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

Ewout J. Hoorn¹, Michiel G.H. Betjes¹, Joachim Weigel² and Robert Zietse¹

¹Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands and ²Department of Intensive Care, Erasmus Medical Center, Rotterdam, The Netherlands

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 (SNa) of hospitalized patients ordered in 2005 were reviewed. The
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 (Hitchi 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 randomly chosen 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 $\geq 40$ 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 $\pm$ SD, except not normally distributed variables (reported as median and range and log-transformed before analysis) and fluid balance data (mean $\pm$ SEM). For all analyses, a $P$-value of $\leq 0.05$ 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 $\pm$ 3 to 156 $\pm$ 6 mmol/l in 48 $\pm$ 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 $\pm$ 8 versus 155 $\pm$ 4 mmol/l, $P = 0.005$). Twenty-nine additional cases died during the resolution of hypernatraemia ($S_{Na}$ at death 143 $\pm$ 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 $\pm$ 5 mmol/l), whereas 42 cases (30%) developed hyponatraemia after their hypernatraemic episode (lowest $S_{Na}$ 130 $\pm$ 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...
Hypernatraemia in critically ill patients

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  |
|                   | Hypernatremia 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 hypernatremia.

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 hypernatremia (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, hypernatremia, the APACHE II score, GCS and renal dysfunction in the model. Age (1.0, 1.0 to 1.1), hypernatremia (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 hypernatremia emerged, except for hypokalaemia (data not shown).

Fluid balance studies in cases

During the development of hypernatremia 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 toxicity balances of two cases with complete balance data are shown in Figure 3.

Discussion

In this study on hypernatremia in critically ill patients, the following principal results were obtained. First, the majority of patients developed hypernatremia in the ICU (93%, Figure 1), suggesting that ICU-related factors contributed to its genesis. The patients with ICU-acquired hypernatremia were generally sicker on admission to the ICU (higher APACHE II, lower GCS) and had a five-fold higher mortality rate (Table 2). Hypernatremia was an independent predictor for mortality, as were age and renal dysfunction. In the patients who died, hypernatremia was both more acute and more severe, while no association was found between mortality and the generally modest correction rates of hypernatremia. The matched case-control study found that hypernatremia 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<sup>a</sup> | 9 (7) | 12 (5) | 0.3 |
| | Drugs associated with NDI<sup>b</sup> | 29 (22) | 39 (15) | 0.08 |
| | Hypokalaemia (≤3.5 mmol/l) | 69 (53) | 89 (34) | <0.001 |
| | Hypercalcaemia (≥1.29 mmol/l)<sup>c</sup> | 22 (17) | 14 (5) | 0.001 |
| | Loop diuretics | 29 (22) | 65 (25) | 0.4 |
| | Renal dysfunction<sup>d</sup> | 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<sup>e</sup> | 12 (11) | 7 (5) | 0.2 |
| | | Hypoalbuninaemia (<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.
<sup>a</sup>Includes: any neurotrauma, pituitary adenoma and craniopharyngeoma [6].
<sup>b</sup>Includes: amphotericin B, dexamethasone, dopamine, ethanol, rifampin and/or triamterene-hydrochlorothiazide [34].
<sup>c</sup>Ionized calcium.
<sup>d</sup>Defined as: serum creatinine ≥100 µmol/l (females) or ≥125 µmol (males).
<sup>e</sup>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 χ² | 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) |
| Hypoalbuninaemia | 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.

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 (hypokalaemia, hypercalcaemia, renal dysfunction, hyperglycaemia, hypoalbuninaemia), 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.
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 defense 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 toxicity of the administered fluids was isotonic (148 $\pm$ 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 x 141)/156 $\approx$ 38 l. This equals a deficit of 4 l or 57 ml/kg, which is almost twice as high as the number we found ($31 \pm 2$ ml/kg, Figure 2). The toxicity 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 toxicity 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 toxicity balances, changes in body weight, water clearance and fractional excretions of sodium and
urea could offer more mechanistic insight. Alternative mechanisms for hypernatremia (not studied here) include high glucocorticoid and/or catecholamine levels, which could also explain concomitant hypokalemia [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 hypernatremia. Other factors that have previously been associated with hypernatremia were not more common or uncommon in our series, including diseases associated with central diabetes insipidus [34], drugs associated with nephrogenic diabetes insipidus [35], burns, citrate dialysis, and the use of charcoal, phenytoin, lactulose and hypertonic saline [5–7].

In conclusion, critically ill patients who develop hypernatremia often have factors promoting renal water loss. Subsequently, hypernatremia 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 hypernatremia and possibly improve outcome.

Acknowledgements. The authors would like to thank N. Tahitu, T. Bontje and G. Lansbergen for their help with data retrieval, and Dr M. ten Berg, Dr P. Stolk and Dr W. Scholte op Reimer for statistical advice.

Conflict of interest statement. None declared.

References

1. Moritz ML, Ayus JC. Dysnatremias in the critical care setting. Contrib Nephrol 2004; 144: 132–157
2. Polderman KH, Schreuder WO, Strack van Schijndel RJ et al. Hypernatremia in the intensive care unit: an indicator of quality of care? Crit Care Med 1999; 27: 1105–1108
3. Aiyagar V, Deibert E, Diringer MN. Hypernatremia in the neurologic intensive care unit: how high is too high? J Crit Care 2006; 21: 163–172
4. Palevsky PM, Bhagrat R, Greenberg A. Hypernatremia in hospitalized patients. Ann Intern Med 1996; 124: 197–203.
5. Adrogue HJ, Madrias NE. Hypernatremia. N Engl J Med 2000; 342: 1493–1499
6. Halperin ML, Goldstein MB. Fluid, Electrolyte, and Acid-Base Physiology,. Philadelphia: W. Saunders 1999
7. Rose BD, Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders,. New York: McGraw-Hill, 2001
8. Cox P. Insensible water loss and its assessment in adult patients: a review. Acta Anaesthesiol Scand 1987; 31: 771–776
9. Hoorn EJ, Geary D, Robb M et al. Acute hypernatremia related to intravenous fluid administration in hospitalized children: an observational study. Pediatrics 2004; 113: 1279–1284
10. Carlotti AP, Bohn D, Mallie JP et al. Tonicity balance, and not electrolyte-free water calculations, more accurately guides therapy for acute changes in natremia. Intensive Care Med 2001; 27: 921–924
11. Marples D, Froikia J, Dorup J et al. Hypokalemia-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla and cortex. J Clin Invest 1996; 97: 1960–1968
12. Earm JH, Christensen BM, Froikia J et al. Decreased aquaporin-2 expression and apical plasma membrane delivery in kidney collecting ducts of polyuric hypercalcaemic rats. J Am Soc Nephrol 1998; 9: 2181–2193
13. Bedford JJ, Leader JP, Walker RJ. Aquaporin expression in normal human kidney and in renal disease. J Am Soc Nephrol 2003; 14: 2581–2587
14. Miller PD, Krebs RA, Neal BJ et al. Polyuric prerenal failure. Arch Intern Med 1980; 140: 907–909
15. Teitelbaum I, McGuinness S. Vasopressin resistance in chronic renal failure. Evidence for the role of decreased V2 receptor mRNA. J Clin Invest 1995; 96: 378–385
16. Gennari FJ, Kassiter JP. Osmotic diuresis. N Engl J Med 1974; 291: 714–720.
17. Sharshar T, Blanchard A, Paillard M et al. Circulating vasopressin levels in septic shock. Crit Care Med 2003; 31: 1752–1758
18. Baylis PH, Thompson CJ. Osmoregulation of vasopressin secretion and thirst in health and disease. Clin Endocrinol (Oxf) 1988; 29: 549–576
19. Milionis HJ, Liamis G, Eliaf MS. Hypernatremia in hospitalized patients: a sequel of inadvertent fluid administration. Arch Intern Med 2000; 160: 1541–1542
20. Liamis G, Kalaitzidis R, Eliaf MS. Hypernatremia during correction of hypercalcaemia. Nephron 2000; 86: 358
21. Snyder NA, Feigal DW, Arteff AI. Hypernatremia in elderly patients. A heterogeneous, morbid, and iatrogenic entity. Ann Intern Med 1987; 107: 309–319
22. Qureshi AI, Suri MF, Sung GY et al. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2002; 50: 749–756
23. Daggert P, Deanfield J, Moss F et al. Severe hypernatremia in adults. Br Med J 1979; 1: 1177–1180
24. Peterson B, Khanna S, Fisher B et al. Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. Crit Care Med 2000; 28: 1136–1143
25. Lindsay RS, Seckl JR, Padfield PL. The triple-phase response—problems of water balance after pituitary surgery. Postgrad Med J 1995; 71: 439–441
26. Sterns RH. Hypernatremia in the intensive care unit: instant quality—just add water. Crit Care Med 1999; 27: 1041–1042
27. Kahn T. Hypernatremia with edema. Arch Intern Med 1999; 159: 93–98
28. Weisberg LS, Szerlip HM, Cox M. Disorders of potassium homeostasis in critically ill patients. Crit Care Clin 1987; 3: 835–854
29. Rouch AJ, Kudo LH. Alpha 2-adrenergic-mediated inhibition of water intake in acute and chronic heart failure. Am J Physiol 1997; 272: F150–F157
30. Sonnenblick M, Alguir N. Hypernatremia in the acutely ill elderly patients: role of impaired arginine–vasopressin secretion. Miner Electrolyte Metab 1993; 19: 32–35
31. Pappas CE, Sladek CD, Raff H. Corticosterone inhibition of osmotic-stimulated vasopressin secretion in hypothalamic-neurohypophyseal explants. Am J Physiol 1997; 272: R158–R162
32. Gropius RC. Adjustment of the osmostat in primary aldosteronism. Mayo Clin Proc 1994; 69: 1108–1110
33. Jochberger S, Mayr VD, Luckner G et al. Serum vasopressin concentrations in critically ill patients. Crit Care Med 2006; 34: 293–299
34. Garofalou CG, Weir M, Rosas-Arellano MP et al. Causes of reversible nephrogenic diabetes insipidus: a systematic review. Am J Kidney Dis 2005; 45: 626–637

Received for publication: 15.9.07
Accepted in revised form: 24.10.07