Therapy of Experimental Hydrazine Poisoning. (20743)

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The increased use of hydrazine in industry has caused a renewed interest in the nature and treatment of poisoning from hydrazine. Convulsions are characteristic of early severe poisoning; with large doses of hydrazine, such as used in this study, the convulsions invariably produce death. With the prevention or amelioration of the convulsions by the use of barbiturates a depression develops beyond that due to the treatment agent, and the animals die during the depression usually with severe pulmonary edema(1). In less severe poisoning the convulsions are absent, the depression is mild and death occurs in a few days from central necrosis of the liver(2). The object in this study was to find some agent or agents which would prevent the deaths due to pulmonary edema and liver damage while using the barbiturates to control the convulsive phase. Some of the products of intermediate metabolism of glucose were selected for study as treatment agents. These were selected because Underhill had related the poisoning process to disturbances in glucose metabolism(3-5), and the brain tissue from rabbits poisoned by hydrazine gave a greater oxygen uptake with succinate than the brain tissue from normal rabbits(6).

Methods. Adult albino mice were used in all experiments. Hydrazine was given intraperitoneally. The susceptibility of this strain to hydrazine administered intraperitoneally was as follows: 50 mg/kg killed 0 of 10, 6.25 mg/kg killed 5 of 10, 75 mg/kg killed 8 of 10, and 100 mg/kg killed all of 50. The concentration of hydrazine and agents used for treatment was such that the dose of each for a 20 g mouse was contained in 0.5 ml of solution.

For screening experiments female mice were used 4 to a group, with 4 groups for each organic acid studied. Two groups received 250 mg/mouse of glucose subcutaneously before the start of the experiment, the other 2 groups received nothing. All groups then received hydrazine 195 mg/kg followed immediately by a mixture of thiopental Na 25 mg/kg and pentobarbital Na 12.5 mg/kg also given intraperitoneally. One group of the glucose treated and one group not receiving glucose received subcutaneously the sodium salt of an organic acid involved in the intermediate metabolism of glucose. The doses are indicated in Table I. The time of injection of hydrazine and time of death was noted in each mouse. The mean survival time of each treated group was divided by the mean survival time of its control group. When the quotient was 1.4 or more the experiment was repeated either with or without glucose, whichever gave the higher quotient. For the study of treatment groups of 12 mice each were used. Both males and females were used, as indicated in Table II. Hydrazine was given in doses of 100 mg/kg or 125 mg/kg. All mice received thiopental Na 50 mg/kg intraperitoneally immediately after hydrazine. Treated animals received Na pyruvate 1 g/kg subcutaneously immediately following the barbiturate, and 3 more

TABLE I. Effect of Sodium Salts of Organic Acids on Hydrazine Poisoning Treated with Barbiturates.

	Ratio of survival times, Treated / Control			
	No glucose		Glucose, 250 mg/mouse	
Citric	1.2		.4	
Glutamic	.7		1.2	
Lactic	.9		1.0	
Malic	1.5	1.0	1.4	
Fumaric	1.4	1.7	1.0	
Pyruvic	1.9	2.3	1.0	
Oxaloacetic	.9		2.0	1.5
Succinic	1.4		1.6	1.9

All mice received intraper. 195 mg/kg of hydrazine, 25 mg/kg of thiopental Na and 12.5 mg/kg of pentobarbital Na. Sodium salts of the acids were given subcut. 0.5 g/kg for Na glutamate, 1 g/kg of the acid for succinic and oxaloacetic acid, and 1 g/kg of the sodium salts for the remainder. Each group consisted of 4 mice.

TABLE II. Treatment with Thiopental Na and Na Pyruvate.

Sex	Pyruvate, hr after hydrazine	Hydrazine I.P., mg/kg	No. surviving of 12 mice Controls	Treated
♀	1, 3, 5	100	0	9
♀	2, 4, 6	100	0	12
♀	2, 4, 6	125	0	8
♂	2, 4, 6	125	0	10

Thiopental Na 50 mg/kg given I.P. at time of hydrazine inj., at 1, 3, and 5 hr, 0.5 mg/mouse given to treated animals. All doses of Na pyruvate were 1 g/kg given subcut., first one immediately following hydrazine and the others as stated. Each group consisted of 12 mice.

doses at the times indicated in Table II. In addition the treated mice received thiopental Na 0.5 mg/mouse (average dose 25 mg/kg) at 1, 3, and 5 hours after the hydrazine.

Results. In hydrazine poisoned mice there was no difference in survival time between mice which received pentobarbital Na 25 mg/kg and those which received a mixture of thiopental Na 25 mg/kg and pentobarbital Na 12.5 mg/kg. However, when thiopental Na 50 mg/kg was compared with pentobarbital 25 mg/kg the average survival time for thiopental Na was 1.3 times that for pentobarbital Na. There is one chance in 20 that this difference is not significant. A potential advantage to the use of a short acting barbiturate with a poison such as hydrazine which gives a convulsant phase followed by a depressed phase also influenced us to use thiopental Na when developing the treatment, although the mixture was used in the preliminary study on survival time. Sodium citrate, glutamate, and lactate were eliminated from the study after the first 2 experiments, because average survival times of treated mice were less than 1.4 times that of the controls (Table I). After the third experiment it was seen that Na pyruvate without glucose gave the highest average survival time of approximately twice that of the controls, so pyruvate was selected for further study. It was possible by using 3 or 4 injections of the same dose of pyruvate along with added barbiturate to increase the survival time up to 6 times that of a single dose of barbiturate, but it was impossible to prevent death with any combination of pyruvate and barbiturate with the dose of hydrazine at 195 mg/kg. The use of repeated doses of pyruvate seemed to increase the need for barbiturate, but when the barbiturate was given in the same amounts to the controls the average survival time was somewhat less than with a single dose.

The final treatment was then developed using a dose of hydrazine of 100 mg/kg with thiopental Na 50 mg/kg as the anesthetic (Table II). All controls died. There were 9 of 12 survivors when pyruvate was given at one, 3, and 5 hours, at the same time as the additional thiopental Na was given, and 12 of 12 survivors when the pyruvate was given at 2, 4, and 6 hours. When the schedule of treatment was held the same as in the latter instance and the dose of hydrazine was raised to 125 mg/kg there were 8 of 12 survivors in the female mice and 10 to 12 survivors in the male. The exact mechanism of action of this treatment is not known but the severe liver damage so characteristic of hydrazine poisoning is not seen in the surviving mice and the pulmonary edema was either reduced or eliminated.

Summary. Severe hydrazine poisoning in the mouse was successfully treated by the use of thiopental Na and Na pyruvate.

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