBZ on convulsive thresholds in the vehicle or lithium pretreated groups is shown in Table I. The median baseline threshold (± SD) was found to be 2.5±1.7 mA. In animals treated with lithium alone for 9 days, there was no significant change in threshold as compared to baseline. CBZ 10 *mg/kg* significantly raised the median convulsive threshold by 3.21±1.55 mA ($P<0.05$), i.e. threshold was increased to 5.71 mA. The increase in median threshold produced by CBZ after lithium pretreatment was by 3.17±1.28 mA, i.e. it was increased to 5.67 mA which was not significantly different from the increase produced by CBZ alone. Thus lithium did not alter the anticonvulsive effect of CBZ on MET.

TABLE I : Effect of carbamazepine on minimum electro convulsive threshold on vehicle or lithium pretreated rats. Values expressed are the median thresholds (± S. D.)

Basal	*Control*		*Increase in median threshold by*	
	Vehicle of lithium + Vehicle of CBZ	*Lithium + Vehicle of CBZ*	*Vehicle of Lithium + CBZ*	*Lithium + CBZ*
2.50 ± 1.7 mA	2.50 ± 1.7 mA	2.46 ± 1.7 mA	3.21 ± 1.55 mA*	3.17 ± 1.28 mA*

*P <0.05 as compared to basal and controls but not significantly different from each other.

PTZ : The percentage of animals protected from PTZ convulsion by the various doses of CBZ in control and test groups is shown in Fig. 2. Low doses of CBZ 2.5, 5 and 10 *mg/kg* when given alone offered no protection against PTZ convulsions, whereas when the animals were pretreated with lithium, the protection given by the same doses of CBZ increased to 25%, 87.5% and 87.5% respectively. The protection provided by CBZ 15 and 20 *mg/kg* alone was 75% and 75% respectively. When the animals were pretreated with lithium, the percentage protection of these same dosage was increased to 100% in both dosage groups. Thus lithium potentiated the anticonvulsant effect of CBZ against PTZ induced oonvulsions. In the parallel control group lithium alone had no anticonvulsant effect.

DISCUSSION

In the present study we report a synergism between lithium and CBZ against PTZ induced convulsions. The combination did not show any synergism against the HLE component or seizure threshold in electrically induced convulsions. Evidence that biogenic amines and neuroactive purines are involved in the pathophysiological mechanim

of experimental seizures produced by ECS or PTZ is accumulating (1). It has been shown that electrically induced seizures are very sensitive to change in NE transmission and that

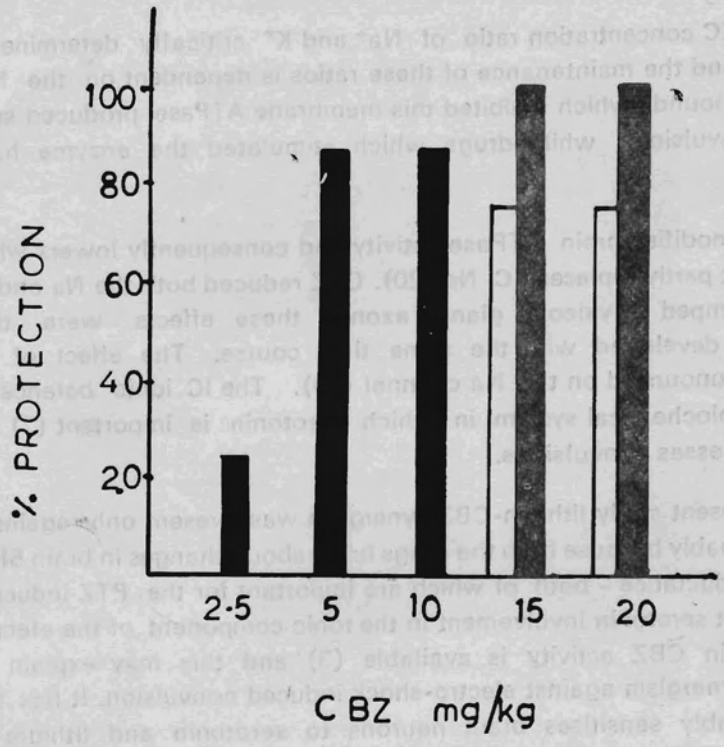

Fig. 2 : Effect of various doses of carbamazepine in control (□) and lithium pretreated (■) animals against pentylenetetrazol induced convulsions. % protection, n=6-8 (2.5, 5 and 10 *mg/kg* CBZ in controls did not show any protection and is therefore not shown in the figure).

they are not significantly modified by procedures aimed at changing 5HT transmission (3,8,17). On the other hand PTZ induced convulsions are more sensitive to increases in brain 5HT levels which have an inhibitory effect (10). Further PTZ induced seizures are related to increase in K^+ permeability and drugs which prevent this increase inhibit the convulsions (7).

CBZ is a potent anticonvulsant which inhibits MES, raises MET and blocks PTZ induced convulsions (18). The mechanism of its action. however, remains obscure. It has been suggested that inhibition of neuronal catecholamine uptake may be involved (16). CBZ 5-100 *mg/kg* (ip, has been shown to increase the concentration of 5HT and

5 HIAA in brain, which may be due to a decrease in utilization of 5HT without altering synthesis (15). Lithium also has been reported to increase brain 5HT after chronic administration (14,23).

The IC-EC concentration ratio of Na^+ and K^+ critically determines resting action potentials (5) and the maintenance of these ratios is dependent on the Na-K- activated ATPase. Compounds which inhibited this membrane ATPase produced seizure discharge leading to convulsions, while drugs which stimulated the enzyme had the opposite effect (12).

Lithium modifies brain ATPase activity and consequently lowers whole brain Na in mice (9), also it partly replaces I.C, Na (20). CBZ reduced both the Na and K conductance of voltage clamped Myxicola giant axons; these effects were dose-dependent, reversible and developed with the same time course. The effect of the drug were slightly more pronounced on the Na channel (19). The IC ionic balance is also in turn regulated by a biochemical system in which serotonin is important (2) and increase in brain 5HT suppresses convulsions.

In the present study lithium-CBZ synergism was present only against PTZ induced convulsion, probably because both the drugs bring about changes in brain 5HT and interfere with ionic conductance - both of which are important for the PTZ induced convulsions. Evidence against serotonin involvement in the tonic component of the electrically induced convulsion and in CBZ activity is available (3) and this may explain the failure of a lithium - CBZ synergism against electro-shock induced convulsion. It has been suggested that CBZ probably sensitises brain neurons to serotonin and lithium enhances the activity of serotonin containing neurons, thus, bringing about a synergism (4), Our findings support this hypothesis. De Montigny *et al.* (4) have reported that manic patients not responding to CBZ showed 50% improvement within 48 hrs when lithium was added to the treatment regimen. It would be worth investigating whether lithium-CBZ anticonvulsant synergism observed in this study can be extrapolated to a clinical situation, i.e. whether addition of lithium to the treatment regimen of those patients not responding to CBZ would produce beneficial effects, especilly in petitmal epilepsy.

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