

MERCUHYDRIN SENSITIVITY

REPORT OF A CASE

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MERCURIAL diuretics have become indispensable therapeutic agents in the management of congestive heart failure. Fortunately, the incidence of undesirable reactions resulting from their use is low, and the majority have taken place after intravenous injection.¹

Recently we have observed a systemic allergic reaction to the intramuscular administration of Mercuhydrin. This compound,² which became available for clinical use in 1945, is the sodium salt of meralluride (mercurated allylsuccinyl-urea) and theophylline. Each cubic centimeter contains the equivalent of 39 mg. of mercury in organic combination and 48 mg. of theophylline (U.S.P.). Its chief advantage has been the absence of irritation upon intramuscular injection, although administration by this route has not prevented entirely the occurrence of severe reactions. Even so, the relative safety of this drug is attested by the paucity of unfavorable clinical reports in seven years of extensive use.

CASE REPORT

P. S. M., a 68-year-old male school principal, was admitted to St. Luke's Hospital on Dec. 18, 1949, in congestive cardiac failure due to arteriosclerotic and hypertensive heart disease. There was a history of generalized urticaria in 1944 following the use of sulfanilamide, but this episode had been the only manifestation of allergic disease.

The patient was an extremely large man of more than six feet and well over two hundred pounds. The temperature was 98.2° F., the pulse 68, and the blood pressure 180/66. He was dyspneic on the slightest exertion and when flat in bed. Examination disclosed pallor of skin and mucous membranes, distended neck veins, cardiac enlargement, forceful heart sounds, a soft systolic murmur at the apex and over the base, regular rhythm with occasional extra-systoles, signs of considerable fluid in the right pleural space, an enlarged liver extending well below the costal margin, marked edema of the abdominal wall, sacral region, and thighs, and massive swelling of the lower legs and feet. The rectum contained large internal hemorrhoids, one of which was thrombosed. Proctoscopy revealed no abnormality as far as the sigmoid flexure. Hematologic study revealed a moderately severe hypochromic anemia which had apparently been produced by chronic blood loss from the hemorrhoids. Immediate supportive measures and hemorrhoidectomy later were sufficient to correct this abnormal state. Other laboratory data included a normal leukocyte count and differential, a normal urinalysis, and stools positive for occult blood. Blood chemical determinations gave values of 34 mg. per 100 ml. for nonprotein nitrogen, 5.6 Gm. per 100 ml. for total protein (albumin, 3.4, globulin, 2.2), and 7 units for icteric index. Electrocardiographic interpretation indicated nodal rhythm, myocardial degeneration, and digitalis effect. Chest roentgenogram confirmed the impression of a large right hydrothorax and generalized increase in size of the cardiac shadow. Barium study of the entire gastrointestinal tract failed to demonstrate any abnormality.

The usual measures for treatment of heart failure were instituted and a maintenance dose of digitalis was continued. The admission weight was 245 pounds. Two milliliters of Mercuhydrin were given intramuscularly on the first and second hospital days; 1 ml. on the third and

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fourth. There was excellent diuretic response, twenty-seven pounds being lost during a five-day period. One liter of straw-colored fluid was aspirated from the right pleural space the day after the patient was hospitalized.

A fifth dose of Mercuhydrin (1 ml.) was administered intramuscularly at 10:00 A.M. on December 23, the sixth day after the initial injection. Ten hours later at 8 P.M. there was a shaking chill. The patient became intensely cyanotic, extremely dyspneic (lungs were clear except for residual fluid in the right pleural cavity), apprehensive, confused, and incontinent of urine. Morphine and oxygen were administered immediately. The acute symptoms subsided within an hour. However, the temperature had risen to 102.8° F. at 10:00 P.M. By 4:00 P.M. of the next day the temperature had receded to 99.6° F. and continued at about this level for twenty-four hours, being entirely normal thereafter. The nonprotein nitrogen was 40 mg. per 100 ml. on December 24 and the patient appeared to have completely recovered. The significance of this episode was not accurately interpreted.

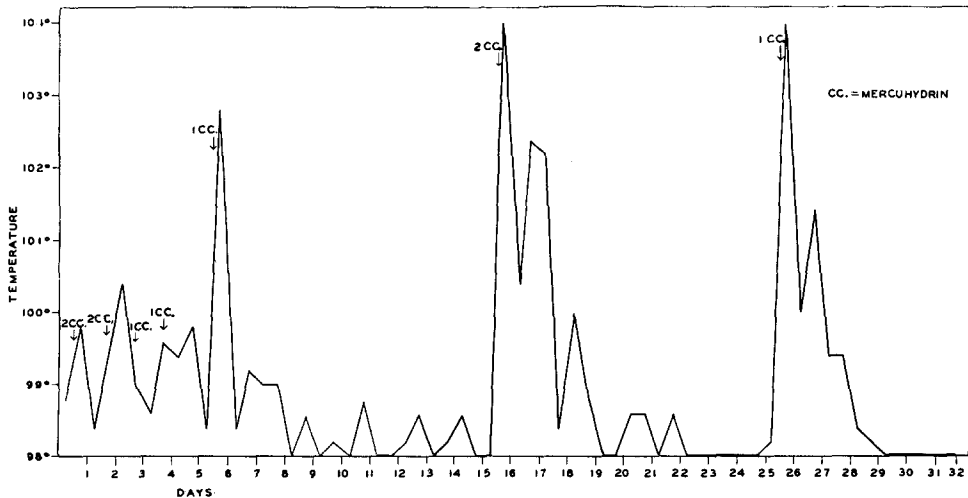


Fig. 1.

The course was uneventful and no fever was recorded until January 3, the sixteenth hospital day. On this date the temperature at 8:00 A.M. was 98° F. Two milliliters of Mercuhydrin were injected intramuscularly at 10:30 A.M. Approximately three hours later, at 1:40 P.M., the patient was suddenly seized with a severe, hacking, nonproductive cough. There followed in rapid succession a shaking chill, intense cyanosis, shortness of breath (the lungs remained clear), and mental confusion. The blood pressure was 150/0. Oxygen and morphine relieved the symptoms promptly. The temperature rose progressively to a peak of 104° F. by 8:00 P.M. and remained at this level for five hours, gradually receding to 100° F. by the next morning. Another rise occurred on January 4 to 102.4° F., but by 4:00 P.M. of the following day the temperature had returned to a normal level. Moderately severe hiccoughs developed on January 4. There appeared to be complete recovery by the afternoon of January 5. Again the significance of this reaction was not fully understood.

Subsequently, the patient was afebrile and without symptoms. Because of a gradual weight increase to 225½ pounds, 1 ml. of Mercuhydrin was again injected intramuscularly at 11:30 A.M. on January 13, the twenty-sixth hospital day. He complained of chilliness two hours later at 1:35 P.M. When examined at 2:30 P.M., he had vomited copiously, was undergoing a shaking chill, and appeared exceedingly apprehensive. There was intense cyanosis and marked dyspnea. He gave the appearance of one who was about to expire. The blood pressure was recorded as 160/40. The pulse was 96 and grossly irregular. The respiratory rate was 32. Oxygen was started and morphine was given immediately. Within an hour the

patient was considerably improved, cyanosis and apprehension having subsided, and the respiration was less rapid. The lungs were clear at all times. The temperature rose to 102° F. at 4:00 P.M. and reached a peak of 104° F. at 5:00 P.M. The fever then subsided gradually, being 100° F. at 7:00 A.M. on January 14. There was a second rise to 101.4° F. at noon on this date but a return to normal by 8:00 P.M. Again there was complete recovery.

We were now convinced that further administration of Mercuhydrin would be most hazardous. Consequently, no reaction occurred during the remainder of his stay in the hospital. The patient was discharged on Feb. 2, 1950.

During the ensuing year the patient remained well compensated and ambulatory on salt restriction, digitalis, xanthines, and ammonium chloride. These measures have not been sufficient, however, in recent months. When it became evident that mercurial diuresis would be necessary again, Salyrgan-Theophylline was given intramuscularly in gradually increasing dosage from 0.1 ml. to 1 ml., and at the time of writing this drug was being administered in a dosage of 1 ml. every two to four weeks. There has been no reaction and the diuretic effect has been excellent. It will be noted that Gelfand's³ patient also tolerated Salyrgan intramuscularly without evidence of hypersensitivity after similar violent reactions to Mercuhydrin.

The striking febrile reaction, the associated cardiorespiratory and cerebral symptoms which followed by several hours the intramuscular injection of 1 ml. of Mercuhydrin on the sixth day after the first dose of this drug, and the occurrence of identical febrile reactions after each subsequent injection indicate that our patient had become sensitized to Mercuhydrin.

The patch-abrasion test⁴ was utilized in an attempt to establish more specifically an allergic basis for the clinical manifestations observed. This procedure produced no local or systemic effects to full strength ampule solution of Mercuhydrin. Since it was not carried out until twelve months after hospital discharge the failure to elicit a positive response may possibly have been due to delay in testing.

Approximately twenty-seven months had elapsed since the third and last violent febrile paroxysm when, in accordance with the Leftwich technique¹⁰ as successfully used by Gelfand,³ we obtained blood serum from a patient receiving Mercuhydrin intramuscularly for the treatment of chronic heart failure. The intradermal injection of 0.05 ml. of this serum into the skin of the right forearm of our patient produced within fifteen minutes an area of edema with surrounding erythema and even small pseudopodia, which persisted for approximately twenty minutes before beginning to fade. Normal serum injected simultaneously in the opposite forearm as a control caused only a transient erythema which disappeared rapidly. From the result of this investigation it would seem logical to conclude that our patient remained allergic to Mercuhydrin for more than two years after the sensitizing dose.

COMMENT

Reactions resulting from acquired sensitivity to Mercuhydrin have been reported in eleven patients. Cohn⁸ observed four; Wallner and Herman,⁷ two; Modell, Gold, and Clarke⁵; Gelfand,³ Fineman and Rosenberg,⁶ Shatan,¹ and Reeves,⁹ one each. There was one fatality.⁷

Typical of this group is the patient observed by Gelfand³ who developed apprehension, difficulty in breathing, palpitation, choking, chest oppression, chills, fever, and sweating after Mercuhydrin intramuscularly, but was able to tolerate Salyrgan without reaction. Reducing the dose of the drug did not alter the patient's response, thus indicating, Gelfand believes, a qualitative allergic effect rather than a quantitative toxic one. As in our patient, Mercuhydrin had been administered a number of times before any untoward signs appeared. Direct skin tests with undiluted ampule solution of Mercuhydrin and Salyrgan gave negative results. The Leftwich technique,¹⁰ in which blood serum obtained from another patient previously treated with Mercuhydrin was used for testing, provoked a positive skin reaction with marked erythema and pseudopodia.

From a review of these eleven cases certain outstanding features can be listed:

1. Febrile paroxysms usually accompanied by chills occurred repeatedly in seven patients.^{1, 3, 5, 6, 7, 9}

2. Cutaneous phenomena appeared in a few instances.^{6, 7, 8} The Negro woman reported by Fineman and Rosenberg,⁶ in addition to febrile reactions following the eleventh, thirteenth, fourteenth, fifteenth, and sixteenth injections, developed an exfoliative dermatitis which lasted two to three weeks. Wallner and Herman's⁷ patient had a transient cutaneous erythema on two occasions before the fatal dose. In one of Cohn's⁸ cases there appeared a diffuse erythematous rash which progressed to exfoliation.

3. Reactions do not follow the initial injection but occur at variable intervals, usually six to seven days, thereafter. Often during this period there have been several well-tolerated doses. Gelfand³ is of the opinion that "the preliminary administration of the drug sensitizes the patient, thus setting the stage for the outburst of the allergic response."

4. The severity of toxic response is independent of the amount given.

5. Mild subjective symptoms, slight temperature rises, and transient cutaneous eruptions must be considered as danger signals, sufficient to warrant discontinuance of the drug. Acute specific febrile reactions obviously contraindicate its further use.

6. Hypersensitivity to Mercuhydrin may not necessarily extend to other mercurial diuretic drugs. Salyrgan,³ Mercupurin,⁵ and Thiomerin⁹ have been administered successfully to patients who previously reacted violently to Mercuhydrin.

7. Skin testing in patients who have developed sensitivity is rarely helpful.

8. A desensitization program may be successful as Shatan's¹ case has demonstrated. After being desensitized this patient tolerated Mercuhydrin without ill effect once or twice weekly until his death from heart failure six months later.

Mercuhydrin is an excellent product and one of several which play an exceedingly important role in the treatment of heart failure. We do not wish to convey the impression that its exhibition in clinical practice should be curtailed. However, it behooves us to be aware of the potential allergenicity of this drug when administered by the intramuscular route and to familiarize ourselves with the undesirable effects which occasionally may be severe and serious.

SUMMARY

1. A patient who experienced violent delayed febrile reactions after the fifth, sixth, and seventh intramuscular injections of Mercuhydrin has been reported.

2. The literature dealing with the manifestations of acquired hypersensitivity to intramuscularly administered Mercuhydrin has been reviewed.

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