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Osmotic diuresis due to urea as the cause of hypernatraemia in critically ill patients

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Abstract

Background. Hypernatraemia is common in critically ill patients and has been shown to be an independent predictor of mortality. Osmotic urea diuresis can cause hypernatraemia due to significant water losses but is often not diagnosed. Free water clearance (FWC) and electrolyte free water clearance (EFWC) were proposed to quantify renal water handling. We aimed to (i) identify patients with hypernatraemia due to osmotic urea diuresis and (ii) investigate whether FWC and EFWC are helpful in identifying renal loss of free water.

Methods. In this retrospective study, we screened a registry for patients, who experienced intensive care unit (ICU)-acquired hypernatraemia. Among them, patients with hypernatraemia due to osmotic urea diuresis were detected by a case-by-case review. Total fluid and electrolyte balances together with FWC and EFWC were calculated for days of rising serum sodium and stable serum sodium.

Results. We identified seven patients (10% of patients with ICU-acquired hypernatraemia) with osmotic diuresis due to urea. All patients were intubated during development of hypernatraemia and received enteral nutrition. The median highest serum sodium level of 153 mmol (Q1: 151–Q3: 155 mmol/L) was reached after a 5-day period of rise in serum sodium. During this period, FWC was −904 mL/day (Q1: −1574–Q3: −572), indicating renal water retention, while EFWC was 1419 mL/day (Q1: 1052–Q3: 1923), showing renal water loss. While FWC did not differ between time of stable serum sodium and development of hypernatraemia, EFWC was significantly higher during rise in serum sodium.

Conclusion. Osmotic urea diuresis is a common cause of hypernatraemia in the ICU. EFWC was useful in the differential diagnosis of polyuria during rising serum sodium levels, while FWC was misleading.

Keywords: critically ill; hypernatraemia; osmotic diuresis; sodium; urea

Introduction

Intensive care unit (ICU)-acquired hypernatraemia is a common problem in ICUs with incidence rates of ~10% and was described to be independently associated with mortality [1]. Causes of hypernatraemia in critically ill patients are various but in general, its development is either a result of a gain of sodium or a loss of free water [2]. Since critically ill patients are often intubated and/or sedated or have other reasons for a lack of free access to water, fluid and electrolyte balance is mainly managed by the physician [3]. Thus, the development of hypernatraemia in a critically ill patient indicating that too little water has been provided was proposed as an indicator of poor quality of care [4].

Given the multitude of adverse effects of hypernatraemia/hyperosmolality ranging from neurologic dysfunction to decreased left ventricular contractility [2, 5–7], an early identification of the causes of a rising serum sodium in critically ill patients is crucial for causal treatment and the avoidance of aggravating or relapsing hypernatraemia.

Osmotic diuresis can lead to significant losses of free water and can cause or at least contribute to the development of hypernatraemia. Osmotic diuresis caused by urea is often not identified under circumstances of rising serum sodium levels since the high urine osmolality in comparison to the serum osmolality can be mistaken for renal retention of free water. Free water clearance (FWC) is often calculated in order to quantify renal water handling [8]. However, the calculation of FWC is based on osmolality (which is influenced by the concentration of urea) and therefore might be prone to failure in patients with urea diuresis. In contrast, electrolyte free water clearance (EFWC) is based on the relation of sodium and potassium in urine to serum sodium concentration and therefore is not prone to failure under circumstances of osmotic diuresis.

In this study, we wanted to (i) identify and characterize patients with ICU-acquired hypernatraemia due to osmotic urea diuresis and (ii) evaluate the benefit of using FWC and EFWC in the differential diagnosis of polyuria and hypernatraemia.

Materials and methods

We screened a database of patients who were admitted to a medical ICU of a tertiary university hospital between June 1 2001 and April 30 2004. Only patients with hypernatraemia were included. Hypernatraemia was defined as a serum sodium exceeding 149 mmol/L [1, 9]. Of these patients,

demographic data, admission diagnosis, severity of disease as measured by the simplified acute physiology score (SAPS II), daily measurements of electrolytes, urinalysis, serum and urine osmolality, detailed information on administered infusion and nutrition solutions were obtained. In order to identify patients with hypernatraemic episodes due to osmotic urea diuresis, we performed a case-by-case review of the days in the ICU during which serum sodium was rising prior to hypernatraemia. In a first step, screening for patients with polyuria (urine output >2.000 mL/day at least once during rise of serum sodium) was performed. In a second step, water diuresis (urine osmolality < 150 mmol/L) was excluded [10]. Patients were considered to have solute diuresis when urine osmolality was >300 mmol/L at time of polyuria [10, 11]. Additionally, a total daily osmole excretion of >1000 mmol as calculated by the following equation: daily osmole excretion = $\text{osmolality}_{\text{urine}} \times \text{volume}_{\text{urine}}$ (in liters), was necessary for the presence of solute diuresis at least once during rise in serum sodium.

To differentiate the cause for the solute diuresis, the following steps were performed to rule out osmotic diuresis due to glucose; only patients with negative tests for glucose in urine during the time of rising serum sodium levels were included. Cases were reviewed for the administration of mannitol in order to rule out solute diuresis due to mannitol. In order to differentiate between an electrolyte diuresis from a urea diuresis, concentrations for both were calculated from urinalysis. Osmotic diuresis due to urea was considered present in a patient if urea concentration in urine was exceeding 250 mmol/L [10, 12]. Additionally, the fraction of the osmolality in the urine caused by urea had to be outweighing the fraction caused by sodium and potassium. For all identified patients, in order to discriminate whether urea stems from protein out of the administered enteral nutrition or from catabolism, we calculated protein balances as follows.

In a first step, protein equivalent was calculated from daily urea output. In order to convert urea in urine (in mmol) to blood urea nitrogen (BUN, in mg/dL), we calculated:

$$\text{BUN} = \text{Urea}_{\text{urine}} \times 2.8 \times 0.467.$$

The product was multiplied with the urine volume, which gave us daily nitrogen output which finally was multiplied by 6.25 to receive the protein equivalent.

Finally, protein intake as calculated from enteral nutrition and protein equivalent allowed calculation for protein balances.

Moreover, we calculated FWC and EFWC as modified by Kurtz for the days during which serum sodium rose [8, 13]:

$$\begin{aligned}\text{FWC} &= \text{Vol}_{\text{urine}} \times \left[1 - \left(\text{Osmo}_{\text{urine}}/\text{Osmo}_{\text{plasma}}\right)\right] \text{ and EFWC} \\ &= \text{Vol}_{\text{urine}} \times \left[1 - 1.03\left(\text{Na}^{+} + \text{K}^{+}_{\text{urine}}\Big/\left(\text{Na}^{+}_{\text{plasma}} + 23.8 \right.\right.\right. \\ &\quad \left.\left.\left. + \left(1.6/100\right) \times \left(\text{Glucose}_{\text{plasma}} - 120\right)\right)\right)\right].\end{aligned}$$

In order to make our findings more illustrative, we also characterized 10 patients with ICU-acquired hypernatraemia due to sodium gain.

Correlations and paired *t*-tests were computed using Statistica Version 9.1, Statsoft Inc. Tulsa, Oklahoma. Results are presented as counts and percentages and as median, first and third quartile. A P-value <0.05 was considered significant.

Results

Of a total of 981 patients admitted to the ICU during the study period, 69 (7% of all patients) were identified with ICU-acquired hypernatraemia. Of these, seven patients (10% of the hypernatraemic patients) were determined to have hypernatraemia due to osmotic urea diuresis. Patient characteristics are given in Table 1. All patients received enteral nutrition during time of rise in serum sodium and were intubated and sedated. All patients were normonatraemic on admission except for one patient who was hyponatraemic. During ICU stay, serum sodium began to rise to finally reach hypernatraemia. Median duration of rise of serum sodium was 5 days (4–6), mean rise in serum sodium was 12 mmol/L (11–16) and maximum sodium level was 153 mmol/L (151–155). During rise of serum sodium, none of the patients received either furosemide or mannitol. Five patients received hydrocortisone treatment during the rise in serum sodium and six patients received catecholamines. Figure 1 shows the course of serum sodium starting with the day of rise until the maximum sodium concentration.

Table 1. Characteristics of patients with ICU-acquired hypernatraemia due to osmotic urea diuresis

	N
Sex (male/female)	4 (57%)/3 (43%)
Age (years)	61 (SD 12)
SAPSII score on admission	50 (SD 18)
Plasma creatinine on ICU admission (mg/dL)	1.42 (SD 0.6)
ICU length of stay (days)	19 (SD 9)
ICU mortality	29%
Main cause of ICU admission	
Respiratory	3 (43%)
Circulatory	3 (43%)
Gastroenterologic/hepatologic	1 (14%)

During rise of serum sodium, total infused volume was 3948 mL (2753–4918) per day, while total volume output was 2595 mL (1890–3000) per day. Mean central venous pressure was 16 mmH_2O (14–18), not corrected for positive end expiratory pressure. Serum osmolality was 320 mmol/L (317–336) and urine osmolality was 494 mmol/L (454–569). Serum creatinine during rise in serum sodium was 112 μmol/L (93–124) and blood urea nitrogen was 22 mmol/L (16–30). Five patients experienced acute kidney injury during their ICU stay according to the RIFLE criteria (two patients with a rise in serum creatinine ×1.5 and three patients with a rise × 2) [14]. Urea in urine was 369 mmol/L (295–415) and accounted for 71% (60–77) of total osmoles in urine as calculated by the following formula:

$$\left(\text{Urea in urine (mmol/L)}/\text{urine osmolality (mmol/L)}\right) \times 100.$$

Total daily osmole excretion was 1051 mmol (822–1313).

Protein intake during the rise in serum sodium via enteral nutrition was 56 g/day (66–80) and median calculated protein equivalent output was 60 g/day (47–73), resulting in a median protein balance of −10 g/day (−37 to 6). The fractional excretion of sodium was 0.19% (0.12–0.31) and the fractional excretion of urea was 36% (26–47).

During the rise in serum sodium, FWC was negative for all patients and all patient days with a median of −904 mL/day (−1574 to −572), indicating renal water retention. In contrast, EFWC was positive for all patients and all patient days with a mean value of 1419 mL/day (1052–1923), indicating renal water loss. Box plots of FWC versus EFWC during the rise in serum sodium are given in Figure 2. Both, FWC ($R = -0.4$ and $R = -0.4$, $P < 0.05$) as well as EFWC ($R = 0.5$ and $R = 0.8$, $P < 0.05$) correlated positively with total volume loss and urine output in patients. EFWC, but not FWC, significantly correlated with the fraction of urea on total urine osmolality ($R = 0.5$, $P < 0.05$; $R = -0.2$, respectively). Total fluid balances [1415 (107–2427) versus 1091 (−300 to 2096) mL; $P = 0.6$] as well as total urine output [2075 (1653–2763) versus 2475 (1420–3088) mL; $P = 0.2$] did not differ during development of hypernatraemia and times of stable serum

sodium. EFWC during rise in serum sodium was significantly higher than during time of stable serum sodium [1419 [1052–1923) versus 805 (527–1200) mL; $P < 0.01$]. FWC during development of hypernatraemia did not differ from FWC during time of stable serum sodium [−904 (−1574 to −572) versus −987 (−1466 to −525] mL; $P = 0.98$]. Table 2 gives an overview of fluid and electrolyte balances of days of rising serum sodium compared to days with stable serum sodium.

In order to illustrate the pathophysiologic mechanisms leading to hypernatraemia due to osmotic diuresis, we also describe 10 patients with episodes of ICU-acquired hypernatraemia due to sodium gain. Patients with ICU-acquired hypernatraemia mainly due to sodium gain had a similar volume output [1965 mL (1430–2880), $P = 0.44$] compared to patients with osmotic urea diuresis. EFWC was lower with 517 mL (137–778), $P < 0.01$, less urea in urine with 154 mmol/L (108–227), $P < 0.01$, and urea

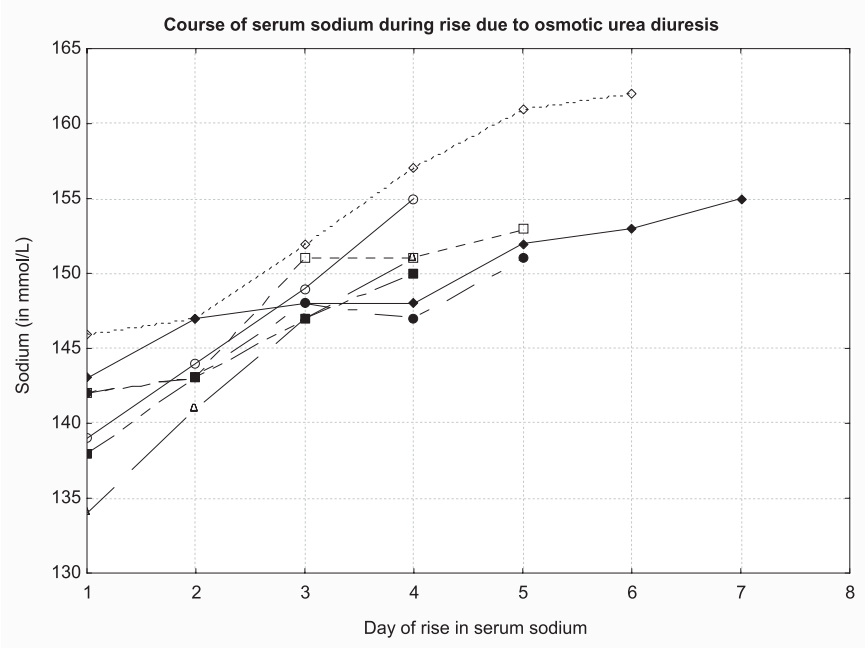

Fig. 1. Rise of serum sodium in seven patients with osmotic urea diuresis.

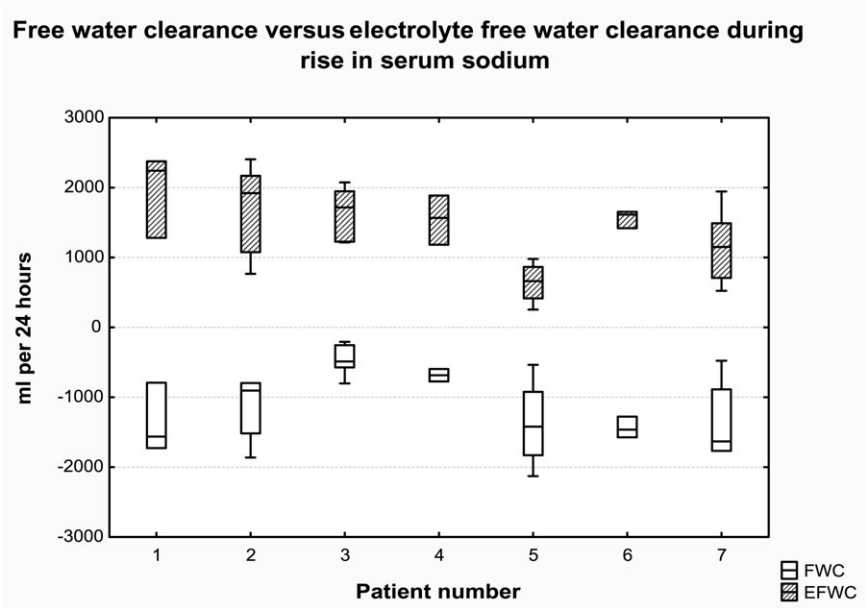

Fig. 2. Box plots of the median FWC versus EFWC calculated while serum sodium was rising to overt hypernataremia.

Table 2. Fluid and electrolyte balances of patients during development of hypernatraemia and during time of stable serum sodium[a]

	Rise of sodium (Q1–Q3)	Stable sodium (Q1–Q3)	P-value
Volume input (mL)	3948 (2753–4918)	3342 (2597–5128)	0.9
Volume output (mL)	2595 (1890–3000)	2480 (1510–3510)	0.4
Urine in 24 h (mL)	2075 (1653–2763)	2475 (1420–3088)	0.2
Volume balance (mL)	1415 (107–2427)	1091 (−300 to 2096)	0.06
Na + K input (mmol)	220 (97–469)	197 (109–339)	0.8
Na + K output (mmol)	146 (89–180)	236 (133–424)	<0.01
Na + K balance (mmol)	50 (−55 to 363)	−65 (−204 to 134)	0.02
FWC (mL)	−904 (−1574 to 572)	−987 (−1466 to 522)	0.9
EFWC (mL)	1419 (1052–1923)	805 (527–1200)	<0.01
Urea in urine (mmol)	369 (295–415)	241 (152–331)	<0.01
Na + K in urine (mmol)	97 (68–156)	188 (130–258)	<0.01
%Urea of osmolality (%)	71 (60–77)	53 (39–66)	<0.01
%Na + K of osmolality (%)	19 (14–27)	43 (25–57)	<0.01

[a]While Na + K stands for sodium and potassium, %urea of osmolality for the fraction of urea on total urine osmolality and %Na + K of osmolality for the fraction of sodium and potassium on total urine osmolality. Values are presented as median and first and third quartiles.

accounted for 37% (28–45) of osmoles in urine, while sodium and potassium was higher with 204 mmol/L (168–227), $P < 0.01$, and sodium and potassium accounted for 57% (39–61) of osmoles in urine.

Discussion

In this study, we characterized a series of patients with ICU-acquired hypernatraemia caused by osmotic urea diuresis. We showed that calculation of FWC as a measure of renal water handling, as often postulated in textbooks and publications [15–17], is misleading in the setting of osmotic urea diuresis. On the contrary, calculation of EFWC explicitly indicated renal loss of free water as the cause of rising serum sodium levels.

The association of tube feeding with hypernatraemia and azotaemia was made early in the literature [18, 19]. However, current studies focusing on the etiology of hypernatraemia in critically ill patients often do not take this important constellation into account [4]. Previous studies could show the association between the occurrence of hypernatraemia in the ICU and an increase in mortality [1, 20–24]. This together with known effects of hypernatraemia on metabolism and cardiac as well as neurologic function should create awareness for rising serum sodium levels [2, 7, 25–27]. When serum sodium begins to rise, a thorough analysis of fluid and electrolyte balance on basis of total infused fluids and nutrition solutions as well as fluid and electrolyte output as measured by urinalysis is indicated.

Urea, given in order to provoke osmotic diuresis, is used as a treatment for hyponatraemia in the syndrome of inappropriate secretion of antidiuretic hormone and was recently described to be complicated by the occurrence of hypernatraemia in some critically ill patients [28–30]. Despite this, osmotic urea diuresis certainly is not the first differential diagnosis in most physicians' minds when confronted with rising serum sodium values. Thus, formulas to assist the physician in making a differential diagnosis of polyuria and rising serum sodium levels are available. FWC has been mentioned in the medical literature for many years as a tool to mark renal water handling [15–17]. However, it is based on the relation of urine osmolality to plasma osmolality and is therefore prone to failure in the setting of osmotic diuresis. In this study, we showed that the calculation of FWC can be misleading in the differential diagnosis of polyuria with rising serum sodium. The Edelman equation [31]

$$\text{Serum } [Na^+]_{serum} = (Na^+ + K^+)_{exchangeable} \Big/ TBW$$

shows that the serum sodium concentration ($[Na^+]_{serum}$ is determined by the relation of total exchangeable sodium and potassium in the body ($[(Na^+ + K^+)_{exchangeable}]$) and the total body water (TBW). Thus, it seems logical that the osmolality-based FWC has no role in the differential diagnosis of sodium disorders.

On the contrary, EFWC, based on the relation of urinary sodium and potassium to serum sodium clearly showed ongoing renal loss of free water in our patients, making it a valuable tool in the differential diagnosis of polyuria and consequently hypernatraemia. Especially in the intensive care setting, where urinalysis and 24 h urine measurement are often performed routinely, the calculation of EFWC under circumstances of rising serum sodium values can be of help in the differential diagnosis of polyuria and hypernatraemia. Additionally, EFWC might help guiding therapy for the correction of hypernatramia. It allows an estimation of how much free water is lost at the moment, which is equal to the minimum amount of free water that has to be given to the patient in order to at least keep the momentary serum sodium. The increasing use of tablet PC's and smartphones allows for rapid bedside calculation of EFWC.

It should also be mentioned that in the ICU losses of electrolyte free water/hypotonic fluids are often substituted by use of isotonic infusions creating a positive sodium balance that ultimately results in a rise of serum sodium. In our patients, the positive fluid balance during rise in

serum sodium is notable since it indicates that a sodium gain contributed to the development of hypernatraemia: Patients lost hypotonic fluid with urine due to the osmotic urea diuresis. At the same time, these losses were replaced by isotonic fluids which in fact were hypertonic compared to the urine thus resulting in a gain of sodium. It might be due to a common fear to create hyponatraemia that hypotonic solutions are only seldom administered in the ICU. However, calculation of EFWC as shown above serves as a guide to find the amount of free water needed to keep the actual serum sodium value at its level. Under normal conditions, the conventional calculation of EFWC as proposed by Rose should be sufficient and is easier to use than the modified formula by Kurtz used in this study [8]:

$$\mathrm{EFWC} = \mathrm{Vol}_{\mathrm{urine}} \times \left[1 - \left(\mathrm{Na}^{+} + \mathrm{K}^{+}_{\mathrm{urine}} / \mathrm{osmo}_{\mathrm{plasma}}\right)\right].$$

In daily clinical practice, when serum sodium starts to rise in a patient who is receiving enteral nutrition (or is in a catabolic state), polyuria combined with a high urea in urine which is exceeding the amount of sodium and potassium in urine should be considered a hint for the presence of osmotic urea diuresis without use of formulas. Under these circumstances, steps should be undertaken to reduce the urea load for the patient or if this is not possible to provide enough free water (e.g. via enteral tube) to avoid a further rise in serum sodium. Nevertheless, calculation of EFWC will rapidly answer the question of whether renal loss of free water is present or not. In any case of rising serum sodium, urine chemistry is necessary to determine the cause.

In our patients, we tried to differentiate whether urea stemmed from enteral nutrition or catabolism, which was difficult since five of the patients experienced acute kidney injury during their ICU stay, making the comparison of actual protein intake by enteral nutrition and the calculated protein equivalent output difficult. Moreover, administration of steroids as often performed in critically ill patients led to an increase in protein catabolism. It should be mentioned that five of the patients fulfilled RIFLE criteria for acute kidney injury. However, the absolute rise in creatinine in these patients makes a significant concentration defect unlikely so this should not be influencing our results.

Our study is limited by its retrospective design and the small patient number. The potentially helpful role of calculation of EFWC in the differential diagnosis of hypernatraemia in critically ill patients should be examined in a prospective study. Fractional excretion of sodium was quite low in our patients potentially indicating volume contraction. On the other hand, central venous pressure was 16 mmH_2O, which at least should rule out more severe hypovolaemia.

In conclusion, we present a series of seven critically ill patients with ICU-acquired hypernatraemia with the often neglected diagnosis of osmotic urea diuresis. We could show that calculation of EFWC identifies ongoing renal loss of free water, while the classic FWC indicates water retention by the kidney. Physicians should be aware of osmotic diuresis due to urea as the cause of polyuria and rising serum sodium values.

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