THE DISTRIBUTION OF CHLORMERODRIN (NEOHYDRIN®) IN TISSUES OF THE RAT AND DOG[1]

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No less than three lines of evidence suggest that organic mercurial compounds exert a diuretic action by virtue of their specific accumulation in renal tubular cells. Govaerts (1) showed that a kidney, removed from a donor animal at the peak of mercurial diuresis, maintains a high rate of urine flow when transplanted into a nondiuretic recipient animal. Bartram (2) demonstrated that the injection of a minute dose of a mercurial diuretic into the artery supplying one kidney causes a prolonged diuresis limited to that kidney alone. Immediately following an intravenous injection of a mercurial diuretic Weston, Grossman, Lehman, Ullmann, Halperin, and Leiter (3) observed that the rate of removal of mercury from the arterial blood by the kidney exceeds the rate of excretion of mercury into the urine.

It is now generally agreed that mercurial diuretics block the renal tubular reabsorption of some limited fraction of the sodium and chloride ions filtered through the glomeruli (4). The elimination of this increased urinary load of osmotically active ions obligates the excretion of water, hence induces polyuria and loss of weight (5, 6). It is probable that mercurial diuretics interfere with some enzyme system or systems concerned either directly with the active tubular transport of ions or with the supply of energy to the transport mechanism. Although blockade of succinic dehydrogenase has been implicated in mercurial diuresis (7–10), evidence is by no means so conclusive as to demand general acceptance (11, 12).

The study described here provides quantitative information on the degree to which mercury is concentrated in the kidney and in other tissues following the injection of a mercurial diuretic, both as a function of time and as a function of administered dose. We have, in addition, studied the action of dithiopropanol on the distribution and excretion of mercury. Ease, rapidity, accuracy and sensitivity of analytic methods directed the use of a diuretic tagged with radiomercury (Hg^{203}) and quantified by gamma emission in a well-type scintillation counter. The rat was chosen as the major experimental animal because of its extensive use in recent histochemical and enzymatic studies (7–10) bearing on site and mode of action of mercurial diuretics. Limited data on the dog have been obtained for comparison. Because of the simplicity with which radiomercury can be incorporated, Chlormerodrin, 3-chloromercuri-2-methoxypropylurea (Neohydrin®) has been chosen for study. Although the analytic method employed quantifies mercury, not the diuretic molecule *per se*, this constitutes no serious drawback for two reasons. First, the significant component of the diuretic is no doubt mercury. Second, the carbon-mercury bond is strong and most probably is not ruptured in the body. Thus Weiner and Müller (13) have shown that Mersalyl is stable in the body and is quantitatively excreted in the urine as a cysteine-like sulfhydryl complex, no detectible mercury being eliminated in inorganic form. The same is probably true of Chlormerodrin (Neohydrin®) (14).

METHODS

3-Chloromercuri-2-methoxypropylurea has been synthesized in our laboratory following directions supplied by Dr. H. L. Friedman of the Lakeside Laboratories. It has been tagged with Hg^{203} and during its useful life has exhibited an activity of from 4000 to 800 counts per minute per microgram mercury in a well-type scintillation counter. The diuretic agent, prepared as the hydrochloride, has been neutralized to phenol red and injected deep into the thigh muscles of rats. We have used female albino rats, weighing roughly 200 gm., obtained from the Charles River Farms. Food and water were permitted *ad lib.* until the start of an experiment

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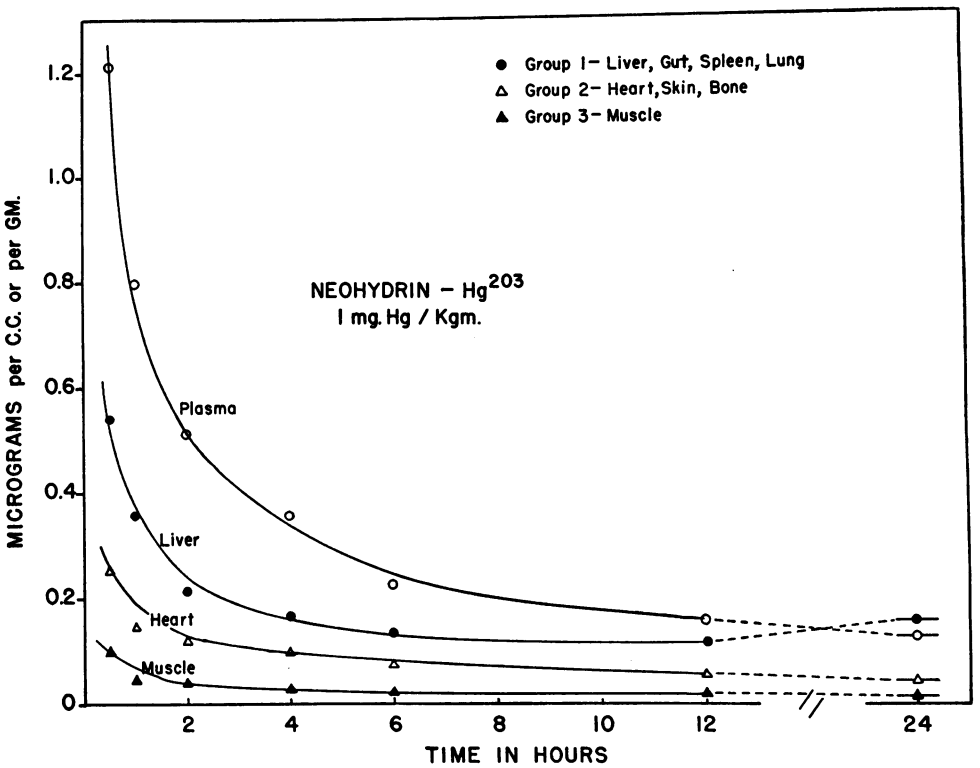

FIG. 1. PLASMA AND TISSUE CONCENTRATIONS OF MERCURY IN RATS FOLLOWING THE INTRAMUSCULAR ADMINISTRATION OF 1.0 MG. Hg^{203} PER KILOGRAM AS CHLORMERODRIN (NEOHYDRIN®)

To avoid confusion, results on only three tissues are included, namely liver, heart, and muscle. Concentrations of mercury in the tissue making up groups 1 and 2 were comparable to those illustrated for liver and heart, respectively. Each datum is a mean value derived from observations on 6 rats.

but not thereafter. Immediately after injection, the rats were placed in individual glass metabolism cages.[3] At the end of the experimental interval (*i.e.*, at ½, 1, 2, 4, 6, 12, or 24 hours), urine was expressed from the bladder by pressure over the lower abdomen, the animal was etherized and blood was rapidly drawn from the inferior vena cava. The animal was then killed and tissue samples were removed, weighed on a torsion balance, and inserted into standard test tubes for counting. One or 2 cc. of plasma, similar volumes of diluted urine and up to 2 grams of tissue were counted. Because we were more interested in total recovery of mercury excreted in the urine than in an estimation of the magnitude of the diuresis, the cage and screen were washed down with some 30 cc. of distilled water and the urine and washings diluted to known volume. One of the two kidneys was decapsulated, weighed, minced and placed in a glass homogenizer with teflon pestle. Sufficient fluid was added to form a 1:10 dilution and the kidney was thoroughly ground. After further dilution, an aliquot was removed for counting. For the most part, sufficient counts were accumulated to ensure an accuracy of from 1 to 5 per cent. For tissues of low activity at 12 and 24 hours, it did not seem worthwhile to prolong counting times to attain this degree of accuracy. Each datum presented is based on the average of individual determinations on six rats. In all, some 72 rats were used.

Data are also presented from two experiments on dogs sacrificed at the peak of diuresis some two hours after an intravenous dose of 1.0 mg. of mercury per kilogram as Chlormerodrin.

[3] These cages were prepared by Dr. Frank Carpenter from 1-liter pyrex beakers by sealing a tube into and drawing down the bottom to form a funnel. A stainless steel screen floor was inserted to prevent contamination of urine with feces.

RESULTS

In Figure 1 are summarized the concentrations of mercury in plasma and in representative tissues other than kidney following the intramuscular injection of roughly 1.0 mg. of mercury per kilogram

TABLE I

Plasma and kidney concentrations of mercury and per cent of the dose bound by the kidneys and excreted in the urine following the intramuscular administration to rats of 1.0 mg. Hg^{203} per kilogram as Chlormerodrin (Neohydrin®)

Number of rats	Time *hours*	Mean body weight *gm.*	Mean weight kidneys *gm.*	Plasma conc. *μ gm./cc.*	Kidney conc. *μ gm./gm.*	Kidney / Plasma	Per cent dose in kidneys	Per cent dose excreted
6	1/2	212	1.494	1.210	42.3	35.0	31.6	0.11
6	1	206	1.504	0.796	55.6	69.9	41.8	0.20
6	2	209	1.436	0.508	75.2	148.0	54.0	0.43
6	4	205	1.458	0.352	97.7	277.0	71.2	1.27
6	6	211	1.480	0.225	108.	480.0	80.0	2.10
6	12	223	1.582	0.154	94.0	610.0	74.3	11.6
6	24	210	1.376	0.124	97.5	786.0	67.1	21.8

of body weight as radio-chlormerodrin.[4] Obviously, absorption from an intramuscular deposit is rapid for the peak plasma concentration was reached within the first half an hour after injection. Thereafter plasma concentration decreased, rapidly for the first six hours and then more slowly over 12 and 24 hours. In all, samples of eight different tissues, other than kidney, were removed from each rat. Since these eight tissues fell into three groups with respect to mercury content, results on only one tissue from each group are included in Figure 1. Thus, liver, gut, spleen, and lung fall into one group exhibiting a moderate concentration of mercury relative to plasma. This group is exemplified by liver. Similarly, a second group, including heart, skin, and bone, is exemplified by heart. Skeletal muscle stood alone in exhibiting a very low concentration of mercury. In general, all tissue concentrations other than kidney, varied in parallel with plasma concentration. Only in the case of liver at 24 hrs. did the tissue concentration definitely exceed the plasma concentration. Probably the most variable tissue of all was gut. The sample, which included duodenum and jejunum, was variably contaminated with bile, although the gut was stripped to remove its contents prior to weighing and counting.

In Table I are summarized the data on the renal uptake and excretion of the mercury of Chlormerodrin from those same experiments presented in Figure 1. Of special interest are the kidney concentrations, expressed in micrograms per gm. of tissue, the kidney/plasma concentration ratios, and the per cent of the dose bound by the kidneys and excreted in the urine. It is evident that within a half-hour after the injection of 1 mg. per kilo of mercury as Chlormerodrin, 32 per cent of the dose was taken up by the kidneys at a concentration of 42 micrograms per gm. tissue. The kidney/plasma concentration ratio was 35. From 4 to 12 hours some 70 to 80 per cent of the dose was fixed in the kidneys at a concentration of approximately 100 micrograms per gm. of tissue.

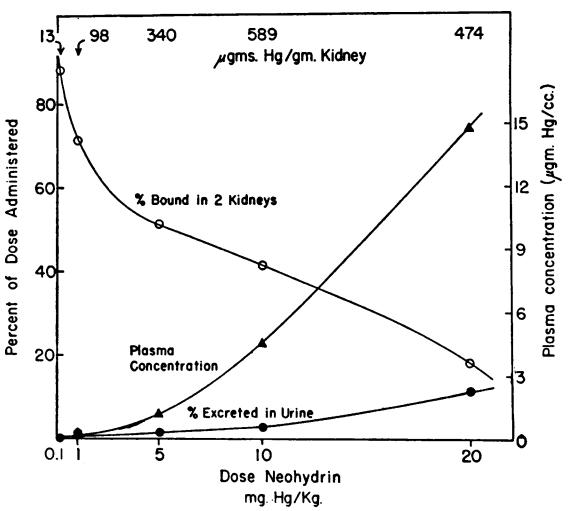

FIG. 2. RELATIONSHIPS AMONG PLASMA MERCURY CONCENTRATION, THE PER CENT OF THE MERCURY BOUND BY THE KIDNEYS, AND THE PER CENT OF THE MERCURY EXCRETED IN THE URINE FOUR HOURS AFTER THE INTRAMUSCULAR INJECTION IN RATS OF 0.1, 1.0, 5.0, 10.0 OR 20.0 MG. HG^{203} PER KILOGRAM AS CHLORMERODRIN (NEOHYDRIN®)

At the top of the chart, absolute concentrations of mercury are given in terms of micrograms per gram of kidney. Each datum is a mean value derived from observations on 6 rats.

[4] 1.83 mg. of Chlormerodrin contains 1.0 mg. of mercury. Each rat received 200 micrograms of mercury and since the weight of the rats used in this group of experiments averaged 211 gm., the dose administered was slightly less than 1.0 mg. of mercury per kilogram, the usual therapeutic dose of most mercurial diuretics in man.

TABLE II

Effects of BAL (dithiopropanol) on renal uptake and excretion of mercury by the rat *

Condition	Number of rats	Mean body weight gm.	Plasma conc. μ gm./cc.	Kidney conc. μ gm./gm.	Kidney / Plasma	Per cent dose in kidneys	Per cent dose excreted
Diuretic only	6	205	0.352	97.7	277	71.2	1.27
Diuretic plus BAL	6	221	0.549	27.7	50	20.0	27.2

* Each rat received 1.0 mg. Hg^{203} per kilogram as Chlormerodrin (Neohydrin®) intramuscularly. Half of the rats received five times a molar equivalent of 10 per cent BAL in oil intramuscularly.

This is equivalent to a concentration of 5×10^{-4} molar mercury. Mercury *in vitro* in such concentration is capable of blocking a number of enzyme systems (15).

The kidney/plasma concentration ratio steadily rose throughout the 24-hour period. However, it should be noted that from the fourth to the twenty-fourth hour, the increase in ratio was due to the drop in plasma concentration, for the kidney concentration remained essentially constant. Urinary excretion was negligible for the first six hours and even after 24 hours only 22 per cent of the dose had been eliminated. In this respect, the rat differs radically from both man (16, 17) and dog (*vide infra*) for in these forms as much as 40 or 50 per cent of the total dose administered may be excreted within two hours.

In Figure 2 are summarized results obtained four hours after the intramuscular injection of 0.1, 1.0, 5.0, 10, and 20 mg. of mercury per kilogram as Chlormerodrin. Each datum is the average of the values obtained in six rats. At the top of the graph are given the concentrations of mercury in kidney tissue at each dose level. It is apparent that concentration increased from 13 to 589 micrograms per gram of kidney as dose was increased from 0.1 to 10 mg. per kilogram body weight. Since the increase in concentration was less than proportional to the increase in dose, the per cent of the dose bound by the kidneys progressively fell. The largest dose of 20 mg. per kilogram was frankly toxic and the animals appeared in poor condition. One was anuric. The fact that the kidneys bound less mercury at this dose level than at 10 mg. per kilogram is no doubt a reflection of their poor physiologic state.

Dithiopropanol (BAL) is an effective antidote in mercury poisoning (18) and has been shown to abolish mercurial diuresis (19). Both actions are presumably due to the formation of an inactive mercaptide, in the one instance, with the two free valences of inorganic mercury, in the other instance, with the single free valence of the organically combined metal. In Table II are summarized the effects of BAL on the binding and excretion of mercury by the kidneys. In the first group of six rats, the diuretic alone was administered in the amount of 1 mg. of mercury per kilogram. In the second group of six rats, the same dose of diuretic was given, but simultaneously five times a molar equivalent of 10 per cent BAL in oil was injected into the opposite thigh. Four hours later, both groups of rats were sacrificed. As a consequence of treatment with BAL, only 20 per cent of the administered dose of mercury was bound in the kidneys at a concentration of 27.7 micrograms per gm. In contrast, in the untreated animals, 71.2 per cent of the dose was bound in the kidneys at a concentration of 97.7 micrograms per gm. The BAL treated animals excreted 27.2 per cent of the administered dose in four hours,

TABLE III

Effects of BAL (dithiopropanol) on the uptake of mercury by liver and muscle of rats *

	Number of rats	Mean body weight gm.	Plasma conc. μ gm./cc.	Liver conc. μ gm./gm.	Liver / Plasma	Muscle conc. μ gm./gm.	Muscle / Plasma
Diuretic only	6	205	0.352	0.165	0.47	0.028	0.08
Diuretic plus BAL	6	221	0.549	0.393	0.72	0.170	0.31

* Data from same experiments presented in Table II.

whereas the untreated animals excreted only 1.27 per cent.

In Table III are summarized the effects of BAL on the distribution of mercury in liver and muscle of rats. These data are from the same experiments summarized in Table II. A variety of tissues were studied but since all behaved in a qualitatively similar fashion, presentation of data will be limited to these two. The plasma concentration of mercury was higher in the BAL treated animals than in those receiving the diuretic only. Similarly, the liver and muscle concentrations were higher in the BAL treated group. However, tissue concentrations increased more than plasma concentration. Accordingly the liver/plasma and the muscle/plasma ratios rose in consequence of BAL treatment. It is obvious that the effect of BAL on the accumulation of mercury in kidney tissue is exactly opposite to its effect on all other tissues. In kidney, BAL reduces the tissue accumulation of mercury. In all other tissues studied, namely liver, spleen, lung, gut, heart, skin, bone, and muscle, BAL increases the tissue accumulation of mercury. Perhaps it would be better to say that BAL increases the tissue penetration of mercury.

In Table IV are summarized results obtained in two dogs in which a dose of 1 mg. of mercury as Chlormerodrin per kilogram was administered intravenously.[5] Two hours later the animals were sacrificed. Several differences of a quantitative nature between the rat and the dog as well as obvious qualitative similarities are evident from an inspection of this table. Thus, 40 per cent of the administered dose of Chlormerodrin was excreted in two hours by the dog. Less than 1 per cent was excreted by the rat during the same time interval. In the dog, several tissues other than the kidney, namely liver, spleen and adrenal, may concentrate mercury relative to plasma, *i.e.*, exhibit a tissue/plasma ratio greater than 1.0. In the dog, mercury is highly concentrated in the outermost layer of the renal cortex, whereas in the papillary part of the medulla it is concentrated only moderately with respect to the plasma and indeed is less concentrated than it is in the urine excreted just prior to sacrifice.

[5] We acknowledge our indebtedness for these data to two groups of Second Year Medical students who performed these experiments under our supervision in the course of Project Teaching in Physiology.

TABLE IV

Plasma and tissue concentrations and rates of excretion of mercury in two dogs two hours after the intravenous injection of 1.0 mg. Hg^{203} per kilogram as Chlormerodrin (Neohydrin®)

Tissue	Dog A		Dog B	
	μ gm./gm. or/cc.	Tissue / Plasma	μ gm./gm. or/cc.	Tissue / Plasma
Plasma	0.91	—	1.02	—
Kidney				
Outer cortex	163.	179.	131.	128.
Medullary papilla	2.17	2.38	3.38	3.31
Liver	2.82	3.10	2.30	2.26
Spleen	1.93	2.12	0.86	0.84
Intestine	0.71	0.78	—	—
Adrenal	0.51	0.56	1.66	1.63
Heart	0.27	0.30	0.29	0.28
Muscle	0.16	0.18	0.11	0.11
Excretion in 2 hours	40.3% of dose		40.8% of dose	

DISCUSSION

The most impressive feature of our observations is that in both rat and dog the mercury of Chlormerodrin is highly concentrated in the kidneys relative to the blood plasma and in comparison with any other tissue. While others (20, 21) have observed some concentration of mercury in the kidneys of man and the rabbit following organic mercurial diuretics, none made his observations at times of maximum uptake. If one makes the logical assumption that organic mercurial compounds combined reversibly with certain cellular enzymes to render them inactive, the predominant renal action of these compounds is understandable on the basis of their high concentration in renal tubular cells. According to Greif, Sullivan, Jacobs, and Pitts (22), the mercury is most highly bound per mg. of nitrogen by the soluble protein fraction of the cells of the outermost layers of the renal cortex. However, mercury is firmly fixed, though in somewhat lesser concentration, in the mitochondrial fraction of these cells. The nature of the proteins or the organelles of renal cortical cells which bind mercury and the reasons why they, rather than the proteins and organelles of other tissues, preferentially bind mercury are factors of significance to an understanding of diuretic mechanism. Unfortunately we can shed no light on them at the moment.

It is tempting to postulate that the delay in onset of diuresis following administration of an organic

mercurial diuretic is related 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. In the rat, the slow excretion and the sustained high cell content of mercury would argue for a prolonged diuretic action. In fact, according to Fawaz and Fawaz (11), mercurial diuresis in the rat is slow in onset and prolonged in duration. In contrast, the brisk onset of diuresis in the dog may be correlated with very rapid uptake of mercury and the relatively brief duration of diuretic action may be correlated with rapid excretion of mercury (23). We must however, temper our enthusiasm for this thesis by noting that the rat still retains a major part of the mercury in the kidneys after 24 hours, yet according to Fawaz and Fawaz (11), is not diuretic at that time. In both rat and dog, the inhibition of diuresis by BAL is associated with reduced renal binding and more rapid excretion of mercury.

Both Meralluride (24) and Chlormerodrin (25) are known to be highly bound to plasma proteins. Hence only insignificant traces of these diuretics enter the urine in the glomerular filtrate. Weiner and Müller (13) have shown that Mersalyl and Chlormerodrin as well (14) are excreted in the urine of the dog in combination with some short chain sulfhydryl compound such as cysteine and postulate that this complex is a detoxification product. If the uptake and concentration of mercury within the tubular cell is associated with diuresis, then the combining of the diuretic with cysteine and the secretion of the complex in the urine may be associated with the restoration of normal reabsorptive function of the tubular cells. It is possible that the cysteine metabolism of the rat kidney is much less active than that of the dog kidney and hence that the excretion of mercury is proportionately slower. The administration of BAL to either the rat or dog provides a large excess of sulfhydryl groups with which to complex the diuretic. Accordingly, renal concentration is reduced and rate of excretion increased. However, BAL must have some additional action, for it increased the concentration of mercury in all tissues other than kidney. It might do so by reducing binding to plasma proteins and by increasing diffusibility across cell membranes, perhaps by increasing lipid solubility.

Adam (26) has recently shown that the kidney of the rabbit concentrates mercury administered as the bichloride salt. Fitzsimmons and Kozelko (27), have made similar observations in rhesus monkeys. Both groups have shown that BAL reduces renal binding, Adam emphasizing great enhancement of urinary excretion by the dithiol, Fitzsimmons and Kozelko pointing out that it increases penetration of all tissues other than kidney by mercury.

CONCLUSIONS

1. Following the intramuscular administration of 1 mg. of mercury per kilogram as Chlormerodrin (Neohydrin®) to rats, renal uptake of mercury reached a peak within six hours. Some 80 per cent of the administered dose was bound by the two kidneys at a concentration of approximately 100 micrograms of mercury per gm. of tissue.

2. The concentration of mercury in the kidneys of rats was sustained at a high level for more than 24 hours. Excretion was slow; only 21 per cent of a dose of 1 mg. per kilogram was eliminated in the urine in 24 hours.

3. Increasing the dose of Chlormerodrin from 0.1 to 10.0 mg. of mercury per kilogram failed to saturate the renal mechanism which binds mercury, although the per cent of the administered dose bound by the kidneys fell progressively.

4. No tissue studied bound mercury in a concentration even vaguely approaching that of the kidney.

5. Dithiopropanol (BAL) administered simultaneously with Chlormerodrin reduced the renal binding of mercury and augmented the rate of excretion of mercury. BAL likewise increased the diffusibility of mercury and caused an increase in the content of the metal in all tissues other than kidney.

6. The kidney of the dog similarly binds mercury in high concentration. Two hours after a dose of 1 mg. of mercury per kilogram as Chlormerodrin and at the peak of diuresis, the outer cortex of the kidney contained 130 to 160 micrograms of mercury per gm. The papillary portion of the medulla contained relatively small amounts of mercury. The dog differs from the rat in having somewhat higher concentrations of mercury in

liver and spleen and in excreting the mercury very rapidly in the urine.

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