Opposite Changes in Serum Sodium and Potassium in Patients in Diabetic Coma

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Abstract. We studied the changes in serum sodium (Na) and potassium (K) levels in seventeen patients in diabetic ketoacidosis and nine patients in non-ketotic hyperosmolar coma, who had marked hyperglycemia (707.4±75.6 mg/dl, mean±SEM) and dehydration. The disorder characterized two types of alteration. The one group was hyponatremia with hyperkalemia in 17 patients in diabetic ketoacidosis (132.9±2.0 and 5.7±0.2 mEq/l), and 4 patients in non-ketotic hyperosmolar coma (125.8±4.3 and 5.2±0.5 mEq/l). The other was hypernatremia (162.5±1.8 mEq/l) with hypokalemia (3.4±0.2 mEq/l) in 5 patients in non-ketotic hyperosmolar coma. Intensive therapy with insulin and fluid administration improved the diabetic hyperglycemia and associated abnormalities. The vectors showing the normalization of serum Na and K levels was in quite opposite directions between the patients with hyponatremia with hyperkalemia and those with hypernatremia with hypokalemia. The amounts of loss of circulatory blood volume exceeded 20% in three groups of patients, a loss greater in the hypernatremic patients than in the hyponatremic ones. These results indicate that serious body water depletion produces hypernatremia instead of hyponatremia in patients in diabetic coma. The disorder may be caused by the altered distribution of electrolytes between the intra- and extra-cellular spaces.

Key words: Serum Na, Serum K, Diabetic coma.

MARKED HYPERGLYCEMIA is common in diabetic coma including diabetic ketoacidosis and non-ketotic hyperosmolar coma. Pseudohyponatremia has been described in such a disorder, because serum sodium (Na) levels are expected to decrease at the rate of 1.6 mEq/l per 100 mg/dl increase in plasma glucose [1]. A remarkable increase in plasma glucose accompanies marked glucosuria and osmotic diuresis. The patients thus suffer from serious dehydration. We have demonstrated that such a volume-depleted state increases plasma arginine vasopressin (AVP) levels in patients in diabetic coma, an increase contributing to circulatory homeostasis [2]. In addition, plasma renin activity (PRA) and plasma aldosterone concentration increase in diabetic coma [3]. In our preliminary study and in the literature [4] the change in serum potassium (K) level as well as that in serum Na is focused on as the disorder of serum electrolytes in patients in diabetic coma.

In the present study we determined the characteristics of the disorder of serum Na and K in patients in diabetic coma. Also, what mechanisms are involved in the disorder was evaluated by studying associated changes.

Subjects and Methods

Seventeen patients in diabetic ketoacidosis and nine patients in non-ketotic hyperosmolar coma were examined between September, 1982 and Sep-
tember, 1992. They were 12 males and 14 females whose ages ranged from 19 to 79 years. They were admitted to Jichi Medical School Hospital because of disordered consciousness or dehydration. Physical examination at the time of hospitalization showed normal blood pressure (125±5/76±4 mmHg) and tachycardia of 106±4 beats/min. All the patients had dry skin and tongue. Laboratory data are shown in Table 1. The patients were divided into 3 groups according to the levels of serum Na on admission. Serum Na levels in the patients in non-ketotic hyperosmolar coma were unsuccessively plotted, as shown in Fig. 1, and they could apparently be put into two groups of hypernatremia more than 159 mEq/l and hyponatremia less than 135 mEq/l. There were a group of patients in diabetic ketoacidosis (n=17), a group of hyponatremic patients in non-ketotic hyperosmolar coma (n=4) and a group of hypernatremic patients in non-ketotic hyperosmolar coma (n=5).

Therapeutic protocol

After hospitalization, intensive care was immediately started. A small dose of short-acting insulin (0.05–0.1 U/kg/h) and a large volume of physiological saline or 0.45% (v/v) saline were infused. When plasma glucose had decreased to below 300 mg/dl, the saline was replaced by solutions containing glucose and K. The saline was infused in a volume of more than 2 liters during the initial 6-h period, followed by 1–2 liters infusion during an additional 18 h period on day 1 of the hospitalization. The infusion was continued with the electrolyte-balanced solutions (131 mEq/l Na+, 4 mEq/l K+, 3 mEq/l Ca2+, 110 mEq/l Cl– and 28 mEq/l lactate) containing glucose in a volume of 1.5–2.5 liters on days 2–3, and then oral intake of food and water was begun. K+ was infused at approximately 30 mEq and 40–50 mEq within the first 24 and 48 h, respectively. All the patients were confined to bed for at least the initial 24 h after the hospitalization. During the 7-day observation period we determined the serum levels of Na, K and chloride, plasma glucose, hematocrit, serum protein, creatinine, blood urea nitrogen (BUN), plasma osmolarity (Posm), arterial blood pH and bicarbonate. All of the above parameters except arterial pH and bicarbonate were determined before the start of therapy, at 1, 2, 3, 4, 5, 6, 12, 24 and 48 h and on day 7 after the hospitalization. In addition, plasma AVP, PRA and plasma aldosterone concentrations were determined before the start of therapy, at 24 h and on day 7 of the hospitalization. The percent change in circulatory blood volume was calculated taking the data on day 7 of the hospitalization as zero, which was determined by the change in hematocrit (Ht); (Ht2 - Ht1)/Ht1 × 100 (%) [2].

Hormonal assays

Blood was collected in chilled tubes containing EDTA-Na2 (1 mg per ml blood) and centrifuged at 3000 rpm at 4°C for 15 min. The supernatants were decanted and frozen at −20°C until the time of assay for plasma AVP, PRA and plasma aldosterone. Plasma AVP was measured by RIA using AVP RIA kits (Mitsubishi Yuka Co., Tokyo, Japan) [5, 6]. PRA and plasma aldosterone concentration were determined by RIA using PRA RIA kits (Midori-Juji Co., Tokyo, Japan) [7], and Aldosterone RIA kits (Dainabott Lab., Tokyo, Japan) [8]. The normal value of plasma AVP is 0.5–2.2 pg/ml, that of PRA 0.3–2.9 ng/ml/h, and that of plasma aldosterone 1.1–6.3 ng/dl.

Statistical analysis

Serum Na levels were compared with the associated parameters. All values were compared with Scheffe’s analysis of multiple variance and Student’ t test. A P value of less than 0.05 was considered significant.

Results

Table 1 shows the laboratory data for 26 patients in diabetic coma. Plasma glucose levels were 707.4 ±75.6 mg/dl, hemoglobin A1c was 11.9 ±1.2%, and Posm was 355.3 ±7.2 mOsm/kg H2O. The patients in diabetic ketoacidosis had ketonuria, increased blood ketone body concentrations and metabolic acidosis with an arterial pH of 7.13 ±0.03 and HCO3 of 7.3 ±1.1 mEq/l. The patients in non-ketotic hyperosmolar coma had an arterial blood pH of 7.36 ±0.02 and HCO3 of 21.2 ±2.6 mEq/l. Percent changes in circulatory blood volume ranged from −24.5±2.6 to −34.4±3.2% in
all the three groups of patients. The percent change in circulatory blood volume was significantly greater in the hypernatremic patients in non-ketotic hyperosmolar coma than in the hyponatremic patients.

Figure 1 shows serum Na levels at hospitalization in the patients in diabetic ketoacidosis and non-ketotic hyperosmolar coma. As mentioned earlier, we divided the patients into 3 groups according to the levels of serum Na at hospitalization. The serum Na levels was 132.9 ± 2.0 mEq/l in a group of patients in diabetic ketoacidosis. Apparently there were two subgroups of the patients in non-ketotic hyperosmolar coma, namely, the hypernatremic group of 162.5± 1.8 mEq/l and the hyponatremic group of 125.8±4.3 mEq/l. It was noted that there was an inverse change in serum Na and K levels, as shown in Table 2. Hyperkalemia of 5.7±0.2 and 5.2±0.5 mEq/l were found in the groups of hyponatremic patients and, inversely, hypokalemia of 3.4±0.2 mEq/l in a group of hypernatremic patients.

Such a finding is very easy to understand when the relationship of serum levels of Na and K is illustrated in Fig. 2. As shown in closed circles, the patients in diabetic ketoacidosis were distributed below 144 mEq/l of serum Na and 4.2 mEq/l of serum K. The hyponatremic patients in non-ketotic hyperosmolar coma were also distributed in an area similar to that of the patients in diabetic ketoacidosis. In contrast, the hypernatremic group of patients in non-ketotic hyperosmolar coma was

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**Table 1.** Laboratory data of 26 patients in diabetic coma at admission

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age</th>
<th>Blood pressure (mmHg)</th>
<th>Pulse rate (/min)</th>
<th>Plasma glucose (mg/dl)</th>
<th>HbA1c (%)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic ketoacidosis</td>
<td>17</td>
<td>39.1 ± 4.3</td>
<td>130.1 ± 6.1/75.1 ± 3.9</td>
<td>104.3 ± 4.6</td>
<td>808.2 ± 48.6</td>
<td>12.5 ± 1.0</td>
<td>7.13 ± 0.03</td>
</tr>
<tr>
<td>Non-ketotic hyperosmolar coma</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hyponatremic group</td>
<td>4</td>
<td>56.0 ± 5.3</td>
<td>110.8 ± 17.2/83.3 ± 5.8</td>
<td>92.5 ± 8.8</td>
<td>955.8 ± 167.4</td>
<td>14.0 ± 3.4</td>
<td>7.39 ± 0.01</td>
</tr>
<tr>
<td>Hypernatremic group</td>
<td>5</td>
<td>65.0 ± 7.1</td>
<td>122.8 ± 8.7/75.6 ± 6.2</td>
<td>110.8 ± 2.1</td>
<td>856.8 ± 165.6</td>
<td>8.6 ± 0.9</td>
<td>7.34 ± 0.02</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
isolated from the other two groups of patients. They were distributed in the left upper quadrant, an area residing above 159 mEq/l of serum Na and below 3.9 mEq/l of serum K.

Intensive therapy with insulin and fluid administration effectively improved the diabetic hyperglycemia and associated abnormalities in all the 26 patients. Plasma glucose gradually decreased to approximately 300 mg/dl 5–6 h after the start of intensive therapy, followed by a further stable decrease in plasma glucose (data not shown).

Figure 3 shows the changes in serum Na and K levels after the therapy with a small dose of insulin and a large amount of fluid. The vectors showing the recovery of serum Na and K levels were in approximately the same direction as for two groups of the patients in diabetic ketoacidosis and the hyponatremic patients in non-ketotic hyperosmolar coma. Serum Na and K levels finally reached 139.9 ± 1.0 and 5.1 ± 0.5 mEq/l, respectively, in the diabetic ketoacidosis, and 139.0 ± 2.1 and 4.1 ± 0.2 mEq/l, respectively, in the hyponatremic patients in non-ketotic hyperosmolar coma. In contrast, the vector was in the opposite direction in a group of the hypernatremic patients in non-ketotic hyperosmolar coma. The levels of serum Na and K on day 7 of the hospitalization were 140.0 ± 1.7 and 4.2 ± 0.1 mEq/l, respectively, values similar to those for the other two groups of patients.

Changes in serum Na and plasma glucose levels after the therapy with a small dose of insulin and a large amount of fluid are depicted in Fig. 4. Serum Na level was normalized in 12 h after the start of intensive therapy in two groups of the patients in diabetic ketoacidosis and the hyponatremic patients in non-ketotic hyperosmolar coma. The changes in the hypernatremic patients in non-ketotic hyperosmolar coma were different from those of two groups of patients. The normalization of plasma glucose proceeded that of serum Na level, as the serum Na level remained as high as 160 mEq/l at 12 h. At that time plasma glucose decreased to less than 273.6 mg/dl. Serum Na levels normalized in at least 7 days in the hypernatremic patients in non-ketotic hyperosmolar coma.

Plasma AVP, PRA and plasma aldosterone concentrations are shown in Table 3. At hospitalization all three parameters were quite high in all the

| Table 2. Serum levels of Na, K and Chloride (Cl) in 26 patients in diabetic coma on admission |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | n   | Na (mEq/l) | K (mEq/l) | Cl (mEq/l) |
| Diabetic ketoacidosis           | 17  | 132.9 ± 2.0 | 5.7 ± 0.2  | 94.8 ± 2.0  |
| Non-ketotic hyperosmolar coma   |     |             |           |             |
| Hyponatremia group              | 4   | 125.8 ± 4.4 | 5.1 ± 0.5  | 90.0 ± 4.1  |
| Hyponatremia group              | 5   | 162.5 ± 1.8b| 3.4 ± 0.2c | 122.4 ± 2.1b|

*, P<0.01 vs. the patients with diabetic ketoacidosis; †, P<0.01; ‡, P<0.05 vs. the patients in the hyponatremic group of non-osmotic hyperosmolar coma. Values are means ± SEM.
Discussion

The present study demonstrated the disorder of serum Na and K in diabetic coma at hospitalization. The disorder characterized two groups of alteration, namely, the one group is hypotremia with hyperkalemia in the patients in diabetic ketoacidosis and non-ketotic hyperosmolar coma. The other is hypernatremia with hypokalemia in the patients in non-ketotic hyperosmolar coma. The alterations in serum Na and K levels are in opposite directions to each other. To our knowledge, this is the first report to note such a disorder in diabetic coma.

A marked increase in plasma glucose is common in ketotic and non-ketotic diabetic coma. Serum Na levels are expected to decrease at the rate of 1.6 mEq/l per 100 mg/dl increase in plasma glucose [1]. This change is dependent on a relative increase in extracellular fluid, which is derived from the intracellular space by osmotic gradient. Therefore,
Hypernatremia is not infrequently found in the patients in diabetic coma [9–12]. Hyperglycemia accompanies with marked glucosuria and osmotic diuresis. The patients are thus suffering from serious dehydration. The amounts of loss of circulating blood volume was estimated to exceed 20% in the present study. The volume contraction was greater in the hypernatremic patients in non-ketotic hyperosmolar coma than in the hyponatremic patients in diabetic ketoacidosis and non-ketotic hyperosmolar coma. Such volume-depleted states increased plasma AVP levels, PRA and plasma aldosterone concentrations [2, 3]. The alteration in serum Na was compared with the plasma glucose levels, Posm, percent change in circulating blood volume, plasma AVP, PRA and plasma aldosterone, and it was closely related to the depletion of circulating blood volume, particularly the depletion of body water. These results suggest that serious depletion of body water produces hypernatremia instead of hyponatremia in patients in non-ketotic hyperosmolar coma. In the case of non-ketotic hyperosmolar coma the hypernatremic patients tended to be older than the hyponatremic ones. Aging might be an another factor in dividing serum Na levels into such two groups, because the homeostatic ability to possess body Na may be reduced in the elderly subjects.

In the state of diabetic ketoacidosis considerable amounts of Na and K are probably excreted from the kidney. Since the patients were admitted to our hospital in the condition of diabetic coma, it is hard to determine the urinary loss of Na and K during the prestate of diabetic coma. Also, urinary excretion of Na and K was not adequate to evaluate after hospitalization because a large volume of saline solution was infused for therapeutic approach.

As shown in Fig. 3, the intensive care normal-ized serum Na and K levels. The patients with hypernatremia with hypokalemia took much more time to normalize serum Na and K levels into the normal ranges when compared with those with hyponatremia with hyperkalemia. The feature is that the vectors showing the normalization of serum Na and K levels were totally in a opposite direction in the patients with hypernatremia with hypokalemia from that in those with hyponatremia with hyperkalemia. The present study did not mention the exact mechanism for the opposite alteration in serum Na and K levels in diabetic coma. Though urinary losses of Na and K could not be evaluated in the present study, changes in the distribution of the electrolytes between intra- and extracellular spaces are speculated. In the state of diabetic ketoacidosis there is an absolute deficiency of insulin. Such a state can not stimulate Na+/K+-ATPase activity and promote active transport of Na and K across plasma membrane, because insulin activates Na+/K+-ATPase [13, 14]. Also, the cell membrane Na+/H+ exchanger is activated by acidosis [15, 16]. Hyperosmolarity produces cellular dehydration, increasing K+ efflux from cells. These factors are involved in the hyperkalemia and hyponatremia in the patients in diabetic ketoacidosis and in non-ketotic hyperosmolar coma. Hypokalemia was found in the hypernatremic patients. Additional undetermined factors, including insulin and catecholamines, may affect the inverse distribution. Further study will be necessary to explore the exact mechanism.

In summary, we demonstrated two opposite types of the disorder of serum electrolytes at hospitalization in the patients in diabetic coma. Hyponatremia with hyperkalemia was found in the patients in diabetic ketoacidosis and non-ketotic hyperosmolar coma, and hypernatremia

### Table 3. Plasma renin activity (PRA), plasma aldosterone and plasma arginine vasopressin (AVP) in patients in diabetic coma at hospitalization

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PRA (ng/ml/h)</th>
<th>Plasma aldosterone (ng/dl)</th>
<th>Plasma AVP (pg/ml)</th>
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</thead>
<tbody>
<tr>
<td>Diabetic ketoacidosis</td>
<td>8</td>
<td>22.7±4.7</td>
<td>26.6±3.0</td>
<td>6.9±1.0</td>
</tr>
<tr>
<td>Non-ketotic hyperosmolar coma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia group</td>
<td>3</td>
<td>20.9±5.0</td>
<td>24.9±7.3</td>
<td>8.8±2.4</td>
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<tr>
<td>Hypernatremia group</td>
<td>4</td>
<td>28.4±7.9</td>
<td>29.1±8.8</td>
<td>9.4±3.0</td>
</tr>
</tbody>
</table>

Values are means±SEM.
with hypokalemia in non-ketotic hyperosmolar coma. The disorder may be based on the altered distribution of electrolytes between intra- and extracellular spaces, but the exact mechanism for the disorder has not been determined.

References