# THE EFFECT ON THE PLASMA VOLUME OF DEHYDRATION PRODUCED BY A LOW-SALT DIET AND AMMONIUM CHLORIDE

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IT HAS been accepted[1, 2] that the plasma volume remains relatively constant with dehydration because it is protected by the much larger extracellular fluid volume. With the use of improved techniques, however, it has been found that the plasma volume is not constant, but shows considerable fluctuation. It has been demonstrated in animal experiments that the plasma, as well as the interstitial fluid, contributes to the water lost in dehydration induced by the removal of gastrointestinal secretions[3] or by the intraperitoneal injection of glucose.[4] In the early stages of diabetic acidosis,[5] the plasma volume decreases before significant dehydration develops. In cardiac edema, where there is a great excess of interstitial fluid, the plasma volume is not constant, but will show a considerable decrease after diuresis, even though edema persists.[6, 7]

The mechanism of the action of ammonium chloride has been well established as a result of carefully controlled balance studies on normal and abnormal subjects.[8] In general, these persons were on fixed diets, usually low in sodium chloride and limited in fluid intake. Considerable variation is noted in the diuretic effect of ammonium chloride on the normal subjects, as reported in the literature; this is due, in part, to the use of different doses of the drug and to variations in the duration of the observation period. The diuresis varied from none[8b] to 2.5 kilograms, or 3.6 per cent of the body weight.[8c] Little information is available concerning the change in plasma volume, even as judged by changes in concentration of serum proteins or hematocrit values.

Since ammonium chloride is a frequently used diuretic, it would appear helpful to know how much diuresis it produces in normal persons in order to evaluate the diuretic response of patients. The studies in the literature are not closely comparable to the usual hospital method of employing ammonium chloride as a diuretic because the subjects had been on a fixed regimen for some days before the administration of the drug.

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This work was supported by grants from the Board of Governors of the Horace H. Rackham School of Graduate Study and from The Upjohn Company.
Received for publication April 16, 1943.

TABLE I

THE PERCENTAGE CHANGE IN PLASMA VOLUME, HEMATOCRIT VALUE, SERUM PROTEIN CONCENTRATION, AND BODY WEIGHT AFTER THE CONTINUOUS ADMINISTRATION OF 9 GM. OF AMMONIUM CHLORIDE DAILY

| SUBJECT | DAYS ON 9 GM. OF AMMONIUM CHLORIDE | PERCENTAGE CHANGE IN PLASMA VOLUME | PERCENTAGE CHANGE IN CONCENTRATION OF SERUM PROTEIN | PERCENTAGE CHANGE IN HEMATOCRIT VALUE | PERCENTAGE CHANGE IN TOTAL BLOOD VOLUME | PERCENTAGE CHANGE IN BODY WEIGHT | ACTUAL CHANGE IN PLASMA CARBON DIOXIDE COMBINING POWER IN VOLUME PER 100 C.C. |
|---|---|---|---|---|---|---|---|
| 1 | 3 | −10.8 | ---- | 0 | −10.7 | −6.1 | −18.0 |
| 2 | 3 | − 8.1 | + 7.3 | + 1.8 | − 6.6 | −4.7 | −11.2 |
| 12 | 3 | − 9.3 | ---- | + 2.8 | − 5.0 | −4.2 | ---- |
| 13 | 3 | −13.8 | ---- | + 3.7 | − 9.0 | −2.4 | ---- |
| 3 | 4 | −13.7 | ---- | −10.5 | −15.3 | −5.8 | − 8.0 |
| 4 | 4 | −14.1 | + 5.3 | + 1.1 | −13.3 | −5.1 | − 6.7 |
| 5 | 4 | −31.0 | + 6.5 | +18.5 | −19.3 | −7.6 | ---- |
| 6 | 4 | −12.5 | +11.2 | − 3.6 | −12.4 | −3.3 | 0 |
| 14 | 4 | −20.0 | ---- | + 3.3 | −11.8 | −4.9 | ---- |
| 15 | 4 | − 4.2 | − 8.0 | + 2.2 | − 2.5 | −0.1 | ---- |
| Average 3-4 | | −13.75 | + 6.5 | + 1.9 | −10.6 | −4.4 | ---- |
| 7 | 6 | −24.4 | +27.6 | − 7.4 | −25.1 | −4.4 | ---- |
| 8 | 6 | ---- | +15.7 | ---- | ---- | −2.9 | ---- |
| 9 | 6 | − 4.9 | + 7.5 | ---- | − 5.6 | −2.8 | −12.2 |
| 10 | 6 | − 6.8 | +14.2 | − 6.7 | −11.7 | −2.6 | − 0.2 |
| 11 | 7 | −23.0 | ---- | 0 | −16.0 | −1.3 | − 1.0 |
| 5 | 8 | −18.6 | − 3.7 | +15.5 | − 7.2 | −9.3 | ---- |
| 6 | 9 | − 7.1 | − 1.9 | − 8.1 | − 9.1 | −3.5 | − 4.0 |
| 9 | 10 | + 4.9 | + 6.2 | + 3.0 | + 5.6 | −3.5 | −21.8 |
| 10 | 10 | + 0.6 | + 2.9 | − 8.7 | − 6.7 | −3.0 | −23.6 |
| 8 | 13 | − 4.4 | + 6.1 | − 7.9 | − 9.2 | −3.6 | ---- |
| 11 | 15 | −16.7 | ---- | − 7.0 | −15.2 | −1.8 | −19.0 |
| 6 | 16 | −14.3 | + 1.8 | − 7.0 | −16.3 | −3.6 | − 1.0 |
| 9 | 16 | −11.6 | +10.0 | + 3.0 | −11.1 | −5.1 | −25.4 |
| 10 | 16 | − 1.3 | 0 | − 4.1 | − 4.9 | −3.6 | −19.8 |
| 8 | 19 | − 2.3 | + 8.4 | − 9.8 | − 8.3 | −4.3 | ---- |

In an effort to evaluate the response of normal subjects to a low-salt diet and ammonium chloride, and to further study the effects of dehydration on the plasma volume, the following observations were made.

## METHODS

Fifteen hospital patients without evidence of cardiovascular or renal disease, who had never had edema and who were not ill at the time of the observations, were selected as normal subjects for study. Each patient had been on the routine hospital diet for several days before the observations were started. The subject was carefully weighed on a beam balance, accurate to 2 grams, in the postabsorptive state, on the morning of the observations. After the weighing he was placed on a comfortable stretcher and blood samples were taken for the determination of the plasma volume,[9] hematocrit value, serum proteins,[10] and, in some cases, $CO_2$ combining power.[11] After the initial observations were made, the subject was kept at rest in bed on a diet low in salt (about 2.5 Gm.), with 70 Gm. of protein, and the caloric content of the diet was adjusted to 40 per cent above the estimated basal caloric consumption. Fluids were permitted ad libitum. As far as could be ascertained, the diet was consumed completely, so that it can be assumed that changes in weight closely reflected changes in the water content of the body. At the start of this diet, 3 Gm. of ammonium chloride in 0.5 Gm., enteric-coated tablets were taken with each meal, so that 9 Gm. of ammonium chloride were ingested daily.

In the postabsorptive, rested state, the plasma volume of the normal subject is remarkably constant. In this laboratory the estimation of plasma volume was repeated fourteen times on successive mornings on twelve normal subjects in the rested, postabsorptive state, and showed an average variation of plus 0.88 per cent; the greatest variations, in one instance each, were plus 6 and minus 5 per cent. These results are in accord with those of others.[12, 13]

## RESULTS

The observations on the majority of the subjects were completed after three or four days on ammonium chloride, chiefly because either they were no longer available for study or an adequate diuresis was produced. The alterations in total blood volume, plasma volume, hematocrit value, serum protein, and weight, expressed as percentage change from the initial determinations, are given in Table I. Plasma volume varies considerably with the size of the body, so that changes in the plasma volume of a group of persons of different size cannot be directly compared.

Ten subjects who received the drug for three or four days experienced an average diuresis of 4.4 per cent of their body weight, with a fall in plasma volume of 13.8 per cent. The hematocrit and serum protein values increased, although these changes were considerably less than the change in plasma volume, and failed to reflect accurately the fall in plasma volume. The actual change in plasma volume in these people averaged 436 c.c., with an average weight loss of 3 kilograms. The decrease in plasma volume accounted for $12.2 \pm 1.2$ per cent of the

total weight lost. The greatest change was noticed in Case 5, i.e., a decrease in plasma volume of 1,120 c.c. and a 4.6 kilogram weight loss.

Six subjects who received ammonium chloride for six to eight days showed a considerably greater variation in response which was in part the result of the selection of the cases. Some subjects who did not show an adequate diuresis after three or four days were allowed to continue the drug for a longer period before the observations were repeated.

Subsequent observations after nine to nineteen days on ammonium chloride indicated that the plasma volume was in part restored after its initial fall, in spite of the continued loss of water from the body as judged by the progressive weight loss. These fluctuations in the plasma volume are recorded in Table II.

TABLE II

THE PERCENTAGE CHANGE IN PLASMA VOLUME, HEMATOCRIT VALUE, SERUM PROTEIN CONCENTRATION, AND BODY WEIGHT AFTER THE CONTINUOUS ADMINISTRATION OF 9 GM. OF AMMONIUM CHLORIDE DAILY

| SUBJECT | DAYS ON 9 GM. OF AMMONIUM CHLORIDE | PERCENTAGE CHANGE IN PLASMA VOLUME | PERCENTAGE CHANGE IN CONCENTRATION OF SERUM PROTEIN | PERCENTAGE CHANGE IN HEMATOCRIT VALUE | PERCENTAGE CHANGE IN BODY WEIGHT |
|---|---|---|---|---|---|
| 5 | 4 | −31.0 | + 6.5 | +18.5 | −7.6 |
| | 8 | −18.6 | − 3.7 | +15.5 | −9.3 |
| 6 | 4 | −12.5 | +11.2 | − 3.6 | −3.3 |
| | 9 | − 7.1 | − 1.9 | − 7.1 | −3.5 |
| | 16 | −14.3 | + 1.8 | − 7.0 | −3.6 |
| 8 | 6 | ---- | +15.7 | ---- | −2.9 |
| | 13 | − 4.4 | + 6.1 | − 7.9 | −3.6 |
| | 19 | − 2.3 | + 8.4 | − 9.8 | −4.3 |
| 9 | 6 | − 4.9 | + 7.5 | ---- | −2.8 |
| | 10 | + 4.9 | + 6.2 | + 3.0 | −3.5 |
| | 16 | −11.6 | +10.0 | + 3.0 | −5.1 |
| 10 | 6 | − 6.8 | +14.2 | − 6.7 | −2.6 |
| | 10 | + 0.6 | + 2.9 | − 8.7 | −3.0 |
| | 16 | − 1.3 | 0 | − 4.1 | −3.6 |
| 11 | 7 | −23.1 | ---- | 0 | −1.3 |
| | 15 | −16.7 | ---- | − 7.0 | −1.8 |

Of considerable interest was the actual weight lost by these patients who had no suggestion of edema. The average weight loss of the group of fifteen subjects after receiving the diet and ammonium chloride for three to seven days was 2.47 kilograms. Continuation of the drug over a longer period was associated with a continued loss of weight, although the changes were quite small.

## DISCUSSION

It is apparent from the results of these studies that the plasma volume shares in the dehydration induced by ammonium chloride. It is, of course, true that the majority of the water lost was derived from the reservoirs other than the plasma volume, but in certain instances there was a profound reduction of plasma volume.

Since sodium and potassium balance studies were not carried out on these subjects, it is not known whether the majority of the water lost under these circumstances came from the interstitial fluid or from the cells. However, others[8] have found that both sodium and potassium are lost in the urine, which suggests that the lost water must come from both the extracellular and intracellular fluid compartments. Gamble indicated that at first the water loss comes largely from the extracellular fluid and later the intracellular fluid.

The fluctuations in plasma volume after the initial fall continued in spite of progressive loss of body water. In general, these subsequent changes were toward a restoration of the plasma volume, and suggest that considerable shifts of water must occur within the body as diuresis continues, presumably because of removal of water from the cells or from extracellular fluid that is not readily mobilized. Judging from the observations of others,[3, 4, 8] who have found that a considerable amount of potassium is lost in the urine, it would appear that the plasma volume was made up by shift of water from the cells.

There was only a directional relationship in these cases between the intensity of the diuresis and the fall in plasma volume. Some cases, in which the diuresis was large with a relatively small decrease in the plasma volume, would suggest that the plasma volume was well protected by the extracellular fluid. In others, however, the large decrease in plasma volume with little change in weight suggested that there was very little protection of the plasma volume. As far as we could ascertain, all subjects were well hydrated and had been on the same hospital regimen for several days before the observations were made.

The diuresis experienced by some of these subjects was greater than that reported in the literature. These observations, however, represent the response of "normal" subjects who had been on the usual hospital regimen, with salt and water ad libitum, to the low-salt diet, as well as to large doses of ammonium chloride, over a three- to seven-day period. In general, in the cases previously reported,[8] the subjects were on a diet limited in salt and fixed in its constituents for some days before the administration of the drug. Loeb, et al.,[8e] however, noted no difference in the loss of potassium, sodium, magnesium, or calcium with the administration of ammonium chloride in the case of their carefully studied normal subject when he was on a "salt poor" diet and on the same diet with an additional 120 milliequivalents of sodium chloride.

These results suggest that it is not uncommon for a normal, hospitalized patient to have a diuresis of 2 to 4 kilograms on a low-salt diet and 9 Gm. of ammonium chloride per day. Such a diuresis in patients suspected of having edema has often been incorrectly interpreted as evidence of edema, but it represents only the response of a normally hydrated person to the diuretic regimen.

A comparison between the percentage change in plasma volume and the percentage change in hematocrit values and the concentration of

serum proteins shows a considerable discrepancy. Certainly, the changes in hematocrit values completely failed to express the changes in the plasma volume. This can in part be explained by the fact that determinations of the plasma volume require from 50 to 80 c.c. of blood, and, therefore, the loss of erythrocytes which may be expected from repeated determinations would produce a lower hematocrit value. It does not adequately explain the changes noted with the second plasma volume determination, for it seems unlikely that the removal of only 50 c.c. of blood three or four days previously would suffice to produce this loss of erythrocytes. The inability to accurately measure changes in plasma volume by changes in the hematocrit value has been demonstrated before by Ebert and Stead.[14, 15] They have indicated that shifts of blood from the larger to the smaller vessels may produce such changes in the hematocrit value without alterations in the number of erythrocytes in the circulation.

The changes in the concentration of serum proteins were consistently less than the changes in plasma volume, although in the same direction. As with the hematocrit, the changes in the concentration of serum proteins failed to express the extent of the dehydration of the plasma. This has been noted by others,[3, 16, 17] and suggests that a change in the concentration of serum proteins as an index of the change in plasma volume is not reliable. A change in the concentration of serum proteins may indicate only a directional shift in the plasma volume, but not a quantitative change, for the change in plasma volume is generally greater than the change in serum protein concentration. The failure of the serum proteins to follow more closely the changes in plasma volume is in accord with the concept of Madden and Whipple[18] that the serum protein is in a state of "dynamic equilibrium." It suggests that a decrease in the volume of the plasma induced over several days may be associated with decreases in the total amount of protein in the plasma.

## CONCLUSIONS

1. Dehydration induced in man by the use of a low-salt diet and 9 Gm. of ammonium chloride daily is associated with a decrease in the plasma volume and a smaller rise in serum proteins and hematocrit values.

2. The amount of water loss varied considerably, but, in general, amounted to 3 or 4 per cent of body weight.

3. Only a directional relationship existed between the decrease in the plasma volume and the amount of diuresis.

4. The difference in the concentration of serum proteins or hematocrit values failed to reflect quantitatively the changes in the plasma volume.

5. Continued administration of ammonium chloride was accompanied by a secondary rise in plasma volume toward the control level, with subsequent fluctuations, although diuresis persisted.

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