Clinical Aspects of Mercurial Diuretics

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FROM the standpoint of the volume of literature, diversity of therapeutic indications and duration of use, mercury in its various forms has no equal among the commonly used drugs of today. Inorganic mercury was employed for its diuretic properties in the sixteenth century. Many references have been made to the combined use of digitalis and mercurous chloride. However, the policy of continuing the administration of mercury until stomatitis appeared was responsible for a decline in its popularity until fairly recently. There were no really significant advances in the use of mercurial diuretics until 1917, when an organic mercurial compound, Novasurol (the double salt of sodium mercurichlorophenyl oxyzacetate with diethyl barbituric acid), was introduced by Zeiler as an antisyphilitic agent. In 1920 Saxl and Heilig first reported an accidental observation on the efficacy of Novasurol as a diuretic.

Extensive search for organic mercurial diuretics of less toxicity resulted in the introduction of several such compounds. Of the more commonly used preparations, Salyrgan (sodium [o-(hydroxy-mercuric-methoxypropyl carbamyl) phenoxy]-acetate) was introduced in 1924, then Mercupurin (Mercuzanthin; sodium trimethyl - cyclopentane - dicarboxonic acid - methoxy - mercury - allylamide - theophylline), Mercuhydrin (sodium salt of methoxy-oxymercuripropyloxyurea with theophylline) and Thiomerin [disodium salt of N - (γ - carboxymethylmercapтомercuri - β - methoxy) propyl camphoric acid] (mercapto-merin sodium), the latest. The introduction of theophylline or a thiol group into the molecule reduced the toxicity without disturbing the diuretic effect of the mercury. The quantity of mercury and the manner in which it is bound in these compounds varies slightly. For example, Mercuzanthin and Salyrgan contain 37 to 42 per cent mercury by weight, Mercuhydrin 39 mg. per cc. and Thiomerin 40 mg.

CHEMISTRY

The chemical properties of mercury determine its biologic actions. For example, the local effect of mercury depends upon the concentration of mercurial ions. Highly ionized inorganic compounds exert greater toxic effects on tissues than do the less ionizable organic mercurial compounds. Solubility of the various mercurial compounds influences the rate of absorption and, in turn, the activity. Their solubility varies with the chemical medium, being less soluble in aqueous solutions containing low concentrations of protein than in those containing large quantities of protein. This latter condition exists in the body in the presence of therapeutic amounts of mercury and affects the rate of absorption from the site of injection. The chemical environment afforded by the body influences the phenomena of solubility, ionization and diffusion, all of which influence the pharmacologic effects of mercury.

The chemical form in which mercury of a
mercurial diuretic exists after injection into man has not been definitely established. Although protein binding of mercury has been demonstrated in vitro and in vivo, this does not exclude the existence of mercury in some combination other than with protein. The ionization equilibrium of protein mercurial complexes which exist in the body is also unknown. Rates of diffusion are certainly influenced by binding of mercury to large protein molecules, and alterations in diffusion affect some of the physiologic responses of the body to injection of mercury. It has been shown that under chemical conditions which exist in the body diffusion of mercury may be enhanced. The strong affinity of mercury and other heavy metals for thiol groups has been demonstrated, but it has not been established that the action of mercury in the body is mediated through reactions with thiol-containing compounds.

The active principle of all mercurial diuretics is the mercury ion. The diuretic action has been demonstrated to be alike for ionizable inorganic mercury, organic mercurials and colloidal mercury, though they vary considerably in toxic properties. The rate, duration and amount of diuresis vary with the particular compound of mercury. Per unit weight of mercury, the highly ionizable compounds are more potent diuretic agents than are the organic mercurial compounds.

PHARMACODYNAMICS

Detailed study of the metabolism of mercury in the body has been hampered by the rather cumbersome and insensitive chemical methods for mercurial analysis. Most methods involve digestion of the organic materials in the presence of reducing agents. Through volatilization of mercury, large amounts may be lost by such technics.

Absorption

Mercury may be absorbed by way of the respiratory and gastrointestinal tracts, the skin, vagina and subcutaneous tissues. The unpredictable nature of the absorption of mercury administered orally and rectally make these routes less dependable. The parenteral route is the most predictable and dependable. Absorption is rapid and satisfactory following intramuscular injection. The presence of theophylline greatly hastens absorption from muscle; DeGraff and associates found that approximately 80 per cent of the injected mercury had been absorbed within 30 minutes and 97 per cent at the end of one hour. Mercupurin and Salyrgan without theophylline were absorbed much more slowly; at the end of 4 hours 50 per cent remained, and at the end of 48 hours about 10 to 20 per cent of the mercury remained at the site of injection. Absorption from edematous or adipose tissue is much less rapid and may result in local reaction. Thiomerin apparently is absorbed satisfactorily from subcutaneous tissue; the curve of absorption from muscle is similar to that for Mercuzanthin and Salyrgan. Merccurial diuretics are absorbed slowly from ascitic fluid.

Studies of transfer of radiomercury of a labeled mercurial diuretic across a blister membrane revealed a reduction in transfer by protein binding of the mercury. The mercury was absorbed more slowly when suspended in a protein medium. No differences existed in rate of absorption or transfer in normal controls and in subjects with congestive heart failure. Elevation of venous pressure by inflating a cuff around the arm had no effect on the rate of absorption.

Distribution

Distribution of mercury throughout the body depends upon the form of the mercurial compound administered and the duration and route of administration. In mercurial poisoning, distribution of mercury in the body may be influenced by "overloading" or injury of the potential mercurial excretory mechanisms. The concentration of mercury attained in the tissues is certainly affected by failure of renal excretion. The excretion, distribution and storage of mercury in the body after a long course of inunction treatments is different from that observed after the single injection usually given for its diuretic effect. With inunction the body is brought into a state of "saturation" by frequent small doses; there is
storage of mercury throughout the body; excretion reaches a maximum at two to three weeks and may continue for 60 days or more after administration has been discontinued. Following oral administration of a mercurial diuretic over a period of four days, there may be continued excretion in the urine for 16 additional days. Such observations indicate that mercury is stored in the body.

Following a single intravenous injection, there is no "state of saturation" nor is equilibrium of distribution achieved if the kidneys are normal. Excretion is so rapid that the observed regression of mercury in the blood is attributable largely to renal excretion. There may be some storage after intravenous injection but it is relatively small by comparison with that following inunction treatments of syphilis, in which about 50 per cent of the administered mercury may be stored.

Mercury is widely distributed in the body. It has been found in almost every organ, including bone. The highest concentration is found in the kidney and the next highest in the liver. It appears in the urine in highest concentrations and in the bile in relatively high concentration. Maximum concentration in the bile is delayed many hours after the peak concentration in the blood is reached. After continuous administration, as by inunction, concentration in the bile may be higher than in the blood, but after a single intravenous injection, the relative concentration depends entirely upon the time of sampling. Thus, if sampling were made 24 hours after injection, when blood concentration is low, concentration in the bile might be higher. This is not true in the hours immediately following the injection.

After a single intravenous injection of a mercurial diuretic labeled with radioactive mercury, this element was found to enter ascitic, pleural and edema fluid and sputum slowly. None was found in sweat, gastric juice or spinal fluid. Washed human red blood cells contained no mercury. The fecal content of mercury varied widely from 0.01 to 26 per cent after intravenous administration of labeled Mercucyanin.15

Immediately after intravenous administration of a mercurial diuretic, concentration of mercury in the blood declines rapidly. If there is renal insufficiency, however, it remains elevated, and the distribution of mercury in the body differs from that found when the kidneys are normal. With normal renal function there is a large unidirectional shift of mercury into the urine. This shift is so rapid that little time is available for the relatively slowly diffusing mercury-protein complex to reach equilibrium of distribution throughout the body. If the kidneys fail to excrete the mercury, equilibrium of distribution may be attained. The extracellular fluid compartment in states of generalized edema may serve as a large storage depot for mercury.

The form in which mercury is stored in the body is unknown, but it is thought by some to be in combination with tissue proteins. This "stored" mercury may remain in the body for varying lengths of time. As with storage of lead, certain chemical environments, such as a high pH, encourage deposition of mercury, whereas acid precursors favor mobilization from storage depots. The concentration of mercury in the blood may be modified by factors which affect storage equilibrium.

Excretion

Although the principal avenue of excretion of mercury from the body is normally by way of the urine, it may occur by way of the saliva, bile, and intestinal mucosa and thus appear in the feces. The latter route becomes more important when the kidneys are diseased or have been injured by an overload of mercury.

The chemical state in which mercury is excreted is unknown. It may be excreted in different chemical forms in the stool and urine, and these forms may vary with time in either of these avenues of excretion. The extent to which the excreted mercurial compound may be influenced by the chemical state in which it is administered, such as the bichloride, succinate, salicylate, colloidal mercury or the organic mercurial diuretics, has not been determined, nor has it been definitely established that mercury is excreted as the same compound in which it was administered.

The pattern of renal excretion for mercury is influenced by the route and duration of
administration and by the rate of absorption. The excretory pattern of mercury administered slowly to the point of saturation is a gradual increase up to a maximum at the end of two to three weeks. The dosage and the blood concentration determine the amount excreted. The “saturation point” of the blood is reported to be 3 mg. per liter; when this level is exceeded, excretion occurs. With the large storage depots in the body, excretion may continue for as long as six months after therapy has been discontinued. Huffman\textsuperscript{14} observed urinary excretion for as long as 16 days after oral administration for four days. The time-course of excretion of mercury in urine following oral administration of a diuretic labeled with radiomercury has been described by Overman and associates.\textsuperscript{9} This involves the variable of intestinal absorption, but the peak excretion of mercury in the urine occurred at approximately 200 minutes after ingestion. Of the mercury which was recovered in the urine, approximately 50 per cent was recovered in the first 400 minutes after administration of the capsules. The last 20 per cent was recovered between 600 to 1500 minutes after ingestion.

Excretion of mercury is most rapid immediately after intravenous or intramuscular injection. The rate and completeness of excretion of the various diuretics are essentially the same. In the presence of normal kidneys, urinary excretion of intravenously administered mercury has been found to be complete in from 24 to 72 hours. Excretion of the last 10 to 20 per cent occurs so slowly that the complete time-course of urinary excretion is difficult to establish by the relatively insensitive chemical methods of analysis for mercury.

Previous studies\textsuperscript{8} indicated a qualitative directional similarity in practically all of the curves between urinary volume, excretion of mercury and concentration of mercury for a variety of mercurial compounds, organic and inorganic. Excretion reached a peak in one to two hours after injection and then descended as a parabolic curve. Curves for mean urinary excretion after intravenous injection were almost identical for many of the mercurial compounds. Diuresis following intramuscular injection was not materially slower than following intravenous injection, but the excretion of mercury was.

The time-course of renal excretion has been studied by means of a mercurial diuretic labeled with radiomercury.\textsuperscript{16,17} After intravenous injection the mercury appeared at the tip of a ureteral catheter in three and one-half to five minutes but the peak concentration was not reached until approximately 20 minutes after injection. The lag in time between renal excretion and extraction of mercury from the serum reflects retention within the kidney. The rate of excretion is slower in subjects with congestive heart failure than in normal subjects and is slower still in those with renal insufficiency, tending to vary indirectly with the degree of renal failure. The time required for one-half of all the administered mercury to be excreted in the urine serves as an index of the differences among normal and diseased subjects. Normal subjects excrete half the administered mercury in about two hours, whether it is given intravenously or intramuscularly; yet some mercury is usually still present in the urine at the end of 24 hours. In some subjects with congestive heart failure more than twice as long is required for excretion of one-half the administered mercury, the time varying considerably with the state of the failure. Renal insufficiency may result in extreme retardation of excretion of mercury. In one subject only 19 per cent was excreted in eight days, although there was a large volume of hyposthenuric urine during this time. It is therefore not correct to assume that excretion is complete in 24 hours simply because urinary volume is large. Daily administration may result in an accumulation of mercury in the body of normal subjects and an even greater accumulation in the presence of disease states such as congestive heart failure and renal insufficiency.

Site and Mode of Action

It has not been definitely established whether mercury possesses extrarenal actions which influence diuresis. Refractometric and blood chemical studies yield findings of hemo-dilution compatible with extrarenal action. There is, however, no evidence of mobilization
of fluids with consequent hemodilution before mercurial diuresis occurs. It is difficult to understand why purely renal action should be associated with hemodilution, since water and electrolytes should enter the circulation no faster than they are removed by the kidneys, were their migration determined entirely by renal excretion and renal action.

Renal effects of mercurial diuretics have been studied rather extensively. When small amounts of mercury were injected into one renal artery, diuresis ensued from the “injected” kidney only. With increasing doses of mercury, diuresis from the opposite kidney developed. Presumably, the extracting capacity of the injected kidney having been exceeded, the excess mercury gained access to the other kidney by way of the blood stream. These observations and those of Govaerts that a kidney taken from an animal at the height of mercurial diuresis continues to reveal diuresis when transplanted into the neck of an untreated animal indicate that the action of mercury can be due solely to direct action upon the kidney. However, extrarenal effects have not been excluded. Such extrarenal changes associated with mercurial diuresis as alteration in size of the extremities and rise in blood pressure may influence the diuretic action of mercury.

The precise site and mode of action of mercury in the kidney have received some attention but neither has yet been definitely ascertained. Abundant evidence tends to indicate that the rate of glomerular filtration is not increased by mercurial diuretics alone. When a xanthine is combined with the mercurial diuretic, there may be a slight rise in rate of glomerular filtration, but it is not considered to be of sufficient magnitude to explain the observed diuresis. Furthermore, if the mercurial diuretics are given in extremely large doses, the rate of glomerular filtration may decline.

Increased urinary excretion of electrolytes and water without antecedent measurable changes in their blood concentration nor significant changes in rate of glomerular filtration supports the concept of a tubular site of action of mercury. Micropuncture studies indicate that mercury “abolished the power of active reabsorption and power of selective retention of diffusible substances by the renal tubule.” Many experimental and clinical investigations have demonstrated reduction of tubular reabsorption with resultant increase in urinary excretion of electrolytes and water, the precise mechanism being unknown. Speculation has been directed at alterations in certain enzymatic processes in the tubular cells which are concerned with transport and selective reabsorption of electrolytes. Mercury has been shown to inactivate certain enzyme systems which may be reactivated by BAI.

Several of the specific functions of the kidneys have been studied during mercurial diuresis: tubular maximum excretory capacity for glucose (Tm), glomerular filtration, renal paraaminohippurate extraction and renal clearances of mannitol, sodium, chloride and uric acid. Weston and associates obtained a depression of glucose Tm and PAH extraction following mercury. TmPAH was depressed and a decrease of 40 to 80 per cent in Tm at the time of maximal electrolyte excretion occurred. Apparently mercury depresses specific proximal tubular function and glucose reabsorption in man. Differences in response between man and dog have been observed. Because of species differences in renal function, correlation and application of data should be made cautiously when different animals are under consideration.

The site of action of the mercurial diuretics has been suggested to be the distal tubule rather than the proximal segment or both. In dogs prepared by saline infusion before and after injection of mercury the sodium excretion was intensified with increasing doses of mercury up to a certain point, beyond which added increments of mercury had no additional effect. With larger doses, the peak of sodium diuresis was reached more quickly. The existence of an upper level of sodium excretion, regardless of the dose of mercury, suggested that only a fraction of renal tubular reabsorptive function was “mercury sensitive.” This fraction has been estimated to be approximately 15 per cent of that reabsorbed during the control periods, a value compatible with the view that 80 to 85 per cent is reabsorbed.
in mercury-insensitive proximal tubules. Because mercury and Pitressin combined did not increase excretion of sodium beyond that obtained with mercury alone, it was concluded that both acted at the same site, the distal segment. The investigators were of the opinion that mercury influences sodium reabsorption in the proximal tubules only when the dose of mercury is sufficient to produce tissue damage.

For numerous reasons it cannot be concluded from these experiments that mercurial diuretics act solely on the distal tubule in man. Experiments were carried out on dogs, which were receiving large amounts of normal saline, the dosage of mercury was large, the difference between therapeutic and toxic levels of mercury cannot be definitely differentiated, and broad assumptions were made by the investigators in order to reach this conclusion.

The most striking response to injection of mercury is the diuretic effect, which is usually complete in 24 hours but occasionally may last as long as 48 hours. The volume of urine excreted varies widely, ranging from 1 to 3 liters, but occasionally as much as 15 liters of urine are passed by patients with anasarca. The specific gravity is lowered for the duration of the diuresis.

More striking than the water diuresis is the preceding outpouring of electrolytes in the urine. Excretion of chloride, sodium, potassium and magnesium is increased, whereas excretion of phosphates and sulfates is not particularly affected.25 The electrolyte excretion depends upon the concentration of chloride and sodium in the blood, since hyponatremia and hypochloremia are associated with little or no diuretic response.26 Following excessive outpouring of sodium, chloride, potassium and water, there is usually decreased excretion of these substances for one to three days or until normal water and electrolyte balance is restored.25

As a result of excretion of large amounts of electrolytes and water, certain chemical changes occur in the blood. Concentration of chloride in serum and extracellular fluid usually declines and that of the bicarbonate rises, that of sodium remaining essentially unchanged.27

Concentration of sodium in the extracellular fluid has been reported to be low in some instances after administration of mercurial diuretics, depending largely upon previous concentration and intake of sodium. Schwartz and Wallace27 found a greater negative balance of chloride than of sodium. Potassium appeared in the urine in greater concentration than could be explained on the basis of its concentration in the extracellular fluid. Additional observations are required to define these effects more precisely, especially for potassium.

The diuretic response to injection of mercury is conditioned by the electrolyte concentration in the body and, therefore, may be influenced by premedication with acidifying salts. The diuretic response may be increased by any measures which enhance renal blood flow and rate of glomerular filtration, such as bed rest and administration of xanthines.

There are many physiologic responses to the intravenous injection of a mercurial diuretic besides excretion of sodium and water. Blood pressure may increase occasionally because of generalized vasoconstriction. The volume of the limbs and of the kidney has been observed to decline, accompanied by a transient decline in renal blood flow with resultant transient antidiuretic effect.28 Changes of hemoconcentration and hemodilution are inconstant. Blood urea is not characteristically altered; it may rise, fall or remain unchanged.

Toxicity

Mercury has long been recognized as a protoplasmic poison. In this respect, the more highly ionized the mercurial compound is, the more toxic it is. Mercury exerts a local toxic effect at the site of contact with the tissues. Gastrointestinal symptoms of nausea, vomiting, abdominal pain and diarrhea, which is occasionally bloody, attest to the toxic local action of mercury when taken orally. Proctitis and ulceration in the rectum may appear when mercurial diuretics are administered as suppositories. Their local irritant effect when given intramuscularly or subcutaneously is well established. It is reduced slightly by the presence of the xanthines and is considerably diminished by the presence of thiol groups.

After mercury gains access to the body, it
tends to become more concentrated in certain organs, although its action is widespread. It is known that large doses of mercury result in necrotic changes in the tubular epithelium of the kidney, and in animals smaller doses acting over a long period of time produce the same changes. The question of damage to the renal tubular epithelium from prolonged frequent injections of therapeutic amounts of the mercurial diuretic has been posed. Enough experience has been accumulated to indicate that mercury may be used in amounts adequate to achieve a diuretic effect without apparent injury. Renal function tests and histologic examination of the kidneys in subjects who had received large quantities of mercurial diuretics have rarely revealed any damage. Occasionally the kidney may exhibit tubular damage following intravenous injection of a mercurial diuretic in the usual doses. When large doses of mercury are administered, toxic changes may also occur in the liver.

Certain differences in reaction to mercurials are known to exist among different species. In animal experiments, amounts of mercury comparable to those used for diuresis in man may produce transient or permanent renal damage. In rats, proteinuria due to injection of a foreign albumin was found to increase renal tubular toxicity of mercury when the mercury and albumin were administered simultaneously. When protein was given prior to the mercury, a protective action resulted. The clinical significance of these observations has not been established.

Toxic reactions of the cardiovascular system to intravenous injection of a mercurial diuretic are more important clinically. The cardiovascular response varies with different dosages of mercury. Generalized vasoconstriction and more serious reactions are blocked by glutathione, cysteine and BAL. One of the most frequent cardiac manifestations of toxicity is a disturbance in cardiac mechanism. Animals exhibit considerable species differences in susceptibility to the cardiotoxic action of mercury. Dilutions of either organic or inorganic preparations of mercury of 1 to 100,000 or greater were sufficient to produce heart block in the turtle; this was reversed by sodium thiosulfate. Farah and his associates found that the monothiols, cysteine and glutathione and dithiol BAL increased the half lethal dose in cats, dogs and mice. Heart failure produced in a heart-lung preparation by infusion of Salyrgan was reversed by these compounds. Large amounts of mercury produced a rapid fall in blood pressure.

Other attempts have been made to protect the cardiovascular system against the toxic action of mercury. Pines and associates were able to reduce the incidence of ventricular fibrillation in dogs by the use of magnesium sulfate in conjunction with the mercurial diuretic. Disturbances in conduction were unaffected. Anoxia of the cardiac muscle was found to intensify its sensitivity to the toxic action of mercury. Quinidine, instead of preventing ventricular fibrillation, appeared to precipitate it. Ventricular asystole has been reported to be the cause of death from an overdose of Mercuhydrin and ventricular fibrillation from Mercurophylline and Mersalyl.

The importance of the toxic cardiovascular reactions is apparent from reports of fatalities following intravenous injection of mercurial diuretics. Death occurs quickly, usually within one to three minutes. The speed of injection is important in these reactions, as a rapid injection may "perfuse" the heart with a sufficiently high concentration of mercury to cause a fatal cardiac mechanism. With slow injection and adequate mixing with the blood, the concentration is relatively low. In some instances death followed the first injection; in others it came suddenly after many previous injections were well tolerated. Sometimes premonitory signs, such as apprehension, dyspnea, substernal discomfort, sweating, pallor, changes in pulse and giddiness, appeared with previous injections. A number of nonfatal convulsions have been reported. In addition to the immediate reactions, certain delayed reactions, such as fever, chills, asthmatic attacks and cutaneous eruptions, have been observed. The relatively large number of deaths which have occurred in children is impressive. The amount of mercury administered to children seems unusually large for the body weight.
Occasionally when some of the "warning signs" or a delayed reaction have been encountered, subsequent injections of a different mercurial diuretic have been well tolerated, but the presence of any reaction, either immediate or delayed, indicates the need for caution in the use of any additional mercurials. If necessity dictates their continued use, a small amount of a different preparation should be tried, preferably not by vein. If well tolerated, the amount may be increased.

There are no significant differences in toxicity among the commonly used mercurial diuretics, Mercuzaanthin, Salyrgan and Mercuhydrin, all of which contain theophylline, but differences in reaction at the site of injection may occur when administration is intramuscular or subcutaneous. The feasibility of reducing the cardiotoxic properties of a mercurial diuretic while retaining the diuretic properties has been demonstrated by the use of monothiol compounds in conjunction with mercury. Thiomerin, in which sodium mercaptoacetate replaces the theophylline, is the latest mercurial diuretic to be introduced. Its diuretic potency is approximately equal to that of other diuretics but the cardiotoxic action and local reaction at the site of injection are minimal. However, some toxic effects other than the acute cardiovascular reactions have been found to be more severe with this drug than with the other organic mercurial diuretics. In regard to delayed deaths occurring from five minutes to seven days after injection, Capps and associates found Thiomerin to be more toxic in rats than Mercuhydrin or Mercurophylline by both intravenous and subcutaneous routes of administration. Observation over a period of four days after injection of Thiomerin into mice revealed delayed toxicity equal to that associated with Mercuhydrin, Mercuzaanthin and Salyrgan. Thiomerin produced a greater decline in rate of glomerular filtration in dogs than did the other mercurials. Stomatitis and diarrhea occurred more frequently among the dogs injected with Thiomerin. Although many enthusiastic reports have appeared about the low toxicity of Thiomerin, it must be remembered that it is a new drug and certain observations in animals indicate that further clinical observations concerning its toxicity are needed.

Clinical Applications

The specific indication for mercurial diuretics is well defined—the need for reduction in size of the extracellular fluid compartment and its maintenance at a desirable level. There are a number of clinical states in which this is desirable, such as congestive heart failure, the nephrotic syndrome and hepatic cirrhosis with ascites. Other clinical states associated with accumulation of fluids in the body, such as lymphedema, malignancy with ascites, and inflammatory states, do not usually respond favorably to mercurial diuretics. Although a reduction in edema may not be concerned with a direct attack upon the primary disease, the patient appears to be improved in most instances.

Studies on the relative efficacy of the various diuretics available commercially are too numerous to cite. As far as volume of diuresis is concerned, there is no particular advantage of one over the other by the intravenous route. Thiomerin, given subcutaneously, produces diuresis approximately equal to that resulting from intramuscular or intravenous injections of the other preparations. A drug which may be administered subcutaneously instead of intramuscularly or intravenously has definite advantages clinically: for example, it is less likely to produce reactions and may be administered by nurses, members of the family or the patient himself. This is particularly important in management of a severe illness like congestive heart failure in which climatic conditions and other factors may make office visits by the patient advisable.

The dosage of a mercurial diuretic varies widely, the ideal being the smallest amount which will produce satisfactory diuresis. In some subjects 2 cc. may be required whereas in others 0.5 cc. may be adequate. The amount used and the frequency of injection have varied considerably in the past. More recently, it has been popular to administer 2 cc. daily in the initial therapy of congestive heart failure. Such a vigorous regimen is usually unnecessary and is frequently unwise. The likelihood of
accumulation of mercury has already been discussed, but more serious are disturbances in electrolyte and water balance which may result from excessive diuresis. If bed rest, administration of oxygen, digitalis and morphine produce the desired effects, then mercury is unnecessary. The amount of mercury which will cause a daily loss of 2 to 3 pounds in the edematous patient is adequate and is indicated only if the other usual procedures fail. Frequency of injections must be dictated by the condition of the patient and his response to previous therapy. The rate of reduction in extracellular fluid should be determined by the clinical state of the patient. This type of therapy is symptomatic, and after the symptoms and signs due to accumulation of extracellular fluid have disappeared, nothing is accomplished by forcing additional diuresis to the point of diminished response. There is, however, considerable danger in depletion of electrolytes and water. Once a relatively asymptomatic state is reached, maintenance at that level should be attempted.

The maintenance dosage of mercury is entirely a matter of trial and error. Generally, smaller, more frequent amounts, such as 1 cc. twice weekly, are more preferable than larger amounts at less frequent intervals. It is much more desirable to maintain the weight below that level at which symptoms appear than to allow an accumulation of fluid and then produce vigorous diuresis with frequent large doses. Even when a maintenance dose is thought to have been established for the individual, it is likely to require alteration. The patient may establish a satisfactory state of compensation so that with reduced salt intake no mercury is necessary. On the other hand, when salt intake is increased either by intention or by accident, the maintenance dose of the mercurial diuretic must often be increased. The onset of disturbances in cardiac mechanism and the occurrence of infections, particularly of the upper respiratory tract, frequently necessitate an increase in the maintenance dose.

Administration by the intravenous and intramuscular routes has been the method of choice because the routes are more dependable. Suppositories containing a mercurial diuretic have been tried but local irritation and unpredictable absorption make this route impractical.

Oral administration of mercurial diuretics has been investigated and the unpredictable absorption by this route has been previously indicated. An average of approximately 1 to 3 per cent of the mercury administered by mouth appears in the urine, the range being 0 to 12 per cent. The oral route is unsatisfactory for early therapy in severe congestive heart failure because the diuretic potency by this route is limited. In addition, the amount necessary to institute diuresis often produces nausea, vomiting and diarrhea. This route may be of benefit in maintenance after initial diuresis has been accomplished by the parenteral route. Even though only a small amount is absorbed from the gastrointestinal tract, the frequent small amounts may be sufficient to prevent formation of edema. The ease of administration by this route, obviating visits to an office or an outpatient department, makes it desirable.

It has been suggested by Olson\textsuperscript{24} that 0.25 to 0.33 cc. of Thimerin administered subcutaneously daily by the patient or a relative may be effective, economical and simpler. Although there may be no apparent diuresis from these small amounts, the subtle changes produced by frequent injections maintain desired weight levels satisfactorily. In patients severely decompensated, large doses may be found necessary to produce the desired effects. This can be determined readily by clinical trial. In some instances, daily administration of the diuretic at home by the subcutaneous route may permit the patient to ingest small quantities of sodium whenever he finds a low salt diet difficult to accept.

Considerable attention has been given to the "low salt syndrome." This usually results from too frequent and injudicious use of mercurial diuretics and is characterized by weakness, apathy, anorexia, vomiting, mental confusion and coma. In addition there may be depression of urinary volume and chlorides, decreased sodium and chloride concentration in the serum, and azotemia. It is often mani-
fested by failure to respond to mercurials. Response to mercurial diuretics is known to be diminished when the concentration of sodium or chloride in the serum is low. The low salt syndrome may be corrected with hypertonic solutions of sodium chloride.

Ammonium chloride increases the diuretic response to mercurials 15 to 25 per cent in normal subjects. When the concentration of chlorides in the serum is low and the response to mercury is poor or absent, administration of ammonium or calcium chloride with restoration of the normal concentration of chlorides in the serum will increase diuresis several fold. Usually ammonium chloride is not necessary, as mercury alone will suffice, but if the individual is subjected to frequent mercurial diuresis, the concentration of chlorides in the serum is likely to be low, and ammonium chloride is indicated.

Other measures which may increase the diuretic response to mercury, apparently by increasing the rate of glomerular filtration, include aminophylline or theophylline, 0.5 Gm. given intravenously with the mercurial diuretic. Rest in bed is important for the patient with severe congestive failure since it may improve renal blood flow. Phlebotomy, with removal of 500 to 750 cc. of blood just prior to the injection of mercury, may result in good diuresis when mercurials have failed previously. Disturbances in electrolytes or renal failure are most commonly responsible for unsatisfactory response to mercurials. As previously stated, the electrolyte state should be corrected and then mercurial diuretics may be tried again.

The use of mercurial diuretics in congestive heart failure will shorten the time required to ameliorate certain aspects of the clinical syndrome. However, clinicians are too often erroneously guided by the time factor rather than by the underlying fundamental cardiac state. Disappearance of edema or most of the symptoms of failure does not indicate complete restoration of cardiac reserve. Mercurial diuretics are not substitutes for digitalis nor are they specific agents which cure cardiac disease. When employed properly, they are useful and when employed carelessly, harmful.

Contraindications

Acute renal disease, such as acute glomerulonephritis, and chronic renal disease with insufficiency are contraindications to the use of mercurial diuretics. It is often difficult to evaluate elevated blood urea nitrogen, albuminuria and hematuria in the presence of congestive heart failure, since they may be present in the absence of any primary renal disease. However, if the blood urea nitrogen exceeds 60 mg. per 100 cc., mercurial diuretics should be used extremely cautiously if at all. The appearance of definite albuminuria, hematuria or oliguria after administration of a mercurial diuretic when they were previously absent is indication for discontinuation of the drug.

One of the most frequently encountered contraindications to the use of mercurial diuretics is failure of response to previous injections. Further use of diuretics should not be attempted until possible electrolyte disturbances have been corrected or until a careful evaluation of the clinical state, including the kidneys, has been made. Further use of mercurials should be undertaken cautiously.

The occurrence of any of the immediate reactions to an intravenous injection of a mercurial diuretic contraindicates further use of this route if mercury has to be given at all. Occasionally, a change in the preparation and in the route of administration may be tolerated. The immediate reactions which may serve as premonitory signs are tachycardia, faintness, pallor, sweatiness and asthmatic episodes. Delayed reactions of fever, chills and cutaneous rashes may also be regarded as warning signs.

Tetany may result from excessive loss of calcium during diuresis. This should be corrected before additional mercury is given. Digitalis intoxication may be precipitated by excessive diuresis. Further use of mercurials should be avoided until the excess of digitalis has been excreted.

Minor reactions, such as cramps in the legs, suggest the need for a smaller dose of the diuretic or possibly less frequent injections but do not contraindicate its continued use. Severe, dangerous reactions almost invariably follow intravenous administration; therefore,
the intramuscular or subcutaneous route should be employed routinely. The intravenous route should be reserved only for absolutely necessary circumstances, such as severe edema and failure, in which impairment of blood flow and absorption may prevent therapeutic responses. Except for the brief statement of Battenman, only one report of a fatal case could be found in which the drug was administered intramuscularly or subcutaneously.

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