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Normal saline to dilute parenteral drugs and to keep catheters open is a major and preventable source of hypernatremia acquired in the intensive care unit☆

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ABSTRACT

Purpose: We wanted to identify modifiable risk factors for intensive care unit (ICU)–acquired hypernatremia.
Materials and Methods: We retrospectively studied sodium and fluid loads and balances up to 7 days prior to the development of hypernatremia (first serum sodium concentration, [Na^+], >150 mmol/L; H) vs control (maximum [Na^+] ≤150 mmol/L; N), in consecutive patients admitted into the ICU with a normal serum sodium (<145 mmol/L) and without cerebral disease, within a period of 8 months.
Results: There were 57 H and 150 N patients. Severity of disease and organ failure was greater, and length of stay and mechanical ventilation in the ICU were longer in H ($P < .001$), with a mortality rate of 28% vs 16% in N ($P = .002$). Sodium input was higher in H than in N, particularly from 0.9% saline to dissolve drugs for infusion and to keep catheters open during the week prior to the first day of hypernatremia ($P < .001$). Fluid balances were positive and did not differ from N on most days in the presence of slightly higher plasma creatinine and more frequent administration of furosemide, at higher doses, in H than in N.
Conclusions: High sodium input by 0.9% saline used to dilute drugs and keep catheters open is a modifiable risk factor for ICU-acquired H. Dissolving drugs in dextrose 5% may partially prevent potentially harmful sodium overloading and H.

1. Introduction

Hypernatremia (ie, serum sodium, [Na^+], >145-150 mmol/L) commonly occurs in the intensive care unit (ICU); it is a risk factor, among others, for delirium, prolonged lengths of stay, and increased mortality [1-18]. Hypernatremia in the ICU is most commonly caused by a positive Na^+ balance exceeding fluid balance. This imbalance results from the frequent need for extensive (Na^+-containing) infusion therapy mismatched to fluid balance, after sedation and impaired intake, impaired renal concentration, use of diuretics and resultant sodium-poor urinary output, or combinations [1-3,5,11,14-16,19-21]. Infusion therapy includes the 0.9% saline for dilution of parenterally administered drugs and to keep lumens of intravenous catheters open. Recently, Bihari et al [22] was the first to report that this may account for about 22% of the total load of Na^+ administered in 20 ICU patients, similar to the 22% originating from resuscitation and maintenance fluids. Indeed, diluting parenteral drugs in 0.9% saline and its use to keep catheters open may be modifiable risk factors for hypernatremia because dextrose 5% in water can be used to dissolve many drugs and to keep catheters open thereby partly circumventing Na^+ overloading.

Accordingly, we studied the sources of Na^+ loading, fluid balance, renal function, and diuretic use to explain the occurrence of hypernatremia ([Na^+] >150 mmol/L) and to identify modifiable risk factors in the ICU. We hypothesized that Na^+ overloading via 0.9% saline to dilute parenterally administered drugs and in drips to keep catheters open is a major factor contributing to ICU-acquired hypernatremia.

2. Patients and methods

Consecutive patients in the ICU of the VU University Medical Center, Amsterdam, staying more than 48 hours with normonatremia ([Na^+] <145 mmol/L) at ICU admission were included for this retrospective study from December 2010 to July 2011. According to Dutch law, informed consent is not required provided that data are treated anonymously. The unit has about 32 operational beds and is a mixed surgical and medical facility also offering postoperative care for neurosurgical and cardiosurgical patients. About 1500 patients are admitted annually and taken care of by full-time intensivists, ordering

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fluids and drugs, according to treatment guidelines in use in the department. Exclusion criteria were prior use of lithium, known chronic renal disease and renal replacement therapy, diabetes insipidus, recent intracranial catastrophe (stroke, bleeding, trauma), and known diseases of the hypothalamic-pituitary-adrenal axis. Data were collected according to a predefined case record from the patient data management system in use in the department, which is connected to the central laboratory.

We collected demographic data, the Acute Physiology and Chronic Health Evaluation score, the Sequential Organ Failure Assessment score, reasons and types of admission, length of stay in the ICU, and duration of mechanical ventilation. Outcome was defined by death in or discharge from the ICU. All sources of Na^+ and fluids via intravenous and enteral routes, such as total parenteral nutrition and 0.9% saline, to dilute drugs and keep catheters open (at 3 mL/h), as well as fluid balances and diuretics used were recorded daily in the patient data management system and collected for this study. Resuscitation fluids include 0.9% saline, gelatins, and other colloids (with $[Na^+]$ of 154 mmol/L). Table 1 contains the top 20 drugs administered at our ICU as well as their potential compatibility with dilution in dextrose 5% in water instead of 0.9% saline. The Na^+ load administered per day was expressed in mmol. We collected plasma $[Na^+]$, which is routinely and daily measured in our ICU and recorded in the patient data management system. This is measured in our unit either in plasma in the central laboratory with an indirect ion selective electrode method (in 90%, using Modular P800; Roche, Basel, Switzerland) or by a direct ion selective electrode method in whole blood using STAT blood gas analyzers (ABL800 FLEX; Radiometer, Copenhagen, Denmark) in the ICU. These systems are calibrated against each other by laboratory personnel. The indirect method of serum $[Na^+]$ measurement generates a slightly lower $[Na^+]$ than in whole blood because blood plasma consists of 93% water and samples are diluted [24,25]. When the water phase of plasma is substantially lowered by an increase in solid substances by hyperlipidemia or hyperproteinemia, for example, the direct method with the blood gas analyzer is used. If [Na+] >150 mmol/L on at least 1 ICU day, the patient was regarded as having hypernatremia (H), so that patients with a lower level were considered normonatremic (N). For H, T0 was defined as the day with the first measured $[Na^+]$ greater than 150 mmol/L. T0 for N patients was defined as the day with the highest $[Na^+]$ (≤150 mmol/L) obtained during admission. If more than 1 $[Na^+]$ per day was available, the highest value was taken. Serum creatinine was measured routinely and daily by a Hitachi Modular P800 (Roche Diagnostics, Mannheim, Germany; n 60-110 μmol/L). All data were collected from 7 days (T7) on prior to T0, in all H and N patients when staying in the ICU.

2.1. Statistical analysis

Data were mostly distributed nonnormally (Kolmogorov-Smirnov test, $P < .05$). Variables in study groups H and N were compared with help of the Mann-Whitney *U* test for continuous data and the Fisher exact test for categorical data. Continuous data are reported as median with interquartile ranges. All tests were 2 sided; a $P < .05$ was considered statistically significant; exact *P* values are given unless less than .001.

Table 1
Top 20 administered drugs

1. Fentanyl	11. Vancomycin
2. Norepinephrine	12. Potassium chloride
3. Propofol	13. Flucloxacillin
4. Midazolam	14. Amphotericin
5. Amiodarone	15. Haloperidol
6. Nicardipine	16. Epinephrine
7. Hydrocortisone	17. Imipenem
8. Calcium glubionate	18. Cefotaxim
9. Clonidine[a]	19. Metronidazole[a]
10. Pantoprazole	20. Acyclovir

[a] Not compatible with dextrose 5% in water.

Table 2
Patient characteristics

	Hypernatremia (n = 57)	Normonatremia (n = 150)	*P*
Age (y)	64.0 (18.0)	64.0 (18.0)	.40
Female, n	21 (37)	62 (41)	.64
APACHE II	25.0 (12.0)	21.0 (10.0)	.02
SOFA	10.0 (5.0)	7.0 (3.0)	<.001
Reason of admission, n			
Postoperative	12 (21)	51 (34)	.09
Respiratory insufficiency	18 (32)	35 (23)	.28
After CPR	9 (16)	32 (21)	.44
Infection/Sepsis	5 (9)	14 (9)	1.00
Shock			
Myocardial infarction	3 (5)	2 (1)	.13
Sepsis	1 (2)	1 (1)	.48
Other	–	1 (1)	–
Liver insufficiency	1 (2)	–	–
Cerebral crisis	1 (2)	–	–
Drug intoxication	–	2 (1)	–
Other	7 (12)	12 (8)	.42
Type of admission			
Elective surgery	17 (30)	47 (31)	.87
Emergency surgery	4 (7)	26 (17)	.08
Other	36 (63)	77 (51)	.16
Outcomes			
Length of stay (d)	14 (17)	6 (6)	<.001
Mechanical ventilation (d)	13 (17)	4 (5)	<.001
ICU mortality	16 (28)	16 (11)	.002

Median (interquartile range) or number (percentage), where appropriate. APACHE indicates Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; CPR, Cardiopulmonary Resuscitation; ICU, Intensive Care Unit.

3. Results

3.1. Patients

The inclusion and exclusion criteria have led to a study population of 207 during study period. Patient characteristics are reported in Table 2; H occurred in 27% of patients, on 1 or more days in the ICU. H patients were sicker than N patients. The duration of mechanical ventilation and length of stay in the ICU were longer in H patients, with a higher mortality rate. There were no differences between H and

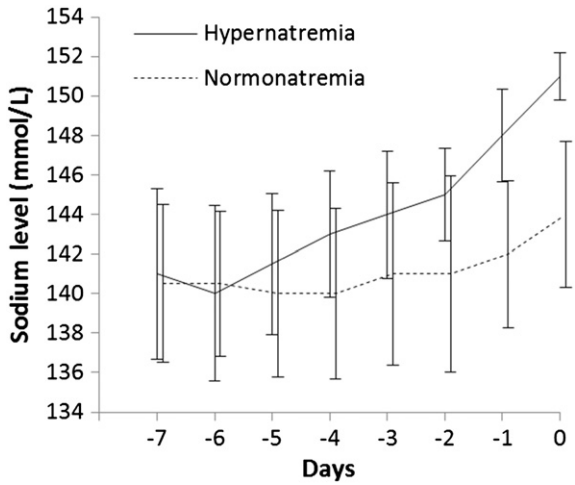

Fig. 1. Plasma $[Na^+]$ (median, interquartile range) in hypernatremia and normonatremia (T7, $P = .30$; T6, $P = .43$; T5, $P = .06$; and T4 until T0, $P = .001$ or lower).