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# Hypernatremia

## Complication of Renal Homotransplantation

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Hypernatremia was observed in five recipients of renal homografts during the first postoperative week. The peak serum levels of sodium varied between 152 and 158 mEq/liter. The postoperative diuresis was associated with sodium concentration in the urine, consistently lower than that in the extracellular water; moderate urinary hypertonicity, with urea being the main urinary solute; and urea excretion exceeding 60% of its filtered load in most instances. The inability of elaborate urine with sodium concentration equal or higher than that in the serum, possibly related to osmotic diuresis and/or altered renal hemodynamics, appears to be the primary cause responsible for the development of hypernatremia in these patients.

Serum sodium concentration under normal conditions is maintained within fairly narrow limits. Salt retention or depletion is usually associated with proportionate variations in water balance, providing a continuous isotonicity of the extracellular fluid. However, excessive losses of water in which sodium concentration is substantially lower than that in the extracellular fluid may induce an increase in serum sodium. Hypernatremia has been observed along with improving renal function during recovery from acute tubular necrosis[1,2] and following relief of prerenal azotemia.[3] In both conditions, the occurrence of diuresis with water being excreted in excess of its isosmotic content of sodium appeared to be the mechanism leading to a rise in serum sodium.

We have observed hypernatremia developing during the restriction of renal function in five recipients of kidney homografts. The data presented in this communication suggest that the postoperative diuresis with inappropriately low urinary sodium concentration was the primary cause for the rise in serum sodium concentration.

### Materials and Methods

Five patients under consideration presented with end-stage chronic renal disease (Table 1). Prior to transplantation, four were treated with periodic hemodialysis and one (patient 5), who maintained a residual creatinine clearance of 3 ml/min, was managed conservatively. This patient required salt supplements to replace excessive urinary losses of sodium. None of the patients had peripheral edema or other evidence of salt and water retention. All received homografts from living donors. The surgical techniques, as well as the immunosuppressive management, were reported elsewhere.[4,5] Four patients were subjected to a bilateral nephrectomy during the transplantation procedure. Urine was collected postoperatively through an indwelling catheter during the first 24 hours. Within the first 24 to 48 postoperative hours, the intake consisted of parenterally administered fluids given to replace urinary losses with equal volumes of 0.45% sodium chloride, alternated with lactated Ringer's solution and additional 200 to 500 ml of 5% dextrose in water, to maintain a patent central venous pressure line (these at least partly could replace insensible water losses). On the second or third postoperative day, varying amounts of liquids and semi-liquid diet were added to the parenterally administered fluids. Salt and water balances were recorded daily throughout the study. Serum and urine specimens were assayed for urea nitrogen, creatinine, and electrolytes by methods reported previously.[6] Urine protein was measured daily. Specific gravity of the urine was determined with the refractometer and corrected for its protein content by subtracting for 1 gm/100 cc of protein present in urine 0.0025 specific gravity units.[7]

### Results

All patients had immediate diuresis following the vascularization of the homografts (Table 2). Creatinine clearances varied between 10 and 21 ml/min on the first postoperative day, and were less than 50 ml/min throughout the study. None of the patients had an acute homograft rejection and the creatinine clearances exhibited progressive increase during the first postoperative month. Sodium concentrations in the serum, in the urine, and in the tubular reabsorbate are shown in Table 2. Serum sodium levels reached their peak values in two patients on the second day and in the remaining three patients on the third, fourth, and fifth postoperative days. Urinary sodium concentration in all determinations was considerably lower than the corresponding serum values, whereas the sodium levels in the reabsorbate were higher than those in the serum. Variations in chloride concentrations paralleled those of sodium both in the serum and in the urine. No apparent correlation could be noticed between the serum levels and urinary excretion of potassium and those of sodium.

Cumulative salt and water balances (in which insensible losses of wa-

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ter are included in the calculation of the water output) for the time interval between the surgery, and the peak sodium values of all patients are presented in Table 3. Water balances ($\Delta H_2O$) were subdivided into sodium isosmotic water ($\Delta Na^+/140 \times 1{,}000$) and sodium free water ($Na^+$ free $\Delta H_2O$). The latter was calculated from the following formula:

$$Na^+ \text{ free } \Delta H_2O = \Delta H_2O - \frac{\Delta Na^+}{140} \times 1{,}000$$

which designates the volume (ml) of water which is lost without corresponding amounts of sodium. All patients exhibited sodium-free water losses ranging from −1,417 to −1,980 ml. This deficit was not associated with substantial losses of body weight in four of five patients (Table 3). None of the patients showed clinical manifestation of dehydration at any time during the study. The return of serum sodium levels to normal range paralled with a considerable rise in urinary sodium concentration in all patients.

The urinary specific gravity consistently exceeded 1.010 and varied between 1.011 and 1.023. The composition of the measured urinary solutes is presented in Table 4. Urea constituted more than 50% of total urinary solute in most instances.

These results are in variance with those observed in patients of a previous report[6] and with the vast majority of our other patients in which electrolytes do contribute more than urea to urinary osmolality, and urinary sodium concentrations very often may exceed those in the serum, reaching values as high as 200 mEq/liter or more.

The clearances of urea (CU) and the percent of filtered urea excreted in the urine (CU/CCr × 100) are shown in Table 2. The CU/CCr × 100 in most instances exceeded 60%. In the normal kidney, it has been believed that approximately 40% of filtered urea is reabsorbed in the proximal tubule and thus normally the excreted amount of urea does not exceed 60% of its filtered load.[8] The finding of more than 60% of urea being excreted in our patients could be consistent with reduced proximal tubular reabsorption similar to that seen in normal humans undergoing osmotic diuresis.[9]

The concentration ratios of urinary creatinine to serum creatinine (UCr/SCr) were less than 8:1 in four patients, only on the first or second postoperative day. It has been postulated that under normal conditions, about seven eighths of glomerular filtrate are reabsorbed in the proximal tubule.[10] Thus, UCr/SCr of less than 8:1 may reflect diminished reabsorption in the proximal tubule.

The aforementioned variations in CU/CCr and UCr/SCr have been used as criteria indicative of osmotic diuresis[8-10] on the basis of the assumption that osmotic diuresis is primarily due to reduced proximal reabsorption.[10,11] However, the results of more recent micropuncture studies in dog and cat question the accuracy of

**Table 1.—Clinical Data**

| Patient | Age | Sex | Diagnosis | Donor | Bilateral Nephrectomy |
|---|---|---|---|---|---|
| 1 | 34 | M | CGN* | Sister | Yes |
| 2 | 48 | M | CGN | Sister | Yes |
| 3 | 29 | M | CGN | Brother | Yes |
| 4 | 11 | F | CGN | Mother | Yes |
| 5† | 17 | M | CGN | Mother | No |

* Chronic glomerulonephritis.
† No hemodialysis prior to transplantation.

**Table 2.—Urinary Excretion and Clearances of Creatinine, Urea, Sodium, and Protein**

| Patient, Day | Urine Volume (ml/24 hr) | Protein (ml/24 hr) | Corrected Specific Gravity | CCr (ml/min) | CU (ml/min) | UCr/SCr | CU/CCr x 100 | Serum Na† (mEq/liter) | Urine Na† (mEq/liter) | Concentrated Na† in Reabsorbed Filtrate (mEq/liter) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1, 1 | 4,270 | 1,900 | 1.015 | 15.1 | 13.8 | 5:1 | 93 | 144 | 96 | 186 |
| 2 | 3,090 | 1,100 | 1.015 | 33.0 | 25.6 | 19:1 | 78 | 144 | 93 | 149 |
| 3 | 2,057 | 3,900 | 1.015 | 44.2 | 19.5 | 24:1 | 44 | 151 | 65 | 155 |
| 4 | 1,420 | 3,700 | 1.023 | 35.2 | 22.1 | 35:1 | 63 | 152 | 66 | 161 |
| 2, 1 | 3,700 | 0 | ... | 21.0 | 10.7 | 8.3:1 | 52 | 133 | 47 | 145 |
| 2 | 3,150 | 0 | 1.011 | 17.6 | ... | 7.9:1 | ... | 147 | 20 | 160 |
| 3 | 3,000 | 0 | ... | 25.0 | 15.9 | 11.9:1 | 64 | ... | 20 | ... |
| 4 | 2,350 | 3,200 | 1.013 | 21.0 | 13.0 | 15.2:1 | 62 | 154 | 27 | 162 |
| 5 | 2,350 | 3,300 | 1.012 | 27.0 | 15.6 | 16.2:1 | 58 | 158 | 24 | 167 |
| 3, 1 | 3,900 | 0 | 1.011 | 15.0 | 12.6 | 6:1 | 84 | 134 | 63 | 149 |
| 2 | 3,961 | 0 | 1.016 | 31.3 | 15.1 | 9.5:1 | 49 | 149 | 82 | 154.5 |
| 3 | 1,983 | 0 | 1.020 | 22.6 | 17.8 | 16:1 | 79 | 152 | 56 | 159 |
| 4, 1 | 1,510 | 0 | 1.020 | 9.9 | 9.4 | 9.4:1 | 95 | 140 | 62 | 161 |
| 2 | 1,782 | 0 | 1.012 | 31.7 | 24.8 | 31:1 | 78 | 153 | 76 | 158 |
| 5, 1 | 2,620 | 1,360 | 1.013 | 12.0 | 9.3 | 6.7:1 | 77 | 143 | 37 | 164 |
| 2 | 1,670 | 760 | 0.021 | 24.6 | 9.8 | 21:1 | 35 | 158 | 50 | 165 |

above considerations by providing evidence that the major effect of an osmotic diuretic is in more distal parts of the nephron.[12,13]

### Comment

This report indicates that hypernatremia is a potential complication immediately after renal homotransplantation. The data presented clearly demonstrate the association of hypernatremia with inordinately low concentration of sodium in the urine (urinary sodium concentration consistently lower than that in the serum) which occurred in the absence of dehydration or extracellular volume depletion. Patients with adequately functioning renal homografts have been shown to be able to elaborate urine with high sodium concentration under comparable circumstances.[6] It is therefore likely that the primary cause underlying the appearance of hypernatremia in our five patients was related rather to the inability to increase urinary sodium concentration than to variations in the intake of water and sodium, although more appropriate adjustments in intake could minimize the rise in serum sodium concentration.

The available data do not define fully the mechanism(s) responsible for these abnormalities; however, a number of factors are worth comment.

**Tubular Defect of Water Reabsorption.**—Ogden et al[14] observed hypernatremia in heterograft recipients who exhibited inordinate water diuresis. The excessive urinary losses of water were attributed by the authors to a possible irresponsiveness of the simian nephrons to the physiologic action of human antidiuretic hormone. The mild-to-moderate urinary hypertonicity in our patients is consistent with an adequate renal response to endogenous antidiuretic hormone. However, partial tubular defect cannot be ruled out completely on the basis of present findings.

**Changes in Renal Hemodynamics.**—Immunologic vascular injury could induce renal hypoperfusion with low urinary sodium concentration[15] similarly to that observed in an ischemic kidney with renal artery constriction.[16] Although none of our patients exhibited definite clinical manifestations of acute homograft rejection, the fact that the creatinine clearance values, which were initially relatively low, assumed higher rates during further postoperative course is consistent with an early state of renal underperfusion.

**Osmotic Diuresis Due to Increased Filtered Loads of Urea.**—Hypernatremia, which is associated with solute diuresis (other than sodium salts), is considered to be secondary to excretion of urine with relatively more water than sodium (the concentration of sodium in the extracellular fluid being used as reference). Solute diuresis, following the administration of exogenous solutes such as mannitol or urea, has been reported to cause hypernatremia.[17,18] Similarly, endogenously retained solutes may induce osmotic diuresis and hypernatremia once the kidney function improves. Leutscher and Blackman[1] described hypernatremia in patients recovering from acute renal failure. Hypernatremia has also been recorded in patients recovering from prerenal azotemia, secondary to congestive heart failure.[6]

Diuresis, following relief of obstructive uropathy, may exhibit an

**Table 3.—Cumulative Water and Sodium Balance**

| Patient | Water (ml) | | Sodium (mEq) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Intake | Output | Intake | Output | Δ $H_2O$ | Δ Na | Na Free Δ $H_2O$ | Δ Weight (kg) |
| 1 | 12,420 | 12,837 | 1,068 | 928 | −417 | +140 | −1,417 | −0.3 |
| 2 | 13,670 | 17,050 | 220 | 417 | −3,380 | −197 | −1,980 | −2.6 |
| 3 | 11,397 | 11,344 | 844 | 681 | +53 | +163 | −1,127 | +0.1 |
| 4 | 4,327 | 4,292 | 456 | 230 | +35 | +226 | −1,595 | +0.2 |
| 5 | 4,110 | 5,000 | 327 | 181 | −890 | +146 | −1,930 | −0.7 |

$H_2O$ indicates net gain or loss of water; Na, net gain or loss of sodium; Na free $H_2O$, Sodium free water loss; weight, changes in body weight.

**Table 4.—Urinary Excretion of Solutes**

| Patient, Day | Electrolytes (mOsm/24 hr) | | | | Urea (mOsm/24 hr) | Urea: Electrolytes |
|---|---|---|---|---|---|---|
| | $Na^+$ | $K^+$ | $Cl^-$ | Total | | |
| 1, 1 | 410 | 34 | ... | ... | 735 | ... |
| 2 | 288 | 68 | 204 | 560 | 700 | 1.25 |
| 3 | 137 | 102 | 39 | 278 | 735 | 2.60 |
| 4 | 94 | 48 | 62 | 204 | 620 | 3.10 |
| 2, 1 | 174 | 233 | 82 | 489 | 675 | 1.38 |
| 2 | 63 | 291 | ... | ... | ... | ... |
| 3 | 60 | 142 | 57 | 259 | 785 | 3.00 |
| 4 | 63 | ... | ... | ... | 620 | ... |
| 5 | 56 | 91 | 25 | 172 | 632 | 3.68 |
| 3, 1 | 245 | 24 | 210 | 479 | 441 | 0.93 |
| 2 | 325 | 40 | 296 | 661 | 541 | 0.82 |
| 3 | 111 | 62 | 66 | 239 | 430 | 1.80 |
| 4, 1 | 94 | 32 | 75 | 201 | 170 | 0.85 |
| 2 | 136 | 68 | 143 | 347 | 395 | 1.14 |
| 5, 1 | 97 | 44 | 16 | 157 | 585 | 3.71 |
| 2 | 84 | 32 | 48 | 164 | 412 | 2.50 |

excretory pattern similar to solute diuresis.[9,19] Maher et al[19] reported urea as the major urinary solute in their patient with postobstructive diuresis. Recalculation of the electrolytes in the latter report showed an increase in serum sodium from 127 to 147 mEq/liter occurring during the diuresis.

In a previous study[6] the diuresis following renal homotransplantation was characterized as solute diuresis, in which electrolytes contributed more than 60% of the urinary osmolar content. In contradistinction, urea was the major urinary solute in our patients. This difference could be due to the fact that the patients in the cited report were moderately overhydrated and possibly volume expanded (this statement is probably also applicable to the vast majority of all renal homograft recipients), whereas our patients being presumably close to their dry body weights had retained more urea than salt. The postoperative diuresis in our patients was modest when compared with that of the patients in the other study. Similar observations were made by Rosenbaum et al[20] who found that sodium loading in their patients had a greater effect on urinary flow than the same osmolar quantity of urea. Kleeman et al,[21] interpreting the above observations, suggested that the striking effect of sodium on urine flow was a result of extracellular volume expansion occurring with salt loading, but not with urea.

The criteria which have been used for years as characteristic of osmotic diuresis[9] were only partially satisfied by our patients (as judged by the urine/plasma creatinine and urea/creatinine clearance ratios). However, the possible occurrence of renal ischemia, as discussed above, and the administration of adrenal corticoids might have modified those ratios.[16,22] Furthermore, as the recent micropuncture studies indicate,[12,13] osmotic diuresis is not necessarily associated with significantly altered proximal reabsorption, in which case the above mentioned criteria cannot be considered anymore as limiting factors in determining the presence of osmotic diuresis. In addition, it is possible that the primary change in our patients was a moderate reduction in proximal sodium reabsorption with subsequent increased volume delivery to the distal nephron. An unimpaired distal sodium reabsorptive capacity might decrease urinary sodium excretion, whereas the urea reabsorptive capacity might be exceeded leading to an increased fractional excretion of urea.

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