

Renal Retention of Mercury-203-Neohydrin

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Since the introduction of ²⁰³Hg—neohydrin as an agent for brain scanning by Blau and Bender (1) in 1959, the postulated ability of previously administered stable mercurial diuretic to reduce renal retention of ²⁰³Hg has been the subject of considerable discussion.

The original work was based on external counting over the kidneys of 17 patients, of whom seven had received one cc mercurhydrin, 39 mg of mercury, the day prior to the radioisotopic injection. These authors reported a three-fold reduction in the renal retention of ²⁰³Hg in most patients receiving prior mercurhydrin. Subsequent reports in the literature have revealed a general acceptance of this statement (2,3,4,5).

Croll *et al* (6) collected 48 hour urines on a group of patients undergoing brain scanning. They found that one cc of stable mercurhydrin given 24 hours prior to 10 μ C/kg ²⁰³Hg—neohydrin caused a three-fold increase in the amount of urine radioactivity.

Other workers, however, have been more skeptical of this *blocking* phenomenon. Pre-dosing with mercurhydrin the day before did not effect ²⁰³Hg retention in a series of 12 patients, according to Sodee, and he discontinued the mercurhydrin injection (7). McAfee noted that pharmacologists have been unable to block the uptake in the kidneys, despite pre-dosing rats with cold mercurials with doses up to 20 mg of mercury per kilogram, a tremendously toxic dose (8).

Although brain scanning with such short-lived isotopes as ^{99m}Tc and ¹⁹⁷Hg is rapidly increasing in popularity and utilization, it was felt that in view of the large percentage of brain scans still being performed with ²⁰³Hg—neohydrin, a more precise answer to the question at hand was indicated. Therefore, a controlled laboratory experiment was conducted to test the hypothesis that previ-

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ously administered stable mercurial diuretic reduces the renal retention of mercury-203. The study was extended to determine if there existed an optimal time of pre-dosing with mercurial.

MATERIAL AND METHODS

Sprague-Dawley 300 gram female rats were used in this study. They were kept four in a cage and fed water and rat chow ad libitum. They were randomly divided into five groups and treated in the following ways:

1. ^{203}Hg -neohydrin IV alone
2. " " " + isotonic saline IP
3. " " " + Mercurhydrin IP 24 hours previously
4. " " " + " " 8 hours "
5. " " " + " " 1 hour "

The ^{203}Hg -neohydrin utilized was the commercially available material from Squibb with an average specific activity of 0.427 mC/mg. Ten microcuries of 0.3 ml volume were injected directly into the saphenous vein. The meralluride (mercuhydrin) was administered intraperitoneally in a volume of 0.3 ml doses ranging from 1 mg Hg/kg body weight to 8 mg/kg were utilized, but the major part of the study was performed with a dose of 4 mg Hg/kg. (This is considered to be the diuretic dose for the rat.) Isotonic saline, 0.3 ml volume, was injected intraperitoneally in one group to act as a control for the intraperitoneal injection of mercuhydrin.

The intravenous injections were done under pentobarbital anesthesia. The animals were kept under normal conditions for seven days and then sacrificed. The kidneys were resected at the hila, weighed, placed in individual test tubes and measured for radioactive content in a standard type sodium iodide well-counter. Radioactivity was recorded for each kidney as counts per minute per milligram of tissue.

RESULTS

1) Mercurhydrin 1/mg Hg/kg body weight:

One preliminary study showed no difference in renal count rates between the control and pre-dosed groups. This was perhaps to be expected with utilization of a sub-diuretic dose of mercuhydrin.

2) Mercurhydrin 6 mg and 8 mg Hg/kg body weight:

In the preliminary studies these doses proved toxic to the majority of the rats so treated, as manifested by increased morbidity and mortality. Further studies at these levels were, therefore, not carried out. Rat experiments performed by earlier investigators substantiate this finding. Fawaz and Fawaz noted maximum diuresis following a dose of 4 mg Hg/kg body weight. Eight mg/kg produced less diuresis and 12 mg/kg caused almost complete anuria, with 100% of the animals in this latter group dying within one week (9). Mercurhydrin at a dose of 10 mg/kg regularly produced renal necrosis, as reported by Wachstein and Meisel (10), and 20 mg/kg was found by Borghgraef and Pitts to be a frankly toxic dose (11).

3) Mercuhydrin 4 mg Hg/kg body weight:

Figure one demonstrates the striking difference in renal count rates between the two control groups and the three groups pre-dosed with mercuhydrin. *There is a three-fold reduction in renal retention of ^{203}Hg in the mercuhydrin injected rats. There is no significant difference in count rate between those rats pre-dosed either one, eight or 24 hours pre- ^{203}Hg injection.*

DISCUSSION

The primary action of the mercurial diuretics is to depress the renal tubular mechanism responsible for the active reabsorptive transport of certain ions, especially chloride, by inhibiting sulfhydryl-activated enzyme systems. Following injection, the organic mercurials are rapidly taken up by the renal cortex, fixed within the proximal tubular cells and excreted into the urine (12). It is postulated that the delay in onset of diuresis following administration of the diuretic is relative to the time required to build up some critical concentration of mercury within the tubular cells. Diuresis might then be sustained for a period of high cell content of mercury and diminish as excretion of mercury began to outstrip cell uptake (13).

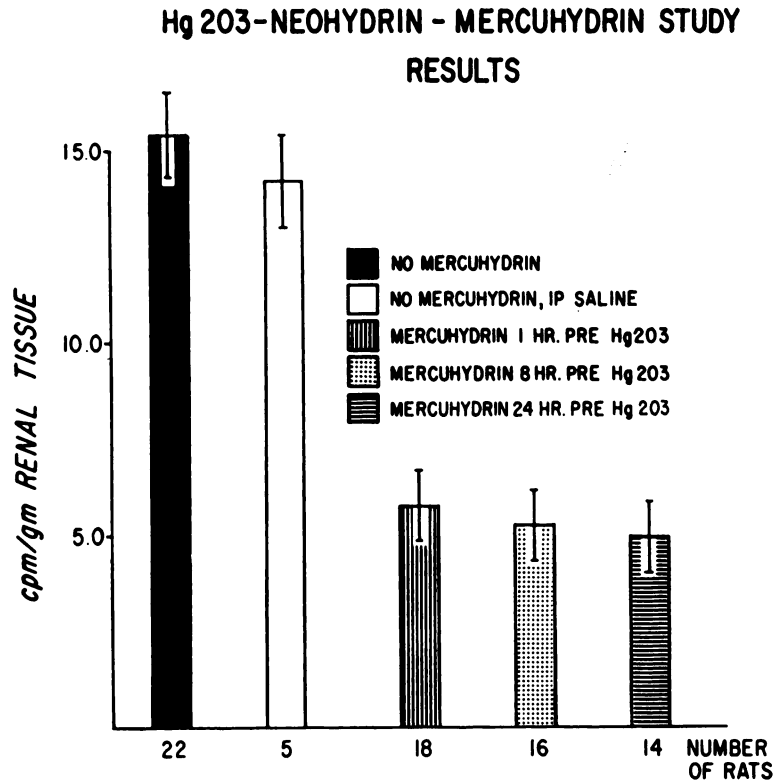


Fig. 1. Renal retention of ^{203}Hg in the control groups and those animals pre-dosed with mercuhydrin, 4 mg mercury per body weight.

The data in this study demonstrate that pre-dosing rats with stable mercurial diuretic in doses of 4 mg of mercury per kilogram body weight reduces the renal retention of subsequently administered ^{203}Hg -neohydrin by a factor of three. No significant difference is noted in the renal retention of those groups pre-dosed at 1, 8, or 24 hours. It seems reasonable to postulate that this *flushing* effect is related in time to the buildup of a critical concentration of mercury within the tubular cells, which as noted above, is deemed a necessary prerequisite for producing a diuresis. This is presumed to be a saturation phenomenon, where the previously administered mercurial saturates most of the available binding sites in the proximal tubules, causing the ^{203}Hg -neohydrin subsequently given, to be excreted in excessive amounts. The importance of these observations would become greatly magnified if they proved valid in the clinical setting. Although this transferral of data cannot be done with total equanimity, there are certain similarities between the rat and human in their handling of mercurial diuretics that may justify it.

Selective concentration of the mercury in the proximal convoluted tubules of the renal cortex in both rat and human has been clearly demonstrated by autoradiography (14), histo-chemical methods (15), and electron microscopy (16).

Calesnick *et al* found in rats 91.7% of the intramuscular dose of ^{203}Hg -mercaptomerin in the kidneys within one hour (1). Blau and Bender noted that in humans the blood level is less than 10% five hours after intravenous ^{203}Hg -neohydrin and that almost 50% is excreted in the urine during the first eight hours.

In the rat, maximum diuresis occurs two to three hours post-injection. It has been shown in humans that following an intramuscular injection of mercurial diuretic, an increased urine flow is evident within one to two hours, reaching a maximum in six to nine hours and is usually complete within 12 to 24 hours.

In a study performed in rats with intraperitoneally injected ^{203}Hg -mercaptomerin, urine collected and counted for radioactivity contained 42% and 78% of the given dose after four hours and 72 hours, respectively (12). In a clinical study with ^{203}Hg -neohydrin, Blau and Bender discovered that the urine contained 50% and 60% of the injected dose at eight hours and 48 hours, respectively (1).

The one major disparity between rat and human is in the dose of mercurial required to produce diuresis. The rat, as has been demonstrated, required approximately 4 mg of mercury per gram body weight. Anything less than 2 to 3 mg per kg is ineffective.

In man, the average diuretic dose is closer to one mg of mercury per kilogram body weight. The explanation of this disparity in diuretic dose between rat and man, despite otherwise similar biologic handling of the mercurial, remains unclear. This difference prevents one from making a more positive statement concerning clinical application of the pre-dosing phenomenon noted in rats. Previously cited clinical studies by such reliable observers as Blau and Bender (1), and Croll *et al* (6), which demonstrate threefold reduction in renal retention of ^{203}Hg following mercurhydrin pre-dosing, certainly lend credence to the probability that these rat data will ultimately prove transferable to man.

A simple and definitive human study is proposed to firmly resolve this question. This consists of giving a randomized group of patients one microcurie of ^{203}Hg -neohydrin, with half of the group receiving mercurhydrin beforehand. Existing differences in ^{203}Hg retention will be recorded by subsequent whole-body counting.

Most of the previous publications dealing with renal irradiation following ^{203}Hg -neohydrin injection assumed uniform renal distribution of the radioisotope. However, auto-radiographic studies performed by Desgrez *et al* (17), Rennels and Ruskin (14), and others have conclusively shown that the ^{203}Hg localized in the renal cortex. The volume of the cortex, calculated on the basis of the cortex being an ellipsoid, has been estimated to be approximately 50% of the total kidney volume. This finding was confirmed in the present study by the dissection of cortex from the rest of the kidney, with its weight being half that of the total kidney.

Earlier work in our laboratory (18) showed agreement with Blau and Bender's estimated renal dose in man of 35-40 rad following a dose of ^{203}Hg -neohydrin, 10 $\mu\text{C}/\text{kg}$ body weight. In view of the above noted auto-radiographic localization of ^{203}Hg and cortical volume calculations, this should be revised to a dose of 70-80 rad to the renal cortex and a much lesser amount to the rest of the kidney.

Assuming that the *flushing* effect is clinically applicable if one precedes ^{203}Hg -neohydrin, 10 $\mu\text{C}/\text{kg}$, injections with stable mercurhydrin, the expected renal cortical dose will be approximately 24-27 rads.

This amount of renal irradiation is not to be lightly discounted and must be weighed against the urgency of the brain scan and availability of preferable alternative radioisotopes. On the other hand, there is no pathophysiologic evidence available to demonstrate that this amount of renal irradiation is of clinical significance. Exteriorized dog kidneys were exposed to 500 rad single blast 200 kvp irradiation by Maier and Casarett (19). Extensive studies performed up to six months later revealed no physiologic alterations and only minimal morphologic changes.

Serious reactions following organic mercurial administration are extremely rare and are usually noted only after intravenous or several previous intramuscular injections. Attesting to the infrequent occurrence of undesirable effects, De Graff and Nadler noted that in 48,000 consecutive injections, mostly intravenous, there were no serious toxic reactions or deaths (20). The only true contraindications to the initial use of mercurial diuretic are known mercury allergy and renal insufficiency; otherwise, the loading dose of intramuscular mercurhydrin can be given with the least possible risk.

SUMMARY AND CONCLUSIONS

- 1) A controlled experiment was performed on rats to test the hypothesis that previously administered stable mercurial diuretic reduces renal retention of ^{203}Hg -neohydrin.
- 2) There was a three-fold reduction in the renal retention of ^{203}Hg -neohydrin following previously administered diuretic doses of mercurhydrin.
- 3) Administration of mercurhydrin 1, 8 or 24 hours before ^{203}Hg -neohydrin affected renal ^{203}Hg retention to an equal degree.

- 4) The probability of these findings being transferable to man is discussed. Assuming this to be the case, pre-dosing with a diuretic dose of mercurhydrin (1-2 cc) should reduce renal cortical irradiation from ^{203}Hg -neohydrin, $10 \mu\text{C}/\text{kg}$, to approximately 24-27 rad. This is felt to be a tolerable and safe dose.
- 5) Organic mercurial diuretics, used on a one-time basis, are considered quite safe and essentially free of risk.

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REFERENCES

1. BLAU, M., AND BENDER, A.: Radiomercury (Hg^{203}) Labeled Neohydrin: A New Agent for Brain Tumor Localization, *J. Nucl. Med.*, **3**:83-93, 1962.
2. BRENNER, M., PIHKANEN, T., AND VOUTILAINEN, A.: Radioisotopic Diagnosis of Brain Tumors, *Ann. Med. Exp. Fenn.*, **42**:145-151, 1964.
3. DUGGER, G. S., AND PEPPER, F. D.: The Reliability of Radioisotopic Encephalography, *Neurology*, **13**:1042-1053, 1963.
4. SELVERSTONE, B., AND GILLESPIE, G.: Localization of Brain Tumors with Radioactive Mercury, *Tufts Folia Medica*, **9**:77, 1963.
5. SKLAROFF, D., et al.: Cerebral Scanning with Radioactive Chlormerodrin (Neohydrin), *Neurology*, **13**:79-85, 1963.
6. CROLL, M., BRADY, L., AND HAND, B.: Brain Tumor Localization Utilizing Mercury-203, *Radiology*, **78**:635-637, 1962.
7. SODEE, B.: *Scintillation Scanning in Clinical Medicine*, Ed., Quinn, J. L., III, Philadelphia: W. B. Saunders Co., p. 228, 1964.
8. MC AFEE, J.: *Scintillation Scanning in Clinical Medicine*, Ed., Quinn, J. L., III, Philadelphia: W. B. Saunders Co., p. 229, 1964.
9. FAWAZ, G., AND FAWAZ, E.: Mechanism of Action of Mercurial Diuretics, II., *Proc. Soc. Exp. Biol. and Med.*, **87**:30-34, 1954.
10. WACHSTEIN, M., AND MEISEL, E.: Protective Action of Certain Amino Acids on Toxicity of Mercurial Diuretics in Rats, *Proc. Soc. Exp. and Biol. Med.*, **76**:523-527, 1951.
11. BORGHGRAEF, R., AND PITTS, R.: The Distribution of Chlormerodrin (Neohydrin) in Tissues of the Rat and Dog, *J. Clin. Invest.*, **35**:31-37, 1956.
12. CALESNICK, B., WASE, A., AND ALTARELLI, V.: Distribution Studies on Radioactive Hg^{203} Sodium Mercaptomerin in Animals, *Proc. Soc. Exp. Biol. and Med.*, **103**:22-25, 1960.
13. WEDEEN, R. P., AND GOLDSTEIN, M. H.: Renal Tubular Localization of Chlormerodrin Labelled with Mercury-203 by Autoradiography, *Science*, **141**:438-439, 1963.
14. RENNELS, E. G., AND RUSKIN, A.: Histochemical Changes in Succinic Dehydrogenase Activity in Rat Kidney Following Administration of Mercurial Diuretics, *Proc. Soc. Exp. Biol. and Med.*, **85**:309-314, 1954.
15. SANABRIA, A.: Ultrastructural Changes Produced in the Rat Kidney by a Mercurial Diuretic (Meralluride), *Brit. J. Pharmacol.*, **20**:352-360, 1963.
16. GOODMAN, L., AND GILMAN, A.: *The Pharmacological Basis of Therapeutics*, Second Ed., New York: The Macmillan Co., 1958.
17. DESCREZ, A., RAYNAUD, C., AND KELLERSHOHN, C.: Le Scintigramme Renal, *La Presse Medicale*, **70**:2194-2196, 1962.
18. MILLER, H.; GREEN, J., AND LEVINE, J.: Metabolism of Chlormerodrin- Hg^{203} , *Investig. Urology*, **1**:112-120, 1963.
19. MAIER, J. G., AND CASARETT, G.: Patho-Physiologic Aspects of Radiation Nephritis in Dogs, *Univ. of Roch. AEC Project*, UR 626, June, 1963.
20. DE GRAFF, A., AND NADLER, J.: A Review of the Toxic Manifestations of Mercurial Diuretics in Man, *J.A.M.A.*, **119**:1007-1011, 1942.