(Acta Anaesth. Belg., 2020, 71, 189-197)

Case Report : Severe Hypernatremia following treatment for Hyperosmolar Hyperglycaemic State : A pragmatic approach used to manage hypernatremia

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Abstract : The Hyperosmolar Hyperglycaemia State (HHS) is an endocrine emergency with a mortality rate between 10 and 50%. The mainstay for the treatment of this condition is vigorous IV fluid replacement with close monitoring of blood glucose, serum osmolality, and electrolytes. However, after initial resuscitation, patients can develop hypernatremia and raised serum osmolality, which have deleterious consequences. While hypernatremia in HHS can be treated with infusions of 0.45% saline or 5% dextrose, alternate measures such as intravenous (IV) hypotonic fluid infusion [e.g. 0.18% sodium chloride (NaCl) containing 4% dextrose and 0.15% potassium chloride (KCl)], or free water administration through a nasogastric (NG) tube can be used. We report the case of a 70-year-old man, who was initially admitted to a medical high care ward (MHC) with HHS, and was transferred to the ICU 72 hours later with an altered level of consciousness and severe hypernatremia. His treatment consisted in an IV hypotonic 0.18% NaCl infusion containing 4% dextrose and 0.15% KCl. He also received free water through a NG tube at a rate that was calculated to correct natremia at an average rate of 0.55 meq L-1 hr-1 over 72 hours. A multipronged approach was instituted to manage this patient, including, in addition to natremia correction, blood glucose control with insulin, appropriate IV antibiotics to treat infected foot ulcers, adequate analgesic medications, low-molecular-weight-heparin (LMWH) for thromboprophylaxis, proton-pump inhibitors, and continuation of patient's ongoing antidepressant drugs at the time of his Glasgow Coma Score improvement. This case report demonstrates the feasibility and success of IV hypotonic fluid (0.18% NaCl - 4% dextrose - 0.15% KCl), alongside NG free water for correcting sodium levels with lower fluid volumes than would have been otherwise required if corrected with 0.45% saline. This treatment seems to be a reasonable choice for correcting sodium levels and osmolality in HHS patients who present with hypernatremia after an initial resuscitation, insofar as it avoids fluid overload and provides dextrose as an energy substrate, in addition to potassium ions. However, while correcting natremia with hypotonic fluid, other aspects of management should not be ignored.

Keywords : Hyperosmolar Hyperglycaemia State (HHS) ; hypernatremia ; IV hypotonic fluid ; nasogastric (NG) free water.

Introduction

Acute severe hypernatremia is associated with a severe prognosis. Indeed, sodium levels higher than 160 mmol L^{-1} carry a mortality rate between 42% and 60% (1). Dysnatremias are com-monly encountered during the management of the Hyperosmolar Hyperglycaemia State (HHS), as sodium plasma concentration is usually modified by the therapeutic measures instituted to manage these patients (2). It has been demonstrated that brain cells are partially permeable to glucose, regardless of insulin action, because of a selective expression of transport proteins (3). Therefore, hypertonicity exclusively due to hyperglycemia is physiologically dampened in the central nervous system (CNS) by glucose penetration into the cells. Hypertonicity due to hypernatremia has a greater impact on the CNS. Hence, it has been suggested that natremia is a better predictor of neuro-logical impairment than plasma glucose itself, since severely hyperglycemic patients can be fully asymptomatic in the absence of hypernatremia (4). While hypernatremia in HHS can be treated with infusions of hypotonic saline (5). other alternative measures, such as intravenous (IV) glucose or sterile water, (6, 7). or the delivery of water through a nasogastric (NG) tube are also possible (8). Among hypotonic saline solutions, 0.45% saline is the most commonly used. However, using this solution often requires large volumes, which has the potential for fluid overload, particularly in elderly patients. Recently, a new brand of IV hypotonic fluid is being increasingly used, namely 0.18% sodium chloride containing 4% dextrose

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Paper submitted on May 11, 2020 and accepted on August 14, 2020
Conflict of interest : None

and 0.15% potassium chloride (KCl). It offers an advantageous correction using lower volumes, and also provides dextrose as an energy substrate, in addition to potassium ions for maintenance. In elderly patient, there is a risk of cerebral edema with the administration of hypotonic solution, whereas under-treatment may be complicated by vascular thrombosis and is associated with a high mortality rate (9). Hence, this hypotonic fluid needs to be administered at a finely calculated rate.

We report here the case of a patient who developed severe hypernatremia after being treated for HHS.

Clinical Case

A 70-year-old male was admitted to our hospital following complaints of vomiting, confusion, abdominal distension, myoclonic jerks, and urinary incontinence. He did not complain of of chest pain and shortness of breath. His past medical history included type-2 diabetes mellitus, chronic elevated blood pressure, and depression. Usual medications included amlodipine 5 mg once-a-day, duloxetine 60mg twice-a-day, gabapentin 300 mg three times a day, gliclazide 160 mg twice-a-day, metformin 500 mg twice-a-day, omeprazole 20 mg once-a-day, trazodone 50 mg twice-a-day, and simvastatin 40 mg once-a-day.

Upon admission, the patient was conscious although confused. His Glasgow Coma Score (GCS) was E4V4M6 (14/15). He was breathing spontaneously room air, and his recorded vital parameters were : pulse rate 82 bpm, blood pressure 154/77 mmHg, respiratory rate 18/min, peripheral saturation in oxygen (SpO_2) 97%, temperature 36.7 °C. Systematic examination was otherwise normal. Laboratory investigations revealed a plasma glucose level of 40.9 mmol L^{-1}, serum osmolality at 339 mOsm Kg^{-1}, plasma ketones at 2 mmol L^{-1}, one cross of urine ketones, a natremia at 134.6 mmol L^{-1}, creatinine at 606 micromol L^{-1}, blood urea (BUN) at 29.3 mmol L^{-1} (see Tables 1, 3, and 6). Arterial blood gases showed a pH at 7.36, a partial pressure in oxygen (PO_2) at 10.25 KPa, a partial pressure in carbon dioxide (PCO_2) of 5.93 KPa, a bicarbonate (HCO_3) concentration of 24.9 mmol L^{-1}, and a saturation in oxygen of 95.5%.

Initial diagnosis of the acute medicine team was HHS, in addition to stage-3 acute kidney injury (AKI-3). A plan was construed to treat HHS in a Medical High Care ward, where the patient remained for 72 hours, as per our internal protocols, which is based on the Joint British Diabetes Societies guidelines on the management of the Hyperosmolar Hyperglycaemia State in adults with diabetes (10), This plan included the infusion of normal saline 1L over 1 hour, and the infusion of insulin at a rate of 0.05 unit Kg^{-1} h^{-1}. A good response was noted to the initial treatment, with an improvement of blood glucose levels. After 60 minutes of treatment, the patient's blood glucose decreased to 36 mmol L^{-1}, and serum osmolality to 336 mOsm Kg^{-1}, while natremia was 136.6 mmol L^{-1} and BUN was 26.3 mmol L^{-1}. Normal saline was instilled at a rate of 0.5 L h^{-1} and the insulin rate was raised from 0.05 unit Kg^{-1} h^{-1} to 0.1 unit Kg^{-1} h^{-1} when the decrease in blood glucose was less than 5 mmol L^{-1} h^{-1}. After 6 hours, the patient's condition further ameliorated with a plasma glucose of 20 mmol L^{-1}, serum osmolality of 324 mOsm Kg^{-1}, natremia of 140 mmol L^{-1}, BUN

Table 1

Upon admission to the Medical High Care

	Admission	After 1 hour	After 6 hours	After 12 hours	After 24 hours	After 48 hours
Blood glucose (mmol L^{-1})	40.9	36	20	15	12.3	12
Serum sodium (meq L^{-1})	134.6	136.6	140	142	144	168
Serum osmolality (mOsm Kg^{-1})	339	336	324	319	318	365
Serum potassium (meq L^{-1})	4.7	4.1	3.8	3.9	4.1	3.6
BUN (mmol L^{-1})	29.3	26.3	24.3	20.0	18	16.8

Table 2

Upon admission to the ICU

	Admission	After 2 hours	After 4 hours	After 12 hours	After 24 hours	After 36 hours	After 48 hours	After 72 hours
Blodd glucose (mmol L^{-1})	11	10.5	11.5	10.6	10	10.2	9.5	8
Serum sodium (meq L^{-1})	180	176	174	171.2	167	160.4	153	141
Serum osmolality (mOsm Kg^{-1})	385	376	373	365	355	341	325	298
Serum potassium (mmol L^{-1})	3.5	3.6	3.8	4.0	4.1	4.2	4.5	4.5
BUN (mmol L^{-1})	14.4	13.8	13.5	12	11	10	9	7.5

Table 3

Bone profile, LFT, and KFT

	Admission to the MHC	24 hours in the MHC	48 hours in the MHC	Admission to the ICU	24 hours in the ICU	48 hours in the ICU	72 hours in the ICU
ALP (U L^{-1})	105	101	90	86	74	70	65
Adj Ca (mmol L^{-1})	2.26	2.22	2.46	2.40	2.32	2.28	2.24
Phosp (mmol L^{-1})	2.11	2.00	1.36	1.08	0.99	1.19	1.42
Total protein (g L^{-1})	77	75	70	65	62	65	67
Albumin (g L^{-1})	42	37	38	36	35	37	39
Globulin (g L^{-1})	33	31	34	30	32	31	33
Total bil (micromol L^{-1})	4	5	4	5	5	4	4
AST (U L^{-1})	8	10	24	63	59	44	34
ALT (U L^{-1})	10	14	16	48	51	37	38
Creat (micromol L^{-1})	606	539	176	150	120	105	99
Magnesium (mmol L^{-1})	0.74	0.83	0.89	0.97	0.95	0.91	0.92
Chloride(mmol L^{-1})	95	101	108	105	102	99	97

Normal values: Adj Ca = 2.2 - 2.6 mmol L^{-1}, Phosp = 0.8 - 1.5 mmol L^{-1}, Total protein = 60 - 80 g L^{-1}, Albumin = 35 - 50 g L^{-1}, Globulin = 21 - 35 g L^{-1}, Total Bil = 3 - 21 micromol L^{-1}, AST = 10 - 45 U L^{-1}, ALT = 5 - 55 U L^{-1}, Creat = 50 - 120 micromol L^{-1}, Chloride = 95 - 108 mmol L^{-1}, eGFR = 60 - 61, Magnesium = 0.7 - 1 mmol L^{-1}.

of 24.3 mmol L^{-1}, and a positive fluid balance of 2 liters. The patient was maintained on IV fluid replacement as per our protocol. After 12 hours, the patient's condition significantly improved with a plasma glucose of 15 mmol L^{-1}, serum osmolality of 319 mOsm Kg^{-1}, natremia of 142 mmol L^{-1}, BUN of 20 mmol L^{-1}, and fluid balance was noted to be positive by 3 liters. The patient was then maintained on IV fluid replacement using normal saline and 5% dextrose, at a rate of 125 mL h^{-1} once blood glucose dropped below 14 mmol L^{-1}.

After 24 hours, the patient was placed on our maintenance protocol, including a variable rate of insulin infusion and a plan to convert insulin administration to a subcutaneous regime once biochemically stable. He appeared to be well responding clinically. Laboratory investigations revealed improving parameters, including a plasma glucose of 12.3 mmol L^{-1}, serum osmolality of 318 mOsm Kg^{-1}, natremia of 144 mmol L^{-1}, BUN of 18 mmol L^{-1} and a positive fluid balance of 4.5 litres. The arterial blood gases revealed a pH at 7.43, a PO_2 of 10.8 KPa, a PCO_2 of 5.14 KPa, a HCO_3 concentration of 25.3 mmol L^{-1}, saturation in oxygen (SO_2) of 95.8%, and a lactate concentration of 1.5 mmol L^{-1}.

Between the 24th and the 48th hour after admission, while being on our maintenance protocol, the patient had improved significantly, except for one vital sign that deserved additional attention, namely a diminished oral intake and an increased urine output. After 48 hours following admission, the patient displayed signs and symptoms of delirium and agitation. He started pulling out his IV lines, exhibited inappropriate speech, and got off the bed. The Sedation Agitation Scale (SAS) Score was recorded at 7. Recorded vital signs were then a pulse rate of 101 bpm, a blood pressure of 108/55 mmHg, a SpO_2 of 98%, and a respiratory rate at 16 min^{-1}. The remaining clinical examination was normal. The recorded input/output volumes were 800 ml/2600 ml. The plasma glucose was 12 mmol L^{-1}, natremia was 168 mmol L^{-1}, serum osmolality was 365 mOsm Kg^{-1}, and BUN was 16.8 mmol L^{-1}. Urine osmolality was noted at 557 mOsm Kg^{-1} thus ruling out diabetes insipidus. A brain CT scan was depicted normal. The inference made by the acute medicine team was a diagnosis of delirium secondary to metabolic encephalopathy, sepsis, and a diuretic phase of recovery from AKI. Lorazepam and haloperidol were administered to control agitation. Blood glucose was controlled by insulin, administered as per a sliding scale. A regimen of antibiotics, namely amoxicillin, as well as antiviral medications was administered for a sepsis of unknown origin. However, correction with half normal saline (0.45% saline) at a rate of 100 mL h^{-1} failed to correct his serum sodium levels, which continued to peak. After 72 hours following admission, the patient continued to be in a state of agitation, and an Intensive Care Unit (ICU) consultation was sought, whereupon patient was transferred to the ICU where he stayed for another 72 hours.

Upon admission to the ICU, the patient had become drowsy, with a GCS dropping to E2V2M5 (9/15). His vital parameters at that time were a pulse rate of 80 bpm, a blood pressure of 105/52 mmHg,

Table 4

Coagulation screen and CRP

	Admission to the MHC	24 hours in MHC	48 hours in MHC	Admission to the ICU	24 hours in the ICU	48 hours in the ICU	72 hours in the ICU
PT (sec)	11	10	9	11	10	12	11
aPTT (sec)	23	24	25	23	22	25	23
Fib (g L^{-1})	3.5	3.4	3.1	3.6	3.5	3.6	3.5
CRP (mg L^{-1})	234	266	141	113	77	25	9

Normal values: CRP = 2 - 10 mg L^{-1}, Fib = 1.8 - 3.6 g L^{-1}, PT = 9 - 12 sec, aPTT = 22 - 28 sec.

Table 5

Full blood count

	Admission to the MHC	24 hours in MHC	48 hours in MHC	Admission to the ICU	24 hours in the ICU	48 hours in the ICU	72 hours in the ICU
RBC ($\times 10^{12}$ L^{-1})	3.86	3.53	3.92	4.09	4.35	3.99	3.90
Hb (g L^{-1})	111	103	112	117	123	112	113
TLC ($\times 10^{9}$ L^{-1})	7.6	6.2	10.9	11.9	14.6	11.7	14.4
Plat ($\times 10^{9}$ L^{-1})	240	217	295	276	250	217	223
Neutro ($\times 10^{9}$ L^{-1})	6.7	5.2	9.1	9.3	7.8	6.4	5.5
Lympho ($\times 10^{9}$ L^{-1})	1.2	1.4	1.5	1.4	2.3	1.9	1.5
Eosino ($\times 10^{9}$ L^{-1})	0	0	0	0	0	0	0
Baso ($\times 10^{9}$ L^{-1})	0	0	0	0	0	0	0

Normal values: RBC = 4.32 - 5.66 × 10^{12} L^{-1}, Hb = 133 - 176 g L^{-1}, TLC = 3.7 - 9.5 × 10^{9} L^{-1}, Plat = 150 - 400 × 10^{9} L^{-1}, Neutro = 1.5 - 6.5 × 10^{9} L^{-1}, Lympho = 1.1 - 5 × 10^{9} L^{-1}, Eosino = 0.1 - 0.7 × 10^{9} L^{-1}, Baso = 0 - 0.1 × 10^{9} L^{-1}.

Table 6

Other tests

Serum protein electrophoresis	No evidence of paraprotein band
ANA	Negative
Serum cortisol level®	361nmol L-1(Normal)
TSH	0.36 mU L^{-1} (0.27 - 4.2 mU L^{-1})
Free T4	2.7 pmol L^{-1} (0.27 - 4.2 pmol L^{-1})
CT Brain	Normal age-related involutional changes. No infarct, hemorrhage, or intracranial lesion noted.
Urine osmolality	557 mOsm Kg^{-1} (after 48 hours in the MHC) 550 mOsm Kg^{-1} (Upon admission to the ICU)

a SPO_2 of 96% in room air. Ulcers were noticed on both feet and swab for culture and sensitivity was taken. Labs revealed a corrected natremia of 180 mmol L^{-1}, a plasma glucose of 11 mmol L^{-1}, BUN at 14.4 mmol L^{-1}, and a serum osmolality at 385 mOsm Kg^{-1}. Urinary osmolality was 550 mOsm Kg^{-1} (see Tables 2 to 6), and an electrolyte-free water excretion was calculated at 600 ml over 24 hours, which suggested that post-AKI polyuria had settled down. Hypernatremia had developed in less than 48 hours, and hence was labelled as acute hypernatremia.

The treatment strategy was devised along following steps :

1. Calculating the free water deficit
2. Determining a suitable serum sodium correction rate
3. Estimating ongoing free water losses (if applicable ~1 L or more)
4. Designing a suitable fluid repletion program that takes into account the estimated free water deficit, the desired serum sodium correction rate, and any ongoing excess of free water losses. Further specific treatment was guided by the presence and severity of signs/symptoms, time of onset, and volume status of the patient.

His airway was patent and not considered to be at risk as his motor function was good. He had strong cough reflexes. Boxing gloves were put on. The arterial blood gases revealed a pH 7.43, a PO_2 at 10.6 KPa, a PCO_2 at 5.04 KPa, a HCO_3 at 25.4 mmol L^{-1}, and a SO_2 at 95.6% (on room air). Hypernatremia was corrected according to the protocol. The replacement fluid was a hypotonic fluid containing 0.18% NaCl, 4% dextrose, and 0.15% KCl, administered intravenously, and free water administered through the NG tube. In order to fully correct sodium within 72 hours at a rate of 0.55 meq $L^{-1}h^{-1}$, the replacement IV fluid had to be given at a rate 99.4 (or 100) mL h^{-1}, and the NG free water at a rate of 50 mL h^{-1}. However, for the first two hours, we allowed the sodium correction to be of 2 meq L^{-1} h^{-1}, followed by a sodium correction rate of 1 meq L^{-1} h^{-1} for the next two hours. Further sodium correction was done at a lower rate of 0.35 meq L^{-1} h^{-1} for the remaining 24 hours, so that the total corrected sodium during the first 24 hours didn't

exceed 13 meq L^{-1} (determined from the original correction rate of 0.55 meq L^{-1} h^{-1}). Thereafter, for the remaining 48 hours, the IV replacement fluid was given at the originally calculated rate of 99.4 (or 100) mL hr^{-1}, allowing full sodium correction within 72 hours. In this context, for the first couple of hours, the replacement IV fluid was given at a rate of 361.45 mL h^{-1} and then at 180.72 mL h^{-1} for the following two hours.

After the first four hours, the replacement fluid was administered at a rate of 63.25 mL h^{-1} for the first 24 hours. Thereafter, during the next 48 hours, the replacement fluid was given at 99.4 (or 100) mL h^{-1}, to allow sodium being corrected steadily at a rate of 0.55 meq L^{-1} h^{-1}. Flucloxacillin was administered on the basis of the identification of a staphylococcus aureus in the swab taken from the toes. Virology revealed negative results, and hence acyclovir was stopped. Adequate analgesia was ensured by the application of lidocaine plasters, the administration of gabapentin 300 mg three times in a day, through the NG tube, and IV paracetamol 1 g twice-a-day. Haloperidol was increased to 1 mg four times a day IV to control agitation.

After two hours, his corrected Na was noted to be 176 meq L^{-1}, serum osmolality to be 376 mOsm Kg^{-1}. After four hours, the corrected Na was 174 meq L^{-1}, and serum osmolality was 373 mOsm Kg^{-1}. At the end of 12 hours, the patient achieved a corrected Na of 171.20 meq L^{-1}, a serum osmolality of 365 mOsm Kg^{-1}, and his GCS had improved to E3V3M6 (12/15). On the 2nd day after ICU admission, i.e. 24 hours after commencing sodium correction in the ICU, the patient's GCS improved further to E3V3M6 (13/15). He was delirious although manageable on haloperidol. Vital signs were a pulse rate of 82 bpm, a blood pressure of 110/56 mmHg, and a SPO_2 of 98% (on room air). Labs revealed a corrected serum Na at 167 mmol L^{-1}, a plasma glucose at 10 mmol L^{-1}, a serum osmolality at 355 mOsm Kg^{-1}, and a BUN at 11 mmol L^{-1}. Arterial blood gases revealed a pH at 7.43, PO_2 at 11.6 KPa, a PCO_2 at 5.44 KPa, a HCO_3 at 26.3 mmol L^{-1}, a SO_2 at 97.4%, and a lactate level at 1.58mmol L^{-1}. Forty-height hours after the commencement of the treatment in the ICU, the patient's GCS improved further to E4V4M6 (14/15). His serum sodium level decreased to 153 meq L^{-1}, serum osmolality to 325 mOsm Kg^{-1}, BUN to 9 mmol L^{-1}, and plasma glucose to 9.5 mmol L^{-1}. He was initiated on a NG low sodium diet at a rate of 30 mL h^{-1}, increased subsequently to 50 ml h^{-1}. Finally, after 72 hours of ICU treatment, the patient's GCS became normal at E4V5M6 (15/15), he was no longer delirious (CAM-ICU score of 0), and his labs revealed a corrected serum sodium at 141 meq L^{-1}, a serum osmolality of 298 mOsm Kg^{-1}, a BUN of 7.5 mmol L^{-1}, and a plasma glucose of 8 mmol L^{-1}. He was transferred from the ICU to the High Dependency Unit (HDU), where he completed his course of antibiotics, tolerated full orals, and was switched on metformin and regular insulin subcutaneously. The patient was subsequently discharged from the hospital.

Discussion

Definition and diagnosis of HHS

The characteristic features of HHS (10) are hypovolemia, marked hyperglycemia(>30 mmol L^{-1}) without significant hyperketonemia (<3 mmol L^{-1}) or acidosis(pH >7.3, HCO_3 >15 mmol L^{-1}), and an osmolality >320 mosmol Kg^{-1} (10).

Hyperglycemia results in an osmotic diuresis, and renal losses in excess of sodium and potassium (11). Fluid losses in HHS are estimated to range between 100-220 ml Kg^{-1}, sodium losses between 5 and 13 mmol Kg^{-1}, chloride between 5 and 15 mmol Kg^{-1} and potassium between 4 and 6 mmol Kg^{-1} (12).

Osmolality is useful both as an indicator of the severity and for monitoring the rate of change with treatment. As frequent measurement of osmolality is not usually available in UK hospitals, osmolality should be calculated as a surrogate, using the formula : 2 sodium concentration + glucose concentration + urea concentration (10).

Changes in mental performance are presorted during HHS (10). Some authors (13) have suggested that changes in mental performance correlates with the severity of hyperosmolality, with confusion being common at an osmolality >330 mosmol kg^{1}. An assessment of cognition should accompany a full history, physical examination, and review of drug therapy upon admission. Of course, tests of cognition must be viewed in comparison to the premorbid state, which in the elderly inpatient is often lacking (10).

Treatment goals in HHS (10)

The treatment goals in HHS are to normalise osmolality, replace fluid and electrolyte losses, normalise blood glucose, prevent arterial or venous thrombosis, prevent other potential complications such as cerebral edema or central pontine myelinolysis, and prevent foot ulcerations. The goal of the initial therapy is the expansion of the intravascular and extravascular volume, and to restore peripheral perfusion. The base fluid that

should be used is 0.9% sodium chloride with added potassium added as required (14). Fluid replacement alone without insulin will lower blood glucose, which will reduce osmolality causing a shift of water into the intracellular space. This inevitably results in a rise in serum sodium (a fall in blood glucose of 5.5 mmol L^{-1} will result in a 2.4 mmol L^{-1} rise in sodium). This is not necessarily an indication to give hypotonic solutions (10). Rapid changes should be avoided (10) – a safe rate of fall in plasma glucose is between 4 and 6 mmol L^{-1}. If the inevitable rise in sodium is much greater than 2.4 mmol L^{-1} for each 5.5 mmol L^{-1} fall in blood glucose (15), it suggests inefficient fluid replacement. Thereafter, the rate of fall of plasma sodium should not exceed 10 mmol L^{-1} in 24 hours (16). The aim of treatment should be to replace approximately 50% of the estimated fluid loss within the first 12 hours and the remainder within the following 12 hours, though this may be in part determined by the initial severity, degree of renal impairment and co-morbidities such as heart failure, which may limit the speed of correction. The aim is to achieve a gradual decline in osmolality, ranging between 3 to 8 mOsm Kg^{-1} h^{-1} (10). Insulin should be started at time zero if ketonemia is present (that is when 3-beta-hydroxybutyrate is >1 mmol L^{-1}). The recommended insulin dose is a fixed rate of IV insulin infusion at 0.05 units Kg^{-1} h^{-1} (10). A target blood glucose between 10 and 15 mmol L^{-1} is a reasonable goal. Complete normalization of electrolytes and osmolality may take up to 72 hours (10). Antibiotics should be given when there are clinical signs of infection or imaging/lab tests. Patients with HHS have an increased risk of arterial and venous thromboembolism (17,18). All patients should receive prophylactic LMWH for the full duration of hospitalization, unless contraindicated (10).

These patients are at increased risk of pressure ulceration. An initial foot assessment should be undertaken, and heel protectors applied in those with neuropathy, peripheral vascular disease, or lower limb deformity. If the patients are too confused or sleepy to cooperate with the assessment of sensation, one should assume that they are at high risk. Feet should be reexamined daily (10).

Management of hypernatremia

The diagnostic criteria (19). of hypernatremia are based on serum sodium concentration. Hypernatremia is defined as a serum sodium concentration >145 mmol L^{-1}. Severe hypernatremia has variously been defined as a serum sodium concentration >152 mmol L^{-1}, >155 mmol L^{-1}, or >160 mmol L^{-1}, no consensus has been reached on the exact level (19-22). Extremely high sodium levels occur in salt poisoning. Time of onset (19). is also important. Patients with hypernatremia that has developed slowly (e.g. over days, weeks, or months) are commonly asymptomatic, while patients with hypernatremia that has developed rapidly (e.g., over a few hours) will be symptomatic. Hypernatremia that develops in <48 hours is usually classified as acute, while hypernatremia that develops over ≥48 hours is chronic (19).

In face of hypernatremia, the useful diagnostic tests (19). include the measurement of a serum electrolyte concentration panel, glucose, urea, and creatinine (10). These tests should be ordered in all patients with suspected or confirmed hypernatremia. They may reveal other electrolyte abnormalities, renal impairment, or uncontrolled diabetes mellitus. Some patients may display associated hypokalemia or, more rarely, hypercalcemia. Patients with hypernatremia often have high serum urea and/or creatinine levels. High urea levels may worsen hypernatremia by causing osmotic diuresis (23, 24).

Urine osmolality (19). should also be ordered in all patients with hypernatremia, as it may help determining the underlying etiology. A low urine osmolality (<150 mmol Kg^{-1}), below or equal to plasma osmolality, suggests diabetes insipidus. When urine osmolality is high (>500 mmol Kg^{-1}), higher or equal to plasma osmolality, it suggests pure volume depletion not due to diabetes insipidus (e.g. gastrointestinal or insensible losses). A urine osmolality not too distant from plasma osmolality (between 200 and 500 mmol Kg^{-1}) suggests a renal concentrating defect, most commonly due to renal failure, osmotic diuresis, and/or use of diuretics.

Unlike hyponatremia, hypernatremia is always associated with serum hyperosmolality (>295 mmol Kg^{-1}) (19).

Urine electrolytes concentration measurement (19), as well as urine flow rate (19) should be ordered in patients with urinary losses to determine electrolyte-free water excretion. The formula $V \times 1-(U_{Na}+U_K/P_{Na})$ can be used, where V = urine flow rate, U_{Na} = urinary sodium concentration, U_K = urinary potassium concentration, and P_{Na} = plasma sodium concentration. The resulting value indicates how much electrolyte-free water is being lost through the urine at any given time (e.g., per hour, per day) (25, 26). However, it does not provide a value for the total amount of free water needed to correct hypernatremia (27). A low value (<0.5 L day^{-1}) suggests an inadequate free water intake, a high

value (≥1 L day^{-1}) suggests large free water losses, and a very high value (>5 L day^{-1}) suggests diabetes insipidus (19).

Other tests can also be considered. A desmopressin challenge test (19). should be ordered in patients with suspected diabetes insipidus. This test helps differentiating between central and nephrogenic diabetes insipidus. It consists in giving a standard dose of desmopressin, and measuring serum osmolality, urine osmolality, and urine volumes hourly over a 4-hour period. Patients with central diabetes insipidus respond to desmopressin with a reduction in urine output and increased serum osmolality. Patients with nephrogenic diabetes insipidus have little or no response. Measuring the serum arginine vasopressin level (19) may also be useful to distinguish central diabetes insipidus from nephrogenic diabetes insipidus, being low in case of central diabetes insipidus. A brain magnetic resonance imaging of CT scan is recommended in all patients with central diabetes insipidus, to find out the underlying cause, such as a pituitary tumor or other abnormalities (19).

Another important point in the management of hypernatremia is the assessment of the extracellular volume of fluids (28). If this volume is low (dehydration signs), it should be restored, if normal, water losses should simply be replaced, and if high (edema), diuresis should be enhanced while replacing lost volumes by hypotonic fluids. If hemodynamic monitoring is available, the intravascular volume status can serve as an estimate of the extravascular volume status, in the absence of hypoproteinemia, which shifts the fluids from the intravascular to the extravascular space (28). The intravascular volume status can be evaluated using the relationship between the cardiac filling pressures and the cardiac output.

The fluid management of HHS is similar to the one described for hypovolemic hypernatremia (28). Volume deficits tend to be more pronounced in HHS than in simple hypovolemic hypernatremia, because of osmotic diuresis that accompanies the glycosuria. Therefore, rapid correction of plasma volume is done by isotonic saline as we did in the reported case. Once the plasma volume is restored, free water deficits are estimated and replaced. Moreover, corrected plasma sodium should be used to guide therapy, insofar as hyperglycemia draws water from the intravascular space (28). The corrected plasma sodium can be calculated as [(current glucose - 100 mg dl^{-1}) / 100) × 1.8)] + measured sodium (28).

The calculation of free water deficit for replacement is based upon the assumption that the product of the Total Body Water (TBW) and plasma sodium concentration (P_{Na}) is always constant, namely current TBW × current P_{Na} = normal TBW × normal P_{Na} (28). Substituting 140 meq L^{-1} for a normal P_{Na} and rearranging terms yields the following relationship : current TBW = normal TBW × (140/Current P_{Na}) (28). The normal TBW in liters is usually 60% of lean body weight in Kg in men, and 50% in females. However, when hypernatremia associated with free water deficits, the normal TBW should be approximately 10% lower than usual (29). Thus, in men, the normal TBW is 0.5 × body weight. Once the current TBW is calculated, the water deficit is taken as the difference between the normal and current TBW : TBW deficit (in L) = normal TBW - current TBW (28). The volume needed to correct the water deficit is determined by the concentration of sodium in the replacement fluid as follows : replacement volume (in L) = TBW deficit × (1/1-x), where 'x' is the ratio of sodium concentration in the resuscitation fluid to the sodium concentration in the isotonic saline (28). The volume deficit should be replaced slowly, so that serum sodium concentration decreases by 0.5 meq L^{-1} each hour, typically requiring 48 to 72 hours to limit the risk of cerebral edema (30). Patients with severe symptoms (i.e., neurological symptoms) require more urgent treatment and more rapid correction of the sodium level during the first 2-3 hours, to prevent long-term neurological complications (e.g., myelinolysis). In that case, the serum sodium concentration should be lowered by 2 mmol L^{-1} h, followed by a correction rate of around 0.5 mmol L^{-1} h^{-1} after 2 to 3 hours (31).

In the patient we report here, we used the IV hypotonic fluid available in our ICU, namely 0.18% sodium chloride containing 4% dextrose and 0.15% KCl, as well as free water instilled through the NG tube. We calculated the total body water deficit as mentioned above, using the Lean Body Mass (LBM) calculated according the James formula for males [eLBM = 1.1 Weight – 128 (Weight/$Height^2$)]. Patient's weight was 96 Kg and height as 182 cm, which leads to a LBW of 70 Kg. In this case, normal TBW is 42 L, current TBW is 42 × 140/180 = 32.6 L, the TBW deficit is 42 - 32.6 = 9.4 L. Considering NG free water replacement at a rate of 50 mL h^{-1}, it equals to 1200 mL over 24 hours and 3600 mL over 72 hours. Thus, for the computation of replacement volume, we deducted 3600 ml from 9.4 L, which equated to 5800 mL. The replacement volume calculated for our IV hypotonic fluid (0.18% sodium chloride containing 4% dextrose and 0.15% KCl) was 5800 × (1/1-x), where 'x' corresponds to the

sodium concentration in the correction fluid divided by the sodium concentration in normal saline, that is 30 / 154 = 0.19. Placing this 'x' value in the above formula reveals that the replacement volume = 5800 × (1/1-0.19) = 7160 mL. In order to fully correct sodium within 72 hours at a rate of 0.55 meq L^{-1}/hr, the replacement fluid had to be administered at 99.4 (approximately 100) mL hr^{-1}. If saline 0.45% had been used instead, our replacement volume would have been 11600 mL, which would have been administered at 161 mL h^{-1}. As a consequence, our replacement fluid provided correction with a lower volume (7160 mL) and a lower rate of administration. During the first two hours, we allowed sodium correction at a 2 meq L^{-1} h^{-1} rate (meaning administering the replacement fluid at 361.45 mL h^{-1}), followed by a sodium correction rate of 1 meq L^{-1} h^{-1} (replacement fluid at 180.72 mL h^{-1}) for the next two hours. After this period, sodium was corrected at a lower rate of 0.35 meq L^{-1} h^{-1} (replacement fluid at 63.25 mL h^{-1}) for the remaining 24 hours, so that the total corrected sodium during the first 24 hours didn't exceed 13 meq L^{-1} (determined from the original correction rate of 0.55 meq L^{-1} h^{-1}). Thereafter, for the remaining 48 hours, the replacement fluid was given at an originally calculated rate of 99.4 (or 100) mL h^{-1}, allowing full sodium correction within 72 hours. After commencing the administration of the replacement fluid, at the end of first 24 hours, the patient's GCS considerably improved to E3V4M6 (13/15), as did his serum osmolality, though he continued to be in a state of manageable delirium. After 48 hours, his GCS further improved to E4V4M6 (14/15), and he was placed on a low sodium NG diet, which was initiated at 30 mLh^{-1} and increased subsequently to 50 mLh^{-1}. Interestingly, this low sodium diet didn't change the sodium correction rate. Sodium continued to decrease as per our calculated anticipated rate. Finally, 72 hours after the beginning of the treatment in the ICU, GCS became normal E4V5M6 (15/15) and his CAM-ICU (delirium) score was 0. He was then transferred from the ICU to the HDU, where he was switched on Metformin and regular subcutaneous insulin, before being discharged from the hospital.

Conclusions

Serum sodium is a better indicator of neurological impairment than blood glucose levels, as demonstrated in our patient who, when brought into the ICU, had attained stable blood sugar levels between 10 and 15 mmol L^{-1}. However, his corrected sodium level was still substantially deranged at 180 meq L^{-1}. Using 0.18% sodium chloride containing 4% dextrose and 0.15% KCl provided correction with lower fluid volumes and rates of infusion than 0.45% saline. In addition, this fluid provided not only dextrose for energy substrate but potassium ions for maintenance. By deducting the free water administered through the NG tube from the replacement volume of the correction fluid, the calculated replacement volume worked as anticipated to lower the serum sodium level. Furthermore, NG feed was added low sodium as the patient's condition improved, and this had no impact on the anticipated sodium correction rate or osmolality. We therefore advocate a multipronged approach for dealing with those patients and regarding sodium correction, using hypotonic IV fluids, NG free water, monitoring of blood glucose levels, and their maintenance within a normal range using regular insulin as per a sliding scale (32). Other important aspects of treatment should also be instituted, namely antibiotics to treat infection (in this case, infected foot ulcers), adequate pain relief (in this case with paracetamol, lidocaine plasters, and analgesic drugs like gabapentin), control of delirium (in this case with haloperidol), prevention of thrombosis using LMWH, and prevention of peptic ulcers using proton pump infibitors (in this case omeprazole). In our opinion, the IV hypotonic fluid we used alongside NG free water appears to be a reasonable choice for correcting the sodium levels and osmolality in HHS patients who present with hypernatremia after initial resuscitation. While correcting sodium with hypotonic fluid, other aspects of management should not be ignored.

Acknowledgements

We would like to thank ICU nurses and paramedic staff who work tirelessly in caring for these critically ill patients.

It is hereby declared that there is no potential conflict of interest of any author of the manuscript with regard to the content of this case report in any form, including honoraria, grants, and commercial interest from and into any commercial entity.

Patient's perspective : Patient was happy that doctors all over the world are going to learn from his case and its discussion will add valuable points to medical literature.

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