Toxicity of Sodium Tetrathionate. (17380)

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Sodium tetrathionate monohydrate ($Na_2S_4O_6 \cdot H_2O$) was first proposed by Theis and Freeland[1] for use in the treatment of thrombo-angiitis obliterans. Their object was to provide a greater and more prolonged effect than that obtained by sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$). These substances comprise an oxidation-reduction system but thiosulfate will not oxidize SH groups while tetrathionate does have this action. It has been suggested by Philips *et al.*,[2] Goffart and Fischer[3] that the kidneys may be damaged by this fundamental reaction.

The Council on Pharmacy and Chemistry of the American Medical Association[4] quoted the work of Chen, Rose, and Clowes,[5] also that of Gilman and his associates,[6] on the toxicity of this substance. It was stated that the intravenous LD_{50} in the dog was 250 mg per kilo and in the rabbit 75 mg per kilo. The animals died from renal failure due to severe necrotizing lesions in the proximal convoluted tubules. A later report of the Council consisted of communications from Theis and DeTakats,[7] who emphatically stated that the clinical dose of sodium tetrathionate was only a small fraction of the lethal dose in animals. They advocated a review of the toxicity of this drug from a clinical standpoint.

In an effort to determine the toxicity of sodium tetrathionate (Tetrathione, Searle) clinically, we decided on the following experiment.

Method of study. A group of 30 patients, admitted to the Medical Service of the Medical College of Virginia, Hospital Division, some with peripheral vascular disease, and others with various other maladies, were subjected to routine blood non-protein nitrogen, Mosenthal concentration and phenolsulphonphthalein tests. These patients were then given 0.6 g (10 cc) of tetrathione, intravenously twice daily, for a period of 7 days. This dosage was equivalent to that of the usual course of treatment of peripheral vascular disease, lasting 7 weeks. At the end of the 7 day period, the non-protein nitrogen, Mosenthal concentration, and phenolsulphonphthalein studies were repeated. The results are given in Table I.

There were no untoward reactions to the drug. None of the patients manifested nausea, vomiting, abdominal pain, or weakness, which have been reported following too rapid injection or during the course of clinical treatment. The changes in the laboratory findings were mostly of a minimal character. In 15 cases the non-protein nitrogen showed a slight increase, in 8 cases there was a slight decrease, and in 7 cases there were no changes. The Mosenthal concentration test showed an increase in specific gravity in 10 cases, a decrease in 7 cases, and in 13 cases there were no changes. The phenolsulphonphthalein test showed an increased concentration of the dye in 6 cases, in 15 cases there was less concentration, and in 9 cases there were no changes. The maximum increase in the non-protein nitrogen was from 20 mg% to 35 mg% in case 18, a patient with thrombo-angiitis obliterans. We consider 35 mg % within the normal range. The Mosenthal concentration test in case 6 showed a variation from a maximum specific gravity of 1.032 prior to tetrathione to 1.018 follow-

1 Theis, F. F., and Freeland, M. R., *Arch. Surg.*, 1940, **40**, 190.

2 Philips, F. S., Gilman, A., Koelle, E. S., and Allen, R. P., *J. Biol. Chem.*, 1947, **167**, 209.

3 Goffart, M., and Fischer, P., *Archives Internationales de Physiologie*, 1948, **55**, 258.

4 Council on Pharmacy and Chemistry, *J.A.M.A.*, 1947, **133**, 693.

5 Chen, K. K., Rose, C. L., and Clowes, G. H. A., *Am. J. Med. Sci.*, 1937, **188**, 767.

6 Gilman, A., Philips, F. S., Koelle, E. S., Allen, R. P., and St. John, E., *Am. J. Physiol.*, 1946, **147**, 115.

7 Supplemental Report on Sodium Tetrathionate, *J.A.M.A.*, 1947, **134**, 1092.

TABLE I.
Sodium Tetrathionate Experiments.

Case No.	P.S.P. control, %	P.S.P. after, %	N.P.N. control, mg %	N.P.N. after, mg %	Mosenthal (highest) Control	Mosenthal (highest) After
1	80	63	24	32	1.022	1.022
2	85	75	23	35	1.024	1.020
3	60	55	36	27	1.022	1.020
4	55	55	28	38	1.022	1.025
5	70	60	33	32	1.022	1.020
6	60	70	30	33	1.032	1.018
7	58	50	26	30	1.020	1.018
8	55	55	25	30	1.018	1.016
9	60	55	35	35	1.018	1.018
10	45	50	30	27	1.020	1.020
11	60	60	44	40	1.015	1.016
12	83	65	23	27	1.013	1.016
13	60	53	29	27	1.017	1.018
14	90	62	23	27	1.020	1.018
15	55	55	32	27	1.022	1.022
16	55	55	41	32	1.017	1.016
17	75	60	33	29	1.026	1.026
18	51	34	20	35	1.016	1.023
19	70	60	25	27	1.012	1.012
20	53	50	24	24	1.012	1.017
21	47	45	30	33	1.012	1.012
22	50	45	31	36	1.016	1.015
23	40	45	36	36	1.012	1.021
24	50	58	33	30	1.021	1.018
25	105	55	27	26	1.018	1.016
26	75	70	26	37	1.012	1.019
27	60	60	32	30	1.022	1.022
28	70	60	47	50	1.020	1.022
29	Incomplete					
30	40	45	36	37	1.014	1.012
Avg	63 ± 2.7	57 ± 1.7	30 ± .11	32 ± 10	1.018 ± .009	1.019 ± .0006

ing the drug. In all other cases the variation in Mosenthal concentration was minimal in either direction. The phenolsulphonphthalein test showed the most marked variations. It was decreased by 18% in case 12 and decreased by 27.5% in case 14. The most unusual change was in case 25, in which there was a decrease of 50%. There was no correlation in any separate case between the changes in the various tests.

A statistical analysis[8] of the data is outlined in Table I. It will be noted that the phenolsulphonphthalein control excretion 63.1% ± 2.75. After sodium tetrathionate the excretion was 56.8% ± 1.69. The "t" value for the difference of these means is 1.955 which, with a normal deviate of 1.96, gives a probability of 0.05. The values for the non-protein nitrogen before and after sodium tetrathionate were 30.3 mg% ± .115, and 32.1 mg% ± 0.97. This indicates no significant difference. The Mosenthal values consider only the highest concentration obtained. They were 1.018 ± 0.009 and 1.019 ± 0.0006. This indicates very little difference. The statistical analysis demonstrates that for the dosage employed sodium tetrathionate does not materially affect kidney function as regards the non-protein nitrogen and Mosenthal tests. The phenolsulphonphthalein excretion might be interpreted as definitely reflecting some changes in kidney function.

Summary. Thirty patients were chosen at random from the routine admissions to the Medical Service of the Medical College of Virginia Hospital Division and given 0.6 g sodium tetrathionate twice daily for 7 days, intravenously. The effect on kidney function was studied by following changes in blood non-protein nitrogen, Mosenthal concentration and phenolsulphonphthalein excretion values. The blood non-protein nitrogen and the Mos-

[8] Snedecor, G. W., Statistical Methods, fourth edition, Iowa State College Press, 1946.

enthal concentration values indicated little disturbance in kidney function. However, these tests would not be expected to show much change unless there was a rather extensive impairment in renal function. The phenolsulphonphthalein excretion test was our most sensitive test of tubular function and in several instances showed evidence of diminished tubular capacity following sodium tetrathionate administration. On the basis of these clinical studies it would seem that sodium tetrathionate probably should not be used if there is any pre-existing renal disease.

Received August 18, 1949. P.S.E.B.M., 1949, **72.**

Glycogen in Basophilic Leucocytes in Human Blood Smears. (17381)

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In a recent study of the occurrence of the periodic acid-Schiff reaction in various normal cells of the blood and connective tissue by Wislocki, Rheingold and Dempsey,[1] small clear red dots were observed in the pale pink cytoplasm of the basophilic leucocytes. These investigators were not able to identify the basophiles in control blood smears digested by saliva. They therefore concluded that the red stained material in the undigested smears may have been glycogen but that the "apparent finding needs further verification." Similarly, Gibb, and Stowell[2] decided that "Because myeloid cells which were free from glycogen were not observed in normal peripheral blood and bone marrow films, basophils, although not specifically identified, may also contain glycogen."

To make certain that basophils could be identified in smears digested by saliva before treatment with periodic acid and leucofuchsin, dried smears of human blood were stained in Wright's blood stain in absolute methyl alcohol for 3 minutes. This step was not followed by the usual one of the diluted stain. For the most part, the smears were very quickly rinsed in 95% ethyl alcohol although at the beginning of the study a few were dipped in running water. Basophils were located and each cell was ringed by means of an object marker. A map was made giving its position in the circle. The smears were then fixed in absolute ethyl alcohol for 5 minutes, rinsed in 95% and 70% alcohol and stained by the periodic-leucofuchsin technic of McManus[3] with ½% periodic acid, or, as modified by Wislocki, Rheingold and Dempsey,[1] with 1% periodic acid. The smears to be digested were covered with saliva for 45 to 60 minutes after fixation in absolute alcohol and rinsed in running water. After the smears had been examined with no nuclear stain, they were stained in Mayer's hematoxylin for 10 minutes.

In the undigested smears, the glycogen in the neutrophiles was stained a deep to pale red-pink, either evenly throughout the cytoplasm, or more deeply either around the periphery of the cell or off at one side. The 29 basophilic leucocytes examined were, in contrast, much paler, a difference seen clearly when the two kinds of cells were found next to each other. There was a marked variation in the amount of glycogen in the basophiles even on the same slide. In some cells rather large clear red granules were seen in groups with finer grains distributed more regularly among the unstained basophilic granules. In others only these dust-like particles of glycogen were visible. A third variety had a hazy pink background which outlined the colorless basophilic granules A few had no color at all.

[1] Wislocki, G. B., Rheingold, J. J., and Dempsey, E. W., *Blood*, 1949, **4**, 562.

[2] Gibb, R. P., and Stowell, R. E., *Blood*, 1949, **4**, 569.

[3] McManus, J. F. A., *Stain Tech.*, 1948, **23**, 99.