Mercurial Diuretics: The Replacement of Parenteral Administration by a New Oral Preparation in Ambulatory Patients with Chronic Congestive Heart Failure

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Improvement in the usage of an effective therapeutic agent is highly desirable especially when the method of administration is simplified, the total dosage reduced, the toxicity of the drug diminished and the cost of medical care lessened. The replacement of parenteral injections of the mercurial diuretics by an oral preparation in ambulatory patients in chronic congestive heart failure represents a step forward in the management of this type of patient.

The induction of diuresis in chronic congestive heart failure by injection of mercurial preparations is the most rapid, effective and reliable method available today. Very often the control of the symptoms can be sustained only by so-called “maintenance doses” of the diuretic at frequent intervals. The chief hazards of this form of therapy arise because of hypotension and digitalis intoxication due to the mobilization and loss of fluid from body tissues. Because the widespread use of self-administered parenteral diuretics remains to be established many patients must seek the services of a doctor or nurse at frequent intervals.

In an attempt to overcome these objections, and yet retain the efficiency of the mercurial diuretics, oral preparations have been introduced. However, even this method has its drawbacks. To be effective, large doses of the drug must be ingested, the amounts used commonly causing nausea, vomiting, diarrhea, melena or stomatitis. The occurrence of uremia and other types of renal intoxication has been reported. Unpredictability of action still remains a problem. Because of these very real obstacles the search for a less objectionable oral mercurial diuretic continues.

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Methods and Materials

The purpose of this study was to attempt replacement of parenteral mercurial diuretics by a new oral drug labeled Ex 1431. Thirty-five patients who had been in congestive failure ranging in duration from 1 month to 11 years were observed at the Adult Heart Clinic of the Los Angeles County Hospital. There was no selection of patients. All were ambulatory, and most of them had been receiving maintenance doses of digitalis preparations, and had also been placed on low-sodium diets.

The dosage of the tablets varied; most often it was one tablet three times per day, twice weekly three or four days apart. Some patients received one tablet three times per day, once weekly, others three times weekly. On occasion one tablet twice daily, five days a week was given.

The period of observation varied from 1 to 11 months. At first patients were observed weekly for signs and symptoms of gastrointestinal or renal toxicity or other signs of intolerance, later they were seen at intervals of one month or more.

It is to be emphasized that prior to substitution by tablets, most of the patients had been receiving Mercuhydrin injections once or twice per week in order to control the congestive failure. The severity of failure was therefore of moderate to marked degree. Most patients were classified grade III C, or D, as to heart function and therapy according to American Heart Association standards.

The patients studied had advanced heart disease and significant limitation of physical activity. They were comfortable at rest. Their ordinary physical...
activity had been limited due to unusual fatigue, dyspnea, angina or palpitation. They had been advised to discontinue their more strenuous everyday activities and habits.

The etiologic types of heart disease listed in table 1 indicate the presence of the four most common types. Age groups include patients from the third decade through the ninth. There were 19 males and 16 females.

Criteria for Determination of Results

Table 1† shows details of the study and summary of results. The response to the oral drug was considered as having satisfactorily replaced the response to parenteral mercurial injections if there was clinical evidence of maintenance of “dry weight” and prevention of progression of the symptoms of congestive failure. In addition, the result was good if at the end of the period of observation functional classification was the same or better than at the time of substitution of therapy. In those patients who responded well, edema and rales were minimal or absent. Some of the patients had hepatomegaly due to chronicity of their failure. If this decreased in size or remained stationary along with the other criteria, the result was considered satisfactory.

The drug was a failure if congestive symptoms progressed, or reoccurred after having been in abeyance under previous injection therapy. If the patient showed signs of intolerance or toxicity the result was also classified as unsuccessful. Control of congestive failure by oral therapy for at least one month was required before the result was considered good. Many of our patients had been getting intramuscular Mercuhydrin four or eight times a month. If this number of injections could safely be avoided, we believed this to be worthwhile.

Results

On the basis of the above criteria, 28 of the 35 patients showed good response to the mercury tablets. (See table 1.) This is equivalent to 80 per cent of this series.

Analyzing the results further, it was noted that of 14 patients with rheumatic heart disease, 11 responded satisfactorily. Other etiologic groups represented in the successful category included three of four patients with arteriosclerotic heart disease, two with cor pulmonale, two with syphilis and hypertension, seven with hypertension. Of six patients with both hypertension and arteriosclerosis three showed good results.

† At the request of the Editor, table 1 is being omitted from the published paper. This table will be furnished upon request.

From the standpoint of age, 19 of the 35 patients were in the age group 50 to 70 years; 17 showed good diuresis. Two patients aged 20 to 29, and one aged 80 also showed good response.

In studying patients on the basis of duration of congestive symptoms, 11 patients responded well whose failure was from 5 to 15 years in duration, four patients in failure less than one year, and seven who had been failing from one to two years responded. Hence the effectiveness of the drug manifested itself in recent as well as longstanding failure.

Intolerance to the tablets was noted in six instances. The chief discomfort was gastrointestinal, consisting of cramping in the abdomen, nausea, occasional vomiting and diarrhea. A sour and burning sensation was noted in the mouth by one patient. It is interesting that another patient (case 9, table 1) noted that while parenteral mercurials had previously caused abdominal cramps, the oral form for a period of nine months did not do so, and that in general she felt “the best she ever has” since taking mercurial therapy. There was no evidence of renal injury.

Case Reports

Case 12. This patient had been getting mercurials for seven years. She developed congestive failure 11 years ago because of hypertensive heart disease. The number of injections summarized are: In 1944, 19; in 1945, 47; in 1946, 86; in 1947, 101; in 1948, 96; in 1949, 64; in 1950, 62; and in 1951, first seven weeks, 16.

She was placed on the tablets with a dosage equivalent to 10 mg. of mercury three times a day, twice a week; and for the 11 succeeding months was able to maintain “dry weight” as well as keep all symptoms of congestion in abeyance. There was no evidence of toxicity. She volunteered the information that she had “felt the best in a long, long time.” This case points out the ease of control in some patients with 60 mg. of mercury per week. On the basis of having received about eight injections a month prior to the initiation of oral treatment, it is estimated the oral mercurials during 1951 replaced about 96 injections. Even should this have proved one-half the estimated amount, the results with tablet therapy would be considered gratifying.

Case 13. This patient had shown a gradually progressive failure in the preceding 13 years. Mercury injections had been given intermittently for the
last five years. The congestive symptoms were especially severe in the four months prior to oral therapy. Weekly Mercuhydrin was necessary. She was given one tablet three times a day, twice weekly; later this dosage was increased to three times weekly. She was observed on this regimen for the succeeding 11 months, with evidence of good control, and absence of toxicity.

This case and case 9 illustrate the value of this new oral mercurial in instances of congestive failure of more than 10 years duration in middle-aged and elderly persons.

Case 10. This patient illustrates response to the drug in a patient with rheumatic valvular disease who had been in failure two years. In 1950 the patient had received 60 Mercuhydrin injections. In the first two months of 1951, just prior to tablet therapy, he was given 15 injections. For the following 10½ months he was given the tablets in dosage of 10 mg. three times a day, twice weekly. His weight decreased from 134 pounds to 129. Six months later his weight increased to 132 pounds; the liver was palpable three fingerbreadths below the costal margin. The dosage was then increased to 10 mg. three times a day, three times per week with improvement. This was maintained in the succeeding four months. Then his weight increased to 138 pounds and hepatomegaly recurred. He was given Mercuhydrin intramuscularly with return to previous weight. There was no toxicity while on oral therapy. Control of congestive symptoms for 10½ months in this instance indicated a satisfactory response. The probable replacement of 50 Mercuhydrin injections during 1951 is good therapeutics.

Case 24. A 60 year old hypertensive woman had been in failure three years. She had received Mercuhydrin twice weekly in the previous year. Three weeks after she was placed on oral therapy of 10 mg. three times a day, three times a week, sudden abdominal distention appeared. She was returned to Mercuhydrin twice weekly for two months with good results. She was then again started on the tablets, 20 mg. three times a day, three times per week. She did well for the following six months. Then she began to cough up bloody sputum and became increasingly dyspneic. Because of the suddenness of this occurrence she was given Mercuhydrin injections and symptoms were relieved. She did not show toxicity during the course of oral therapy.

This case illustrates the sudden storms in the course of congestive failure which can be better managed with the use of the injectable mercurial than by the oral form. However, the interim therapy with oral mercury was satisfactory.

Case 4. This patient had been in failure for one year, during which time he had been getting weekly Mercuhydrin injections. He was given 10 mg. in oral tablets three times a day, once weekly. After three and one half months his initial weight had been reduced from 172 pounds to 169, and there was no progression of failure. He then noted mild nausea and diarrhea. One month later, after deviating from his low salt diet, his weight increased to 173 pounds and ankle edema appeared. The dose of tablets was increased to 10 mg. twice a day for five days of the week. He began to complain of abdominal cramps and a “burning taste in the mouth.” He was unable to tolerate the increased dosage. He was given Mercuhydrin intramuscularly with relief of symptoms, and disappearance of his gastro-intestinal complaints.

This case also emphasizes the importance of continued subsidiary therapy, such as low-salt diet, along with the mercurial diuretics. Straying from his diet, in this instance, may have decreased the effectiveness of the diuretic drug. He also illustrates one type of toxicity seen in six of our patients. It was not severe, and decreasing the dosage or stopping the drug caused disappearance of toxic symptoms.

Case 16. This patient had been in failure four years. During the year before oral therapy he had received 40 Mercuhydrin injections. He was changed to tablets in dosage of 10 mg. three times a day, once a week. Two months later this was increased to two times a week. He continued satisfactorily for the succeeding five months, when recurrent rheumatic fever was suspected. He refused hospitalization, discontinued medication, and later died.

This case emphasizes the importance of patient cooperation. The necessity of close observation for factors other than inadequate dosage of the drug which contribute to progression of the congestive state, such as discontinuation of medication, or possible recurrence of rheumatic fever, is well illustrated.

There was no means by which one could determine beforehand which patient would be a favorable candidate for oral mercurial diuretics. Close observation of weight and changes in signs and symptoms is very important in determining the effect and adequacy of drug dosage. The most common effective dosage in this series was one tablet of 10 mg. of mercury three times a day, twice weekly three or four days apart. This could be increased to three times weekly, or be given twice a day five times weekly. We did not give the drug in daily continuous doses.

**Comment**

Ten years ago Batterman, DeGraff and Rose2 published their observations on an oral mercurial diuretic, Mercupurin-theophylline. Each tablet contained the equivalent of 30 mg. of mercury. They found the most effective dosage to be two tablets daily for an average
of 19 days.\textsuperscript{9} Successful diuresis was accomplished in 77 per cent of ambulant patients. However, toxicity occurred in 33 per cent of the same group. The most common toxic effect was digitalis intoxication following the diuresis. Gastrointestinal intolerance symptoms appeared in the form of nausea, vomiting and diarrhea. Two patients became uremic. In another study they reported 50 per cent toxicity with the same drug used in 13 patients.\textsuperscript{8}

Derow\textsuperscript{1} and Wolff\textsuperscript{32} reported "uniformly excellent results" in 11 patients, using Mercupurin tablets. Albuminuria and a variety of gastrointestinal symptoms including vomiting, bloody diarrhea, abdominal cramping and pains in gums and teeth were reported in 50 per cent of their case studies. One patient died of mercurialism. It was of interest to note that in spite of the above gastrointestinal symptoms the drug was continued, and in time the symptoms decreased or disappeared.

The interpretation of the gastrointestinal toxicity in oral mercurial therapy is confusing. Batterman and associates\textsuperscript{8} believed it to be due to digitalis, since on decreasing or stopping the digitalis, but continuing the mercurial, the symptoms improved or disappeared. On the other hand Derow and Wolff,\textsuperscript{32} without changing digitalis dosage, and still maintaining the oral Mercupurin, noted the same improvement in their toxic patients.

Another study of Mercupurin-theophylline was made by Vander Veer, Clark and Marshall.\textsuperscript{12} In 34 ambulatory patients they noted that 79.4 per cent showed good results. Fourteen patients or 41 per cent showed symptoms of drug toxicity. Five showed slight albuminuria.

Studies have also been reported on Salyrgan-theophylline.\textsuperscript{11, 14, 15, 16} Borg,\textsuperscript{11} studying ambulatory and hospitalized patients observed good results in 71 per cent. Toxicity was found in 35 per cent. Carryer and associates,\textsuperscript{14} using the same drug in a very brief study of hospitalized patients, reported toxicity in 22 per cent.

Shaffer and associates reported 60 to 70 per cent success in treating cardiac failure with Mercuhydrin-ascorbic acid tablets. Each tablet contained the equivalent of 19.5 mg. of mercury and they advised dosage of one to three tablets daily. Toxicity occurred in 25 per cent of the cases. It was primarily of gastrointestinal origin.

The findings in our series compare favorably with the above reports, although the comparisons cannot be absolute due to differing criteria of success among the various studies. It is of interest that Ex 1431 showed the lowest toxicity of any oral preparation. Only 6 of our 35 patients, or 14 per cent, developed toxic symptoms. The intolerance was gastrointestinal. There was no evidence of renal injury.

This relatively infrequent toxicity is probably due to the smaller amounts of mercury in this preparation. The average initial and maintenance dose was equivalent to 10 mg. of mercury three times a day, two or three times a week: a total of 60 to 100 mg. of mercury per week in divided doses. Batterman\textsuperscript{8} and his co-workers found that 60 mg. daily for 19 days was the most effective mercury dosage. This equalled 420 mg. per week. Derow and Wolff prescribed as high as the equivalent of 600 mg. of mercury per week, and on occasion gave the parenteral preparation with it. Vander Veer\textsuperscript{13} and his associates gave as much as 180 mg. daily for six weeks, or the total of 1200 mg. per week, in some instances.

Carryer\textsuperscript{14} could obtain diuresis with Salyrgan tablets only if the equivalent of 150 mg. of mercury were given daily. Using the same drug, Borg\textsuperscript{11} advises the equivalent of 180 to 270 mg. of mercury daily.

It is obvious that Ex 1431 achieves just as good results as other preparations, with less toxicity. It is our belief that Ex 1431 oral mercurial tablets are of value in the following situations and for the following purposes: (1) For the maintenance of "dry weight" and control over the symptoms of congestive failure after the initial acute phase has been treated with parenteral mercurials, along with other adjuncts of therapy. In the acute, suddenly changing, rapidly progressive phase of congestive failure the oral mercurials are too slow and unpredictable, and therefore unreliable.\textsuperscript{1} Once the peak of the storm has levelled off the tablets can be used for interim
“maintenance therapy.” (2) In some instances of early, mild, or slowly progressive congestive failure. Not infrequently this form of failure can be initially treated with oral in place of injection therapy. Our experience and that of others cited above is not in agreement with the pronouncement of Gold and his co-workers that "oral tablets rarely suffice..."2, 18

Oral mercurials are contraindicated: (1) In the presence of uremia and renal disease. It must be remembered that often albumen and casts in the urine may be due to congestive failure itself, and mercurials would help instead of harm the congested kidney. (2) When significant gastrointestinal disease is present. (3) In sudden, rapidly changing or progressive heart failure.

SUMMARY

Results in treatment of 35 ambulatory patients in chronic congestive heart failure with a new oral mercurial, Ex 1431, are presented.

This drug was found to replace intramuscular Mercuhdrin effectively in "maintenance therapy" of mercurial diuresis for periods from 1 month to 11 months, in 80 per cent of the patients studied.

Toxicity was observed in six patients, or in 14 per cent. Because of the relatively small amount of mercury necessary to attain diuresis, toxic reactions were less than those reported after the use of other oral mercury preparations.

SUMARIO ESPAÑOL

Mejoramiento en el uso de un agente terapéutico efectivo es conveniente especialmente cuando el método de administración se simplifica, la dosis total se reduce, la toxicidad de la droga disminuye y el costo del cuidado médico se reduce. La substitución de inyecciones parenterales de diuréticos mercuriales por una preparación oral en pacientes ambulantes con decompenación cardíaca crónica representa un paso hacia delante en el manejo de esta clase de paciente.

REFERENCES


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