The Prolonged Use of an Oral Mercurial Diuretic in Ambulatory Patients with Congestive Heart Failure

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Tablets of an oral mercurial diuretic were utilized in the management of patients with severe congestive failure over a prolonged period of time. The need for parenteral mercurial diuretics was eliminated or greatly decreased by this therapy. The individual dosage was established by clinical trial. Minor toxic effects were encountered in several patients but in all instances it was possible to resume the therapy. Severe toxicity was not seen and there were no symptoms of salt depletion. Ease of administration, a more sustained diuresis, and good patient cooperation are advantages of this type of therapy.

The most effective diuretic agents which we have today, organic mercurial compounds, were introduced by German investigators in the early 1920's. These compounds are effective in promoting diuresis in over 90 per cent of edematous patients when given intravenously or intramuscularly. In recent years, they have been found to promote satisfactory diuresis when given orally. The diuretic effect of mild mercurous chloride (calomel) has been recognized for many decades and used for this purpose in Addison's pill. Because its action was uncertain and because adequate dosage caused untoward effects such as diarrhea, stomatitis, albuminuria, and hematuria, the drug was not wholly satisfactory.

The first clinically valuable organic mercurial compound, Novasurol, was introduced by Zeiler in 1917 for the treatment of syphilis. Linking mercury with an organic compound reduced the undesirable effects of mercury while preserving its antitreponemal action. In this form, it was found possible to give the drug parenterally. The strong diuretic action of the compound was soon observed, but was unsuitable for general use because of its undesirable effect on the kidneys. In 1924, Bernheim introduced Salyrgan, a more powerful and less toxic diuretic than Novasurol. Further research resulted in the preparation of another mercurial compound, Novurat or Mercurpurin. It was introduced in 1928 by von Issekutz and von Veghn, who claimed the drug to be less toxic than Salyrgan. They found that by combining the xanthine, theophylline, with Salyrgan the diuretic effect of the mercurial was augmented and untoward reactions at the site of injection and in the kidneys were reduced. These benefits were amply substantiated in the observations of deGraff, Nadler, and Batterman. Theophylline is combined with the three organic mercurial compounds (Mercuzanthin, Mercuhydrin, and Salyrgan-theophylline) which are in common use today as parenteral diuretics. Although each of these drugs has its enthusiasts, there is no evidence that one is preferable to another under all circumstances.

The mercurial-theophylline compounds are reliable, powerful, and safe diuretics when given parenterally in office, clinic, and hospital practice. There are many reports in the literature of their continued use for months or years; however, there are disadvantages and limitations to the parenteral administration of these preparations. Administration usually requires the service of a physician. Pain at the site of injection is not uncommon, particularly when given intramuscularly. Reactions secondary to their potent and sudden diuretic effect are not unusual. These include muscle cramps, weakness, giddiness, and sometimes prostration. Digitalis toxicity may occur in digitalized patients following the prompt and copious diure-
resis. On rare occasions, sudden death has followed the intravenous administration of a mercurial diuretic. Administering the diuretic by rectal suppository has been attempted, but irritation of the rectal mucosa occurs frequently.  

In 1941 Batterman, deGraff and Rose reported favorably on the diuretic effect of Salyrgan-Theophylline by oral administration. Previously there had been inconclusive reports from Germany on the similar use of Novasurol, Salyrgan, and Novurit (Mercupurin). Since 1941 there have been other reports demonstrating that Salyrgan-theophylline and Mercuzanthylin are effective diuretics when given orally. In single doses they are not as potent as the usual intravenous or intramuscular dose; however, they are more powerful than the xanthines or the acid salts. The purpose of the present study has been to determine the usefulness of an orally administered mercurial diuretic in ambulatory patients with congestive heart failure when administered over a prolonged period of time. Particular attention was directed toward the value of this mode of administration in decreasing the need for parenteral mercurial therapy, in relieving patients of the signs and symptoms of congestive failure, in decreasing the need of hospitalization for heart failure, in observing patients for possible toxic effects coincident with the prolonged use of mercury, and in arriving at some idea as to the optimum daily dosage.

**Material**

A total of 34 patients was found suitable for final analysis. No patient was included in this study who had received the oral mercurial preparation for less than thirty days. Of the 34 patients, 27 had required parenteral mercurial therapy prior to using the oral drug. The remaining 7 had never received parenteral mercury. Thus, for the purpose of comparing the period on parenteral therapy with the period on oral therapy, the 34 patients were divided into two groups; those who had had a previous period of parenteral mercurial therapy and those who had not.

Five etiologic diagnoses were represented among the 34 patients and all patients had chronic congestive heart failure. Arteriosclerotic heart disease comprised the largest group and included 17 patients. There were 9 patients with rheumatic heart disease, 5 with syphilitic heart disease, 2 with hypertensive heart disease, and one patient with congenital heart disease (Lutembacher's syndrome). Hypertension was found in 16 patients. The average age was 58 years. The youngest patient was 19 years of age and the oldest 81 years. In the group studied, 23 were male patients and 11 were female.

Ambulatory patients, most of whom attended the Adult Heart Clinic of the Pennsylvania Hospital, were selected for study. The patients suffered from rapidly recurring edema due to chronic heart failure. Many had been followed for several years and had required parenteral mercurial therapy. With few exceptions, the patients had been digitalized and were instructed in a low sodium diet.

**Method**

All patients had complete blood counts, urinalyses, blood serology, and urea nitrogen determinations done at varying intervals while under observation. The urine and blood urea nitrogen were watched carefully for signs of renal damage which might be related to the mercurial therapy. An electrocardiogram and orthodiagram were done when the patient was admitted to the clinic and thereafter as indicated. Each patient was examined in the clinic at weekly or biweekly intervals. The physical examination, interval history, weight and vital capacity were recorded on each visit.

At the beginning of the study, patients were placed on a dosage schedule of 1 tablet of the mercurial diuretic daily. On this regimen, it was found that appreciable diuresis was not obtained for two or three weeks. For this reason and because the drug was well tolerated by the patients, the dose was subsequently increased to 3 and as high as 6 tablets daily. More rapid and pronounced diuretic effects were noted with the increased dosage. There was little tendency towards an increased intolerance to the drug.

If prompt diuresis was desired, the patient was started on 6 tablets daily (2 tablets three times daily). Satisfactory diuresis was usually evident in one to three days. This regimen was continued for three to six days and then reduced to a maintenance dose of 2 or three tablets daily. Occasionally patients were maintained on 6 tablets daily for as long as six weeks. Some patients, however, required no more than 1 tablet daily after the initial diuresis.
We found that the optimum daily maintenance dose had to be established individually for each patient by observing his clinical response. Seventeen patients required maintenance doses of 1 to 3 tablets daily. Nine patients required doses varying between 3 and 4 tablets daily. The remaining 8 patients received doses of 1 to 6 tablets daily, the optimum daily dosage varying considerably during the period of observation.

It is well known that ammonium chloride augments the diuretic effect of mercurial compounds. DeGraff and his co-workers employed this drug in most of their patients in conjunction with the mercurial therapy. As a rule, this drug was not given to our patients in order that the side effects of the drug might not be confused with toxic manifestations of the oral mercurial.

The average period of observation for 27 patients on parenteral mercurial therapy prior to using the oral mercurial was 290 days. The shortest observation period was fourteen days and the longest was 1092 days. Among the 34 patients who received the oral mercurial, the average period of observation was 284 days; the minimum was thirty-two days, and the maximum was 742 days. It was necessary to interrupt the oral therapy at one time or another in 10 of the 34 patients. These interruptions were for the following reasons: (1) possible drug toxicity; (2) failure of the patient to obtain the drug when clinic appointments were neglected; (3) the desire of the physician to determine the clinical progress of the patient following drug withdrawal; and (4) hospitalization of the patient. The 10 patients did not receive the drug for an average of eighty-three days in an average total observation period of 367 days. Medication given during hospital admissions were excluded in this study on ambulatory patients.

RESULTS

The response of each patient receiving the oral mercurial diuretic was classified as good: fair, or poor. In evaluating the patient and placing him in the category deemed most applicable, the following questions were posed: (1) Were the clinical signs and symptoms of congestive failure improved, unchanged, or worse when the patient was receiving the oral mercurial as compared to the observation period when the patient received parenteral mercurial therapy? (2) Did the need for parenteral mercurial therapy decrease? (3) Did the need for hospitalization for cardiac reasons decrease when the patient received an oral mercurial diuretic? (4) Was the oral mercurial well tolerated by the patient and were there any manifestations of progressive renal impairment which might be attributed to mercury?

In the group of 27 patients who had previously been receiving parenteral mercurial therapy, 22 patients were classified as having good responses, 3 fair responses, and 2 patients were classified as responding poorly since they showed no improvement. Of 7 patients who had received no parenteral mercury prior to the oral preparation, 5 had good responses and 2 showed fair responses. None in this group did poorly. Thus, in the total group of 34 patients, 94.4 per cent were benefited while receiving the oral mercurial, and 79.4 per cent revealed responses which can be classified as clinically good. In addition to the beneficial results of the oral mercurial, the patients were more satisfied with this mode of administration. The weakness, muscular cramps, and prostration which occasionally follow parenteral mercurial therapy were not observed.

The following case report is cited as an example of the exceptional benefit derived from oral mercurial therapy.*

W. O., a 65 year old white woman, had arteriosclerotic heart disease, cardiac enlargement, mitral insufficiency, and auricular fibrillation. She was hospitalized with congestive heart failure for the first time in 1941. Despite digitalization at this time and maintenance digitalis therapy thereafter, further hospitalizations for heart failure was necessary in July, 1944, and November, 1945. Sodium restriction and the use of ammonium chloride were not sufficient to prevent edema and the patient received her first injection of intravenous mercury on December 15, 1945, with injections every two or three weeks thereafter. A gradual increase in the weight of the patient from 135 pounds in December, 1945 to a weight fluctuating between 150 and 156 pounds in May and June of 1947 occurred. The frequency of parenteral mercurial injections was increased in July, 1947 despite the marked weakness and muscular cramps which the patient usually experienced following the diuresis.

On November 3, 1947, the patient was started on an oral mercurial preparation, following which, she improved clinically and symptomatically. With the sustained diuresis, her weight decreased to a quite constant new low level (fig. 1). An initial daily dose of 3 tablets was given, and this was increased to 6 tablets daily after five days. A maintenance dose of 2 tablets daily was established as the patient improved. In December, 1947, following an unexplained weight increase, the daily dose was increased

* We are indebted to Dr. Arthur M. Rogers for permission to include the case report of this patient.
again to 6 tablets daily for four days. One parenteral injection of mercury was given, the first injection in six weeks, and the mercury tablets were reduced to 1 daily thereafter. The weight remained at the low level of 139 to 142 pounds without further parenteral therapy until the sudden death of the patient on January 20, 1948. A postmortem examination was not obtained and death was attributed to a cerebral embolus.

All 27 patients who had received parenteral mercurial therapy prior to the oral mercurial diuretic revealed a decreased need for parenteral therapy during the administration of the oral preparation. Previously, 12 of these patients required injections every five to thirteen days; 6 required injections every fifteen to twenty-three days; 4 received injections every thirty to forty-one days; and the remaining 5 received infrequent injections at intervals from forty-nine to eighty-four days.

In determining the decreased need for parenteral injections in each patient, the first thirty days of oral mercurial therapy were...
excluded to permit a reasonable lapse of time to achieve the fullest drug effect. Sixteen of the 27 patients required no parenteral therapy while receiving the oral preparation. Seven of these had previously required injections every five to eleven days. Seven other patients revealed a marked decrease in the need for parenteral mercury, and the 4 remaining patients showed only a slight decreased need. Thus, 85.1 per cent of patients previously requiring parenteral mercury showed a significant decrease in the need for this mode of therapy while receiving an oral mercurial preparation. Of the 7 patients who had no trial period on parenteral mercury, none required mercury injections while receiving the oral mercurial.

The comparative frequency of hospital days relative to the number of days that the patient was observed on parenteral mercurial and oral mercurial therapy was studied. Hospitalizations for cardiac reasons alone were considered. Twenty of the 34 patients were not hospitalized at any time. Nine patients requiring hospitalization while receiving parenteral mercury needed no hospitalization when receiving the oral preparation. Four patients showed a decreased percentage of time spent in hospital confinement while on oral therapy. Only one patient revealed an increased period of hospital days. Of the 7 patients who received no course of parenteral mercury, none required hospitalization during the period of study.

The patients were closely observed for signs and symptoms which might be attributed to toxic effects of the oral mercurial. For the purpose of the study, all such suggestive signs or symptoms were assumed to be related to mercury although it was recognized that similar manifestations might be due to other causes. Of the total group of 34 patients, 20 presented no suggestive signs or symptoms of drug toxicity. The remaining 14 patients presented signs and symptoms which might be attributed to drug toxicity. The most common manifestations were nausea, vomiting, and diarrhea, occurring singly or in combination. These occurred in 10 instances. Three patients developed stomatitis, and 2 others a Vincent's ulcer of the tonsil. Digitalis toxicity was observed in 2 patients. In 9 of the 14 patients, signs and symptoms suggestive of drug toxicity disappeared although the treatment was not interrupted. In none of the 14 patients did the reactions necessitate a permanent interruption of the oral mercurial therapy.

Serial blood urea nitrogen levels in 19 patients and urinalyses in 21 patients furnished no evidence to suggest progressive renal impairment. One patient who had been hospitalized for benign prostatic hypertrophy and uremia prior to the period of oral mercurial therapy was rehospitalized for uremia. This patient received 1 to 3 tablets of the oral mercurial daily for 105 days. Because of neglected clinic appointments, he received no oral mercurial therapy for three weeks prior to his hospitalization. The uremic state improved considerably but the patient died suddenly and unexpectedly in the fourth hospital week. His death was attributed to cardiac disease. Necropsy permit was not granted.

Five patients developed albuminuria while receiving the oral mercurial. Four of these 5 patients revealed only a faint trace to a trace of albumin. The uremic patient mentioned above progressed to a 3 plus albuminuria, which decreased to 1 plus as therapy was continued. Most patients revealed minor urine abnormalities at one time or another during the period of observation as might be anticipated in patients with advanced cardiac disease and congestive failure.

Ten of the 34 patients studied died. Six died during the course of oral mercurial therapy. Four died after periods of two to six months following discontinuation of the oral mercurial therapy.

Discussion

It was not the concern of this study to appraise the relative potency of oral and parenteral mercurial preparations. Undoubtedly mercurial diuretics are more rapidly effective when given by the parenteral rather than the oral route of administration. We have found, however, that the oral administration of an organic mercurial compound over prolonged periods of time is a useful, safe, and effective
method for promoting and maintaining diuresis in ambulatory patients with congestive heart failure. This was illustrated in the decreased need for parenteral mercury in all patients when receiving an oral mercurial preparation, and the absence of serious toxic manifestations.

Mild toxic reactions similar to those reported elsewhere were encountered in this study. Occasionally the drug was discontinued when such reactions occurred, but usually the therapy was continued. Nausea, vomiting, and diarrhea were always of transitory duration. It was difficult to be certain that mercury toxicity rather than transient gastroenteritis, digitalis toxicity, or disturbed physiology of the gastrointestinal tract secondary to congestive failure was the exact cause. In 3 patients who developed gingivitis, pre-existing pyorrhea had been observed. By periodic urinalyses and blood urea nitrogen determinations, the patients were observed for renal damage. Batterman, DeGraff, and Schorr reported 2 cases of uremia which were apparently related to an oral mercurial. We are not certain, in the single case of uremia which we encountered, that the oral mercurial was responsible, particularly in view of the previous uremic history of the patient. Minor evidences for renal damage were not considered to be of sufficient significance to warrant interruption of the therapy. In keeping with advanced cardiac disease, many patients in this study revealed impaired renal function as evidenced principally by albuminuria and urea nitrogen retention.

While receiving the oral mercurial preparation, the patients in this study impressed us as maintaining a more constant diuresis and more stable weight than when receiving parenteral mercurial therapy. Symptoms of hypopitremia, seen occasionally with parenteral mercurial therapy, were not present in patients receiving the oral mercurial drug. A more constant and sustained relief from the symptoms of congestive failure was noted by most patients, in contrast to the fluctuating states of relative comfort and discomfort experienced when receiving periodic injections of parenteral mercurial preparations alone. Thus, it is under-

standable that the majority of the patients in this study preferred the mercurial tablets rather than parenteral mercurial therapy.

Summary

1. Thirty-four selected patients with chronic congestive heart failure were given tablets of an organic mercurial preparation in addition to digitalis therapy and restriction of sodium chloride.

2. Twenty-seven of these patients had previously received parenteral mercurial therapy. In 25 of these patients the need for parenteral therapy was eliminated or greatly reduced.

3. A greatly decreased incidence of hospitalization for cardiac reasons was noted during the period of study.

4. No serious toxic manifestations were observed.

5. Oral mercurial tablets are a valuable adjunct to the therapy of chronic congestive heart failure.

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Circulation. 1950;1:516-522
doi: 10.1161/01.CIR.1.4.516

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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