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Salt depletion syndrome with mercurial diuresis in circulatory failure

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SALT DEPLETION SYNDROME WITH MERCURIAL DIURESIS IN CIRCULATORY FAILURE

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INTRODUCTION

The past two to three decades have brought great advancement of knowledge of the therapy of congestive circulatory failure by a dehydration regime, which almost invariably utilizes the organic mercurial diuretics. So, it has become extremely important that all clinicians involved in the use of this dehydration regime become aware of its dangers.

The purpose of this paper is to point out one of these dangers, the salt depletion syndrome, and explain its etiologic, diagnostic and therapeutic factors, so that life-saving preventive and therapeutic measures may be taken.

HISTORY

It is appropriate in a paper dealing with the affects resulting from the use of mercurial diuretics to discuss briefly the evolution of our present powerful mercurial diuretics.

The use of Calomel, a mild mercurous chloride, as a diuretic was initiated about 1886 by Jendrassik (14). It was used to decrease the edema in cardiac conditions, producing a marked diuresis and excretion of chlorides. Calomel became popular as a diuretic, however the diarrhea which it produced caused it to be abandoned and nonmercurial compounds substituted.

An organic mercurial, merbaphen, was demonstrated by Saxl and Heilig (22) in 1920 to have an affect very similar to Calomel - increased excretion of water and chlorides - without so marked gastrointestinal affects.

Another organic mercurial, salyrgan, with powerful diuretic affect but with less toxic properties largely displaced merbaphen. Mercupurin is perhaps more powerful than salyrgan and is now widely used. It is a complex organic mercurial combined with about five percent theophyllin.

Thiomerin is the newest widely used mercurial diuretic. It is an organic mercurial containing sulphur and is held by many clinicians to be more effective and less toxic than previous mercurials.

The recognition of the syndrome of hypenatremia in persons with congestive heart failure and with hypertension following the institution of a salt-poor diet and the use of mercurial diuretics is not new. The salt depletion syndrome was reported as early as 1898 by Eichhorst (9) who, with the use of digitalis and diuretin produced marked diuresis after which somnolence, disorientation, delirium and apathy developed in certain cases. The problem had not at that time reached the importance it now holds, for not until 1920 were organic mercurials used. In the literature of the past twenty years are reported increasing numbers of cases of the syndrome.

Sprague and Graybiel (26) reported in 1931 a case of malignancy with acites in which they believed death was hastened with the use of salyrgan. Binger and Kieth (3) in 1933 reported that of 216 persons with heart failure treated with vigorous dehydration regime an increase in blood urea nitrogen developed in eighty nine cases. Steiglitz (28) noted that many patients appeared more toxic after diuresis than when they were edamatous.

Srnetz (27) in 1934 mentioned somnolence and mental confusion following diuresis and stressed the necessity for care in administering salyrgan in severe cardiac insufficiency.

McCance (18) in 1936 described symptoms of aberration of taste, cramps, weakness, lassitude and severe cardio-respiratory distress on exertion in normal experimental human subjects who were subjected to loss of 25 to 30 percent of the body's extracellular ions by low sodium chloride intake and sweating.

Poll and Stern (20) in 1937 reported a series of seven cases and discussed at length a syndrome which occurs with diuresis and is characterized by preliminary restlessness and mental confusion, delirium, or even a psychotic state, followed in some instances by apathy, coma and death. Extreme thirst with exceedingly dry tongue and loss of tissue turgor were observed.

Klinghoffer (16) noted three instances of serious dehydration with one death from mercurials within one year on a single hospital ward. Symptoms observed were nausea, anorexia, muscle cramps and vascular collapse.

Evans (10) was able to abolish the symptoms by stopping the use of diuretics and increasing fluids. DeGraff and Nadler (8) in their review of the toxic affects of mercurials in human beings mentioned the occurence of chloride depletion and azotemia after

diuresis.

Ben-Asher (2) in 1946 reported observation of eighteen cases of toxicity of mercurial diuretics. Of these eighteen cases, ten were said to be due to dehydration and nine of the cases recovered with administration of salt and water.

Soloff and Zatuchni (25) saw four instances within one month in which dehydration following mercurial therapy contributed to the death of patients in congestive failure.

Schroeder (24) in 1949 has described the "low salt syndrome" in various conditions. Boone (5) in 1944 described a remarkably high incidence of death among patients with renal disease and congestive heart failure who had received salyrgan.

ETIOLOGY

The factors in the etiology of the syndrome of salt depletion are the treatment of the disease process; including the type of drugs used, the indications for diuresis, the amount and duration of the drug used, diet, age of patient, and the underlying disease process.

The age groups most often seen with this syndrome are the age groups in which congestive failure takes place and are treated with a dehydrating regime, including organic mercurials. The age group observed by Poll and Stern (20) in their series of seven cases was a range from 57 to 67 years of age. All of this group manifested myocardial insufficiency secondary to cononary arteriosclerosis.

Jaffee, Master and Dorrance (13) in eight cases which manifested the syndrome after therapy for congestive failure with organic mercurial diuretics noted an age incidence from 57 to 81 years. These were cases with primary disease of hypertension. One patient had had an acute posterior cardiac wall infarct and another acute urinary retention.

Soloff and Zatuchni (25) reported a series of cases of the syndrome. The ages of the patients with an underlying rheumatic heart disease ranged from 39

to 42 years. They also reported two cases of hypertension, ages 40 and 49 years, in which the syndrome appeared.

The organic mercurial diuretics have been found to be used nearly universally prior to the onset of the salt depletion syndrome. The amount of drug used varies widely, as may be noted by comparison of two cases reported by Soloff and Zatuchni (25). In one case, age 39 years, one cubic centimeter of mercuhydrin injected once was sufficient along with ammonium chloride and low salt diet to produce the syndrome, as observed both clinically and from a laboratory standpoint. Another patient, age 35 years, reported by them had been on a similar dehydrating regime for six months prior to developing symptoms which were diagnosed as the syndrome. By these same cases may be seen that the speed of the onset of the syndrome cannot be determined on basis of age. The underlying disease processes involved in the syndrome include those producing congestive circulatory failure, which include in the cases reported generalized and coronary arteriosclerosis, hypertension, rheumatic heart disease, posterior cardiac wall infarction and cardiac disease of undetermined type.

The indications for diuresis should be carefully checked in an evaluation of etiology. Pulmonary edema, ankle edema or generalized edema, liver engorgment, dyspnea and orthopnea are signs and symptoms commonly used as indications for diuresis. However, other measures must be instituted before safe diuresis can be carried out. These include tests of blood, non-protein nitrogen or blood urea nitrogen, blood sodium level and renal tubule reabsorption. The presence of dyspnea, hepatic congestion and edema as indications used alone may sometimes be an etiologic factor in production of the syndrome, since poor kidney function may already have developed and the body could be low in its stores of sodium ion. Previous dehydration, if to a dangerous level will be shown by the blood sodium levels and blood nitrogen levels, and if diuresis and dehydration is carried out without this check of patient's status, the depletion syndrome may result.

Poll and Stern (20) state that they have the impression that elderly atherosclerotic individuals may be less able than others to effect an automatic readjustment of salt and fluid balance after diuresis, particularly if they are thin and cachectic; thus probably with a reduced kidney reserve and reduced margin of salt and fluid safety.

The amount intensity and the duration of diuretic drugs used and of other dehydration measures are important etiological factors in the development of the syndrome. First of all, the organic mercurials are the drugs being specifically discussed in this paper, and since they are all of somewhat nearly equal diuretic potency, will be discussed together. It is worthy of note at this place that the salt depletion syndrome has been said to occur in the absence of the mercurials. However, this paper will be confined to the cases of the syndrome encountered in the presence of mercurials, and therefore, they will be considered to be an etiologic factor.

Soloff and Zatuchni (25) cite a case of the depletion syndrome which was brought on by a single cubic centimeter of mercuhydrin, combined with a very minimal dosage of ammonium chloride; thus, showing that a very small amount of diuretic and a very mild dehydration therapy may cause the snydrome. Another case demonstrating mild dehydration measures over a period of several years, which eventually developed the depletion syndrome, was reported by Jaffe, Master and Dorrance (13) in 1950. The patient was a 70 year old male who had been receiving weekly or semi-monthly injections of mercurials forfour years. He was then

placed on two cubic centimeters of mercupurin intravenously for ten days, at which time he developed the syndrome and succumbed 26 days after institution of the intensive treatment.

From these two extreme cases one may conclude that the duration and the amount of the drug given are not particularly important etiological factors. More important by far than the amount and duration of diuretic therapy is the intensity with which it is administered. This is demonstrated by the case noted above, which has been reported by Jaffe, Master and Dorrance (13) in which four years of weekly or semimonthly mercurial injections had not produced the syndrome or any indications of it, but when daily mercurial injections were used for ten days, the patient developed lethargy, disorientation, vomiting, trembling hands, finally coma and death. Other cases possibly not so dramatic but very similar are reported.

THEORIES OF MECHANISM OF SYNDROME

Since the syndrome of salt depletion is closely associated with diuresis, a definition of diuresis and general points about it, such as the following given by Blumgart et al (4), are important in the understanding of the syndrome. Diuresis is a loss of water and cations in the proportions in which they occur in blood plasma and extracellular fluids, i. e., 145 milliequivalents of sodium, 4 milliequivalents of potassium and 4 milliequivalents of calcium per liter. Chloride is excreted in larger amounts than the basic ions, i. e., 190 milliequivalents. The length of time required to restore the body to its normal amount of fluid is proportional to the amount of diuresis. The diuretic response is proportioned to the size of the body. Poll and Stern (10) state that the presence of edema is no assurance that the patient is not suffering from a lack of available salt and water.

The mode of action of the organic mercurial diuretics is important in explaining the syndrome, but to the present time no completely satisfactory explanation of the action of the diuretics has been arrived at. However, there are three theories:

(1) The first theory holds that the hydrophilic properties of tissues are diminished; i. e., an antidotal effect of supplying fluids to the body and an effect similar to giving posterior pituitary extract. This theory would postulate an initial blood dilution which cannot be borne out of fact.

(2) A second theory is that of an adrenalin-like action of prolonged duration. This is based on the studies of Jackson (12) who noted that salyrgan is analogous to adrenalin in its action upon the heart, blood vessels and kidney.

(3) The third theory of the mode of action of organic mercurial diuretics is that of depression of the renal tubular epithelium. This depression prevents resorption of threshold substances, notably sodium chloride and water.

Of the three, possibly the best evidence lies with the latter theory. Of the experimental evidence on this theory, Govaerts (11) contributed some of the best with his experiment with novasurol on transplanted dog kidney. In this experiment a kidney from a dog at the height of novasurol diuresis was transplanted to the neck of a dog that had not received the drug. The

transplanted kidney eliminated far more urine than did the original kidneys of the animal. A similar experiment was performed by transplanting a non-novasurol treated kidney into the neck of an animal that had previously received novasurol. The original kidneys eliminated much more urine than the transplanted organ. Bartram (1) further added to the evidence of this theory with his experiment in which small quantities of mercurial were injected directly into the left renal artery of a dog. The urinary output of the left kidney increased, but little increase was noted in the output of the right.

Experimental work has been done supporting the theory of an extrarenal action of organic mercurials by demonstration of dilution of the blood prior to onset of diuresis. Saxl and Heilig (22) have found that the concentration of hemoglobin and plasma proteins fall, indicating a mobilization of fluids from the tissues into the blood when organic mercurials are injected into animals whose kidneys have been damaged or removed. Other experimentations showing similar dilution of blood contents have been made.

Claussen (7) further elucidated the extrarenal action theory by his observation that after salyrgan injection, the blood of the hepatic vein is more dilute than that of the general circulation, indicating mobilization of water from the liver.

As a nearly direct refutation, Schmitz (23) and Bryan and his associates (6) by various measures, including refractive index of plasma, specific gravity, total nitrogen content and colloidal osmotic pressure, found that prior to diuresis after injection of salyrgan that none of the above values changed and that after diuresis had begun all values rose showing hemoconcentration and pointing to a renal action of the drug.

This experimental work which has been sited would suggest strongly a predominant renal factor as responsible for the diuresis.

Whatever may be the mechanism of the diuresis, we know that there is a diuresis and that by the definition previously stated by Blumgart (4) that a diuresis involves a loss of water and cations in the proportions in which they occur in blood plasma and extracellular fluids. We further know that the salt depletion syndrome ensues following an active diuresis regime. Newburg (19) has emphasized that a salt-poor diet may require work of the tubule cells that they are incapable of performing. If this occurs, salt-leakage continues, drastic dehydration occurs, and uremia and the picture of shock may appear.

In an attempt to explain the symptoms of the salt depletion syndrome on the basis of a diuresis, i. e.,

loss of water and cations, a comparison can be made of the symptoms of the syndrome with the symptoms manifested in the subjects of McCance's experiment.

McCance (18) used several normal, healthy human subjects and forced loss of sodium and chlorine by a very low sodium chloride intake and sweating. At least 25 to 30 percent of the body's extracellular ions were removed in this manner. He did not limit the fluid intake.

This deprivation led to aberrations of taste, cramps, weakness, lassitude and severe cardiorespiratory distress on exertion. The nitrogen balance became negative and the blood urea rose.

Clinical evidence which may give further evidence of the exact ionic derangement in salt depletion syndrome is offered by Fishberg (29). He notes that in patients receiving ammonium and calcium chloride as adjuvants to diuresis, some, if not all, of the chloride ion is replaced; and yet they may also show some or all the symptoms of low salt syndrome. In fact, a state of acidosis may be produced with depression of the carbon dioxide of the blood. This would indicate that the decreased sodium ion is solely responsible, or at least the main determining factor, in the development of the syndrome.

SYMPTOMATOLOGY AND DIAGNOSIS

The symptoms of the salt depletion syndrome are described by Poll and Stern (20) as restlessness early, followed by mental confusion, delirium, or even a psychotic state, and occasionally by apathy, coma and death. Extreme thirst not satisfied by water is another symptom which is often seen. The symptom of restlessness and confusion may not occur, and the first indication of the syndrome may be apathy. Symptoms which Soloff and Zatuchni (25) warn of as seen in their report of seven cases are weakness, lassitude, anorexia, nausea, vomiting, restlessness and apathy. Further signs and symptoms which must be evaluated are fall in blood pressure, increase in pulse rate, diminution of volume of the pulse, clammy skin, shock and coma.

Very important in the diagnosis of salt depletion syndrome is for the attending physician to be alert to the possibility of its occurence in patients who are being purged of their edema and having a very high index of suspicion when it is noted that a patient has a tendency to do well under such a regime. This is especially true when the patient has only a minimal edema or if the regime is vigorously carried out.

Positive diagnosis of the syndrome may be made when a combination of the signs, symptoms and laboratory data presents itself concomitantly with a dehydra-

tion regime which may have been effective, only partially or entirely non-effective.

Laboratory work which is helpful in the diagnosis of this syndrome includes blood chloride and blood sodium levels, blood urea nitrogen, blood non-protein nitrogen, and carbon dioxide power. Soloff and Zatuchni (25) in their report of seven cases in 1949 noted the following laboratory data: the blood urea nitrogen was determined in all seven patients and it was elevated in each instance. Blood sodium was determined in one patient and blood chlorides in six patients, and the blood sodium and chlorides were decreased in all instances. However, as mentioned previously, Fishberg (29) believes chlorides can remain normal.

DIFFERENTIAL DIAGNOSIS

In a differential diagnosis of salt depletion syndrome an evaluation of the previously stated symptoms must be carried out. Soloff and Zatuchni (25) list in their differential diagnosis excessive sedation, digitalis, unrelated infection, thrombo-embolic phenomena and natural progression of cardiac disease.

Poll and Stern (20) include a somewhat augmented and more definitive list to this differential, including irremedial myocardial insufficiency, a fresh coronary thrombosis, exacerbation of acute rheumatic carditis, pulmonary infarction, respiratory tract infection, cerebral vascular accident, true renal insufficiency, oversedation and acidotic coma from the use of acidifying salts in cases with impaired renal function.

Any one of these conditions could explain some of the symptoms. But when the symptoms appear in a patient who is being subjected to diuretic therapy, and who appears to be going down hill, and since it is known that the depletion syndrome can be responsible, it should be possible to distinguish the cause of the patient's course.

PROPHYLAXIS

There are two periods in which prophylactic evaluations must be done. First is the careful evaluation of the patient for diuretic and low salt therapy before institution of the therapy, and second is careful revaluation during therapy. This first evaluation must include study for presence of senility, advanced atherosclerosis and cachexia. Also, the renal function determined on concentrating power is extremely important. Initial determination of blood non-protein nitrogen and possibly either blood sodium or blood chlorides are measures which can point to dangers of intensive dehydration therapy. The amount of edema on a symptomatic basis is also an index which can be used for a mild non-symptomatic edema but does not warrant the risk of the syndrome.

Prophylactic measures to be carried out concomitantly with the dehydrating regime are observation of patient for symptoms suggestive of the syndrome, physical examination and check of edema symptoms with which in part to determine the vigor of dehydration therapy. Equally important and perhaps more reliable are laboratory tests of blood non-protein nitrogen for elevation and blood sodium and chloride for depression.

Poll and Stern (21) caution that dehydration should proceed slowly, and too many procedures (such as phlebotomy, thoracentesis, paracentesis abdominis) should not be carried out at one time.

THERAPY

Therapy of the salt depletion syndrome is simple when once the condition is recognized. The first step is cessation of diuretic measures and removal of the salt restriction of the diet. Poll and Stern (20) suggest three steps in further therapy, which consist of oral administration of water, oral administration of sodium chloride in capsules and later as a 0.1 percent solution, and if these methods are impossible, intravenous and subsutaneous administration of salt solutions must be done.

PROGNOSIS

The prognosis in the syndrome is determined by the stage at which treatment is instituted and the ability of the individual to readjust his ionic balance. It is difficult to determine the prognosis, but there are two facts which have been noted.

First, there is a point in the process of the syndrome beyond which, if it is permitted to progress, there is no amount or intensity of therapy which will save the patient from death.

The other fact is that debilitated senile or atherosclerotic patients are more difficult to treat successfully than patients without these handicaps.

CONCLUSIONS

I Though the mechanism of action of mercurial diuretics has not been completely ascertained, it has been shown quite conclusively that the major affect is on the renal tubules in preventing resorption of threshold ions, including especially sodium, and also that there is a minor extrarenal affect.

II The intensity of the dehydration regime as determined on the basis of the individual patient is the most important etiologic factor.

III Diagnosis of the syndrome in a patient on a dehydration therapy may be based on a symptom and sign complex of mental confusion, apathy, weakness, lassitude, anorexia, nausea, vomiting, thirst not relieved by water, increased pulse rate, decreased blood pressure, shock, coma and elavation of blood non-protein nitrogen and decreased blood sodium level.

IV Prophylaxis lies in individualizing dehydration treatment of the patient and careful analysis of his condition before and during treatment.

V Therapy consists of replacing sodium chloride by the most rapid route to the extent that signs and symptoms disappear.

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