EFFECT OF PSYCHOTROPIC DRUGS ON THE PHARMACOKINETICS OF LITHIUM

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UDC 615.31:546.34].015.23:615.214

KEY WORDS: lithium; psychotropic drugs; pharmacokinetics.

During the treatment of affective states by lithium salts in conjunction with chlorpromazine, levomepromazine, haloperidol, diazepam, and clozapine, an increase in the frequency of appearance of signs of lithium poisoning has been observed, together with complications which are not found as a result of administration of lithium salts in the same doses alone [3-5, 7, 8], possibly on account of the ability of the psychotropic drugs to modify the pharmacokinetics of Li^+.

The present investigation was undertaken for the experimental verification of this hypothesis.

EXPERIMENTAL METHOD

Experiments were carried out on 147 noninbred albino mice of both sexes weighing 18-23 g. Once a day for 3 days the animals were given an injection of 100 mg/kg LiCl, either alone or together with chlorpromazine (15 mg/kg), trifluoperazine (60 mg/kg), haloperidol (15 mg/kg), tofranil (50 mg/kg), fluacizine (50 mg/kg) or phenazepam (100 mg/kg). LiCl was injected intraperitoneally, phenazepam was given by gastric tube, and all the other drugs were injected subcutaneously. The mice were decapitated 1 and 24 h after a single dose or 24 h after three doses of the drugs, and the Li^+ concentration in blood, cerebral cortex, cerebellum, pons, medulla, mesencephalon and diencephalon, kidneys, and liver was determined by flame photometry [1].

EXPERIMENTAL RESULTS

The Li^+ concentration 1 h after a single injection of LiCl was lower in the various brain structures tested, but in the kidneys it was higher than in the blood and, in particular, in the liver (Table 1), in agreement with data in the literature [2, 6]. After 24 h the Li^+ concentration was reduced in the kidneys, showed little change in the liver and blood, and was increased in the brain tissues (Table 2). These changes were evidently due to excretion of Li^+ and its redistribution in the body of the mice.

In mice killed 1 h after a single dose of LiCl and chlorpromazine the Li^+ concentration in the cerebellum, kidneys, and liver was higher than in the same organs of control animals receiving only LiCl (Table 1). Trifluoperazine increased the Li^+ concentration in the cerebral cortex, cerebellum, kidneys, and liver; haloperidol had the same effect in the kidneys and liver, tofranil in the kidneys, fluacizine in the cerebral cortex, medulla, and kidneys, and phenazepam in the cerebral cortex, medulla, mesencephalon, and liver. The Li^+ concentration 24 h after a single dose of LiCl and trifluoperazine was higher in all parts of the brain studied and in the kidneys and liver than in animals of the control group. The remaining psychotropic drugs studied had a less marked effect on the Li^+ concentration in the mice, and they can be arranged in the following order of diminution of this effect: tofranil, haloperidol, fluacizine, chlorpromazine, and phenazepam (Table 2). At both periods of the investigation the psychotropic drugs did not change the blood Li^+ concentration (Tables 1 and 2).

During a course of injections of LiCl into mice accumulation of Li^+ took place in the organs and blood, but this process differed in its intensity. For instance, in mice killed 24 h after a 3-day course of injections, each of 100 mg/kg LiCl, the Li^+ concentration was higher in the diencephalon (2.42 ± 0.04 meq/kg), cerebral cortex (2.36 ± 0.07 meq/kg), mesencephalon (2.32 ± 0.05 meq/kg), cerebellum (2.31 ± 0.04 meq/kg), and pons (2.22 ± 0.05 meq/kg) than in the medulla, liver, kidneys and, in particular, in the blood (1.84 ± 0.06; 1.80 ± 0.03; 1.80 ± 0.05; and 1.01 ± 0.04 meq/kg, respectively).

Department of Civil Defense, Bryansk Pedagogic Institute. Laboratory of Drug Toxicology, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 89, No. 6, pp. 696-698, June, 1980. Original article submitted October 10, 1979.

 0007-4888/80/8906-0784$07.50 © 1980 Plenum Publishing Corporation

TABLE 1. Li^+ Concentration (in meq/kg) in Tissues of Mice 1 h after a Single Injection of 100 mg/kg LiCl Alone (control) and Together with Psychotropic Drugs (M ± m)

Tissue tested	Control	Chlorpromazine	Trifluoperazine	Haloperidol	Tofranil	Fluacizine	Phenazepam
Cerebral cortex	0,43±0,05	0,59±0,07	0,63±0,03*	0,47±0,06	0,47±0,06	0,60±0,06*	0,68±0,10*
Cerebellum	0,52±0,05	0,67±0,05*	0,67±0,05*	0,56±0,08	0,57±0,08	0,58±0,07	0,61±0,08*
Medulla	0,44±0,07	0,60±0,05	0,61±0,06	0,45±0,07	0,53±0,06	0,63±0,06*	0,72±0,08
Pons	0,53±0,07	0,58±0,06	0,63±0,05	0,52±0,06	0,57±0,07	0,61±0,05	0,62±0,07
Mesencephalon	0,44±0,05	0,52±0,05	0,48±0,07	0,47±0,07	0,54±0,06	0,44±0,07	0,68±0,08*
Diencephalon	0,57±0,07	0,68±0,06	0,54±0,08	0,58±0,08	0,62±0,08	0,62±0,08	0,61±0,08
Kidneys	2,19±0,12	3,59±0,10*	3,22±0,08*	2,95±0,11*	2,94±0,11*	3,13±0,07*	2,33±0,13
Liver	0,61±0,06	1,35±0,05*	1,19±0,07*	1,12±0,06*	0,71±0,08	0,88±0,08	0,97±0,08*
Blood	0,97±0,06	1,12±0,09	1,06±0,07	1,09±0,07	1,01±0,07	1,06±0,07	0,94±0,07

Legend. Here and in Table 2, asterisk indicates that differences compared with control values are statistically significant at $P < 0.05$ level.

TABLE 2. Li^+ Concentration (meq/kg) in Tissues of Mice 24 h after a Single Injection of 100 mg/kg LiCl Alone (control) and Together with Psychotropic Drugs (M ± m)

Tissue tested	Control	Chlorpromazine	Trifluoperazine	Haloperidol	Tofranil	Fluacizine	Phenazepam
Cerebral cortex	0,96±0,04	1,17±0,05	1,32±0,08*	1,24±0,05*	1,32±0,04*	1,16±0,07	1,02±0,07
Cerebellum	0,98±0,04	1,07±0,06	1,43±0,09*	1,32±0,04*	1,25±0,07*	1,17±0,07	1,16±0,07
Medulla	0,72±0,06	0,90±0,07	0,95±0,06*	0,89±0,07	0,92±0,08	0,85±0,11	0,82±0,10
Pons	0,91±0,09	0,98±0,07	1,24±0,09*	1,00±0,06	1,04±0,08	1,05±0,07	0,97±0,08
Mesencephalon	0,82±0,07	1,11±0,04*	1,34±0,07*	1,16±0,05*	1,15±0,07*	1,00±0,09	1,14±0,06*
Diencephalon	0,98±0,05	1,16±0,04*	1,58±0,04*	1,27±0,04*	1,29±0,05*	1,23±0,11*	1,09±0,07
Kidneys	0,91±0,10	0,99±0,08	1,57±0,11*	1,11±0,09	1,17±0,07*	1,35±0,06*	1,08±0,11
Liver	0,52±0,08	0,63±0,03	0,76±0,07*	0,67±0,08	0,65±0,06	0,76±0,06*	0,74±0,06*
Blood	0,81±0,05	0,74±0,03	0,94±0,13	0,87±0,06	0,86±0,06	0,76±0,07	0,79±0,05

Repeated combined administration of LiCl and psychotropic drugs to mice had effects which differed in degree of Li^+ accumulation, depending on the type of tissue and the preparation. This effect was more marked in the case of haloperidol than of trifluoroperazine and, in particular, chlorpromazine and phenazepam. For instance, in mice killed 24 h after three injections of LiCl and haloperidol, the Li^+ concentration in the cerebellum (2.52 ± 0.07 meq/kg), pons (2.47 ± 0.10 meq/kg), mesencephalon (2.64 ± 0.05 meq/kg), diencephalon (2.74 ± 0.04 meq/kg), kidneys (2.13 ± 0.11 meq/kg), and blood (1.15 ± 0.05 meq/liter) was significantly higher than in animals receiving LiCl only. Trifluoperazine increased Li^+ accumulation in the cerebellum, mesecephalon, and blood (to 2.72 ± 0.04, 2.55 ± 0.07, and 1.17 ± 0.03 meq/kg, respectively), chlorpromazine increased it in the medulla (2.07 ± 0.09 meq/kg), and phenazepam in the kidneys (2.01 ± 0.07 meq/kg). Under the same experimental conditions, tofranil and fluacizine caused no change in Li^+ accumulation in the blood and organs of the mice.

Psychotropic drugs (tofranil, fluacizine) thus lead to the more rapid achievement of the maximal Li^+ concentration in the tissues (but not the blood) of mice in the case of their combined administration with LiCl. Haloperidol and, to a lesser degree, trifluoperazine, chlorpromazine, and phenazepam, promote accumulation of Li^+ in certain organs above the level which can be achieved by administration of lithium chloride alone.

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*As in Russian original – Consultants Bureau.