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Original Article

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Hypernatraemia in critically ill patients: too little water and too much salt

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Abstract

Background. Our objective was to study the risk factors and mechanisms of hypernatraemia in critically ill patients, a common and potentially serious problem.

Methods. In 2005, all patients admitted to the medical, surgical or neurological intensive care unit (ICU) of a university hospital were reviewed. A 1:2 matched case-control study was performed, defining cases as patients who developed a serum sodium ≥150 mmol/l in the ICU.

Results. One hundred and thirty cases with ICU-acquired hypernatraemia (141 ± 3 to 156 ± 6 mmol/l) were compared to 260 controls. Sepsis (9% versus 2%), hypokalaemia (53% versus 34%), renal dysfunction (53% versus 13%), hypoalbuminaemia (91% versus 55%), the use of mannitol (10% versus 1%) and use of sodium bicarbonate (23% versus 0.4%) were more common in cases ($P < 0.05$ for all) and were independently associated with hypernatraemia. During the development of hypernatraemia, fluid balance was negative in 80 cases (−31 ± 2 ml/kg/day), but positive in 50 cases (72 ± 3 ml/kg/day). Cases with a positive fluid balance received more sodium plus potassium (148 ± 2 versus 133 ± 3 mmol/l, $P < 0.001$). On average, cases were polyuric (40 ± 5 ml/kg). Mortality was higher in cases (48% versus 10%, $P < 0.001$), for which hypernatraemia was an independent predictor (odds ratio 4.3, 95% confidence interval 2.5 to 7.2).

Conclusions. Hypernatraemia seems to develop in the ICU because various factors promote renal water loss, which is then corrected with too little water or overcorrected with relatively hypertonic fluids. Therapy should therefore rely on adding electrolyte-free water and/or creating a negative sodium balance. Adjustments in intravenous fluid regimens may prevent hypernatraemia.

Keywords: electrolyte disorders; intensive care; intravenous fluids; mortality; renal dysfunction

Introduction

Hypernatraemia is recognized to be a common and important electrolyte disorder in critically ill patients [1]. However, thus far no controlled studies have investigated hypernatraemia in the intensive care unit (ICU), hindering the development of effective management strategies. Previously, Polderman *et al.* described a case series with 34 patients who presented with hypernatraemia in the ICU, and 22 patients who developed hypernatraemia in the ICU, demonstrating delayed or inadequate treatment in the latter group [2]. More recently, Aiyagari *et al.* studied 339 patients with hypernatraemia in the neurological ICU and found that hypernatraemia was associated with the use of mannitol, renal insufficiency, mechanical ventilation and an increased mortality rate [3]. In non-ICU patients, Palevsky *et al.* [4] identified a urinary concentrating defect, increased insensible and enteral losses, in addition to inadequate fluid management as responsible factors for the development of hypernatraemia.

In the present study, our objective was two-fold. First, we aimed at investigating the risk factors for hypernatraemia in the medical, surgical and neurological ICU using a matched case-control study design. Second, we pursued fluid balance studies in patients who developed hypernatraemia, hypothesizing that hypernatraemia not only developed because of a negative water balance, but also because of a positive sodium balance. If so, this would contradict with the general assumption that hypernatraemia usually develops because of a negative water balance [5–7]. It would also have implications for the diagnostic and therapeutic approach to the critically ill patient with hypernatraemia.

Materials and methods

Patient population and laboratory measurements

The study protocol was approved by the Institutional Review Board (MEC-2005-190) of the Erasmus Medical Center, an 813-bed urban university hospital in Rotterdam, The Netherlands. All serum sodium values (S_{Na}) of hospitalized patients ordered in 2005 were reviewed. The

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study group was selected from the medical, surgical and neurological ICU (42 beds, one medical team). S_{Na}-values were determined by the clinical chemistry department with ion-selective electrodes (Hitachi 917, Roche) and on-site with a blood gas analyser (ABL 725, Radiometer). For clinical significance, hypernatraemia was defined as $S_{Na} \geq 150$ mmol/l measured at least once by ion-selective electrodes. The definitions of other biochemical disorders are shown in Table 3. We also analysed how often hyponatraemia (defined as $S_{Na} < 136$ mmol/l) was present before or after hypernatraemia.

Data collection

The following data were recorded: reason of admission, Acute Physiology And Chronic Health Evaluation II (APACHE II) score, Glasgow Coma Score (GCS), vital signs, peripheral oedema, biochemical parameters, medication and fluid balances (in cases only). These data were available for all patients. They were retrieved from the ICU data management system (PICIS Care Suite 7.1, Wakefield, MA, USA) and reviewed manually. A review of charts and discharge letters was also performed.

Matched case-control study

To analyse which risk factors contributed to ICU-acquired hypernatraemia, a retrospective matched case-control study was performed. The following risk factor categories for hypernatraemia were defined: urinary concentrating defect, osmotic diuresis, shift of water, sodium gain and non-renal water loss (Table 3). Cases consisted of patients who were admitted to the ICU with $S_{Na} < 145$ mmol/l, and who subsequently developed hypernatraemia in the ICU. Patients who had hypernatraemia on admission to the ICU were excluded. Each case was matched to two control patients. The matching criteria for controls were normonatraemia (S_{Na} between 136 and 145 mmol/l), admission to the same ICU type (to account for ICU-specific diseases and treatments) and ICU exposure (meaning that the ICU admission time of controls needed to be at least as long as the time that hypernatraemia developed in cases). If more than two controls were available, they were chosen randomly using a random number generator (www.random.org). Risk factors were recorded in cases in the period between the last normal S_{Na} and the highest S_{Na}, and in controls using an equivalent time period.

Fluid balance studies in cases

Fluid balances were calculated during the development of hypernatraemia (in ml/kg/day), using all input (intravenous [IV] fluids, oral intake, nutrition, blood products) and output (24-h urine, insensible and enteral losses, blood loss and wound drains) values. Fluid balance data were carefully recorded in an automated data management system by experienced nursing staff. For insensible loss, an average of 14 ml/kg/day was used, adding 3.5 ml/kg/day per degree above 37°C [8]. The tonicity, defined as the amount of sodium (Na^+) plus potassium (K^+), and electrolyte-free water (EFW) of the fluids administered through the IV and/or oral routes were calculated, as described previously [9]. Polyuria was defined as urine output ≥40 ml/kg/day [6]. Tonicity balances were calculated for two patients with complete balance data (Figure 3, see the legend for details) [10].

Statistical analysis

Data were analysed using SPSS (version 15.0, Chicago, IL, USA). Cases were compared to controls using conditional logistic regression to allow a comparison between cases and controls in the same matched set. Two multivariate analyses (using a backward conditional approach) were performed to identify independent predictors for hypernatraemia and for mortality. A subanalysis was performed leaving out all neurological patients and their matched controls, because hypernatraemia could have been a therapeutic objective in these patients to control intracranial pressure. Data are expressed as mean ± SD, except not normally distributed variables (reported as median and range and log-transformed before analysis) and fluid balance data (mean ± SEM). For all analyses, a P-value of ≤ 0.05 was considered significant.

Results

Study group

Figure 1 shows the selection of the study group and outcomes. Hypernatraemia was usually acquired in the ICU (130/140 patients, 93%). In cases, S_{Na} increased from 141 ± 3 to 156 ± 6 mmol/l in 48 ± 4 h. Hypernatraemia was observed for a median of 45 h (range 0.25–603 h). Thirty-three cases (24%) were hypernatraemic when they died. Compared to the other cases, these 33 deaths had a more acute rise in S_{Na} (median 14 versus 6 mmol/l/day, $P = 0.002$) and reached a higher peak S_{Na} (160 ± 8 versus 155 ± 4 mmol/l, $P = 0.005$). Twenty-nine additional cases died during the resolution of hypernatraemia (S_{Na} at death 143 ± 6 mmol/l). The correction rates did not differ between the 29 cases who died during the resolution of hypernatraemia compared to those who survived (median 1.7 versus 1.4 mmol/l/day, $P = 0.2$). Finally, 45 cases (32%) had hyponatraemia prior to hypernatraemia (lowest S_{Na} 130 ± 5 mmol/l), whereas 42 cases (30%) developed hyponatraemia after their hypernatraemic episode (lowest S_{Na} 130 ± 4 mmol/l). The differences in S_{Na} between the measurements with ion-selective electrodes and the blood-gas analyser did not exceed 2 mmol/l.

Characteristics of cases and controls

Patients were admitted to the medical ICU (26 cases, 52 controls), surgical ICU (43 cases, 86 controls) and the neurological ICU (61 cases, 122 controls). The reasons of admission to the ICU are listed in Table 1. Cases were more often admitted directly to the ICU with higher APACHE II scores and lower GCS (Table 2). Cases were more often admitted to ICU after emergency surgery, and more often ventilated during hospitalization. With regard to outcomes, cases had a longer ICU stay and a higher mortality rate.

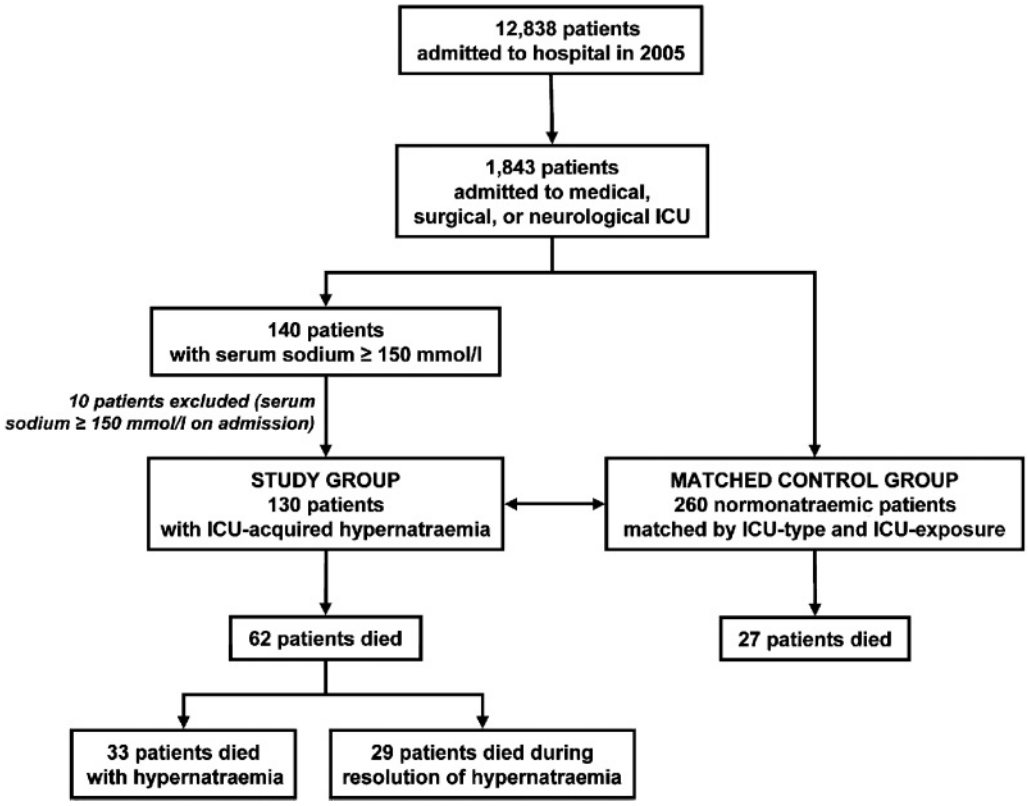

Fig. 1. Flow diagram showing study group selection and outcomes. The majority of patients developed hypernatraemia in the intensive care unit (ICU, 130/140 patients, 93%). These patients formed the study group and they were 1:2 matched to control patients based on the type of ICU and ICU exposure. The mortality rate in cases was significantly higher than in controls (62/130 or 48% versus 27/260 or 10%, $P < 0.001$).

Table 1. Reasons of admission to the intensive care unit

Reason of ICU admission	Cases ($n = 130$) n (%)	Controls ($n = 260$) n (%)	P-value
Abdominal aneurysm surgery	8 (6)	10 (4)	0.3
Brain tumour surgery	2 (2)	31 (12)	0.002
Cerebral haemorrhage	17 (13)	32 (12)	0.8
Subarachnoid haemorrhage	9 (7)	16 (6)	0.2
Gastro-intestinal surgery	24 (18)	54 (21)	0.6
Intoxication	1 (1)	9 (3)	0.2
Respiratory insufficiency	16 (12)	32 (12)	1.0
Sepsis	12 (9)	6 (2)	0.005
Trauma	20 (15)	21 (8)	0.02
Miscellaneous[a]	30 (23)	65 (25)	0.8

ICU, intensive care unit.
[a]Includes: status epilepticus, gastro-intestinal haemorrhage, decompensated diabetes mellitus, malignant hypertension and monitoring after other surgical procedures.

Factors contributing to hypernatraemia

In Table 3, the possible causes of hypernatraemia categorized by mechanism were analysed, showing that cases more often had hypokalaemia, hypercalcaemia, renal dysfunction, hypoalbuminaemia and hyperglycaemia, and more often received mannitol and sodium bicarbonate during the development of hypernatraemia. Except for hyperglycaemia, these factors remained significantly more common in cases ($P < 0.05$) when the APACHE II score and GCS were included in the comparison. In cases, biochemical disorders were more severe for hypokalaemia (lowest serum potassium 3.1 ± 0.4 mmol/l versus 3.2 ± 0.2 mmol/l, $P = 0.01$), hypercalcaemia (highest ionized calcium 1.45 ± 0.25 mmol/l versus 1.34 ± 0.07 mmol/l, $P < 0.001$), hypoalbuminaemia (lowest serum albumin 22 ± 6 versus 26 ± 5 g/l, $P < 0.001$) and hyperglycaemia (highest serum glucose 14.5 ± 9.1 mmol/l versus 11.9 ± 1.8 mmol/l, $P = 0.03$). Of the patients with renal dysfunction, serum creatinine was 217 ± 121 μmol/l in cases and 189 ± 99 μmol/l in controls ($P = 0.2$). Twenty-seven cases (39%) and four controls (11%) had a serum urea to creatinine ratio greater than 20. In 15 cases (12%) and 49 controls (19%), only

Table 2. General characteristics and outcomes of cases and controls

Category	Variable	Cases ($n = 130$)	Controls ($n = 260$)	P-value
Demographics	Age (years)	57 ± 18	54 ± 18	0.2
	Female sex, *n* (%)	53 (41)	117 (45)	0.4
Admission	Directly to ICU, *n* (%)	74 (57)	121 (47)	0.04
	APACHE II score	22 (6–44)	16 (2–35)	<0.001
	Glasgow Coma score	7 (3–15)	10 (3–15)	<0.001
Vital signs[a]	Heart rate (bpm)	91 ± 16	82 ± 15	<0.001
	Systolic BP (mmHg_	130 ± 22	130 ± 20	0.9
	Diastolic BP (mmHg)	66 ± 12	67 ± 12	0.5
	Temperature (°C)	36.8 ± 0.8	36.6 ± 0.6	0.04
Physical signs	Oedema	39 (30)	27 (10)	<0.001
Interventions	Elective surgery, *n* (%)	24 (19)	86 (33)	0.003
	Emergency surgery, *n* (%)	36 (28)	19 (7)	<0.001
	Ventilation, *n* (%)	120 (92)	151 (58)	<0.001
Outcomes	Duration ICU (days)	11 (1–152)	3 (1–75)	<0.001
	Mortality, *n* (%)	62 (48)	27 (10)	<0.001
	Hypernatraemia at death, *n* (%)	32 (25)	–	–

ICU, intensive care unit; APACHE II, Acute Physiology And Chronic Health Evaluation; BP, blood pressure.
[a]Average values during the development of hypernatraemia.

urea and not creatinine levels were increased. Hypomagnesaemia, metabolic and respiratory acid–base disturbances were not more common in cases (data not shown). In patients with hypokalaemia, hypomagnesaemia, acid–base disturbances and/or diuretic use were not more common (data not shown).

Multivariate analyses and subanalysis

In the first multivariate analysis, we analysed which factors were independently associated with hypernatraemia (Table 4), including in the model the significant factors from the univariate analyses (Tables 1 and 3). In the second multivariate analysis predictors for mortality were studied, including age, gender, hypernatraemia, the APACHE II score, GCS and renal dysfunction in the model. Age (1.0, 1.0 to 1.1), hypernatraemia (4.3, 2.5 to 7.2) and renal dysfunction (2.0, 1.0 to 3.9) were found to be independent predictors of mortality in our patients. The subanalysis excluding all neurological patients showed that the same significant risk factors for hypernatraemia emerged, except for hypokalaemia (data not shown).

Fluid balance studies in cases

During the development of hypernatraemia in the ICU, 80 patients (62%) had a negative fluid balance (−31 ± 2 ml/kg/day, body weight 77.6 ± 19.6 kg), while 50 patients (38%) had a positive fluid balance (72 ± 3 ml/kg/day, body weight 74.0 ± 13.4 kg) (Figure 2). The risk factors listed in Table 3 were evenly distributed between cases with negative and positive fluid balances, except for renal dysfunction, which was more common (52/80 versus 17/50, $P = 0.001$), but not more severe (204 ± 125 versus 209 ± 88 μmol/l, $P = 0.4$) in cases with a negative fluid balance. Patients with a positive fluid balance received more sodium plus potassium (148 ± 2 versus 133 ± 3 mmol/l, $P < 0.001$), but a similar small amount of electrolyte-free water (3.5 ± 0.6 versus 4.7 ± 0.9 ml/kg/day, $P = 1.0$). Administered fluids included normal saline, colloids, Ringer's lactate, nutrition and blood transfusions. Voluntary drinking was negligible, and water administration (mostly through the nasogastric tube) was minimal both in cases with a positive (0.21 ± 0.21 ml/kg) and a negative fluid balance (0.56 ± 0.33 ml/kg). No cases were treated with hypertonic saline. Excreted fluids were largely comparable, and included urine, blood loss and losses from the gastro-intestinal tract and from wounds. On average, both cases with a negative fluid balance (40 ± 4 ml/kg) and with a positive fluid balance (41 ± 6 ml/kg) were polyuric. Separate analyses of urine output in cases with hypokalaemia (45 ± 4 ml/kg/day), hypercalcaemia (55 ± 7 ml/kg/day), mannitol use (57 ± 5 ml/kg/day) and hyperglycaemia (40 ± 4 ml/kg/day) showed that these were all in the polyuric range. The available urinary sodium concentrations and urinary osmolality were 67 ± 10 mmol/l and 499 ± 47 mOsm/kg in 6 patients with a negative fluid balance and 64 ± 19 mmol/l and 427 ± 59 mOsm/kg in 21 patients with a positive fluid balance. The tonicity balances of two cases with complete balance data are shown in Figure 3.

Discussion

In this study on hypernatraemia in critically ill patients, the following principal results were obtained. First, the majority of patients developed hypernatraemia in the ICU (93%, Figure 1), suggesting that ICU-related factors contributed to its genesis. The patients with ICU-acquired hypernatraemia were generally sicker on admission to the ICU (higher APACHE II, lower GCS) and had a five-fold higher mortality rate (Table 2). Hypernatraemia was an independent predictor for mortality, as were age and renal dysfunction. In the patients who died, hypernatraemia was both more acute and more severe, while no association was found between mortality and the generally modest correction rates of hypernatraemia. The matched case-control study found that hypernatraemia was associated with underlying diseases (sepsis, trauma), accompanying biochemical disorders

Table 3. Potential factors contributing to hypernatraemia

Mechanisms	Observed causes	Cases ($n = 130$) n (%)	Controls ($n = 260$)n (%)	P-value
Concentrating defect	Diseases associated with CDI[a]	9 (7)	12 (5)	0.3
	Drugs associated with NDI[b]	29 (22)	39 (15)	0.08
	Hypokalaemia (≤3.5 mmol/l)	69 (53)	89 (34)	<0.001
	Hypercalcaemia (≥1.29 mmol/l)[c]	22 (17)	14 (5)	0.001
	Loop diuretics	29 (22)	65 (25)	0.4
	Renal dysfunction[d]	69 (53)	35 (13)	<0.001
Osmotic diuresis	Mannitol	13 (10)	3 (1)	0.001
	Hyperglycaemia (≥10 mmol/l)	56 (43)	81 (31)	0.04
Shift of water	Creatine kinase ≥2000 IU/l[e]	12 (11)	7 (5)	0.2
	Hypoalbuminaemia (<35 g/l)	118 (91)	126 (55)	<0.001
Sodium gain	Sodium bicarbonate use	30 (23)	1 (0.4)	<0.001
Non-renal water loss	Lactulose	14 (11)	18 (7)	0.2

CDI, central diabetes insipidus; NDI, nephrogenic diabetes insipidus.
[a]Includes: any neurotrauma, pituitary adenoma and craniopharyngeoma [6].
[b]Includes: amphotericin B, dexamethasone, dopamine, ethanol, rifampin and/or triamterene-hydrochlorothiazide [34].
[c]Ionized calcium.
[d]Defined as: serum creatinine ≥ 100 μmol/l (females) or ≥125 μmol (males).
[e]Creatine kinase was available in 113 cases (87%) and 135 controls (52%).

Table 4. Results of multivariate conditional logistic regression showing independent predictors for ICU-acquired hypernatraemia

Variable	Parameter estimate	Standard error	Wald χ^2	P-value	OR (95% CI)
Sepsis	1.7	0.8	4.2	0.04	5.7 (1.1–30.2)
Hypokalaemia	1.0	0.5	4.6	0.03	2.7 (1.1–6.7)
Hypoalbuminaemia	1.0	0.5	3.7	0.05	2.6 (1.0–6.9)
Renal dysfunction	1.8	0.5	11.5	0.001	6.3 (2.2–18.4)
Use of mannitol	2.8	1.2	5.9	0.02	16.9 (1.7–164.0)
Use of sodium bicarbonate	3.5	1.1	9.5	0.002	32.5 (3.5–297.8)

OR, odds ratio; CI, confidence interval.

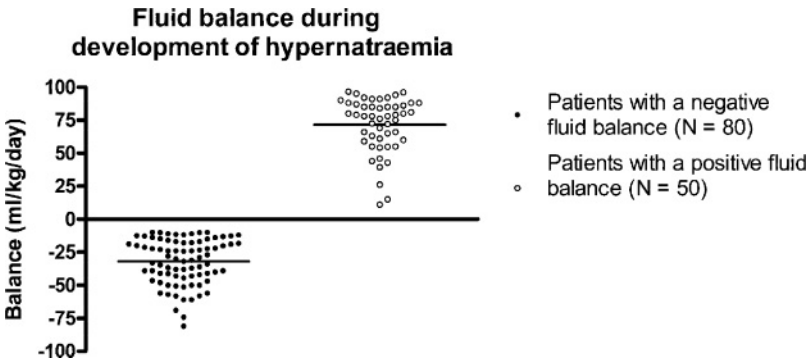

Fig. 2. Fluid balance during the development of hypernatraemia. Fluid balances were calculated during the development of hypernatraemia using all input (intravenous fluids, oral intake, nutrition, blood products) and output (24-h urine, insensible and enteral losses, blood loss and wound drains) values.

(hypokalaemia, hypercalcaemia, renal dysfunction, hyperglycaemia, hypoalbuminaemia), and/or therapy (mannitol, use of sodium bicarbonate, Tables 1 and 3). Multivariate analysis showed that these associations were independent of the severity of disease (based on APACHE II and GCS), suggesting a causal relationship with hypernatraemia. Finally, during the development of hypernatraemia, fluid balance was negative in two-thirds of the cases, but positive in one-third, which is higher than previously appreciated [5–7] and has potential therapeutic implications for IV-fluid management.

Based on these results, we propose the following three-step hypothesis for the pathogenesis of ICU-acquired hypernatraemia. First, most of the identified risk factors for ICU-acquired hypernatraemia share the ability to promote renal water loss. Hypokalaemia [11], hypercalcaemia [12] and renal dysfunction [13–15] can cause a urinary concentrating defect, whereas hyperglycaemia [16] and mannitol [3] can cause osmotic diuresis. Vasopressin deficiency can develop in late stages of sepsis and therefore also contribute to renal water loss [17]. Further evidence for renal water loss comes from the fact that approximately half of the cases were polyuric, even when fluid balance was negative, and that the available urine osmolalities were comparable to those of a previous cohort of patients with hypernatraemia and renal water loss [4]. Regardless of the underlying

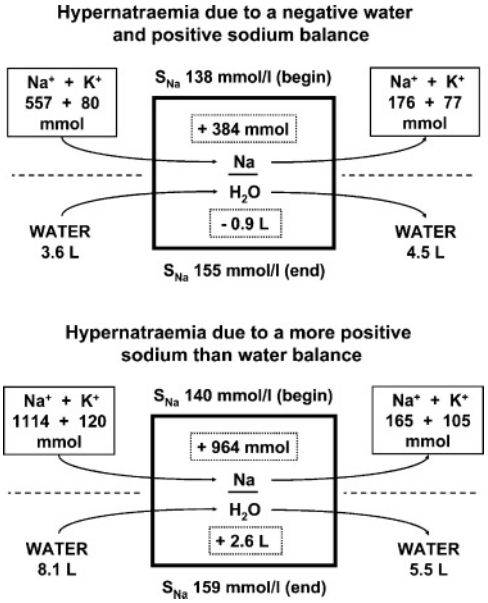

Fig. 3. Tonicity balances illustrating two mechanisms of hypernatraemia. Two mechanisms of hypernatraemia are shown in two representative patients. The large darker rectangles represent total body water with the serum sodium concentration measured at the beginning and end of the observation shown on top and bottom of this rectangle, respectively. The quantities of sodium (Na^+) plus potassium (K^+) infused and excreted are shown in the two flanking rectangles, and the volumes of water (H_2O) infused and excreted are depicted below. The first patient (top) was a 50-year-old female (body weight 75 kg) who was admitted with respiratory insufficiency due to pneumonia. Hypernatraemia developed in 4 days and was attributed to a combination of a negative water balance and a positive sodium balance due to the infusion of isotonic fluids and renal water loss from hyperglycaemia, hypercalcaemia and hypokalaemia. The second patient (bottom) was a 47-year-old male (body weight 95 kg) who was admitted after cystectomy for bladder cancer, which was complicated by faecal peritonitis. Hypernatraemia developed in 1day and was attributed to a positive sodium balance due to large isotonic volume resuscitation for sepsis, the administration of hypertonic fluids (sodium bicarbonate), renal water loss from renal insufficiency and hyperglycaemia and non-renal water loss from wound drains and colostomy.

mechanism, the initial rise in S_{Na} is known to produce a strong thirst stimulus [18]. The second step therefore consists of an inability to express thirst and access water. Indeed, water intake in cases was negligible, likely because cases were more often unconscious and more often required ventilation than controls (Table 2). Consequently, the defence of their water homeostasis depended completely on the treating clinicians. Therefore, the third and final step in the development of hypernatraemia appeared to be inadequate IV-fluid administration, which did not prevent, or even aggravate hypernatraemia. Previously, several studies [2,4,19,20], including ours [9], have shown the relationship between inadequate IV-fluid therapy and the development of dysnatraemia, and some authors consider it a negative indicator of quality of care [2].

We emphasize that the precise mechanisms of hypernatraemia could not be analysed, because urinary values were not regularly recorded, so that water and sodium balances could not be calculated. However, indirect evidence suggests that not only a negative water balance, the classical explanation for hypernatraemia [5–7], but also a positive sodium balance contributed to hypernatraemia. For example, the tonicity of the administered fluids was isotonic (148 ± 4 mmol/l), while patients at the same time had reasons to excrete a hypotonic urine (Table 3), and also lost other hypotonic fluids, such as gastro-intestinal fluids. A positive sodium balance likely also contributed to hypernatraemia in patients with a negative fluid balance, because a negative water balance alone cannot completely account for the rise in S_{Na}. For example, for S_{Na} to rise from 141 mmol/l to 156 mmol/l in a 70-kg patient due to a negative water balance, total body water would need to be reduced from 42 l to $(42 \times 141)/156 = 38$ l. This equals a deficit of 4 l or 57 ml/kg, which is almost twice as high as the number we found (-31 ± 2 ml/kg, Figure 2). The tonicity balances of two cases with complete balance data also illustrate the role of a positive sodium balance in the pathogenesis of ICU-acquired hypernatraemia (Figure 3).

The association between hypernatraemia and a high mortality rate, as shown by others [4,21–23], remains striking. However, it remains difficult in studies like these to determine whether hypernatraemia, the underlying disease, or both contributed to mortality. In addition, the induction of hypernatraemia sometimes is a therapeutic objective, for example to reduce intracranial pressure [24], although a recent study showed that too high serum sodium values in these settings increase mortality [3]. Although not a specific subject of this study, another interesting observation was that hyponatraemia preceded or followed hypernatraemia in approximately one-third of the patients. This could be related to fluctuations in vasopressin release [25], but overcorrection of dysnatraemia might be an alternative explanation.

Clinically, an important question is how these results could aid in preventing and treating hypernatraemia in critically ill patients. To prevent hypernatraemia, close monitoring of factors that could result in the excretion of a hypotonic urine appears indicated. If polyuria develops, the amount and tonicity of the IV-fluids should be matched to the urinary output and composition to maintain fluid and electrolyte balance. If a water or osmotic diuresis is present, isotonic fluids should be switched to more hypotonic solutions to prevent a positive sodium balance from developing. Although aggressive fluid resuscitation to defend the extracellular fluid volume may have been required initially in patients who developed a positive fluid balance (e.g. because of on-going blood loss), it seems advisable to reduce the infusion rate once haemodynamic stability is achieved. The most logical and practical treatment of hypernatraemia is to increase EFW administration [26]. However, in patients with a positive sodium balance, the infusion of hypotonic IV-fluids may cause even more fluid overload. In these patients, the goal of therapy should also be to create a negative balance of $Na^+ + K^+$ [10]. Therefore, one might consider using diuretics, for example a combination of loop diuretics and water or thiazide diuretics only, provided that there is haemodynamic stability. Therapy should also focus on causes of a low effective circulating volume, which are often present in patients with hypernatraemia, and a positive fluid balance [27].

Because our study was retrospective, the identified risk factors should be followed up in a prospective study, in which complete tonicity balances, changes in body weight, water clearance and fractional excretions of sodium and

urea could offer more mechanistic insight. Alternative mechanisms for hypernatraemia (not studied here) include high glucocorticoid and/or catecholamine levels, which could also explain concomitant hypokalaemia [28]. These hormones can inhibit the release or actions of vasopressin [29–31] or cause an upward resetting of the osmostat [32]. Although vasopressin is usually elevated during critical illness [33], it would be interesting for future research to measure circulating vasopressin and assess its renal concentrating ability in critically ill patients with hypernatraemia. Other factors that have previously been associated with hypernatraemia were not more common or uncommon in our series, including diseases associated with central diabetes insipidus [6], drugs associated with nephrogenic diabetes insipidus [34], burns, citrate dialysis, and the use of charcoal, phenytoin, lactulose and hypertonic saline [5–7].

In conclusion, critically ill patients who develop hypernatraemia often have factors promoting renal water loss. Subsequently, hypernatraemia develops either when insufficient water is given (negative water balance) or when hypotonic losses are overcorrected with isotonic fluids (positive sodium balance). Therapy should therefore rely on adding electrolyte-free water and/or creating a negative sodium balance. Adjustments in intravenous fluid regimens may prevent hypernatraemia and possibly improve outcome.

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