THE SYNERGISM BETWEEN POLYSULFIDES AND ANESTHETICS

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Polysulfide compounds of the thiuram group (tetraethylthiuramdisulfide and tetramethylthiuramdisulfide) have found application in industry as vulcanizers in the production of various types of rubber. In recent years these compounds and their semimolecules (sodium diethyldithiocarbamate and dimethyldithiocarbamate) have begun to be widely used in agriculture in the protection of various crops from blight, molds, oscochitosis of peas and so on [2, 6, 7].

As we have previously shown, these preparations exert a well-marked action on the blood and hemopoietic organs of animals [4, 5]. One of them – tetramethylthiuramdisulfide – conventionally known as "tetrathion" has been recommended for clinical trial as a drug superior in many of its properties to embikhin, novembikhin, etc.

Antabuse (tetraethylthiuramdisulfide) has found application in medicine in the treatment of chronic alcoholism [1, 9, 10, 11, 12]. The mechanism of its therapeutic action is not yet fully understood. It is thought to be based on the principle of potentiated synergism [3, 8, 15]. By blocking the xanthine oxidase of the liver, antabuse increases and distorts the effect of alcohol [15].

We have found that the three other compounds mentioned above have the property of increasing and prolonging the action of alcohol. The problem of the combined action of these compounds with other narcotics has not been investigated at all, although such a study would be of great interest in view of the widespread use of derivatives of thiuram in agriculture, industry, and medicine.

On the basis of the few papers [13, 14] published on antabuse, it may be considered that thiuram derivatives in all probability enhance the action of other narcotics besides alcohol.

In the present research we studied the combined action of antabuse, tetrathion, and sodium diethyldithiocarbamate and dimethyldithiocarbamate with narcotics (hexobarbital, sodium amytal, chloral hydrate, and urethane).

EXPERIMENTAL METHODS

Experiments were carried out on 200 mice (mainly males) weighing from 16 to 28 g. Polysulfides were introduced into the stomach of the animals on two occasions (once a day) in the form of a 1% suspension in 2% starch mucilage, in a dose of 100 mg/kg. In this dose it gave rise to no visible changes in the mice. Before the experiment the animals were divided into groups, each of 10 mice. During the first day one group of animals received antabuse, another – tetrathion and the following groups received the other polysulfides. The control group (10 mice) received the same volume of 2% starch mucilage. On another day, 30 minutes after the second administration of these compounds, all the mice including the controls) received subcutaneous injections of narcotics in a dose sufficient to cause narcosis: hexobarbital – 35 mg/kg, sodium amytal – 80 mg/kg, chloral hydrate – 400 mg/kg and urethane – 1500 mg/kg.

TABLE

Results of a Study of the Combined Action of Polysulfides and Narcotics

Narcotic	Experiment								Control	
	polysulfides									
	tetrathion		Na dimethyl-dithiocar-bamate		antabuse		Na diethyl-dithiocar-bamate		2% starch mucilage	
	1	2	1	2	1	2	1	2	1	2
Hexobarbital	70	—	38	—	31	—	24	—	26	—
Sodium amytal	709	1	752	—	732	—	807	2	164	1
Chloral hydrate	249	—	900	6	627	5	148	—	107	—
Urethane	491	10	954	7	3 314	5	1 296	2	517	1

Note: 1) Duration of LP in minutes; 2) number of dying mice.

Synergism between the test compounds and narcotics was judged by the duration of narcosis and by death of the animals. The duration of narcosis was deduced from the "lateral position" (LP); the end of narcosis was considered to be the moment when the animal began to wake spontaneously and to show its ability to move about. Careful records were kept of the results of the experiments. The mean duration of narcosis was obtained from these findings (see Table).

EXPERIMENTAL RESULTS

The experiments showed that a well-marked synergism existed between the polysulfides and narcotics. This was shown not only by the prolongation but, in some cases, by the intensification of the narcotic action of the drugs tested.

Combined action of polysulfides with hexobarbital. It may be seen from the table that tetrathion had the strongest action in prolonging the narcotic effect of hexobarbital. The duration of narcosis in the presence of tetrathion was increased from 26 minutes (control figure) to 70 minutes. Antabuse and sodium dimethyldithiocarbamate caused a very slight prolongation of not more than 5-12 minutes by comparison with the controls.

Combined action of polysulfides with sodium amytal. In this series of experiments all the preparations brought about a roughly equally marked prolongation of the narcotic action of sodium amytal. Sodium diethyldithiocarbamate lengthened narcosis 4.9 times (from 164 to 807 minutes), sodium dimethyldithiocarbamate — 4.5 times (from 164 to 752 minutes), antabuse — 4.4 times (from 164 to 732 minutes) and tetrathion — 4.3 times (from 164 to 709 minutes) by comparison with the controls.

Combined action of polysulfides with chloral hydrate. It can be seen from the table that sodium dimethyldithiocarbamate and antabuse, in prolonging the course of the narcosis, considerably enhanced the narcotic action of chloral hydrate; this was shown by the death rate among the animals of these groups by comparison with the controls. In the presence of sodium dimethyldithiocarbamate, for instance, the duration of narcosis was lengthened 8.4 times (from 107 to 900 minutes) and 6 of the 10 mice died, but not one control animal died. When combined with antabuse, narcosis was prolonged from 107 to 627 minutes (5.9 times); 5 of these mice died. In the presence of tetrathion the duration of narcosis rose from 107 to 249 minutes, and of sodium diethyldithiocarbamate — from 107 to 148 minutes.

Combined action of polysufides with urethane. In these experiments, just as in those with chloral hydrate, synergism was observed in both strength and duration of the effect. When antabuse was combined with urethane 5 mice died and one in the control group. The duration of narcosis increased from 517 minutes (controls) to 3314 minutes (by 6.4 times). With sodium diethyldithiocarbamate narcosis was prolonged 2.4 times (from 517 to 1296 minutes). In association with the action of sodium dimethyldithiocarbamate the duration of narcosis increased from 517 to 954 minutes. At the same time many of the animals were observed to die: 7 of the 10 mice taking

part in the experiment died (6 mice more than in the control series). When tetrathion was combined with urethane all 10 mice died, but only one in the control series. The period of narcosis was shortened from 517 to 491 minutes, i.e., by an average of 26 minutes.

SUMMARY

It may be concluded from these experiments that polysulfides of the thiuram group (antabuse, tetrathion, sodium dimethyl- and diethyldithiocarbamates) prolong and, in some cases also enhance the action of narcotics. Care must be exercised when prescribing sodium amytal, chloral hydrate, and urethane to alcoholics under treatment with antabuse. These narcotics must not be prescribed in cases of accidental poisoning by polysulfides of the thiuram group.

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