Hypersensitivity to Mercuhydrin

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Specific hypersensitivity to the mercurial component of meralluride sodium was induced by a series of intramuscular injections in 12 patients who were being treated for congestive heart failure. Reactions were characterized by fever and systemic symptoms and were precipitated in hypersensitive patients by minute amounts of the drug. No untoward effects resulted from administration of full therapeutic doses of two other mercurial diuretics. Reactions appeared to be modified or inhibited by the action of tripelennamine hydrochloride and British anti-lewisite (BAL); eventual disappearance of the allergic response was demonstrated in two patients.

Recent accent on the use of mercurial diuretics in the treatment of congestive heart failure has made it increasingly apparent that these preparations occasionally induce unfavorable side effects. The manifestations of toxicity have been attributed, in various instances, to the direct effect of the mercurial drug on the myocardium, to disturbances in water and electrolyte metabolism, to mobilization of digitalis from extracellular fluid, to the protoplastic toxicity of the mercury ion, and to the specific sensitivity to the material used. Information concerning reactions of an allergic nature1-10 has been confined largely to isolated reports of cases in which urticaria, erythematous eruptions, exfoliative dermatitis, chills, fever, bronchial asthma, or anaphylactoid collapse occurred after the injection of an organic mercurial compound. The present report concerns 12 patients in whom hypersensitivity to Mercuhydrin (meralluride sodium), manifested by systemic reactions, developed during treatment for congestive heart failure.

Material and Results

The age of the 12 patients ranged from 48 to 71 years. Five had arteriosclerotic heart disease, three hypertensive heart disease, and two rheumatic heart disease. A precise etiologic classification was not possible in two cases. The treatment employed included a diet containing not more than 500 mg. of sodium, a fluid intake of 2000 to 3000 cc. daily, adequate digitalization, and daily intramuscular injections of the mercurial diuretic. There was satisfactory diuresis in all patients, and no untoward symptoms were noted for an average of nine days (range 6 to 13 days), by which time an average of 13.5 cc. (range 6.5 to 19) of Mercuhydrin had been administered. Patients were usually free from demonstrable edema prior to the first reaction after having lost 7 to 26 pounds in weight.

In each of the 12 patients, a reaction characterized by fever and systemic symptoms occurred after 6 to 11 injections of Mercuhydrin, and recurred after each subsequent administration of the drug. (See fig. 1.) The temperature rose to an average of 102.6 F., and in each instance returned to normal within 24 hours. The time interval between the injection and the peak of the febrile reaction averaged 6.2 hours. In one case fever was noted within one hour. Eight patients experienced chills, and profuse sweating frequently accompanied the fever. Anorexia was usually present, and five persons reported nausea. Vomiting occurred in three of the latter. Eight patients complained of general malaise and aching in the legs. Transient erythema of the skin most noticeable over the face, neck, and upper trunk appeared in five patients. Three patients had vague anterior chest pain and three others dyspnea. In all instances the symptoms subsided within 12 to 18 hours.

Measurements of the serum sodium in five cases gave normal values in all. The blood urea was measured in seven patients and was found to be elevated in only one. This patient reacted more violently than any of the others. Minute amounts of Mercuhydrin were given

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to six patients, 0.05 cc. to five patients and 0.01 cc. to one. In each instance, the resulting reaction was only slightly less severe than that which followed conventional therapeutic doses. The elevation in temperature averaged 101.6 F. and the systemic complaints were the same as in the patients' earlier reactions.

Mercuhydrin is supplied in the form of a sodium salt, each cubic centimeter of which contains 39 mg. of mercury in organic combination with 48 mg. of theophylline. A solution containing 48 mg. of theophylline sodium per cubic centimeter was obtained, and 2 cc. of this preparation was administered to eight patients who had experienced repeated reactions to Mercuhydrin. In none of these did a systemic or febrile response occur.

Mercuzanthine (mercuphylline) was administered by intramuscular injection to three of the patients, and Thiomerin (mercaptomerin sodium) to each of the 12 in doses of 1 cc. or 2 cc. In no instance did a reaction occur.

Fifty milligrams of BAL was given by intramuscular injection to one patient two hours before administering 1 cc. of Mercuhydrin. Mild malaise and nausea were experienced but there was no febrile response. A second patient was given a similar dose of BAL at the same time as the diuretic drug, and no reaction was observed.

One patient was studied again two months after having demonstrated sensitivity to Mercuhydrin and, at that time, 1 cc. of the drug caused a rise in temperature to 102.4 F. On the following day, a similar dose was given and Pyribenzamine (tripelennamine hydrochloride) was administered orally in 50 mg. doses every four hours for four doses, the first dose being given at the same time as the diuretic. The temperature reached a maximum of 99.4 F.

Two patients, each of whom had repeatedly experienced reactions to Mercuhydrin, even in small test amounts, were given gradually increasing doses of the drug 12 months after the original study. Neither experienced a reaction.

CASE REPORTS

The following abstracts of the reactions in three patients are presented to illustrate the phenomenon described and typify the observations made on the other patients in the group.

Case 1. Figure 2 demonstrates the febrile response to Mercuhydrin administered to a 57 year old white man who had severe hypertension, hypertensive and arteriosclerotic heart disease with cardiac enlargement, auricular fibrillation, and congestive failure and who had been experiencing paroxysmal nocturnal dyspnea. The daily temperature was normal prior to the period illustrated in the graph, which begins with the fourth hospital day. Of particular significance are the low grade elevations of temperature following the daily administration of Mercuhydrin prior to the tenth hospital day, at which
time it was decided to give the diuretic on alternate days. Normal temperature was maintained throughout the tenth and twelfth hospital days, on which no diuretic was given, but significant elevations followed the injections on the eleventh and thirteenth days. On the fourteenth, fifteenth and sixteenth hospital days, the patient received 96 mg. of theophylline sodium, 2 cc. of Mercuazanthin, and 1 cc. of Thiomerin respectively with no reactions. On the seventeenth day, he was given 0.05 cc. of Mercuhydrin, and a fever of 101 F. resulted. On the eighteenth day he received simultaneous injections of 50 mg. of BAL and 1 cc. of Mercuhydrin without subsequent reaction. The next day he was given 0.5 cc. of Mercuhydrin alone and failed to experience a reaction.

**Case 2.** The patient whose reactions are presented graphically on figure 3 was a 49 year old woman who had arteriosclerotic heart disease with angina pectoris and angina decubitus. During the first seven days of hospitalization, she was given five doses of Mercuhydrin and no febrile response was noted. Despite the absence of fever, she had experienced ill described discomfort, which included pain in the chest and left shoulder, weakness, and generalized muscular aching, following the last few injections. The patient associated these symptoms with the receipt of the diuretic and the medication on the seventh hospital day. She recalled that she had experienced similar symptoms during a series of mersalyl injections six months previously. On the eighth hospital day she was given 2 cc. of Mercuhydrin at 9 a.m. and at 4 p.m. had a temperature of 103.5 F., chills, and severe muscular aching. This reaction was followed on the tenth, eleventh and twelfth days by injections of 2 cc. of Thiomerin, 96 mg. of theophylline sodium and 1.1 cc. of Mercuazanthin, respectively, none of which caused an untoward reaction. On the fourteenth day, the administration of 0.05 cc. of Mercuhydrin produced severe systemic symptoms and a fever of 103.2 F.

**Case 3.** A 50 year old white woman having rheumatic heart disease of functional class III with cardiac enlargement, aortic insufficiency, mitral stenosis and insufficiency, auricular flutter and mild congestive failure was hospitalized for treatment of the arrhythmia and decompensation. As represented in figure 4, she received Mercuhydrin intramuscularly at 9 a.m. daily for seven days prior to her first reaction on the sixth hospital day. The peak of the febrile response occurred at 4 p.m. and the reaction was characterized by a chill, diaphoresis, “drawing sensation” in the muscles and generalized malaise. Similar episodes followed the diuretic injections on the seventh and eighth hospital days. Mercuhydrin was discontinued on the ninth day. Fever-free days followed, during which she was given 96 mg. of theophylline sodium on the eleventh and 2 cc. of Thiomerin on the twelfth and thirteenth days. On the fourteenth day, she had a rather severe reaction following 0.05 cc. of Mercuhydrin but, on the following day, the injection of 2 cc. of Mercuazanthin caused no symptoms.

![Fig. 3. Case 2. Temperature reactions](image)

**Fig. 3. Case 2. Temperature reactions**

![Fig. 4. Case 3. Temperature reactions](image)

**Fig. 4. Case 3. Temperature reactions**

**DISCUSSION**

The fact that the reactions to Mercuhydrin occurred after a series of 6 to 11 apparently well tolerated injections suggested that they were due to hyponatremia or the development of hypersensitivity to the drug. Hyponatremia was not demonstrated in any case in which the serum sodium was determined. The development of typical reactions to minute amounts of the drug and the absence of any reaction to other mercurial diuretics support the hypothesis of specific hypersensitivity to the mercurial compound. The absence of reaction to theophylline sodium indicates that the hypersensitivity is to the mercurial component of the organic combination. The modification of the response to Mercuhydrin after the administration of Pyribenzamine, is further evidence of the allergic nature of the reactions.
British anti-lewisite has been reported to inhibit the diuretic effect of organic mercurial drugs, and to counteract the acute cardiac and renal toxicity of mercury in the laboratory. The administration of BAL also appears to prevent the development of typical hypersensitivity reactions to Mercuhydrin. The lack of reaction to Mercuhydrin on the day following administration of BAL in one case is difficult to explain.

Eventual disappearance of the allergic response was demonstrated in two patients. Hypersensitivity to Mercuhydrin was also observed by Gelfand in a patient whose reactions were similar to those described and in whom a positive skin reaction was elicited with blood serum from another patient who was receiving and tolerating Mercuhydrin. The skin reaction became negative several months after the cessation of therapy.

The administration of mercurial diuretics forms an integral part of the effective management of cardiac decompensation, and there are few contraindications to their administration. Although thousands of injections of these drugs have been given without observed adverse effect, there exists a small number of patients who develop sensitivity after multiple well tolerated doses. During the period from March 1949 to January 1951 more than 16,000 cc. of Mercuhydrin were dispensed at the direction of the Cardiovascular Department of the Cleveland Clinic, and the reported cases represent the total evidence of intolerance so far as we are able to determine. It is important that one be cognizant of the manifestations of hypersensitivity to mercurial diuretics and regard even mild reactions as an indication for re-evaluation of therapy. Failure to appreciate the danger of continued administration may well result in fatalities. If there is need for further diuresis in a patient who has become hypersensitive to a given preparation, simply changing to another product appears to be a satisfactory solution.

**SUMMARY**

The observations reported indicate that, in certain individuals, hypersensitivity to the mercurial component of Mercuhydrin is induced by a series of intramuscular injections of the drug. An investigation is in progress to ascertain whether or not the similar use of other mercurial diuretics will result in the development of analogous reactions.

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