Excretion of Water by Normal Subjects

L. G. WELT AND W. P. NELSON, III. From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

The rate of flow of urine is the resultant of the rate of glomerular filtration minus the water reabsorbed in the proximal and distal portions of the nephron. The proximal reabsorption of water is, presumably, a passive and obligatory consequence of the active reabsorption of solutes. The distal tubular reabsorption of water is promoted by the antidiuretic hormone of the posterior pituitary gland and is limited by the unreabsorbed solutes. Hypotonicity of the body fluids induced by a positive balance of water promotes the excretion of a dilute urine owing, presumably, to suppression of the secretion of the antidiuretic hormone. The question may be raised whether hypotonicity of the body fluids may modify the rate of excretion of water through some mechanism in addition to suppression of the secretion of antidiuretic hormone.

It has been reported (1) that a maintained positive balance of water induces an initially high rate of excretion of water followed by a gradual decline in this rate. This latter phenomenon has been attributed to a decrease in the rate of excretion of salt. The positive balance of water was attained and maintained by the oral ingestion of water in that study. The nature of the exchanges between the body fluids and the gastrointestinal tract during the continuous ingestion of plain water suggested an alternative explanation for the decline in the rate of excretion of water that had been observed.

The present studies were designed to answer the following questions: 1) Is the high rate of flow of urine associated with a positive balance of water dependent on a maintained rate of excretion of salt? 2) Does hypotonicity of the body fluids induced by the administration of water promote the excretion of water by some mechanism in addition to suppression of the secretion of the antidiuretic hormone?

Experimental Procedure and Methods

The subjects of these studies were healthy young adult male physicians. Food and water were restricted for a period of 12 to 14 hours prior to each study. The experiments were conducted with the subject in the recumbent position, except for the brief intervals attending voiding. Samples of blood were collected under oil.

Following a control period a positive balance of water was attained either by the oral ingestion of water or a solution of 5 per cent glucose, or by the infusion of the latter. Minimal glycosuria was occasionally observed in the first few minutes following the start of the infusion. In the experiments employing the oral route a large
volume of water (ML 07/28/50, 8/7/50) or a solution of 5 per cent glucose (WPN
08/31/50) was ingested during the first 90 minutes following the control period. The
positive balance of water achieved in this period was maintained by ingesting fluid at
a rate equal to the rate of flow of urine plus 40 cc/per hour. This latter figure was the
assumed rate of insensible loss of water. An increase in the positive balance of water
was attained by ingesting fluid at a rate greater than its excretion. The intravenous
technique (WPN 11/6/50, LGW 09/25/50) differed only in that the solution of
dextrose in water was administered by vein.

Sensations of fullness and abdominal discomfort were not infrequent when the
oral route was used. One study in which a solution of glucose was ingested (not in-
cluded here) had to be terminated because of severe nausea and eventual emeses.

The chemical methods and calculations have been described in previous publi-
cations from this department (2, 3). In the calculations the value for the initial vol-
ume of the extracellular fluid (chloride space) was assumed to be 20 per cent of the
body weight. The value for total milliosmols in the urine was calculated from the
equation: 2 (Na + K) + urea. The per cent change in plasma volume, PV2/PV1
was calculated from the formula:

\[
\frac{Hgb_2}{Hgb_1} \times \frac{1 - Hkt_2}{1 - Hkt_1} \times 100
\]

RESULTS

The experimental and derived data are presented in table 1A and B. The ad-
ministration of fluid in such a manner as to attain and maintain a significant posi-
tive balance of water promotes the excretion of a large flow of dilute urine. The range
of values for the U/P ratio for creatinine varied between 4.5 and 12.4 with an average
of 8.3. Ratios of this magnitude are commonly observed in patients with diabetes in-
sipidus and indicate that 8.5 to 21.5 per cent (average: 12.5%) of the filtered water
is excreted. A maximum rate of excretion of urine and a minimum U/P creatinine ratio
was achieved with a load of water representing an increase of approximately 1 per
cent of the total body water. The rate of flow of urine was not augmented nor was the
U/P ratio for creatinine decreased by doubling this positive balance of water.

The rate of excretion of water was well maintained when the intravenous route
of administration was employed. This was not the case, however, in the studies em-
ploying the oral ingestion of the fluid. The flow of urine was, perhaps, better main-
tained with the ingestion of the solution of dextrose than it was with plain water.
This decrease in the rate of flow of urine was accompanied by a slight increase in the
U/P ratio for creatinine and a trend in the direction of a decrease in the rates of clear-
ance of endogenous creatinine.

The maintenance of a large flow of urine during the intravenous administration
is not dependent on the maintenance of a constant rate of excretion of salt. Following
a transient increase in the rates of excretion of sodium and chloride during the ascent
of the diuresis, there was a progressive decline in the rates of excretion of these ions.
The rates of excretion of urea and potassium behaved similarly.

There was no gross difference in the time interval between the administration
of water by either route and the attainment of the maximal rate of excretion of water.
There was no evident correlation between the initial concentration of sodium in the
serum, the initial rate of excretion of sodium or urea, or the rate of clearance of en-
dogenous creatinine and the height of the maximal diuresis attained.
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EXCRETION OF WATER BY NORMAL SUBJECTS  

| TABLE I. EFFECTS OF ORAL AND INTRAVENOUS WATER LOADING (5% GLUCOSE) |
|-----------------------------|-----------------------------|-----------------------------|
| SUBJECT                    | CONC. IN SERUM              | RATES OF EXCRETION          |                |
|                            |                            | H2O                        | Clr            | H2O/ 
|                            |                            | Na/P                        | H2O/ 
|                            |                            | Total                       | Hkt.            | Na/P |
|                            |                            |                            | Hgb.            | PVI |
|                            |                            |                            | vol. % mEq/l    | gm.% |
|                            |                            |                            | gm.%           |      |
|                            |                            |                            | mEq/l          |      |
|                            |                            |                            |                 |      |
| A. Oral Water Loading      |                            |                            |                 |      |
| M.L. 7/28/50 (H2O)         |                |                            |                 |      |
| +50 760 101 17.0           | 340 16.2 67.2            | 45.5 16.5 100              |                |      |
| 00 760 91 4.6             | 1208 32.0 100.4          | 47.8 16.2 98              |                |      |
| 10 668 92 4.5             | 1376 11.1 57.4           | 45.5 16.5 100             |                |      |
| 15 667 69 5.5             | 1056 10.2 47.5           | 45.5 16.5 100             |                |      |
| 18 825 81 6.3             | 700 6.7 35.5             | 45.5 16.5 100             |                |      |
| 210 615 69 6.8            | 880 6.7 35.5             | 45.5 16.5 100             |                |      |
| 240 675 92 7.7            | 720 6.5 32.5             | 45.5 16.5 100             |                |      |
| 250 600 88 7.0            | 670 6.8 29.8             | 45.5 16.5 100             |                |      |
| 310 870 84 7.8            | 620 6.4 29.7             | 45.5 16.5 100             |                |      |
| 350 770 86 7.3            | 700 5.2 31.5             | 45.5 16.5 100             |                |      |
| B. Intravenous Water Loading |                |                            |                 |      |
| W.P.N. 8/31/50 (H2O)      |                |                            |                 |      |
| +50 0 122 25.0            | 122 6.0 43.3            | 50.3 14.5 100             |                |      |
| 47 1158 129 25.0          | 570 6.0 43.3            | 49.0 15.7 88              |                |      |
| 87 1110 119 6.5           | 1106 8.3 53.5           | 49.0 15.3 91              |                |      |
| L.G.W. 9/22/50 (5% glucose) |                |                            |                 |      |
| +50 0 127 23.0            | 55 18.0 44.6            | 45.4 15.5 100             |                |      |
| 40 425 128 23.5           | 145 9.6 45.5            | 45.4 15.5 100             |                |      |
| 59 700 229 4.3           | 509 7.2 40.8            | 45.4 15.5 100             |                |      |
| 129 920 229 11.5          | 569 7.1 37.9            | 45.4 15.5 100             |                |      |
| 149 945 223 10.7          | 680 6.7 34.2            | 45.4 15.5 100             |                |      |
| 169 220 118 10.4          | 690 5.9 30.9            | 45.4 15.5 100             |                |      |
| 189 1270 112 11.1         | 648 5.8 26.1            | 45.4 15.5 100             |                |      |
| 229 1320 117 10.8         | 670 7.5 30.6            | 45.4 15.5 100             |                |      |
| 410 1385 219 10.6         | 690 4.7 22.1            | 45.4 15.5 100             |                |      |
| 449 2185 223 22.0         | 700 3.0 23.0            | 45.4 15.5 100             |                |      |
| 500 2175 101 8.8          | 700 3.0 23.0            | 45.4 15.5 100             |                |      |

The route of administration of water promoted certain differences in response. There was a significant fall in the concentration of total proteins in the serum in the two studies employing the intravenous route of administration of water, and this
evidence of hemodilution was reasonably well correlated with the changes in blood volume as indicated by alterations in hematocrit and hemoglobin. In the two studies with oral ingestion of plain water, there was either an early rise or no change in the concentration of total proteins in the serum with corresponding alterations in hematocrit and hemoglobin. This lack of evidence of hemodilution obtained despite significant decreases in the concentration of sodium and chloride in the serum. The data from the study utilizing the oral ingestion of a solution of glucose in water more closely approximated the observation noted when the parenteral route of administration was employed.

In all but one study the decrease in concentration of sodium in the serum was associated with swelling of the red blood cells as indicated by a reduction in the value for: hemoglobin/hematocrit.

The changes in volume of the extracellular compartment as measured by changes in chloride space, and transfers of sodium and potassium between cells and extracellular fluid were derived for the two studies employing the intravenous route of administration of water. There were no significant exchanges of sodium between the cells and extracellular fluid, but there were small transfers of potassium from the cells. These calculations, of course, can not be made in those studies associated with the continuous ingestion of fluid. In these latter instances there is an unknown and unaccountable transfer of ions into the gastrointestinal tract. This represents a negative balance of unknown magnitude which makes the calculation impossible.

**DISCUSSION**

Complete, or nearly complete, suppression of secretion of antidiuretic hormone by the posterior pituitary gland may be achieved in normal subjects by providing a positive balance of water approximately equivalent to 1 per cent of the total body water. The maintenance of this positive balance of water promotes a reasonably steady state which may be described as 'physiological diabetes insipidus' (4) and is characterized by a steady, large flow of urine, with a U/P ratio for creatinine of approximately eight, and a low total solute concentration.

The current concepts of renal physiology imply that in the absence of antidiuretic hormone all, or nearly all, the urine that reaches the distal tubule is excreted. Under these circumstances an increase in the rate of urine flow can only be achieved by the delivery of an increased volume to the distal tubule. This might result from 1) an increase in the rate of glomerular filtration with the delivery of a constant percentage of the filtrate to the distal tubule, 2) the delivery of a larger fraction of filtered water to the distal tubule with an unchanged rate of filtration, or 3) the secretion of water by the distal tubular cells (5-7). It is clear from these studies that none of these possible mechanisms is stimulated by a large increase in the balance of water in excess of that which appears necessary to induce complete suppression of the secretion of antidiuretic hormone. Hypotonicity can not promote the elimination of water by the kidneys beyond the limits permitted by the complete excretion of that moiety of filtered water that gains access to the distal tubule; and, further, the size of this latter fraction is not influenced by an increase in the 'concentration of water.' This is similar to the observation of Findley and White (8) that a water load in well-hydrated subjects with diabetes insipidus did not increase the rate of excretion of water.

There was a decrease in the rate of excretion of water despite persistently maintained hypotonicity in those studies employing the oral route of water loading. The slight increase in the U/P ratio for creatinine suggests either an increase in re-
absorption of fluid in the proximal tubule or some return of antidiuretic activity in
the distal tubule. The discomfort associated with the ingestion of large volumes of
fluid may play a role in promoting secretion of antidiuretic hormone. In addition,
there was a reduction in the rate of glomerular filtration as implied by a decrease in
the clearance of creatinine. The stimuli that may be responsible for these phenomena
must be sought in the alterations that are induced during ingestion of large volumes
of water.

It has been demonstrated that during the 30-minute period following ingestion of
a water load (9) there is a loss of electrolytes from the extracellular fluid into the
gastrointestinal tract. This loss of electrolytes causes a decrease in the concentra-
tions of these ions in the extracellular water, and as a consequence there is a movement
of water from the extracellular compartment into the cells. This, of course, results in
a contraction of the volume of the extracellular fluid. The fact that the concentra-
tion of proteins in the serum did not decrease, and in some instances increased, despite a
decrease in the concentrations of sodium and chloride in the serum, certainly suggests
that such a sequence of events was operative in these studies. Moreover, since water
was continuously ingested, there could have been no opportunity to establish an
equilibrium. These factors which would limit expansion, and even promote a contra-
tion, of the extracellular volume may well have been responsible for the decrease in
the rate of glomerular filtration. This hypothesis helps explain the fact that the
reduction in rate of urine flow was less evident when the ingested fluid was a 5 per
cent solution of glucose. This solution is almost isotonic with the body fluids; glucose
is not absorbed from the stomach and, therefore, very little electrolyte would have to
be transferred into this fluid in the interests of osmotic equilibrium (10). It is clear
at any rate, that the use of the oral route of water loading to establish a steady state
of physiological diabetes insipidus is unreliable.

The constant large flows of urine despite decreasing rates of excretion of sodium
and chloride reassert the independence between the reabsorption of salt and water in
the distal tubule.

**SUMMARY AND CONCLUSIONS**

A 'maximal' diuresis of water is promoted with a positive balance of water ade-
quate to suppress completely the secretion of antidiuretic hormone by the posterior
pituitary gland. A positive balance of water greatly in excess of this does not promote
any further increase in the rate of excretion of water. No mechanism responsible for
the excretion of water other than elimination of antidiuretic hormone responds to
hypotonicity of body fluids. The maximal rate of excretion of water remains fairly
constant for a prolonged period when the route of administration of the load of water
is achieved and maintained by the intravenous route. This does not appear to be
dependent on the rate of excretion of salt. The rate of excretion of water is not main-
tained at high levels when the oral route of water loading is employed. There is evi-
dence that under these circumstances the volume of the extracellular fluid does not
expand and may contract, due, presumably, to the transfer of electrolytes into the
stomach and lower gastrointestinal tract which produces a hyponatremia and con-
sequent movement of water into the intracellular space. These changes may be the
cause of the apparent decrease in filtration rate, and increased reabsorption of water
in the renal tubules.

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REFERENCES