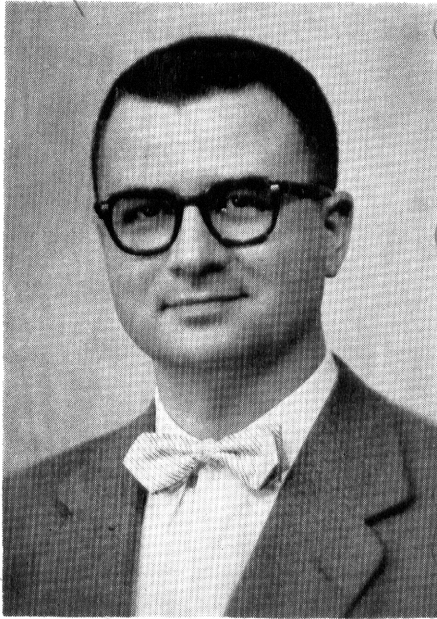


Warning: Thiocyanate Intoxication

BY R. R. GRAYSON, M.D.,

my Sweetheart



Although potassium thiocyanate is rarely used now for the treatment of hypertension, there are still occasional physicians who, because of their experience, feel that in their hands the treatment of patients with high blood pressure can best be affected with this drug. This is evidenced by the present report of a case of severe anemia secondary to potassium thiocyanate therapy.

It is felt that, because of the extreme seriousness of the toxic manifestations of potassium thiocyanate administration in some patients, it is of importance to report the following case of intoxication due to

this drug. This report and the review of the literature on potassium thiocyanate which follows will be of interest to those physicians who still use the drug and to those physicians, also, who occasionally may be called upon to treat patients who suffer from the toxic manifestations which may be thereby induced.

CASE REPORT

The patient, Mrs. T. A., age 66, was first admitted to the Perry County Memorial Hospital October 13, 1956, in severe cardiac decompensation. On admission, it was noted that in addition to her signs of pulmonary edema she also suffered from extreme anemia.

On admission, the hematocrit was 23 mm. (Wintrobe), the leucocyte count 8,900, and the hemoglobin 7.5 grams. The differential count was: Stabs 8; Segs 68; and Lymphs 24. Examination of the red cells on the peripheral blood smear revealed that the erythrocytes were normocytic and normo-chromic. (The normal appearance of the red blood cells was the first clue that the anemia was not due to chronic blood loss.)

PAST HISTORY: The patient stated that she had known of her high blood pressure for 20 years and that her systolic pressure occasionally went as high as 240 millimeters of mercury. She had suffered a stroke 5 years before.

Several days after the patient's admission and therapy for pulmonary edema, a conference with her family physician revealed that he had been administering potassium thiocyanate in the customary dosages to her for the previous month because of her hypertension. In retrospect, it was decided that her symptoms of weakness, pallor, dyspnea, orthopnea, and chest pain began shortly after this therapy had been initiated. It is to be noted that potassium thiocyanate blood levels were not available to the patient and were not performed during her therapy.

Because of the delay in the receipt of the information regarding the thiocyanate, it was felt that blood levels for thiocyanate would not be helpful. Therefore, these tests were not performed in the hospital.

The patient was treated with the usual therapy for pulmonary edema and gradually recovered. Her recovery was hastened by the administration of packed red blood cell transfusions.

A bone marrow examination performed three days after admission revealed a perfectly normal and active bone marrow. Repeated peripheral blood studies during the first hospitalization revealed no evidence of a blood dyscrasia.

Therefore, after recovery from her cardiac decompensation and after correction of her anemia with packed blood cell transfusions, the patient was discharged under her family doctor's care October 27, 1956.

SECOND HOSPITAL ADMISSION

The patient was readmitted to the

hospital January 15, 1957 in much the same condition that she was in on her first admission. She complained of dyspnea for 1½ weeks and anterior chest pain off and on for the same period of time which was getting worse. She also gave a history of not having taken her Digitalis since her discharge from the hospital previously.

In addition to this, she stated that she had had a gradual onset of pallor in recent weeks. Her dyspnea this time was out of proportion to her physical signs. Her physical signs, essentially, were as follows: Extreme air hunger relieved inadequately by the administration of oxygen, a heart rate of 88 which was regular, and rales in the left base. The patient also had a severe cough which was, on several occasions, productive of blood. In view of the essentially normal electrocardiogram and also in view of an episode of severe pleuritic pain in the right chest with dyspnea and hemoptysis one week later, it was decided that the episode which caused her emergency hospitalization this time and the recurrent chest pain and dyspnea later were due to pulmonary emboli. There were no leg signs of thrombophlebitis, however.

The importance of this case study, however, lies in the blood picture and in the renal disease. On admission the second time, her red count was 3,870,500, hemoglobin 70% (10.5 grams), and hematocrit 29 millimeters. The white count and differential again were normal. Thus, it is apparent that her red count again fell following discharge despite the fact that it had been brought to normal by transfusions the first time.

The urinalysis on admission showed two plus albumin and 10 red blood cells per high powered field. The urea nitrogen was 27 milligrams percent (normal 9-15). Further transfusions of packed red blood cells returned the patient's hematocrit and red cell values to normal.

However, continued studies of the urine revealed many casts, white cells per high powered field. The A concentration-dilution test revealed no evidence of concentrating power by the renal tubules. An intravenous pyelogram showed no visualization of the renal pelvis. The diagnosis of nephritis (probably acute) thus was definite.

FINAL COURSE: An upper and lower GI Series was performed to rule out the possibility of any bleeding lesion, and these studies were reported as normal. The patient recovered from her pulmonary emboli after adequate anticoagulant therapy along with the application of elastic stockings to both legs.

She was finally discharged from the hospital on February 8, 1957 in excellent condition. She was ambulant, breathing well, and was asymptomatic. The hematocrit was 37 millimeters.

She has been followed weekly to the date of this writing and her hematocrit has continued to improve upon the administration of oral and parenteral hematinics.

DISCUSSION

It will be seen from the discussion which follows that anemia is one of the toxic manifestations of potassium thiocyanate therapy. It is apparent, moreover, from the foregoing case report that there was no other etio-

logy of this patient's anemia which could be discovered. She had a normal bone marrow and no evidence of bleeding from the upper or lower GI tract or from any other site. There also was no evidence of any other blood dyscrasia.

The author is aware that nephritis can produce a similar type of anemia. The evidence in the present case is not sufficient to incriminate the kidneys, however. For the purpose of illuminating the theme of thiocyanate intoxication, it will be assumed that thiocyanate was the etiology involved. It is possible, however, that the cause could have been the combination of renal and thiocyanate-induced anemia.

It will also be seen in the review which follows that chronic renal disease is a contraindication to thiocyanate therapy. This patient possibly had chronic nephritis which had become exacerbated at the time the thiocyanates were first begun. The type of nephritis is undetermined. It could be argued that it was either chronic glomerulonephritis or chronic nephrosclerosis but the difference remains academic. The point is that in the presence of chronic renal disease of such gravity, the titer of thiocyanate ion will rise precipitously upon the usual dosage schedule and cannot be predicted in advance.

It will be noted that there were no thiocyanate levels done on this patient either during her therapy for hypertension or during her hospitalization for the toxic manifestations of that therapy. Therefore, it will be agreed that the diagnosis of toxicity is presumptive. Regardless of this, the probability of this diagnosis

serves to point up the serious dangers inherent in the use of thiocyanate and to remind practitioners that they may some day see patients with signs and symptoms referable to previous thiocyanate therapy.

REVIEW OF POTASSIUM THIOCYANATE HISTORICAL

Barnett reported, in 1951¹, that during the last half century medical observers have argued for and against the use of thiocyanate. "From a perusal of the voluminous literature that has accumulated, only two things seem firmly established: (1) Its effectiveness either as a symptomatic remedy or as a drug useful in reducing blood pressure is by no means generally accepted. (2) Toxic manifestations are relatively common."

Apparently, thiocyanate fell into disrepute about 1925 but came back into favor again in 1936 when Barker described a rapid and easy chemical method of following the blood level accurately.

DOSAGE AND ADMINISTRATION

Freis² states that it is impossible to predict the dosage required by any patient from the surface area or other available criteria; the dose required to maintain a therapeutic blood level varies from 0.2 to 0.6 grams of potassium thiocyanate daily. He states, "Therefore, under no circumstances may thiocyanate be administered unless there are laboratory facilities available for determining the serum levels of the drug."

Gorman³ states that "the drug is given by mouth in 0.2 gram doses

sufficient to maintain a blood level of 5 to 14 mg. percent."

PHARMACOLOGY

The thiocyanate ion is similar in effect to the iodide ion. When ingested, a high percentage of the drug is distributed to the extracellular fluid and thus influences the colloids in a similar manner to the iodides and other haloids. It is excreted chiefly by the kidneys but more slowly and less completely than are the haloids.

Potassium thiocyanate has a sedative action in moderate dosage. In lethal doses, it is irritating to the anterior horn cells.⁴

EFFECT ON HYPERTENSION

Ruskin and McKinley, in 1957, in a comparative study of potassium thiocyanate and other drugs in the treatment of essential hypertension, concluded that statistically it was possible to demonstrate that the thiocyanate period of therapy when compared with the placebo-therapy interval showed significant drops in systolic and diastolic blood pressures. The diastolic pressures, at least, fell more markedly at serum levels of potassium thiocyanate above rather than below 15 mg. percent. They concluded from their study that its administration is clinically hazardous and unreliable. They stated that the occasional marked drop in blood pressure due to potassium thiocyanate may, apart from any toxicity, cause relative cerebral, renal, and myocardial eschemia.⁵

Gorman³ stated: "In hypertension, thiocyanate reduces the systolic and diastolic blood pressures by 60 and

40 mm. respectively, is effective against headache, and may produce a feeling of general well being." He stated in addition, however, that weekly blood assays are to be made and the patient closely observed for signs of toxicity.

TOXICITY OF THIOCYANATE

The toxicity of potassium thiocyanate is so varied and serious that generally at the present time the drug is not used. It will be noted that the dosage of the drug is uncertain, the blood levels of the drug are unpredictable, the effects of the drug are unreliable, and the toxic manifestations of the drug may be fatal in patients who have had a supposedly normal amount of the drug and who have normal blood levels of thiocyanate.

It will be instructive to quote directly the following statement from a review of the situation in the *Journal of Gastroenterology* in 1949.⁶ "There have been a number of cases of fatal poisoning with thiocyanates and what is most disturbing is that in a number of these the total dosage was low. In eight cases, the amounts given were between 3 and 25 grams total. The sad feature is that in several cases death has resulted when the blood level was within the supposedly safe range.

"In three fatal cases, the titer in the blood was 3.3, 4.2, and 7.0 mg. per 100 cc. The usual symptoms of toxicity at the beginning are dermatitis, psychotic manifestations, enlargement of the thyroid, thrombophlebitis, and convulsive twitchings. Sometimes, coryza-like symptoms appear. There may be pruritis,

a maculopapular eruption, and exfoliative dermatitis. There may be edema of the glottis and larynx. In most of the fatal cases there has been confusion, hallucinations, delusions, and psychomotor agitation."

Gorman³ reviewed 28 articles on thiocyanate in 1945 and listed the following toxic symptoms in the order of their appearance: (1) Muscular fatigue, (2) Nausea and vomiting, (3) Disorientation, (4) Mental confusion, (5) Motor aphasia, (6) Hallucinations of sight and hearing, (7) Delirium, (8) Convulsive twitchings, (9) Death.

Psychosis is extremely common in intoxication with thiocyanate: Almost all fatal cases have been preceded by confusion, hallucinations, delusions, and psychomotor agitation. Others have described the goitrogenic action of thiocyanate. There have been reported acute diffuse goitre with pain and myxedema as well as acute enlargement of an adenomatous nodule of the thyroid and chronic diffuse goitre. Thiocyanate produces goitre by a mechanism similar to that of thiouracil.

The skin manifestations of toxicity include pruritis, a maculopapular eruption, and exfoliative dermatitis.

One patient who received 18 grams of thiocyanate in six weeks developed a skin rash with a high eosinophilia and died. At autopsy, a Fiedler's myocarditis was found.

Kotte⁷ stated that thiocyanate reduces the blood cholesterol, the serum protein, and the red cell count.

Kessler and Hinds⁴ reported that occasionally with serum levels less than 12 mg. per 100 cc. the follow-

ing symptoms occurred: Weakness, fatigue, depression, exhaustion, somnolence, apprehension, nervousness, nightmares, tinnitus, pruritus, dry skin, various dermatitides, nausea, vomiting, abdominal pain, diarrhea, anemia, and goitre.

They also stated that with levels higher than 12 mg. per 100 cc. other more serious effects occurred, such as: Fever, loss of hair, angina, purpura, gastric hemorrhage, vertigo, twitching, convulsions, disorientation, confusion, slurred speech, hallucinations, unsteady gait, motor aphagia, paralysis of the lower extremities, exfoliative dermatitis, collapse, coma, and death.

ANEMIA CAUSED BY THIOCYANATE

Lindberg, et al.⁸ gave twelve normal dogs potassium thiocyanate orally in 5 gram doses. Observation of the blood thiocyanate content at frequent intervals was the guide to daily dosage for the maintenance of toxicosis. They reported that the fall in the erythrocyte count and hematocrit level in their series of dogs was striking. The gradient in most cases was very gradual. In several instances, there was a brief initial rise in the hematocrit value before the fall commenced. The progress of the reduction of the erythrocyte count and the hematocrit value was slow and prolonged, persisting at least beyond the limits of these experiments and long after the thiocyanate had been stopped.

Following the cessation of administration of the drug, there was a slowing of the fall in the erythrocyte count on actual arrest of the fall. The hematocrit value which

showed a much wider response tended to stabilize more quickly after the blood was cleared of thiocyanate. In attempting to classify this type of anemia, they found that there was a definite fall in hemoglobin, hematocrit reading, and erythrocyte count. The color index and volume index ran somewhat less than 0.8. The Price-Jones curves showed a tendency to the left. The differential leukocyte count was normal. The polymorphonuclear leukocytes and other cells of the granulocytic series were normal despite the intoxication. The reticulocyte count was normal; there was no change in the fragility of the cells.

It is to be noted that the above description of the onset of the anemia and of the type of anemia which was present experimentally is completely compatible with the history of the anemia in the case reported upon in this paper. This is further presumptive evidence of the etiology of the anemia.

CONTRAINDICATIONS

Severe renal damage is generally regarded as a contra-indication. In these cases, the drug is apt to accumulate rapidly and may soon reach the toxic level. The danger of toxic effects is said to increase with age.⁹

Connell, et al¹⁰ stated that they believe that thiocyanate is contra-indicated in patients over 60 and also in patients with cardiac or cerebral complications. Also, patients with failing renal reserve may commence suddenly to accumulate the thiocyanate; and this has led to severe intoxication and death within a few days in some cases.

In patients who cannot have blood estimations performed at regular intervals, the treatment is contraindicated.

SUMMARY

An unusual case of severe anemia which was responsible for acute cardiac decompensation is reported. The anemia, in the present case, apparently was due to potassium thiocyanate administration in an aged patient with chronic nephritis and poor renal reserve.

A review of the literature is presented to indicate the catastrophic effects which may be produced by poisoning from potassium thiocyanate therapy and to list the varied symptoms and signs that may be produced.

The production of a severe anemia in humans has been infrequently reported but has been adequately studied in animals.

It is concluded, on the basis of this case study and review of the literature, that potassium thiocyanate therapy is too hazardous for use in the therapy of hypertension. Its use can no longer be recommended in any case of hypertension in view of the probability that the risk of the therapy is greater than the risk of the disease.

Physicians should be warned when they see new patients for the first time who have hypertension and who may have strange signs and symptoms that seem unexplainable, they should keep in mind the possibility of previous thiocyanate therapy.

12 S. Jackson St.
Perryville, Mo.

BIBLIOGRAPHY

1. Barnett, H. J. M., et al.: Thiocyanate psychosis, *J.A.M.A.* 147: 1554-1558 (December 15) 1951.
2. Freis, E. D.: Recent advances in the medical treatment of essential hypertension with particular reference to drugs, *Medical Clinics of North America*, page 1251, September 1948.
3. Gorman, W. F., et al.: Toxicity of thiocyanate used in treatment of hypertension, *Annals of Internal Medicine* 30: 1054 (May) 1945..
4. Kessler, D. L. and Hinds, L. E.: Hazards of thiocyanate therapy in hypertension, *J.A.M.A.* 138: 549-551 (October 23) 1948.
5. Ruskin, A. and McKinley, W. F.: Comparative study of potassium thiocyanate and other drugs in the treatment of essential hypertension, *American Heart Journal* 34: 691-701 (November) 1947.
6. *Gastroenterology*, *J.A.M.A.* 31: 471 (November) 1949.
7. Kotte, H.: Therapy of experimental hypertension with potassium thiocyanate, *Ohio State Medical Journal* 39: 1943.
8. Lindberg, H. A., Wald, M. H., and Barker, M. H.: Observations on the pathologic effects of thiocyanate, *American Heart Journal* 21: 605-611 (May) 1941.
9. Watkinson, G. and Evans, G.: Potassium thiocyanate for hypertension, *British Medical Journal* 4504: 95 (May 3) 1947.
10. Connell, W. F., Wharton, G. K., and Robinson, C. E.: Thiocyanate therapy, *Canadian Medical Association Journal* 62: 20 (January) 1950.

CHEMOTHERAPEUTIC AGENTS used in treatment of urinary tract infection are so potent that frequently the urine is sterilized before the urinary tract lesion heals. Consequently, treatment with reduced drug dosage must be continued for 7 to 10 days after urine cultures are negative.—*Leberman, Intl. Rec. Med.* 169:557, 1956.

new... a more potent, longer-acting progestational agent

DELALUTIN

SQUIBB 17-ALPHA-HYDROXYPROGESTERONE CAPROATE

a single injection provides sustained progestational activity for approximately 2 weeks, when enough estrogen is present, simulating endogenous progesterone production.

Vials of 2 and 10 cc. Each cc. provides 125 mg. of 17-alpha-hydroxyprogesterone-caproate

Comparative effect of single subcutaneous injection of Delalutin and progesterone on the progestational changes (Clausberg Test) in the rabbit uterus



SQUIBB



Squibb Quality—the Priceless Ingredient

*DELALUTIN® IS A SQUIBB TRADEMARK.

for quicker recovery

STRESSCAPS*

Stress Formula Vitamins Lederle

STRESSCAPS provide adequate vitamin supplementation for patients suffering from prolonged stress—surgery, burns, fractures, trauma or shock.

Stress Formula Vitamins promote wound healing, and stimulate antibody production as well as providing a nutritional reserve of water-soluble vitamins.



dry-filled sealed capsules (a Lederle exclusive!) for more rapid and complete absorption.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK



*REG. U.S. PAT. OFF.

