

[CASE REPORT]

Tonicity Matters, Especially in Complex Hyponatremia Resulting from Pseudo-, Trans-locational, and True Hypotonic Hyponatremia: An Educational Case Report

Masatomo Ogata, Satoru Morikubo, Naohiko Imai, Yugo Shibagaki and Masahiko Yazawa

Abstract:

Serum tonicity is defined by the serum concentrations of sodium (sNa) and glucose, which can promote free water movement across intra/extracellular compartments. Rapid changes in serum tonicity can cause brain damage. We herein report an educational case of a patient with hyponatremia (sNa: 112 mEq/L) concomitant with acute alcoholic pancreatitis. The cause of hyponatremia was considered complex. Pseudo- and trans-locational natremia was secondary to hyperglycemia (721 mg/dL) and hypertriglyceridemia (1,768 mg/dL), respectively, and true hypotonic hyponatremia. Regarding sNa correction, rapid correction was suspected. However, this was safely managed by monitoring tonicity (not sNa or osmolality), thereby avoiding brain damage.

Key words: electrolytes, water-electrolyte imbalance, hyponatremia, tonicity

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Introduction

Hyponatremia is a prevalent disorder of water homeostasis in a variety of clinical settings. Hyponatremia is associated not only with falls, fractures, osteoporosis, and kidney stones but also with a higher likelihood of morbidity and mortality, which are significant social issues (1-4).

Serum concentrations of sodium (sNa) and glucose, not blood urea nitrogen (BUN), define serum tonicity, which creates forces responsible for free water movement across intra/extracellular compartments. Rapid changes in serum tonicity (elevation or decline) can cause brain damage. Severe hyponatremia is known to cause brain damage, including convulsions, disturbances of consciousness, cerebral edema, and - in extreme cases - irreversible damage. A proper diagnosis and treatment of hyponatremia are critical. Osmotic demyelination syndrome (ODS) presents a significant challenge when treating hyponatremia, since ODS due to rapid correction of hyponatremia during treatment has been known to carry a rate of high mortality (5, 6).

We herein report an educational case of hyponatremia

caused by a complex combination of factors and the safe correction of hyponatremia to pursue the serum tonicity, but not sNa per se nor even serum osmolality, to avoid ODS.

Case Report

A man in his 40s was transferred from another hospital to our hospital's gastrointestinal (GI) unit for intensive treatment of acute alcoholic pancreatitis. He consumed more than 1 L of Japanese distilled spirit (Japanese shochu) every day. He had smoked 10 cigarettes per day for an unknown number of years. He had a history of untreated hypertension and did not have any allergies or a family medical history of illness.

Four days before visiting the previous hospital, abdominal pain had begun, preventing the patient from achieving adequate food intake. His chief complaint at admission before hospitalization was abdominal pain, with normal serum amylase (98 mg/dL). Computed tomography (CT) showed diffuse enlargement of the pancreas. He was immediately transported to our hospital without specific treatment for acute pancreatitis, only undergoing intravenous infusion with

Table 1. Laboratory Data on Day 1.

	Hospital day 1
Total protein (g/dL)	5.3
Albumin (g/dL)	2.7
Total bilirubin (mg/dL)	9.9
AST (U/L)	197
ALT (U/L)	45
LDH (U/L)	2,352
ALP (U/L)	286
γ -GTP (U/L)	592
Amylase (U/L)	89
Total cholesterol (mg/dL)	348
Triglyceride (mg/dL)	1,768
Creatinine (mg/dL)	2.09
Blood urea nitrogen (mg/dL)	41.6
Estimated GFR (mL/min/1.73m ²)	28.7
C-reactive protein (mg/dL)	29.5
sNa (mEq/L)	112
Potassium (mEq/L)	4.6
Chloride (mEq/L)	73
Calcium (mg/dL)	4.5
Phosphorous (mg/dL)	3.7
Blood glucose (mg/dL)	721
Measured plasma osmolality (mOsm/kgH ₂ O)	287
Urine glucose	(4+)
Urinary Na (mEq/L)	<20
Urinary potassium (mEq/L)	10.7
Urinary chloride (mEq/L)	<50
Urinary osmolality (mOsm/kgH ₂ O)	443

GFR: glomerular filtration rate, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, γ -GTP: γ -glutamyl transpeptidase, sNa: serum Na

sodium bicarbonate ringer solution (total amount of fluid therapy is unknown).

On admission, although his measured sNa was as low as 112 mEq/L, he had no apparent symptoms related to hyponatremia, and his lab findings also showed severe hyperglycemia and hypertriglyceridemia (Table 1). He was administered normal saline (NS) and insulin for presumed volume depletion and hyperglycemia. He was also treated for acute pancreatitis with the administration of ulinastatin, gabexate mesilate, octreotide acetatein, thrombomodulin alfa, and an *Cephalosporin* antibiotic, in addition to intravenous therapy.

After the infusion of 1.5 L of NS, the patient's measured Na increased to 122 mEq/L within 6 hours. The nephrology team was consulted at this point. They suggested replacing NS with 5% dextrose (D5W) for this apparent over-correction of hyponatremia in the setting of significant hypotonic urine excretion (the sum of the urinary sodium and potassium concentrations, 30 mEq/L, was much lower than the sNa). However, his measured sNa increased to 14 mEq/L in the first 24 hours and 20 mEq/L within 48 hours after admission, indicating persistent rapid correction of sNa (Fig. 1). Fig. 1 also shows the use of fluid replacement ther-

apy and urinary volume during the first three days after admission. These findings suggested rapid correction of measured sNa.

However, after re-evaluating the patient's hyponatremia, we considered attempting to correct the tonicity, and not the sNa or serum osmolality, in order to focus on the movement of free water in the brain cells. The measured sNa and serum osmolality (sOsm) values were 112 mEq/L and 287 mOsm/kgH₂O, respectively, which led to a diagnosis of non-hypotonic hyponatremia. The presence of concomitant hypertriglyceridemia and hyperglycemia raised the suspicion of non-hypotonic hyponatremia that the patient has both pseudohyponatremia by hypertriglyceridemia and translocational hyponatremia by hyperglycemia. The correction formula for hypertriglyceridemia-related pseudo-hyponatremia is as follows (7):

True sNa=measured sNa+0.21×[triglyceride (g/L)-0.6]×measured sNa/100

When calculated using the correction formula, the patient's initial true sNa was found to be 116 mEq/L instead of 112 mEq/L.

After correcting for hypertriglyceridemia-related pseudo-hyponatremia, we also considered the presence of hyponatremia due to severe hyperglycemia. His corrected sNa was 130 mEq/L according to the following correction formula (8):

Corrected sNa=measured and true sNa+2.4×[measured blood glucose (BG) (mg/dL)-100 (mg/dL)]/100 (mg/dL)

Based on the above-mentioned true- and corrected sNa values, the patient was eventually diagnosed with coexisting pseudo-, translocational, and true hypotonic hyponatremia, since the sNa was 130 mEq/L after accounting for triglyceride and blood glucose, following the common definition of hyponatremia (sNa<135 mEq/L) (9).

In terms of treatment, particularly with regard to the correction speed, Figs. 2 and 3 show the clinical course of the measured sNa, blood glucose, sOsm, and serum tonicity values. Table 2 summarizes the sNa-related parameters. The sNa itself rapidly increased during the initial treatment using NS infusion and correction of hyperglycemia, suggesting over-correction (sNa increased to 14 mEq/L in the first 24 hours and 20 mEq/L within 48 hours). However, after accounting for tonicity, as defined by the true sNa and BG, it was found to be almost stable, within the 10-mOsm/kgH₂O (replacing with sodium, only 5 mEq/L fluctuation in 3 days). Although we did not perform brain magnetic resonance imaging (MRI) or computed tomography (CT) to detect structural brain damage, such as ODS, no evidence of clinically symptomatic ODS based on neurological presentation was observed during the patient's treatment course.

Discussion

In making a differential diagnosis of hyponatremia, clinicians must first evaluate the sOsm to rule out non-hypotonic hyponatremia (9, 10). Hypertriglyceridemia or hyperprote-

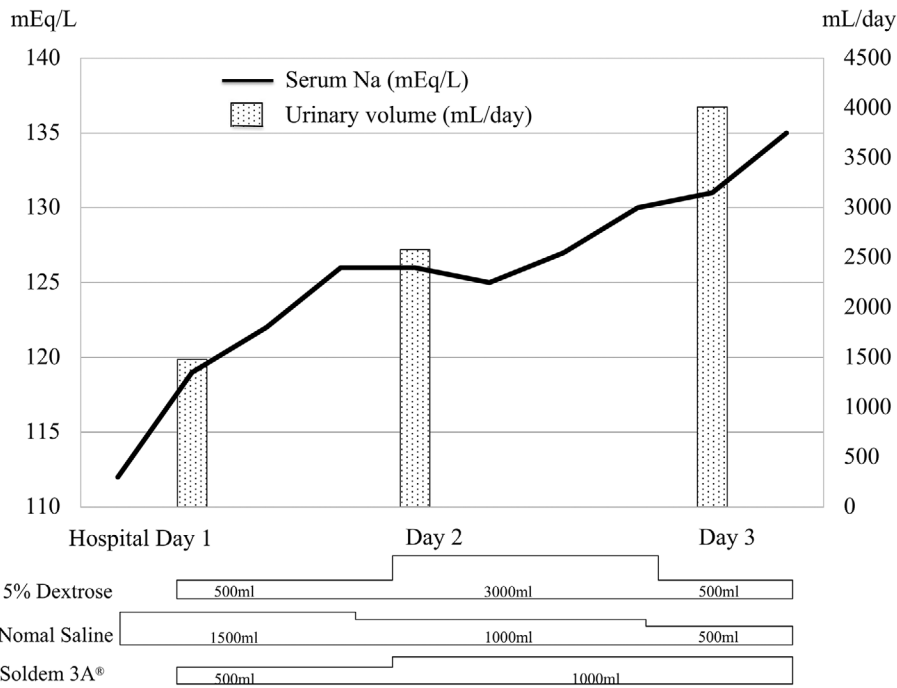


Figure 1. The clinical course of the measured serum Na (sNa) and urine volume values and fluid therapy.

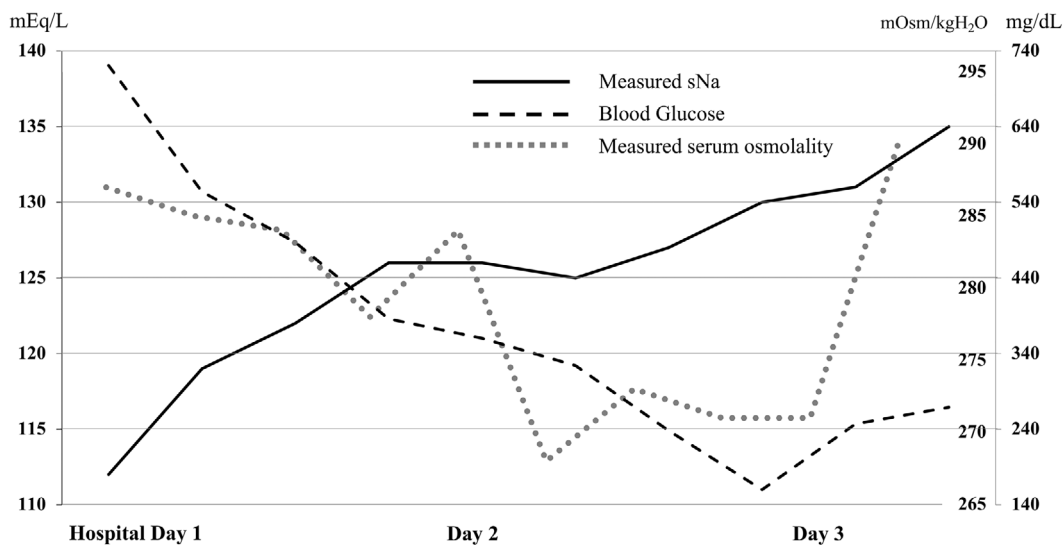


Figure 2. The clinical course of the measured serum Na (sNa), measured serum osmolality, and blood glucose values.

inemia can influence indirect ion-selective electrodes (ISEs), inducing an “incorrectly” low sNa result; this falsely low hyponatremia is known as pseudo-hyponatremia (11). To make the best use of the blood sample, ISEs are tested by diluting the water phase of the sample with a fixed amount of dilution. In hypertriglyceridemia, wherein the quantity of solid phase in the blood increases while that of the water phase decreases, a constant dilution ratio can significantly lower the concentration of ionic contents, leading to a false diagnosis (11, 12). Studies have thus recommended the use of direct ion-selective electrodes to avoid this error (11). Since the calculated sOsm (including blood glucose, BUN,

and sNa values) in the present study was 279 mOsm/kgH₂O, this indicated a slight osmolar gap. This gap should arouse suspicion of pseudo-hyponatremia secondary to hypertriglyceridemia, hyperproteinemia, or hypergammaglobulinemia.

Clinicians should also consider the possible presence of hyponatremia due to severe hyperglycemia. Serum glucose is a driving force for translocating free water from the intracellular component (IC) to the extracellular component (EC) because of the osmolar gradient between the IC and EC. This causes sNa in the EC to be diluted in a hyperglycemic state. This kind of hyponatremia is called “translocational hyponatremia” (10). To exclude this possibility and properly

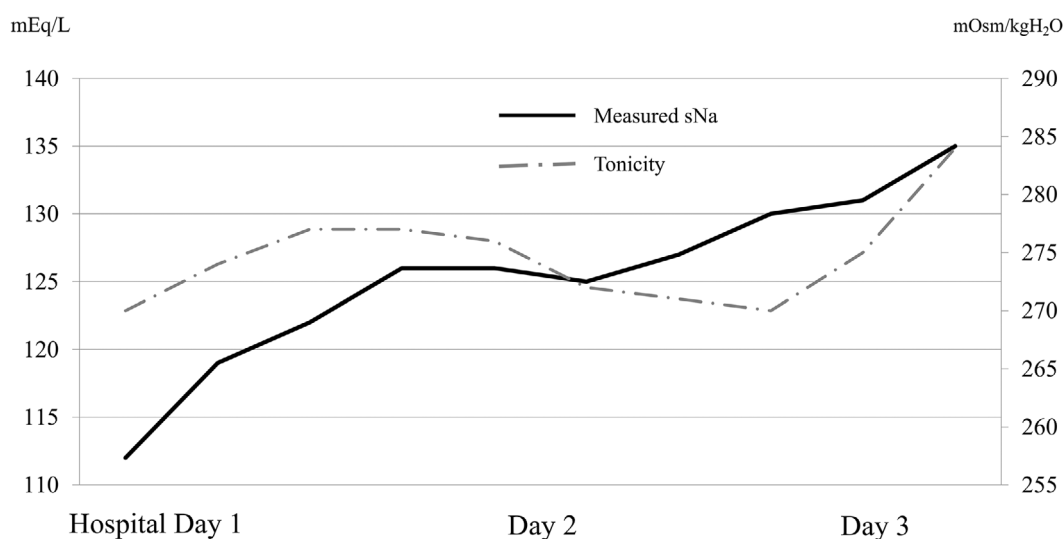


Figure 3. The clinical course of the measured serum Na (sNa) and tonicity values.

Table 2. Serum Na Related Parameters from Hospital Day 1 to Day 3.

sNa related parameters	Hospital day 1	Hospital day 2	Hospital day 3
Measured sNa (mEq/L)	112	126	131
True sNa (mEq/L)	116	129	131
Corrected sNa (mEq/L)	130	135	135
Triglyceride (mg/dL)	1,768	1,066	189
Blood glucose (mg/dL)	721	360	247
Blood urea nitrogen (mg/dL)	41.6	24.1	11.3
Measured serum osmolarity (mOsm/kgH ₂ O)	287	284	271
Serum tonicity (mOsm/kgH ₂ O)	270	276	276
Urinary Na (mEq/L)	<20	<20	51
Urinary potassium (mEq/L)	10.7	32.1	27.9
Urinary osmolarity (mOsm/kgH ₂ O)	443	546	486

sNa: serum Na

diagnose hyponatremia, clinicians must adjust the true or measured sNa to a corrected sNa value.

In the present case, we were unable to identify the exact cause of true hypotonic hyponatremia (after correcting for the effect of hyperglycemia and hypertriglyceridemia; sNa, 130 mEq/L). Of note, the urinary osmolality was extremely high in our patient, despite the presence of true hypotonic hyponatremia; however, glucosuria and iso-osmotic pressure might have accounted for this concentrated urine value. Severe inflammation might also lead to distributive volume imbalances and patient suffering because of abdominal pain, leading to inappropriate vasopressin secretion secondary to osmotic and non-osmotic stimulation. No hypothyroidism or adrenal insufficiency was detected. Eventually, this case was diagnosed with coexisting pseudo-, translocational, and true hypotonic hyponatremia.

We would like to emphasize that a rapid change in sNa can be easily assumed to cause brain damage. However, it should be noted that it is the rapid change in tonicity, and not sNa or sOsm, that leads to brain damage. Tonicity usu-

ally consists of effective osmoles, such as sodium and glucose, but not urea. Mannitol is also a viable substitute for use in balancing tonicity in specific situations. The measured sOsm, calculated by measuring the sNa, blood glucose, and BUN values, does not reflect the force translocating free water throughout brain cells, as observed in azotemia, a state of high osmolarity but normal tonicity, and so does not cause water to shift across the cell membrane. Under normoglycemia conditions, sNa directly reflects tonicity, since a normal BG has a minimal osmotic pressure (nearly 4-5 mOsm/kgH₂O if BG is 90-100 mg/dL). However, the BG as well as the sNa are essential factors for balancing tonicity in cases of severe hyperglycemia. In the present case, although measured the sNa and sOsm values dramatically increased and decreased, respectively (Fig. 2), tonicity remained relatively stable within 10 mOsm/kgH₂O (replacing with sodium, only 5 mEq/L of fluctuation in 3 days). Particularly in cases of non-hypotonic hyponatremia, such as severe hyperglycemia, clinicians must closely monitor serum tonicity, rather than sNa or sOsm, to avoid brain damage. In fact, the

guideline for the diagnosis and treatment of diabetic ketoacidosis (DKA)/hyperosmolar hyperglycemic state (HHS) also emphasizes “effective serum osmolality,” which is consistent with tonicity, in order to distinguish DKA from HHS and consider mental alteration when effective serum osmolality is greater than 320 mOsm/kg (13).

In summary, this patient was afflicted by all three types of hyponatremia - pseudo-, trans-locational, and true hypotonic hyponatremia - in the setting of severe hyperglycemia and hyperlipidemia induced by acute alcoholic pancreatitis. Tonicity, but not sNa or even sOsm, should be monitored when treating non-hypotonic hyponatremia in order to avoid brain damage.

No information identifying the individual patient is published, and personal information is protected. The patient provided his informed consent for the publication of this case report.

The authors state that they have no Conflict of Interest (COI).

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