A method to estimate urinary electrolyte excretion in patients at risk for developing cerebral salt wasting

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Object. Two major criteria are necessary to diagnose cerebral salt wasting (CSW): a cerebral lesion and a large urinary excretion of Na⁺ and Cl⁻ at a time when the extracellular fluid (ECF) volume is contracted. Nevertheless, it is difficult for the physician to confirm from bedside observation that a patient has a contracted ECF volume. Hyponatremia, although frequently present, should not be a criterion for a diagnosis of salt wasting. A contracted ECF volume is unlikely if there are positive balances of Na⁺ and Cl⁻.

The goal of this study was to assess the accuracy of calculating balances for Na⁺ plus K⁺ and of Cl⁻ over 1 to 10 days in an intensive care unit (ICU) setting.

Methods. A prospective comparison of measured and estimated quantities of Na⁺ plus K⁺ and of Cl⁻ excreted over 1 to 10 days in 10 children and 12 adults who had recently received a traumatic brain injury or undergone recent neurosurgery. Plasma concentrations of electrolytes were recorded at the beginning and end of the study period. The total volumes infused and excreted and the concentrations of Na⁺, K⁺, and Cl⁻ in the infusate were obtained from each patient’s ICU chart. The electrolytes in the patients’ urine were measured and calculated. Correlations between measured and calculated values for excretions of Cl⁻ and of Na⁺ plus K⁺ were excellent.

Conclusions. Mass balances for Na⁺ plus K⁺ and for Cl⁻ can be accurately estimated. These data provide information to support or refute a clinical diagnosis of CSW. The danger of relying on balances for these electrolytes measured within a single day to diagnose CSW is illustrated.

KEY WORDS • chloride • hyponatremia • neurosurgery • syndrome of inappropriate antidiuretic hormone secretion • traumatic brain injury

HYPONATREMIA is a frequent finding in neurosurgical patients. Although hyponatremia is a hallmark of SIADH, it should not be viewed as a critical component for the diagnosis of CSW for the following reasons. Hyponatremia develops if there is a source of electrolyte-free water and vasopressin to prevent its excretion. Patients with CSW have multiple stimuli for the release of vasopressin, including central nervous system lesions, pain, stress, high intracranial pressure, and the drugs they have been given. Therefore, if their renal concentration process is intact, they will have very high concentrations of Na⁺ in their urine. If this is combined with the infusion of isotonic saline, electrolyte-free water will be generated by desalination of the intravenous saline and will be retained in the body. Accordingly, hyponatremia will develop, but only as a secondary event. In fact, hyponatremia can be prevented if the concentration of Na⁺ in the intravenous solution is equal to that in the urine. Therefore, with proper treatment, hyponatremia will not be present in a patient with CSW. It is particularly important to avoid making an incorrect diagnosis of CSW or SIADH in these patients because the treatments of these disorders differ. For example, although treatment of CSW includes a large infusion of saline, this therapy can lead to a more severe degree of hyponatremia in a patient due to desalination of the infused saline.

Because the essential feature of CSW is Na⁺ wasting, there should be a negative balance for Na⁺ plus K⁺ and/or for Cl⁻ when the diagnosis of CSW is established. Because urine electrolytes are not usually measured on the first few days the patient spends in the ICU, balance data would not be available when the patient is seen at consultation (usually 3–5 days after the appearance of the CNS lesion).

The objective of our study was to test a method to calculate the amount of Na⁺ plus K⁺ and that of Cl⁻ excreted during the 1st week of hospitalization by using data that should be available in the ICU chart. These data include the total amount of fluid administered, its electrolyte con-
Urine electrolytes

TABLE 1
Characteristics of 22 patients on admission

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Weight (kg)</th>
<th>Diagnosis</th>
<th>No. of Days in ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>pediatric patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-1</td>
<td>14</td>
<td>60</td>
<td>TBI</td>
<td>10</td>
</tr>
<tr>
<td>P-2</td>
<td>8</td>
<td>35</td>
<td>TBI</td>
<td>6</td>
</tr>
<tr>
<td>P-3</td>
<td>4</td>
<td>18</td>
<td>TBI</td>
<td>6</td>
</tr>
<tr>
<td>P-4</td>
<td>6</td>
<td>25</td>
<td>TBI</td>
<td>6</td>
</tr>
<tr>
<td>P-5</td>
<td>10</td>
<td>25</td>
<td>TBI</td>
<td>5</td>
</tr>
<tr>
<td>P-6</td>
<td>4</td>
<td>20</td>
<td>TBI</td>
<td>4</td>
</tr>
<tr>
<td>P-7</td>
<td>5</td>
<td>20</td>
<td>TBI</td>
<td>4</td>
</tr>
<tr>
<td>P-8</td>
<td>5</td>
<td>18</td>
<td>TBI</td>
<td>4</td>
</tr>
<tr>
<td>P-9</td>
<td>7</td>
<td>30</td>
<td>TBI</td>
<td>1</td>
</tr>
<tr>
<td>P-10</td>
<td>6</td>
<td>20</td>
<td>reseected tumor</td>
<td>1</td>
</tr>
</tbody>
</table>

| adult patients | | | | |
| A-1          | 60       | 93          | SAH                | 7                  |
| A-2          | 77       | 68          | SAH                | 7                  |
| A-3          | 60       | 66          | SAH                | 7                  |
| A-4          | 75       | 91          | reseected tumor    | 6                  |
| A-5          | 60       | 83          | SAH                | 5                  |
| A-6          | 20       | 65          | TBI                | 5                  |
| A-7          | 44       | 71          | SAH                | 4                  |
| A-8          | 42       | 100         | SAH                | 4                  |
| A-9          | 55       | 58          | SAH                | 4                  |
| A-10         | 40       | 86          | TBI                | 4                  |
| A-11         | 40       | 80          | SAH                | 3                  |
| A-12         | 71       | 97          | SAH                | 3                  |

TABLE 2
Mean plasma composition in the study population on admission and at the end of the urine collection period*

<table>
<thead>
<tr>
<th>Plasma Composition (mmol/L)</th>
<th>Pediatric Group</th>
<th>Adult Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>140 ± 0.7</td>
<td>141 ± 1.2</td>
</tr>
<tr>
<td>K⁺</td>
<td>3.5 ± 0.1</td>
<td>3.9 ± 0.1</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>107 ± 1.2</td>
<td>108 ± 1.3</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>25 ± 0.8</td>
<td>26 ± 0.7</td>
</tr>
</tbody>
</table>

* All values are reported as means ± standard errors of the means.

Calculations of Electrolyte Measures

We measured concentrations of Na⁺, K⁺, and Cl⁻ in patients’ plasma on admission to the ICU, defining the beginning of the study period and again at the end of the study period. The other information required for the calculations was an estimate of total body water on admission based on the weight and height of the patient.29 Because a diagnosis of CSW is usually made several days after the patient’s arrival at the ICU, measurements and calculations were performed over a 1- to 10-day period. The results we report reveal that there was an excellent agreement between measured and calculated values of urinary electrolytes in both adult and pediatric patient populations.

Clinical Material and Methods

Patient Population

The research ethics boards of the Hospital for Sick Children and St. Michael’s Hospital approved the protocol. In the pediatric group there were nine patients with TBI (Glasgow Coma Scale score < 8) and one patient who had undergone neurosurgery for a brain tumor. The adult group consisted of nine patients who had undergone neurosurgery for an SAH, two who had suffered a TBI, and one who had undergone resection of a meningioma. All patients were admitted to the ICU where Foley catheters and arterial lines were inserted as part of routine case management. Urine and drainage volumes (nasogastric and extraventricular drainage) were noted as were the concentrations of Na⁺, K⁺, and Cl⁻ excreted in the patients’ urine. The electrolyte concentrations in the fluids drained were estimated on the basis of data obtained in the literature; in every case, these volumes were less than 5% of the urine values. Because the stay in the ICU was 6, 6, 6, and 10 days in the first four pediatric patients, respectively, the data in these patients were analyzed for both a 4-day study period and for their entire stays in the ICU.

Analytical Procedures

Both Na⁺ and K⁺ in each urine sample were measured in duplicate by using flame photometry (FLM-3, Radiometer; London, ON, Canada). The concentration of Cl⁻ was measured using electromimetic titration (CMT 10, Chlomideter; London Scientific Ltd., London, ON, Canada). Creatinine, urea, glucose, and bicarbonate, as well as osmolality were measured in a manner previously described.9

Results

In no patient did we measure a blood sugar level exceeding 200 mg/dl (11 mmol/L). The age and weight of the patients as well as the diagnosis and duration of stay in the ICU are provided in Table 1. No children, but all adults were febrile on at least one of the study days. The mean peak for body temperature was 38.5 ± 0.15°C and the mean nadir for body temperature was 37.3 ± 0.2°C.

The mean values of plasma electrolytes in each of the patients on admission and at the end of the study period are provided in Table 2. Overall, there was no consistent change in concentrations of any plasma electrolytes in the pediatric and adult study groups. The maximum rise in the concentration of Na⁺ in plasma was 9 mmol/L, whereas its maximum decrease was 6 mmol/L. Corresponding values
for Cl\textsuperscript{−} were a maximum rise of 11 mmol/L and a maximum fall of 10 mmol/L. For all calculations, we used the change in concentrations of both Na\textsuperscript{+} and K\textsuperscript{+} in plasma, rather than just the concentration of Na\textsuperscript{+} in plasma. The volume infused was 2.2 ± 0.2 L/day (5.8 ± 0.4 L/day/70-kg body weight) in the pediatric group and 3.9 ± 0.5 L/day in the adult group. The solutions infused tended to be slightly hypertonic (175 ± 6 mmol/L) because KCl was added to isotonic saline. The mean concentration of Na\textsuperscript{+} plus K\textsuperscript{+} in the urine was 220 ± 11 mmol/L in the pediatric population and 152 ± 8 mmol/L in the adult population. In six patients, there were negative balances for both Na\textsuperscript{+} plus K\textsuperscript{+} and Cl\textsuperscript{−} on an individual day (Table 3). Nevertheless, the cumulative balances of these electrolytes were positive over the entire period of observation (Table 3).

When calculations were performed in each patient, the measured and calculated values for both Na\textsuperscript{+} plus K\textsuperscript{+} and Cl\textsuperscript{−} were very close to the line of identity for these two parameters in both the pediatric and adult populations (Fig. 1). Notwithstanding, the calculated values for Na\textsuperscript{+} plus K\textsuperscript{+} were somewhat lower than their corresponding measured values; although still evident in the case of Cl\textsuperscript{−}, this difference was smaller in magnitude.

**Discussion**

After a few days in the ICU, patients who have either received a recent TBI or undergone neurosurgery for an SAH or a brain tumor often excrete a very large quantity of NaCl.\textsuperscript{11} On examining their urine, one often finds a negative balance for Na\textsuperscript{+} on one of those days (Table 3), high urinary concentrations of Na\textsuperscript{+} plus K\textsuperscript{+} and of Cl\textsuperscript{−} (>200 mmol/L), and hyponatremia. This constellation of findings provides the usual basis on which to formulate a clinical diagnosis of CSW.\textsuperscript{11} Nevertheless, to make this diagnosis one must ensure that a stimulus to excrete Na\textsuperscript{+} and Cl\textsuperscript{−}, such as expanded ECF volume, is absent. It is important to emphasize that one cannot be certain that the ECF volume, or even more important, the effective vascular volume is contracted on clinical grounds unless changes are quite marked.\textsuperscript{2,17} Therefore, it would be very helpful if there was a bedside test to confirm that a negative balance for Na\textsuperscript{+} plus K\textsuperscript{+} and one for Cl\textsuperscript{−} were present. This would provide a stronger indication that the ECF volume is contracted, because specialized laboratory tests, such as measurement of renin activity in plasma, are not available when the clinical diagnosis of CSW is being considered and decisions concerning therapy must be made.\textsuperscript{11,19} Unfortunately, critical data for balances of Na\textsuperscript{+} plus K\textsuperscript{+} and those of Cl\textsuperscript{−} are often not available because earlier urine collections were discarded. Hence the objective of this study was to determine whether one could obtain a reasonable estimate of these urinary losses without making actual measurements of electrolyte concentrations in the urine. This objective was achieved because there was an excellent correlation between measured and calculated values in individual pediatric and adult patients, even when studies were conducted over a period of 10 days (Fig. 1).
Urine electrolytes

When calculations were performed, two sites of water loss were ignored: the respiratory tract and the skin. The rationale to deduce that loss of water by the respiratory tract should not have an important effect on water balance in this setting is provided in the Appendix. We estimate that there will be a positive balance for water that is equivalent to metabolic water production, which is close to 300 ml/day, because all patients received intubation and mechanical ventilation with humidified air warmed to 36.5°C for the majority of the study period.

The other ignored water loss is via perspiration and this loss cannot be measured accurately. In the absence of fever with excessive heat dissipation, the volume of sweat is probably close to the volume of daily metabolic production of water for the following reasons. First, perhaps one fourth of this loss can be considered to be isotonic saline if the concentration of Na+ in sweat is close to 35 mmol/L.21,22 This is a very small loss that is ignored. Second, the remaining volume is electrolyte-free water and this was not included in our calculations because it is probably offset by the net positive balance for metabolic water in patients inspiring humidified air at 36.5°C. Hence it is not surprising that ignoring these two sources of nonrenal water loss had no important impact on the comparison of calculated and measured urine electrolyte excretions during the study period (Fig. 1).

Extra caution is required to interpret the significance of the excretion of K+ with respect to its potential impact on ECF volume. When K+ is excreted along with inorganic phosphate derived from the intracellular fluid compartment, this excretion should be ignored because it does not reflect a contraction of ECF volume.6 This form of excretion of K+ would pose a problem for an interpretation of directly measured urine electrolytes, whereas this same excretion of K+ would not be detected in, or cause a problem for, interpretation when using our calculation of the amount of urine Na+ plus K+. Parenthetically, this could provide a partial explanation for why the relationship between measured and calculated excretions was more precise for Cl− than for Na+ plus K+ (Fig. 1).

Healthy persons will excrete an amount of Na+ over a 48-hour period of salt restriction that is approximately equal to the preceding day’s intake of NaCl.12,18 Hence, to establish a diagnosis of CSW, the negative balance for Na+ and Cl− should exceed 2 mmol Na+/kg body weight in persons who ingest a typical Western diet because a 70-kg person on average consumes 150 mmol daily NaCl.15,28 In our patients, on the basis of the data we can infer that the large amount of natriuresis may have been stimulated by ECF volume expansion. In the case of patients with SAH, this is particularly relevant, given the large volumes of isotonic saline administered as part of the therapy aimed at preventing vasospasm.13,30

There are two possible limitations for our calculations. If accompanied by a large loss of sweat and/or excessive loss of fluid via the skin in burn victims, fever would lead to a significant underestimation of the calculated losses of Na+ plus K+ and of Cl−. Nevertheless, because one needs large deficits of Na+ plus K+ and Cl− to make a diagnosis of CSW, this is unlikely to cause a clinically important, unrecognized problem. Second, one must have reliable data on all infusions and daily urine volumes to determine a valid calculation.

At times, clinicians use unreliable data such as hyponatremia and the concentration of Na+ in urine to infer that there is salt wasting.11 As mentioned in the introduction to this paper, hyponatremia should not be used as a diagnostic criterion for CSW. It is important to recognize that neither the concentration of Na+ in the urine nor its excretion rate is sufficient to reveal the balance for Na+.16 When only limited data were examined (Table 3), one could incorrectly imply that there was an overall negative balance for Na+ plus K+ and that CSW was present. Only when calculated values for urine electrolytes for the entire time period were examined did it become obvious that the balances for Na+ plus K+ and for Cl− were positive for their entire period of hospitalization, despite the fact that on a single day, negative balances for these ions were present (Table 3). If a diagnosis of CSW were based on this limited 1-day data, it would have been incorrect. Moreover, if an effort was mounted to maintain Na+ balance, a significant degree of hyponatremia might be produced because the urine in these patients had a higher concentration of Na+ plus K+ than in the intravenous infusate (220 ± 11 mmol/L compared with 175 ± 6 mmol/L in the pediatric population, respectively), with possibly a very unfavorable outcome.14 To avoid inducing acute hyponatremia when urine has very high concentrations of Na+ plus K+, the infusate must be as hypertonic as the urine. Alternatively, the concentration of Na+ plus K+ in the urine must be lowered to become equal to isotonic saline that is being infused. The latter can be achieved by giving a loop diuretic4,10 or an osmotic diuretic agent such as urea1 or mannitol.20

Conclusions

The diagnosis of CSW in a patient with a cerebral lesion is dependent on finding ongoing natriuresis in the face of a contracted effective ECF volume and no other cause for the excretion of Na+ and Cl−. One difficulty encountered at the bedside of the patient is that it is not usually possible to determine whether the effective ECF volume is contracted by performing physical examination, even when the deficit of Na+ is close to 30%.19 If inputs and outputs were recorded accurately and one has measurements of the initial and current concentrations of Na+ plus K+ or of Cl− in plasma, one could estimate the excretion of these electrolytes with sufficient accuracy for clinical purposes (Fig. 1). In these patients, one should also include how much Na+ and Cl− were administered by the ambulance crew and by personnel in all hospital areas before the patient arrived at the ICU to be sure that mass balances for Na+ plus K+ and of Cl− were truly negative. We suggest that one should not formulate a diagnosis of CSW unless the balances for Na+ plus K+ and/or of Cl− are appreciably negative.

Appendix

Respiratory and Metabolic Water Balance

Water and CO2 are produced in a 1:1 ratio during the complete oxidation of the major energy fuels5 and all the CO2 produced in 1 day is excreted via the lungs. If there is no respiratory acid–base disturbance, the PH2O and PCO2 should be similar in magnitude in alveolar air (47 and 40 mm Hg, respectively). The PH2O of inspired
air must be assessed. Even if this PH2O is considerably higher than the PCO2 due to humidification of inspired air, the H2O content of humidified air is approximately 15 mol/day in an adult and the molecular weight of H2O is 18 (15 mol H2O = 270 g H2O). Because all patients in this study received intubation and mechanical ventilation with humidified air warmed to 36.5°C for the entire study period, they would retain virtually all of the metabolically produced H2O.

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References