

Tracer Studies of the Urinary Excretion of Radioactive Mercury following Oral Administration of a Mercurial Diuretic

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This report presents experimental evidence of the inefficient intestinal absorption of mercury following the oral administration of a mercurial diuretic. Radiotracer technic was employed using a diuretic prepared with radioactive mercury. Both control subjects and subjects with congestive heart failure were shown to absorb only a small percentage of the mercury administered by the oral route.

REPORTS on the efficacy of oral mercurial diuretics in control of edema in patients with chronic congestive failure have been in general agreement.¹⁻¹¹ Employing the ability to control edema as a clinical index, various workers^{1, 3, 4, 7} have found the preparations used to be effective in from 58 to 77 per cent of trials. The validity of this index, however, is questionable. The efficacy of a mercurial diuretic may also be evaluated from a knowledge of the absorption, blood concentration, and urinary excretion of mercury, the active agent common to this whole class of compounds¹². Opportunities were available during the course of other studies to make these observations by tracing radiomercury chemically incorporated into a mercurial diuretic prepared for oral use. The tracer method permitted quantitative assay of many samples during each experiment.

MATERIALS AND METHODS

The labeled mercurial diuretic "Mercuryhydrin"* was prepared with radioactive mercury ($Hg^{203, 205}$)† such that each capsule of 0.33 Gm. contained ap-

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* The sodium salt of methoxyoximercuri-propylsuccinylurea with theophylline, prepared with radiomercury in this laboratory by Messrs. Harold Krahnke, Darwin Kaestner, and Edwin Sprengler through the courtesy of Dr. H. L. Daiell, Director of Research, Lakeside Laboratories, Milwaukee.

† Radioactive mercury ($Hg^{203, 205}$) was obtained from the Isotopes Division of the Oak Ridge National Laboratories.

proximately 60 mg. of "Mercuryhydrin" (19.5 mg. mercury and 24 mg. theophylline), with lactose as a vehicle. The preparation was placed in plain or enteric-coated (shellac or salol) gelatin capsules. Each capsule was equivalent in mercurial content to 0.5 cc. of the parenteral preparation.

The specific activity of the capsules, as estimated by means of a mica window Geiger-Müller counter and a special mold, varied considerably, owing to individual variations in degree of filling. The activity of five intact capsules was compared with the activity of the content of each of these capsules dissolved in water and measured under conditions employed for the biologic preparations. A high correlation was found between the activity of the intact and dissolved capsules, the maximum deviation from the mean being 10 per cent (fig. 1). Thus, calculations of dosage in terms of radiomercury were possible.

Twenty-two control subjects and 5 subjects with chronic congestive heart failure were selected for study from the medical wards of the Charity Hospital (table 1). The control subjects were apparently free from any cardiovascular, renal, or metabolic disease; the majority had either recovered from an acute respiratory infection or were suffering from a chronic pulmonary disease. Only one subject had ever received a mercurial diuretic; this was a subject with chronic congestive heart failure and edema but he had not received any for two weeks prior to study. Additional therapy for the subjects in his group consisted of restriction of salt, digitalis, bed rest and sedation.

Of the 22 control subjects, 14 received the radioactive mercurial diuretic in plain gelatin capsules, 4 in capsules enteric-coated with shellac, and 4 in capsules enteric-coated with salol. All of the 5 subjects with congestive heart failure received the labeled diuretic in plain gelatin capsules.* The diuretic was administered as a single dose after twelve hours of fasting. Food and liquids were withheld for at least two hours after administration except for water needed to swallow the capsules. The dose for 23 sub-

*One hundred mg. ascorbic acid was added to each capsule given to 5 of the control subjects who received the drug in plain gelatin capsules.

jects was 4 capsules, equivalent to 2.0 cc. of the parenteral preparation or 78 mg. of mercury. This represented approximately 40,000,000 counts per minute (range: 37,246,000 to 43,649,000) or roughly 0.1 millicurie. In 4 subjects the dose was 10 capsules, equivalent to 5 cc. of the parenteral preparation, 195 mg. of mercury, or approximately 100,000,000 counts per minute (range: 98,726,000 to 119,943,000) or 0.25 millicurie.

Samples of blood were obtained from an antecubital vein at ten to fifteen minute intervals from the first subjects studied, at thirty minute intervals from others, and at hourly intervals later in the series. Specimens of urine were collected by catheter in some patients; in others the samples were voided, collections being made until there was no further radioactivity demonstrable. Fecal specimens were obtained from a number of subjects, but accurate

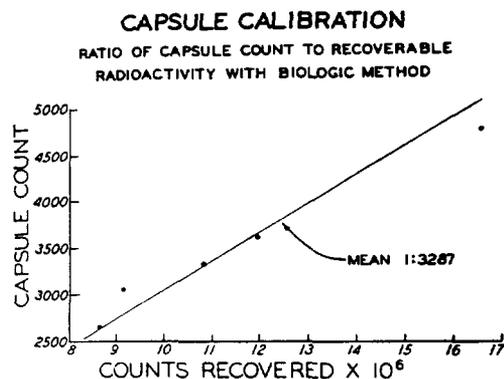


FIG. 1.—High correlation of counts obtained for 5 capsules selected at random and observed in the intact state and then with the counts of each dissolved in water by the use of the method for the biologic specimens. The points represent the values of each capsule and the line their mean.

quantitative determinations of their radiomercurial content were unsuccessful because of problems of self absorption and other difficulties peculiar to the handling of radiomercury.

RESULTS

Total urinary excretion of mercury following oral administration of the diuretic was low both in the control subjects and in the subjects with chronic congestive heart failure (table 1). Urinary recovery of the oral dose varied from 11.79 per cent to 0.00 per cent, with an average of 3.86 per cent. The largest percentage of recoveries was obtained after administration of the drug in plain gelatin capsules (table 1, A, B, and E), and the smallest recoveries occurred following its use in

TABLE 1.—Summary of Results Obtained with Oral Mercurhydrin for All Subjects

Subject	Age (yrs.)	Diagnosis	Urinary recovery (per cent)	Clearance time (min.)
A. Control subjects who received dose of 10 plain gelatin capsules				
E. H.	31	Convalescing pneumonia	3.60	1420
J. H.	14	Pleural effusion, clearing	8.90	1298
W. G.	29	No disease	4.23	1347
W. O.	29	No disease	6.60	1700
B. Control subjects who received dose of 4 plain gelatin capsules				
O. P.	32	Convalescing pneumonia	3.86	1410
F. M.	46	Tuberculous adenitis	4.33	1440
E. M.	28	Convalescing pneumonia	11.79	1350
L. W.	55	Convalescing pneumonia, anemia	0.72	1205
I. B.	54	Convalescing pneumonia	6.41	1630
E. D.	63	Severe nutritional anemia, corrected by transfusion	2.31	1765
S. C.	50	Bronchogenic carcinoma	4.03	1764
I. H.	68	Possible pernicious anemia, normal hemogram	7.07	1690
L. H.	19	Convalescing pulmonary abscess	4.57	837
E. P.	47	Bronchogenic carcinoma	5.53	1513
C. Control subjects who received dose of 4 shellac-coated capsules				
V. D.	29	Sterile synovitis	0.23	325
Jo. H.	31	Pulmonary abscess	0.04	156
J. M.	55	Bronchogenic carcinoma	0.00	0
L. P.	15	Bronchiectasis, afebrile	0.00	0
D. Control subjects who received dose of 4 salol-coated capsules				
A. B.	29	Tuberculous adenitis	1.19	1035
A. J.	20	Convalescing pneumonia	0.06	550
T. J.	44	Guillain-Barré syndrome	1.86	930
H. M.	51	Bronchiectasis, afebrile	2.55	1510
E. Subjects with congestive heart failure who received dose of 4 plain gelatin capsules				
R. C.	50	Hypertensive cardiovascular disease, failure	8.23	1365
L. M.	61	Arteriosclerotic heart disease, hypertensive cardiovascular disease, diabetes, failure	0.18	785
F. N.	50	Rheumatic heart disease, failure, chronic glomerulonephritis	9.40	5045
F. S.	68	Hypertensive cardiovascular disease, failure	3.12	1905
R. W.	66	Syphilitic heart disease, failure	3.38	815

enteric-coated capsules (table 1, C and D). The addition of ascorbic acid to the diuretic in control subjects (last 5 subjects, table 1, B) did not appreciably affect urinary excretion of mercury.

The shellac-coated capsules were extremely resistant to dissolution in the intestine; 50 per cent of those administered were recovered in-

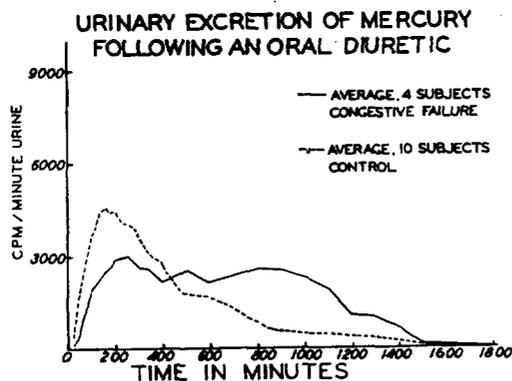


FIG. 2.—Comparison of the time course of the average rate of urinary excretion of mercury in 4 subjects with chronic congestive heart failure with that in 10 control subjects.

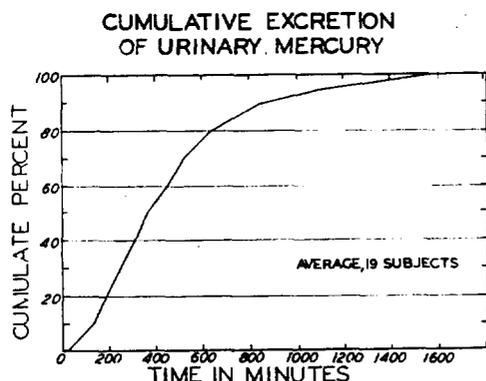


FIG. 3.—Cumulative urinary excretion of mercury for all subjects who received the diuretic in plain gelatin capsules, the 100 per cent value being based upon the total amount excreted in the urine.

tact in the stools. Although the capsules coated with salol dissolved in the gastrointestinal tract, urinary excretion of mercury was essentially one-fourth of that observed following administration of the diuretic in plain gelatin capsules.

Three of the four control subjects who received a single dose of ten capsules experienced toxic reactions manifested by abdominal cramp-

ing and diarrhea. A dose of four capsules produced no toxic symptoms. There was no significant difference noted in percentage of mercury recovered in the urine of the groups receiving these two quantitatively different doses in plain gelatin capsules (table 1, A, B, and E).

The total urinary excretion of mercury following a dose of four plain gelatin capsules was similar both for the control subjects and for those with chronic congestive heart failure (table 1, B and E). The excretion rates were qualitatively different in that the maximum level of urinary concentration was lower and more prolonged for subjects with heart failure than for the control subjects (fig. 2).

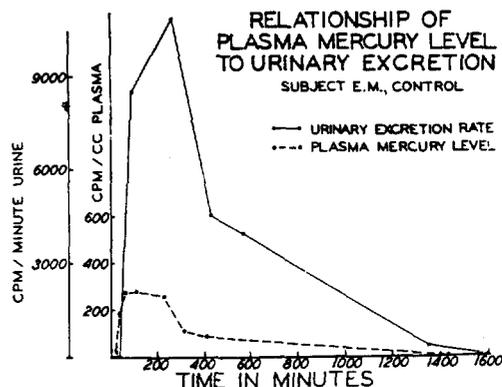


FIG. 4.—Comparison of the concentration time course of radiomercury in the plasma with the time course of the rate of urinary excretion in control subject (E. M.).

The average cumulative time-course of urinary excretion for mercury for all subjects receiving plain gelatin capsules is shown in figure 3. The time course of percentage excreted is based on the total amount recovered in the urine and not on the dose administered. Seventy per cent of the excreted mercury was found within 500 minutes (8.3 hours) after administration of the diuretic. The remainder was slowly excreted over an additional 1,090 minutes (16.2 hours). The average total time for urinary excretion was 1,590 minutes (26.5 hours), the extremes being 785 and 5,045 minutes (13 and 84.1 hours).

Maximum concentrations of radiomercury in the plasma coincided in time with the periods of maximum urinary excretion of the tracer

(figs. 4 and 5). In general, the plasma concentrations were low in comparison with equal doses administered intramuscularly and intravenously,¹³ with one notable exception, a subject with congestive heart failure, chronic glomerulonephritis, and mild uremia (Subject

and rate of urinary excretion observed for all subjects and is illustrated for 2 of these in figures 4 and 5. This would indicate that most or practically all the mercury found in the stool passed through the gastrointestinal tract unabsorbed rather than having been absorbed and

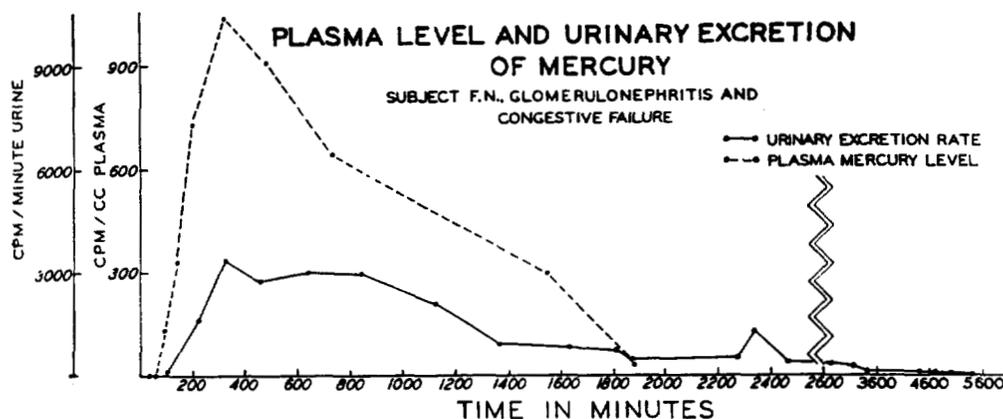


FIG. 5.—Comparison of the concentration time course of radiomercury in the plasma and the time course of the rate of urinary excretion in Subject F. N., who had chronic congestive heart failure and chronic glomerulonephritis.

F. N., table 1). The concentration of mercury in the plasma of this subject was higher and was maintained longer than in the other subjects (fig. 5), the tracer being detectable in the urine over a period three times as long as that of the average, 5,045 minutes or 84.1 hours.

DISCUSSION

Even though the radiomercurial content of the stools could not be accurately quantitated, it was possible to demonstrate the presence of large amounts of mercury in specimens passed in the interval from 240 to 4000 minutes (4 to 66.6 hours) following administration. The large quantities passed in the stools indicate that if there is bodily retention or storage of mercury following oral administration, it is small.

The relatively long duration of detectable levels of radiomercury in the plasma of a patient with impaired renal function who excreted small quantities of mercury in the urine over an extended period of time (fig. 5) suggests that most of the mercury entering the blood stream is eliminated through the kidneys. Evidence supporting such a concept is offered by the close correlation between blood level

then re-excreted into the bowel. Repeated experiments in this laboratory with the labeled diuretic administered parenterally¹³ confirm this opinion. The possibility of an enterohepatic cycle is ignored.

Regardless of the mechanism or mechanisms involved, only small amounts of the radiomercury are recovered in the urine after oral administration of the diuretic. Since the diuretic effect of mercury is dependent to a large extent, if not entirely, upon its action on renal tubules,¹² it would appear that only that mercury which finds its way into the kidney produces diuresis. The degree of diuresis has been reported to be proportional to the amount of mercury excreted in the urine.^{14, 15}

For each of a series of two widely different dosages an average of 5.0 per cent of the mercury administered found its way into the urine.^{14, 15} Theoretically it is possible to administer an oral dose sufficiently large so that 5.0 per cent of it would produce diuresis. Approximately 60 per cent* of the mercury of a comparable mercurial diuretic (Salyrgan) admin-

* Unpublished data from this laboratory indicate this figure is much higher with Mercurhydrin.

istered intravenously is recoverable in the urine.^{14, 16} Therefore, to produce the equivalent urinary excretion of 1.0 cc. of an intravenously administered dose it would be necessary to administer orally an equivalent of 12 cc. or 24 capsules. However, a dosage of 10 capsules was found to produce gastrointestinal irritation in 3 out of 4 control subjects. Multiple doses may solve the problem, but they may still cause gastrointestinal disturbances without resulting in sufficient urinary excretion to produce diuresis, since some mercury remains in the gastrointestinal tract for several days after administration. A patient with renal damage and a prolonged period of urinary excretion for mercury, such as Subject F. N. (table 1 and fig. 5), might accumulate enough mercury following repeated oral administration to achieve diuresis provided mercurialism does not supervene following repeated doses.^{2, 6}

The poor urinary excretion following the use of the salol-coated preparation indicates that when mercury is available, maximum absorption occurs relatively high in the gastrointestinal tract (stomach or duodenum), at a level higher than that at which dissolution of salol occurs.

SUMMARY AND CONCLUSIONS

By means of tracer methods the absorption, blood concentration and urinary excretion of mercury following oral administration of standardized single doses of plain and enteric-coated capsules of a mercurial diuretic were studied in 22 control subjects and in 5 subjects with chronic congestive heart failure.

Enteric coating of the capsules resulted in the lowest blood concentrations and in the poorest urinary excretion of mercury, which indicates that maximum absorption occurred high in the gastrointestinal tract. Even with the more efficient plain gelatin capsules the blood concentration was low compared with intravenous administration, and the amount excreted in the urine averaged only 5.0 per cent of the amount administered orally. The addition of ascorbic acid had no significant

influence on urinary excretion. In no instance did oral administration of the diuretic result in a urinary excretion of mercury equivalent in amount to that following a therapeutic parenteral dose, even though the drug was administered orally in toxic doses to several subjects.

In one subject with chronic glomerulonephritis prolonged retention of mercury was demonstrated, indicating the possibility of toxicity from repeated doses in patients with this disease.

The observations of poor absorption, low blood concentration, and low urinary excretion of mercury following oral administration of this mercurial diuretic precludes its general use in the treatment of chronic congestive heart failure.

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