

THE EFFECT OF LITHIUM ON ACUTE TOXICITY OF CHLORPROMAZINE IN MICE

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Abstract — The effects of chronic administration of lithium, on acute toxicity of chlorpromazine (CPZ) 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 containing 600mg/L lithium chloride for 10 days) the LD50 value (the dose corresponding to probit 5) of CPZ increased significantly from 27.99 ± 0.29 to 45.5 ± 0.47 mg/kg. It seems that concurrent administration of lithium with CPZ decreases the acute toxicity of CPZ in mice. Several interactions between phenothiazines and lithium has been described. It is concluded that concurrent use of lithium and CPZ, decreases the acute toxicity of CPZ in mice and such interaction may reduce CPZ response. The lithium-induced reduction of CPZ lethality may be due to pharmacokinetics and pharmacodynamics interactions.

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in animal models have not been studied, we investigated the CPZ-induced lethality either alone or in combination with lithium in male albino mice.

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

Chlorpromazine hydrochloride and lithium chloride were obtained from Sigma (England) and Merck (Germany) respectively. Solutions of both drugs were prepared in distilled water immediately before use.

Experiments

The animals were divided into two groups. The first group was maintained on drinking water containing of 600mg/L of lithium chloride 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 CPZ injection. CPZ injected ip at doses of 5-80mg/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 normal saline. 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 CPZ in mice has been done by graphic method of Miller and Tainter (15). Results are shown in Table 1 and 2. The CPZ was diluted to give different strengths in the same volume and a fixed volume of different strengths were injected intraaperitoneally per unit body weight bases. Since all the mice in group seven died, group eight has been neglected. Before plotting, the percent for the 0 and 100 are corrected according to the

INTRODUCTION

Lithium that belongs to the alkali metals is the most appropriate drug for the treatment of mania and an effective and specific agent for the prophylaxis of bipolar affective disorders (1,2,3). Neuroleptic drugs are commonly employed as adjuncts to lithium in the treatment of acute mania (4,5). Clinical experience has shown that patients who have manic breakthrough, despite adequate doses of prophylactic lithium, appear to benefit from the concurrent use of neuroleptics with lithium (6). Furthermore neuroleptics such as chlorpromazine (CPZ) and haloperidol are combined with lithium in the initial phases of treatment, although sometimes this combination is used for maintenance therapy (7,8). It has been suggested that the best way to treat the acute manic patients is to administer lithium in combination with CPZ or haloperidol (3). It has been reported that the concurrent use of a neuroleptic drug and lithium has been associated with neurotoxicity (9,10,11) and nephrotoxicity (12). Addonizio and coworkers (13) have also reported that patients treated with lithium and neuroleptics concomitantly show more pronounced adverse effect than patients that lithium alone. Recently it is demonstrated that patients taking a combination of lithium and neuroleptics showed significantly lower lithium ratio and intraerythrocyte lithium concentration as compared with those of lithium alone (14).

Since, the effect of lithium on acute toxicity of CPZ

following correction formula:

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

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

Where n is the number of the animals in the group. The observed percent mortality is converted into probit by refereeing 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 result were statistically analyzed 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 $(0.34 \pm 0.09 \text{ mmol/L } n=30)$. The LD50 value of CPZ in control and lithium pretreated animals were 27.99 ± 0.29 to $45.5 \pm 0.47 \text{ mg/kg}$ respectively. One way ANOVA indicates a significant difference between animals treated with CPZ and those pre-treated with lithium and CPZ [$F(11,684) = 35837, p < 0.0001$]. The results of acute toxicity of CPZ 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 CPZ in the presence of lithium is shifted to right Fig. 1.

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

Group	Dose i.p. mg/kg	Dead	Survived	Dead%	Corrected%	Probit
1	5	0	58	0	0.4	<2.67
2	10	11	47	18.96	18.96	4.1184
3	20	21	37	36.20	36.20	4.6460
4	40	31	27	53.40	53.40	5.0880
5	60	43	15	74.14	74.14	5.6442
6	80	54	4	93.10	93.10	6.4870
7	>80	58	0	100	99.56	>7.33

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

Group	Dose i.p. mg/kg	Dead	Survived	Dead%	Corrected%	Probit
1	5	0	58	0	0.4	<2.67
2	10	0	58	0	0.4	<2.67
3	20	11	47	18.96	18.96	4.1184
4	40	19	39	32.76	32.76	4.5528
5	60	34	24	58.62	58.62	5.2186
6	80	50	8	86.21	86.21	6.0905
7	>80	58	0	100	99.56	>7.33

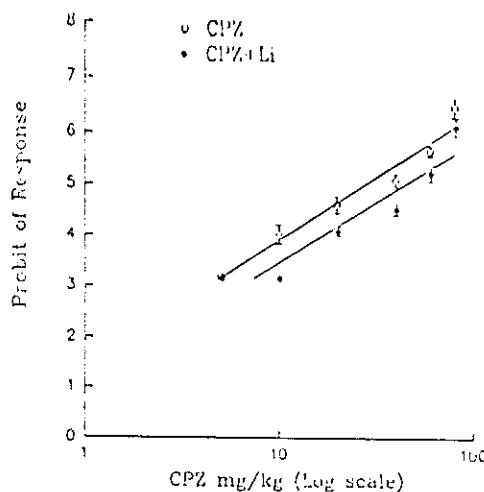


Fig. 1. LD50 values of CPZ in control and lithium pretreated mice. All point with CPZ + lithium-treated are significantly ($P < 0.001$) different from CPZ-treated animals.

DISCUSSION

In this study the influence of chronic lithium on acute toxicity of CPZ in male albino mice has been investigated. Lithium effectively treats acute mania, but it must often be used in conjunction with neuroleptics (5). There are conflicting reports about the safety of the combination of lithium and neuroleptic drugs. For example, in some studies neurotoxicity (9,10,11) and nephrotoxicity (12) have been reported. Whereas in some other study the safety of this combination has been confirmed (16).

Several pharmacokinetics interaction between phenothiazines and lithium have been described; lithium-induced reduction in plasma level of CPZ.; phenothiazines-induced increase in the erythrocyte uptake of lithium. CPZ-induced increase in renal excretion of lithium (17,18).

Our results showed that lithium decreased the acute toxicity of CPZ as revealed a reduction of CPZ-induced lethality compared to the control. It has been shown that patients treated with a combination of lithium and

neuroleptic drugs had significantly lower erythrocyte lithium concentrations and lithium ratios than patients receiving lithium along (13). In conclusion concomitant use of CPZ and lithium decreased the acute toxicity of CPZ in mouse. Although it is difficult to predict the clinical outcome of this interaction, but one should be alert for evidence reduced of phenothiazine response in the presence of lithium.

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