EXPERIMENTAL TREATMENT OF ACUTE LITHIUM CHLORIDE POISONING

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Lithium chloride was given to mice as a single subcutaneous injection (480 or 1000 mg/kg) and to rabbits via gastric tube (850 mg/kg). Treatment with Trilon B (mice in doses of 100, 150, 175, 200, 300, and 400 mg/kg; rabbits 50 mg/kg) began 10–15 min after poisoning. If large single doses of Trilon B were injected the animals developed tetanic spasms and died. A slow test injection of Trilon B had a distinct therapeutic action but did not accelerate the elimination of lithium from whole blood or prevent the decrease in its sodium and potassium concentrations.

The ever-increasing use of lithium salts for the treatment of manic-depressive psychoses has been accompanied in some cases by overdosage of the compound or even acute poisoning [5, 6]. Treatment of poisoning by lithium salts includes overcoming the effects due to disturbance of the water and electrolyte balance. For this purpose large doses of sodium chloride and abundant fluids are given, together with diuretics to promote elimination of the lithium [3, 4, 7]. Other pharmacological agents are given as indicated. There is no specific antidote for severe lithium poisoning [2, 4].

In this investigation the action of Trilon B in lithium chloride poisoning was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 243 albino mice and 24 grey rabbits of both sexes. Lithium chloride was injected subcutaneously into the dorsum of the mice in a dose of 1,000 mg/kg (LD_{90}; series I and II) or 480 mg/kg (series III), and administered to the rabbits by gastric tube in a dose of 850 mg/kg (LD_{90}). Trilon B (the disodium salt of ethylenediaminetetra-acetic acid) was injected intraperitoneally into the mice 10–15 min after the lithium chloride in single doses of 100, 150, 175, 200, 300, and 400 mg/kg in series I, and twice at intervals of 10 and 60 min after injection of the lithium salt in doses of 100 and 150 mg/kg, respectively, in series II and III. Trilon B was injected intravenously into the rabbits in a dose of 50 mg/kg as a 1% solution at the rate of 1 ml per min at the following times after poisoning: 10 min, 2 and 4 h, and 1 and 2 days. The lithium, sodium, and potassium concentrations in the whole blood were determined by flame photometry in the rabbits and the mice of series III. Blood was taken from the marginal vein of the rabbits' ear 1 and 3 h and 1–7 days, and from the mice by decapitation 1, 3, 6, 12, and 24 h after the beginning of the experiment.

TABLE 1. Effect of Trilon B on Survival Rate of Mice with Acute Lithium Chloride Poisoning (1000 mg/kg; M ± m)

Series of experiments	Dose of Trilon B (in mg/kg)	No. of mice: total	No. surviving: abs.	No. surviving: %	P
I	Control	26	6	23±8	—
	100	16	4	25±13	0,5
	150	25	17	68±9	0,001
	175	10	6	60±15	0,05
	200	15	6	40±13	0,5
	300	10	0	0	0,01
	400	10	0	0	0,01
II	Control	20	6	30±10	—
	100×2	31	24	77±7	0,001
	150×2	30	28	93±5	0,001

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TABLE 2. Concentrations of Lithium, Sodium, and Potassium (in mg%) in Whole Blood of Mice Poisoned with 0.5 LD_{50} Lithium Chloride and Treated with Trilon B (M ± m)

Time after poisoning (in h)	Lithium			Sodium			Potassium		
	control	experiment	P	control	experiment	P	control	experiment	P
1	1,71±0,06	2,55±0,10	0,001	142±1,7	147±4,2	0,5	209±5,1	210±7,9	0,5
3	1,29±0,08	1,66±0,06	0,01	161±2,3	156±6,6	0,5	203±4,5	192±4,0	0,5
6	1,29±0,21	1,49±0,13	0,5	165±5,5	176±10,0	0,5	196±6,4	183±5,3	0,5
12	0,75±0,04	0,80±0,08	0,5	158±4,0	169±3,2	0,5	196±7,2	186±6,6	0,5
24	0,26±0,01	0,26±0,05	0,5	160±1,5	159±2,3	0,5	194±3,0	192±3,8	0,5
Intact	0,21±0,02			199±2,5			218±3,1		

Instead of Trilon B, the animals of the control groups received the same volume of distilled water at the same times as the experimental animals. The animals remained under observation for 30 days.

EXPERIMENTAL RESULTS

After subcutaneous injection of 1,000 mg/kg lithium chloride into mice death took place within 1-3 days. Death of the rabbits receiving 850 mg/kg lithium chloride by mouth occurred over a period of 2 weeks. The therapeutic effect of Trilon B depended on the dose and rapidity of its absorption into the body. After a single injection of Trilon B in doses of 150 and 175 mg/kg the survival rate of the experimental mice was increased significantly over that of the controls (Table 1). Trilon B, in a dose of 200 mg/kg, had a less marked therapeutic action, and if single doses of 300 or 400 mg/kg of Trilon B were given all the mice died within a few minutes after injection of the chelating agent. Before death the mice developed severe tetanic spasms, evidently as the result of a deficiency of free calcium ions in the blood because of their binding by Trilon B [1]. The optimal effective dose of Trilon B was thus between 150 and 175 mg/kg.

The experiments of series II (Table 1) showed that administration of large doses of Trilon B, subdivided over several injections, enhanced its therapeutic effect even more and reduced the toxic action of the treatment. For instance, a single injection of Trilon B in a dose of 100 mg/kg did not affect the outcome of the poisoning, while two injections of the same dose at intervals of 60 min increased the survival rate of the experimental mice by 47%. After two injections of 150 mg/kg Trilon B, 93 ± 5% of the mice in the experimental group survived compared with 30 ± 10% in the control, but after a single injection of the same total dose of the compound the corresponding figures were 68 ± 9 and 23 ± 8%. The effectiveness of repeated administration of Trilon B in acute lithium chloride poisoning was also confirmed by the experiments on rabbits. In the control group only one of the 14 rabbits survived, compared with 8 of the 10 experimental animals, i.e., 7 ± 6 and 80 ± 12%, respectively, ($P < 0.001$).

Analysis of the lithium concentration in the whole blood of the experimental and control mice and rabbits showed that Trilon B did not increase the rate of excretion of the lithium (Table 2), and its therapeutic action is probably connected with the formation of a nontoxic complex with the lithium ion. Other mechanisms of the therapeutic action of Trilon B in lithium poisoning are also possible. Trilon B does not prevent the ability of lithium to reduce the sodium and potassium concentrations in the whole blood of mice and rabbits, but it prevents the development of degenerative changes in the stomach wall. For instance, regardless of the time of death, extensive ulcers involving the mucous membrane and muscular layer were found in the stomach of all the control animals. No ulcers were found in the stomach of the 2 experimental rabbits which died on the 3rd and 4th days of the experiment or in 90% of the experimental mice which died.

These experiments showed that the rapid administration of large doses of Trilon B leads to the development of severe complications terminating in death. The slow intravenous injection of repeated doses of Trilon B, such as are used in clinical practice [1], enabled the side effects of the compound to be avoided and led to recovery from acute lithium poisoning.

LITERATURE CITED

1. M. D. Mashkovskii, Therapeutic Substances [in Russian], Moscow (1967).
2. G. M. Rumyantseva and E. B. Margolina, Zh. Nevropat. i Psikhiat., No. 7, 1082 (1970).

3. L. I. Allgen, Acta. Psychiat. Scand. Suppl., 207, 98 (1969).
4. S. Gershon, Clin. Pharmacol. Ther., 11, 168 (1970).
5. R. Noyes, Dis. Nerv. Syst., 30, 318 (1969).
6. M. Schou, A. Amdisen, and J. Trap-Jensen, Nord. Méd., 77, 831 (1967).
7. M. Schou, A. Amdisen, and J. Trap-Jensen, Am. J. Psychiat., 125, 520 (1968).