THE EFFECT OF LITHIUM ON ACUTE TOXICITY OF CARBAMAZEPINE IN MICE

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Abstract — The effects of chronic administration of lithium, on acute toxicity of carbamazepine (CBZ) in male albino mice was studied and the LD50 values were determined from dose-probit curves. The results showed that in lithium pretreated animals (animals consumed drinking water contraining 600 mg/L lithium carbonate for 10 days) the LD50 value (the doese corresponding to probit 5) of CBZ decreased significantly from 212.02 to 190.83 mg/kg. It seems that concurrent administration of lithium with CBZ increases the acute toxicity of CBZ in mice. Several interactions between carbamazepine and lithium has been described. It is concluded that concurrent use of lithium and CBZ, increase the acute toxicity of CBZ in mice and such interaction may increase CBZ adverce reactions. The lithium-induced increase of CBZ lethality may be due to pharmacokinetics and pharmacodynamics interactions.
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Key words: Lithium, carbamazepine, lethality, mice

INTRODUCTION

Lithium is well established in the treatment of mania and is the preferred prophylaxis in bipolar affective disorder (1,2). Carbamazepine (CBZ), an iminodibenzyl derivative, is commonly employed as adjunct to lithium in the treatment of manic-depressive patients (2,3,4,5). It may offer an alternative to treatment with lithium (6). Although lithium appeared to be more effective than carbamazepine in the acute phase of mania but there was no significant difference in the follow-up phase (7). The combination of these two drugs may produce a more rapid response than lithium alone but severe neurotoxicity reported during concomitant therapy with lithium and carbamazepine. This may be due to the drug-drug interaction (2,8,9). Since, the effect of lithium on acute toxicity of CBZ in animal models have not been studied, we investigated the CBZ-induced lethality either alone or in combination with lithium in male albino mouse.

MATERIALS AND METHODS

Animals

Male albino mice weighing 20-30g were used. Animals were housed at a constant room temperature with 12 h light/dark cycle, and were allowed free access to water and standard laboratory chow except during the time of experiments.

Chemicals

Carbamazepine and lithium carbonate were obtained from Ciba (England) and Merck (Germany) respectively. Solution of CBZ was prepared in Glycofurol (Aldrich, USA) and solution of lithium carbonate was prepared in distilled water.

Experiments

The animals were divided into two groups. The first group was maintained on drinking water containing of 600 mg/L of lithium carbonate for 10 consecutive days and the second group had tap water. All experiments were performed between 10 AM till 4 PM. Mice were placed in subgroups according their weight and allowed to habituate for 30 min before CBZ injection. CBZ injected intraperitoneally (ip) at doeses of 83-500 mg/kg. Increasing of dose for each subsequent group was in equal log intervals. Age and weight matched control mice were given for the same period equivalent amounts of glycofurol. Mice were placed in individual cages for observation. The effect of drug on lethality and the survival of mice after drug injection was observed and recorded on each group within a period of 72 hours. Determination of LD50 value of CBZ in mice has been done by graphic method of Miller and Tainter (10). Results are shown in Table 1 and 2. The CBZ was diluted to give different strengths in the same volume and a fixed volume of different strengths were injected intraperitoneally per unit body weight bases. Since all the mice in group eight died, group nine has been neglected. Before plotting, the precent for the 0 and 100 are corrected according to the following correction formula:

For the 0% dead: 100 (0.25/n)

For the 100% dead: 100 {(n - 0.25)/n}

Wheren is the number of the animals in the group. The observed percent mortality is converted into probit by referring to the appropriate table and the values thus obtained are plotted against log dose and the dose corresponding to probit 5 or 50% (median lethal dose or LD50) were found for control and pretreated animals.

Serum Determination

Measurements were made after 10 days chronic lithium administration. Animals sacrificed by decapitation and blood collected from the neck wound into siliconized tubes. Serum was immediately separated by centrifugation in microcentrifuge distilled and deionized water. Lithium level were then determined using Shimadzu AA-670 atomic absorption spectrophotometer (Shimadzu, Japan). Reading were made in triplicated at wave length of 670.8 nm. Peak height measurement were compared with values for standards of known concentration made up in similarly diluted serum.

Data analysis

The results were statistically analayzed by ANOVA followed by student-Newman-Keuls. Differences with $P<0.05$ were considered significant.

RESULTS

In this experiment, when lithium was given chronically at the concentration of 600 mg/L, the serum levels after 10 days were (0.34 ± 0.09 mmol/L). The LD50 value of CBZ in control and lithium pretreated animals were 212.02 and 190.83 mg/kg respectively. The results of acute toxicity of CBZ in control and pretreated mice have been shown in Table 1 and 2 respectively. Comparative curves which are in log dose-probit indicate that dose-mortality curve of CBZ in the presence of lithium is shifted to left (Fig. 1).

Table 1. Results of acute toxicity of CBZ in control mice

	Dose ip					
Group	mg/kg	Dead	Survived	Dead %	Corrected %	Probit
1	<83	0	28	0	0.89	<2.67
2	83	1	27	3.57	3.57	3.1570
3	119	4	24	14.28	14.28	3.9240
4	170	9	19	32.14	32.14	4.5300
5	244	15	13	53.57	53.57	5.0940
6	349	19	9	67.86	67.86	5.4570
7	500	25	3	89.28	89.28	6.2940
8	>500	28	0	100	99.11	>7.33

Table 2. Results of acute toxicity of CBZ in lithium pretreated mice

	Dose ip					
Group	mg/kg	Dead	Survived	Dead %	Corrected%	Probit
1	<83	0	28	0	0.89	<2.67
2	83	4	24	14.28	14.28	3.9240
3	119	6	22	21.42	21.42	4.1810
4	170	12	16	42.85	42.85	4.8120
5	244	20	8	71.42	71.42	5.5810
6	349	23	5	82.14	82.14	5.9470
7	500	27	1	96.43	96.43	6.6910
8	>500	28	0	100	99.11	>7.33

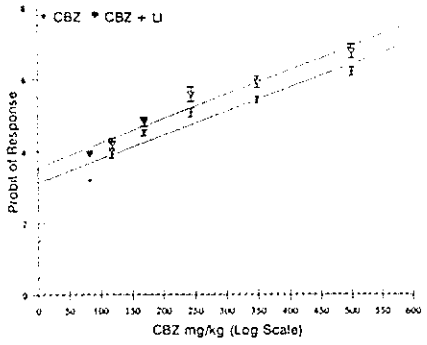

Fig. 1. LD_{50} values of CBZ in control and lithium pretreated mice. All point with CBZ + lithium - treated are significantly different from CBZ - treated animals ($P<0.5$).

DISCUSSION

In this study the influence of chronic lithium on acute toxicity of CBZ in male albino mice has been investigated. Lithium effectively treats acute mania (1,2) but the combination with CBZ may produce a more rapid response in manic-depressive patients (2,8,9). Severe neurotoxicity has been reported during concurrent use of lithium and CBZ (2,12,13). Our results showed that lithium increases the acute toxicity of CBZ as revealed an increase of CBZ - induced lethality compared to the control. The effect may be related to the pharmacokinetics and pharmacodynamics interactions. Since, the therapeutic index of lithium is narrow, TDM is suggested in patients treated concurrently with lithium and CBZ.

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