Comparison of Mercurial Diuretics and Bed Rest in Normal and Toxemic Pregnancies

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Recent reports have indicated that oral organomercurial compounds are effective in promoting diuresis in edematous states. In the majority of these studies, however, salt restriction, bed rest, and other medications were used. Therefore, the diuretic effects of the oral mercurials alone have not been properly assessed. In the present report, the effects of oral mercurials on water and electrolyte excretion were studied in normal and toxemic pregnancies and were compared to effects induced by bed rest and by injectable organomercurial agents.

The effectiveness of mercurial diuretics when given parenterally has been well demonstrated in man and animals. Recently oral organomercurial preparations have been used by several authors in the management of edematous states. Satisfactory results have been reported depending to a large extent on the dose given. In most of these reports, however, low-sodium diet, other diuretic and cardiac medication, or bed rest was also used. Therefore, the efficacy of the orally administered mercurials alone has not been satisfactorily assessed.

The present study was aimed at investigating the action of oral organomercurial agents on the renal excretion of water and electrolytes in the edema of normally pregnant and toxemic patients. The effects of bed rest alone were similarly investigated. These results were then compared to those obtained from a similar group of patients to whom intramuscular organomercurial drugs had been administered.

Material and Methods

A total of 37* patients whose ages varied from 18 to 40 years were studied: 29 had toxemia of pregnancy and 8 were normally pregnant. All patients were in the last trimester of gestation. The criteria for the diagnosis of toxemia have been outlined elsewhere.

The patients were in the hospital at bed rest without any specific medication throughout the periods of study (the normally pregnant patients were permitted to ambulate for 1 to 2 hours a day). They all received the same daily diet, that contained approximately 100 Gm. of fat, 100 Gm. of protein, 200 Gm. of carbohydrate, and 85 mEq. of sodium as sodium chloride.

The study was divided into 3 consecutive periods. The first period lasted from 4 to 5 days and served as a control. During the second period, which lasted from 4 to 5 days, an organomercurial compound was given either orally in 3 doses totaling 6 to 8 tablets or intramuscularly in the dose of 1 to 2 ml. every 24 hours. The third period served as a recovery period and lasted for 3 to 4 days. In assessing the effects of bed rest alone, a group of 4 patients at bed rest without other therapy were studied during the same number of days.

Two oral and 2 injectable organomercurial compounds were used. Neohydrin† (3-chloromercuri, 2-methoxypropyl urea) was given orally to 5 normal and 10 toxemic patients and Metrox† (1-(3-hydroxymercuri-2-methoxypropyl)-biuret) was given to 3 normal and 5 toxemic patients. Mercuhydrin (melonlulide) and Mersoben,‡ 3-[2-hydroxy-3-(d-glucopentalhydroxyhexyl-mercaptop mercuri) - propyl]-d-mannitol were given intramuscularly to 5 toxemic patients each.

† Neohydrin and Mercuhydrin were furnished through the courtesy of Lakeside Laboratories. Each tablet of Neohydrin contains 10 mg. of mercury so the total dose of mercury varied between 60 and 80 mg.
‡ Metrox and Mersoben were furnished by Ciba Pharmaceutical Products. Each tablet of Metrox contains 20 mg. of mercury so the total dose given of this compound varied between 120 and 160 mg. of mercury.
During each period, the patient's weight, blood pressure, and fluid intake and output were recorded daily. Arterialized blood samples were collected anaerobically without stasis from an antecubital vein after soaking the arm in warm water for 10 to 15 minutes. Twenty-four-hour urine specimens preserved with toluene and kept refrigerated were collected throughout the study and served for analyses of ammonia, titratable acids, and electrolytes. The completeness of urine collections was checked by the creatinine excretion. Plasma pH, carbon dioxide content, sodium, chloride, and potassium as well as urinary ammonia, titratable acids, and electrolytes were determined by methods previously described. 7

RESULTS

The administration of oral organomercurial drugs to either normally pregnant or toxemic patients resulted in a weight loss of 1 to 2 Kg. that was not regained after cessation of therapy. A slight increase in urine output along with a moderate increase in sodium, potassium, and chloride excretion was also observed, particularly during the Neohydrin administration. There was no change in either the plasma electrolytes or in blood pH or carbon dioxide. Similarly, urine pH and the excretion of ammonia and titratable acids remained the same. The patients with toxemia of pregnancy excreted significantly less electrolytes than those with normal pregnancy during the control period and continued to do so during the treatment period.

In the group of patients studied with bed rest alone, the changes in weight, urine output, sodium, potassium, and chloride excretion were similar to those observed during the administration of the oral mercurial compounds. Calculation of the significance of the differences between

Fig. 1 Top. Sodium excretion in the urine induced by oral mercurials, bed rest, and injectable mercurials in patients with toxemia of pregnancy.

Fig. 2 Middle. Urinary potassium excretion during the administration of oral and injectable mercurials and bed rest. The difference between oral mercurials and bed rest was not significant.

Fig. 3 Bottom. Urinary chloride excretion produced by injectable and oral mercurials and by bed rest.

* Detailed data on changes in blood and urine compositions are listed in 8 tables that have been deposited with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress. Copies may be obtained from this Service (ADI document no. 5112) for $1.25, or from the author.
tween the mean of the groups of patients treated with oral mercurials and the means of the patients treated with bed rest was made by computing Student's t for each pair of values according to the method of Fisher. The difference between bed rest and oral organomercurials was not significant ($p > .5$).

Intramuscular administration of organomercurial compounds resulted in a weight loss varying from 5 to 8 Kg. over the entire treatment period and the patients continued to lose weight after cessation of therapy. The loss of weight was mainly due to a marked increase in the excretion of water and electrolytes. The statistical difference between the means of the groups of patients given injectable organomercurials and the patients kept at bed rest was highly significant ($p = .001$) and so was the difference between injectable and oral organomercurials.

Figures 1–3 compare the effects of bed rest, and of oral and injectable mercurials on sodium, potassium, and chloride excretions. It is evident that the effects of bed rest and of oral mercurials were very close and they differ markedly from the effects of injectable mercurials irrespective of the type of mercurial compound utilized.

**Side Effects.** The side effects caused by oral administration of organomercurials were more conspicuous when 6 to 8 tablets were given. They consisted mostly of nausea, abdominal cramps, and in a few instances diarrhea and vomiting. These side effects, however, were not severe enough to warrant discontinuation of therapy.

**Discussion**

The present data show that the 2 oral organomercurial compounds did not have a significant diuretic action in normal and toxemic pregnancies and that the slight effects on weight and electrolyte excretion might have been due to bed rest. These results are in contrast to those obtained by Moyer and his co-workers and by others in patients with cardiac edema, and by Dyer and his associates in patients with toxemia of pregnancy. Moyer found a significant weight reduction in ambulatory cardiac patients 2 days after the administration of 6 to 8 tablets of Neohydrin. However, no metabolic data were given by these authors and the conditions of the experiment were entirely different from those carried out here. The group of hospitalized patients studied by Dyer and his associates were on a regime of salt restriction, bed rest, and other specific medications for toxemia, so that it would be difficult to state how much of the weight reduction was due to oral mercurials. Greiner and co-workers assayed 3 oral organomercurials: 2 were found to be ineffective and 1 (Neohydrin) had one fourth of the activity of its injectable form. The patients studied by Greiner were also ambulatory in the outpatient department and reduction in weight was the only criterion of effectiveness utilized.

Two possible explanations could be given for the lack of striking results with oral organomercurials observed in the present study: (a) the dose was too small, and (b) pregnant patients have impairment in the intestinal absorption of mercury. The first hypothesis probably may be discarded, since the dose and mode of oral administration utilized here were not different from those used by others with the exception of Greiner. This author administered the whole amount (1 to 9 tablets) as a single dose, so that the discrepancy between his and our results may be due to this difference in administration.

The second hypothesis receives support from the fact that intestinal absorption is known to be impaired in pregnancy due to the over-all hypotonicity of smooth muscles. So, it is possible that the fraction of mercury absorbed through the intestines was not sufficient to produce the desired diuresis. Studies on blood levels of mercury are in progress in order to elucidate this point. The diuretic effects of injectable mercurials were certainly striking since, regardless of the preparation utilized, the patients invariably lost a significant amount of weight, mainly due to increased loss of water and electrolytes by the kidneys. Furthermore, despite the large dose employed, the side effects were practically nonexistent when the intramuscular route was employed. These properties of excellent diuretic action along with minimal side effects make injectable mercurials particularly suitable in the management of edema of pregnancy.
Nevertheless, the use of mercurials in obstetrics has been condemned by obstetricians on the theory that damage to the kidneys may occur and because the effects on the fetus are not known. In view of our observations and other reports, the fear of using mercurial diuretics in pregnancy does not seem well founded, in fact these agents may well be indicated in the cases of edema of pregnancy resistant to other simpler therapeutic regimens.

SUMMARY

The diuretic effects of oral organomercurials (Neohydrin and Metrox) were compared to those induced by bed rest and by injectable mercurials (Mercurhydridin and Mersoben) in groups of normally pregnant and toxemic patients. No significant difference existed between the effects of oral mercurials and bed rest. Injectable mercurials produced marked diuretic effects, which were significantly different from those induced by oral mercurials and bed rest. It is suggested that the lack of diuresis of the oral mercurials might be due to impairment of intestinal absorption for mercury during pregnancy.

SUMMARIO IN INTERLINGUA

Le effectos diuretic de oral organomercuriales (Neohydrina e Metrox) eseva comparate con le effectos diuretic de allectamento e injicible mercuriales (Mercurhidydrina e Mersoben) in gruppos de gravidas normal e toxemic. Nulle significative differentias esisteva inter le effectos de mercuriales oral e allectamento. Mercuriales del typo injicible produceva marcate effectos diuretic que eseva significative-mente differente ab le effectos inducite per mercuriales oral e per allectamento. Es formulete le possibilitate que le manco de diuresis per mercuriales oral es explicabile per un obstruite absorption intestinal de mercurio durante le pregnancy.

REFERENCES


I observe the physician with the same diligence as he the disease.—John Donne, 1573–1631.
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