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Original Article

Prediction of plasma sodium changes in the acutely ill patients: the potential role of tissue sodium content

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ABSTRACT

Background: Rapid correction of dysnatremias can result in neurological complications. Therefore, various formulas are available to predict changes in plasma sodium concentration ([Na^+]) after treatment, but these have been shown to be inaccurate. This could be explained by sodium acumulation in skin and muscle tissue, which is not explicitly considered in these formulas. We assessed the association between clinical and biochemical factors related to tissue sodium accumulation and the discrepancy between predicted and measured plasma [Na^+].
Methods: We used data from an intensive care unit (ICU) cohort with complete data on sodium, potassium, and water balance. The predicted plasma [Na^+] was calculated using the Barsoum-Levine (BL) and the Nguyen-Kurtz (NK) formula. We calculated the discrepancy between predicted and measured plasma sodium and fitted a linear mixed-effect model to investigate its association with factors related to tissue sodium accumulation.
Results: We included 594 ICU days of sixty-three patients in our analysis. The mean plasma [Na^+] at baseline was 147±6 mmol/L. The median (IQR) discrepancy between predicted and measured plasma [Na^+] was 3.14 mmol/L (1.48, 5.55) and 3.53 mmol/L (1.81, 6.44) for the BL and NK formulas, respectively. For both formulas, estimated total body water ($p=0.027$), initial plasma [Na^+] ($p<0.001$) and plasma [Na^+] change ($p<0.001$) were associated with the discrepancy between predicted and measured plasma [Na^+].
Conclusion: In this ICU cohort, initial plasma [Na^+], total body water, and plasma [Na^+] changes, all factors that are related to tissue sodium accumulation, were associated with the inaccurateness of plasma [Na^+] prediction.

1. Introduction

Dysnatremias, disorders of plasma sodium concentration ([Na^+]), are frequently encountered in daily clinical practice and pose a diagnostic and therapeutic challenge for many clinicians[1]. Rapid correction of dysnatremias is a major concern during treatment, as this might be accompanied by neurological complications such as central pontine myelinolysis in the case of hyponatremia and cerebral oedema in hypernatremic patients[2,3]. These complications are mainly a concern when plasma [Na^+] alterations exceed eight mmol/L within 24 hours. Therefore, it is crucial that physicians can predict the effect of infusion strategies on plasma [Na^+]. For this purpose, various formulas, such as the Barsoum-Levine and Adrogué-Madias equations, have been developed. These formulas are based on experiments performed by Edelman et al. more than 60 years ago, who correlated plasma [Na^+] to exchangeable sodium, exchangeable potassium and total body water in patients with varying plasma [Na^+][4].

Unfortunately, the formulas currently available to predict plasma [Na^+] changes are not accurate [1,5,6]. Previous studies demonstrated that the mean discrepancy between predicted and measured plasma [Na^+] was 6.7 mmol/L within 24 hours in patients with hypernatremia [1]. A potential explanation for this discrepancy is the recently discovered 'third tissue compartment' for sodium accumulation, which is not explicitly taken into account in these formulas and has been shown to

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interfere with osmoregulation in hypernatremic patients [7]. It has been suggested that the Nguyen-Kurtz formula, which incorporates the y-intercept and slope of the Edelman equation into their formula, partly accounts for the non-exchangeable sodium in the skin, muscle, cartilage, and bone [8].

Intervention studies have demonstrated that tissue sodium accumulation is a dynamic process which is affected by the infusion of hypotonic and hypertonic solutions [9-11]. Because the original Edelman study only assessed differences among subjects instead of intra-individual changes following treatment, the dynamics of tissue sodium accumulation and release are not incorporated into their formula. Therefore, this study aims to evaluate which clinical and biochemical factors related to tissue sodium accumulation are associated with the discrepancy between predicted and measured plasma [Na^+] after treatment of dysnatremias.

2. Method

We used data from a hypernatremic intensive care unit (ICU) cohort consisting of 66 patients [1]. The total daily input and output of fluid and electrolytes were meticulously recorded for all patients during their entire ICU stay, and plasma and urine sodium, potassium and osmolality were measured. We excluded ICU days with incomplete fluid and electrolyte balances, such as ICU admission days and days with dialysis or severe diarrhoea.

We used the Barsoum-Levine (BL) and the Nguyen-Kurtz (NK) formula to predict the plasma [Na^+] at the end of a 24-hour balance period. For the fluid balance, we accounted for a variable amount of insensible water loss via skin and respiratory system using a frequently used formula taking into account body temperature and intubation status [12]. In a sensitivity analysis, we recalculated our data without insensible water loss and with a fixed amount of 800 ml/day insensible water loss [13]. We calculated the discrepancy between predicted plasma [Na^+] and measured plasma [Na^+] for both formulas.

2.1. Variables of interest

We selected patient characteristics that have been associated with tissue sodium accumulation, including age, sex, total body water (TBW), hypertension, inflammation, infection, kidney disease and hypernatremia [7,14-20]. TBW was estimated to be 60% of the body weight for males and 50% for females, corrected for fluid balances on subsequent ICU days.

In our model, we included the initial plasma [Na^+] at the start of the 24-hour period, as we previously demonstrated that the Edelman equation was different for hypo- and hypernatremic subjects [21]. Because the tissue sodium compartment has shown to respond differently to increasing (i.e. sodium accumulation) and decreasing plasma [Na^+] (i.e. sodium release), we included the change in plasma [Na^+] as a covariate and we investigated the interaction between initial plasma [Na^+] and the change in plasma [Na^+] [9-11]. Additionally, we compared subgroups of sex, eGFR ($<$ and $\geq$60 ml/min/1.73m^2), initial plasma [Na^+] ($\leq$ or $>$140 mmol/L) and plasma [Na^+] change ($>$2 mmol/L increase, $>$2 mmol/L decrease or stable).

2.2. Statistical analysis

Baseline characteristics and laboratory results are expressed as mean plus standard deviation (SD) for variables with a normal distribution and median plus interquartile range for variables with a non-normal distribution.

We fitted a linear mixed-effect model to investigate the association between the discrepancy between predicted and measured plasma [Na^+] and the variables age, sex, mean arterial blood pressure (MAP), eGFR CKD-EPI 2021, C-reactive protein (CRP), albumin, TBW, initial plasma [Na^+], change in plasma [Na^+] and the interaction between initial plasma [Na^+] and change in plasma [Na^+]. These variables were incorporated as fixed effects in the model, whereas the subjects were introduced as a random effect. All analyses were performed using R version 4.3.2 using the "ggeffects", "nlme", "gtsummary", "ggplot2" and "tidyverse" packages.

3. Results

3.1. Study population

The original cohort consisted of 66 ICU patients, which constituted a total of 1034 ICU days [1]. Our analysis included 594 ICU days for 63 patients (Supplemental Fig. 1). At admission, the mean age was 59 years, two-thirds of the subjects were male, the mean eGFR was 52±29 ml/min/1.73m^2, and the mean plasma [Na^+] was 145±9 mmol/L. The average ICU stay was 15±5 days (Table 1).

In this cohort, 527 of the ICU days corresponded to a plasma [Na^+] $>$140 mmol/L, while 67 days had a plasma [Na^+] $\leq$140 mmol/L (Supplemental Table 1). Compared to the previous day, plasma [Na^+] remained stable on 254 ICU days, increased on 174 days, and decreased on 166 days.

The median Na^++K^+ input was 217 mmol/day (IQR 114, 411), whereas the median daily Na^++K^+ output was 224 mmol (IQR 126, 371). The median volume administered via infusion and through enteral/ parental solutions within 24 hours was 3.5L (IQR 2.6, 4.8). The median 24-hour volume excreted via urine and drains was 2.7L (IQR 2.1, 3.8).

3.2. Formulas to predict plasma [Na^+]

The BL formula accurately assessed alterations in plasma [Na^+] within a 2 mmol/L range in 30.5% of the cases (median discrepancy 1.00 mmol/L (IQR 0.44, 1.43)), an underestimated and overestimated plasma [Na^+] in 52.2% and 17.3% of the cases, respectively. In the underestimation group, the median discrepancy was 4.34 mmol/L (2.93, 6.88), whereas the overestimation group had a median discrepancy of 4.12 mmol/L (3.13, 7.43). For the NK formula, we observed similar data with 27.1% of the changes in plasma [Na^+] being accurately predicted within a 2 mmol/L margin (median 0.95 mmol/L (0.43, 1.44)), whereas 56.1%

Table 1
Clinical characteristics of the study population at inclusion

	N = 63, 594 ICU days
Male sex, no. (%)	41 (65%)
Age (years)	59 ± 15
Height (cm)	171 ± 11
Weight (kg)	84 ± 22
Mean ICU days analysed (days)	15 ± 5
Mean plasma [Na^+] at baseline (mmol/L)	145 ± 9
Plasma [Na^+] at baseline, no. (%)	
Plasma ≤140 mmol/L	16 (25%)
Plasma >140 mmol/L	47 (75%)
eGFR CKD-EPI (ml/min/1.73m^2)	53 ± 29
Syst. BP (mmHg)	117 ± 30
Diast. BP (mmHg)	58 ± 12
MAP (mmHg)	78 ± 17
Reason for admission, no. (%)	
Respiratory	20 (31.7)
Neurologic	5 (7.9)
Gastroenterological+ hepatological	10 (15.9)
Cardiologic	25 (39.7)
Nephrological	3 (4.8)

Categorical data are presented as n (%), and continuous data are presented as mean ± SD unless stated otherwise. CRP: C-reactive protein, Diast. BP: Diastolic blood pressure, eGFR: estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration, MAP: mean arterial pressure, Plasma [Na^+]: measured plasma sodium concentration, Syst. BP: Systolic blood pressure, TBW: total body water.

was underestimated (5.08 mmol/L (3.35, 7.47) and 16.8% was overestimated (4.01 mmol/L (2.95, 7.60)). After correction for insensible water loss, the overall median absolute discrepancy was 3.14 mmol/L (IQR 1.48, 5.55) for the BL formula and 3.53 mmol/L (IQR 1.81, 6.44) for the NK formula (Supplemental Table 2).

3.3. Factors associated with the discrepancy between predicted and measured plasma [Na^+]

TBW, initial plasma [Na^+], change in plasma [Na^+], and the interaction term for initial plasma [Na^+] and change in plasma [Na^+] were significantly associated with the discrepancy between predicted and measured plasma [Na^+] when the BL formula or NK formula were used to predict plasma [Na^+] (Table 2). eGFR was only a significant contributing variable for the BL formula.

These associations remained significant when we did not correct for insensible water loss. When incorporating a fixed amount of insensible water loss for all subjects, TBW was not significantly associated with the discrepancy between predicted and measured plasma [Na^+] in the BL formula model (p=0.11).

3.4. Subgroup analysis

Blood pressure and TBW were higher in the subset of ICU days on which plasma [Na^+] was >140 mmol/L versus ICU days with a plasma [Na^+] of ≤140 mmol/L. In contrast, eGFR and CRP were significantly lower on ICU days with a plasma [Na^+] >140 mmol/L. The absolute discrepancy between predicted and measured plasma [Na^+] was also significantly higher on the ICU days with a plasma [Na^+] under 140 mmol/L (p=0.002) (Supplemental Table 1). When plasma [Na^+] was >140 mmol/L, TBW (p=0.032) and the plasma [Na^+] change (p<0.001) were significantly associated with the discrepancy between predicted and measured plasma [Na^+] (Supplemental Table 3). The number of observations with a plasma [Na^+] ≤140 mmol/L was too small for a separate analysis (n=67).

The observed direction of plasma [Na^+] change greatly influenced the discrepancy between predicted and measured plasma [Na^+] and the variables associated with this discrepancy (Fig. 1, Supplemental Table 4).

The distribution of the discrepancy between predicted and measured plasma [Na^+] for the BL and NK formula is displayed in supplemental Fig. 2.

On the ICU days with a stable (p=0.016) or a decreasing plasma [Na^+] (p=0.003), we found a significant association for initial plasma [Na^+]. In contrast, no associations were found on days with an increasing plasma [Na^+] (Supplemental Table 4).

Table 2
Association between the discrepancy between predicted and measured plasma [Na^+] and factors related to tissue sodium content

	Barsoum-Levine formula N=587			Nguyen-Kurtz formula N=587		
Fixed effects	Value	SE	p	Value	SE	p
(intercept)	24.97	5.60	<0.001	20.14	6.07	0.001
Age	-0.02	0.02	0.47	-0.01	0.02	0.70
Sex	0.74	0.71	0.30	0.59	0.73	0.43
MAP	-0.02	0.01	0.19	-0.01	0.01	0.39
eGFR	-0.02	0.01	0.012	-0.01	0.01	0.12
C-reactive protein	-0.03	0.02	0.17	-0.04	0.02	0.08
Total body water	0.04	0.02	0.027	0.06	0.02	0.004
Initial plasma [Na^+]	-0.18	0.04	<0.001	-0.17	0.04	<0.001
Change in plasma [Na^+]	-2.84	0.59	<0.001	-3.05	0.65	<0.001
Plasma albumin concentration	0.04	0.05	0.51	0.10	0.06	0.10
Initial plasma [Na^+] * Change in plasma [Na^+]	0.02	0.00	<0.001	0.02	0.00	<0.001

CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, MAP: mean arterial pressure, TBW: total body water. SE, standard error; N, number of ICU observations with complete data on all variables used in the model

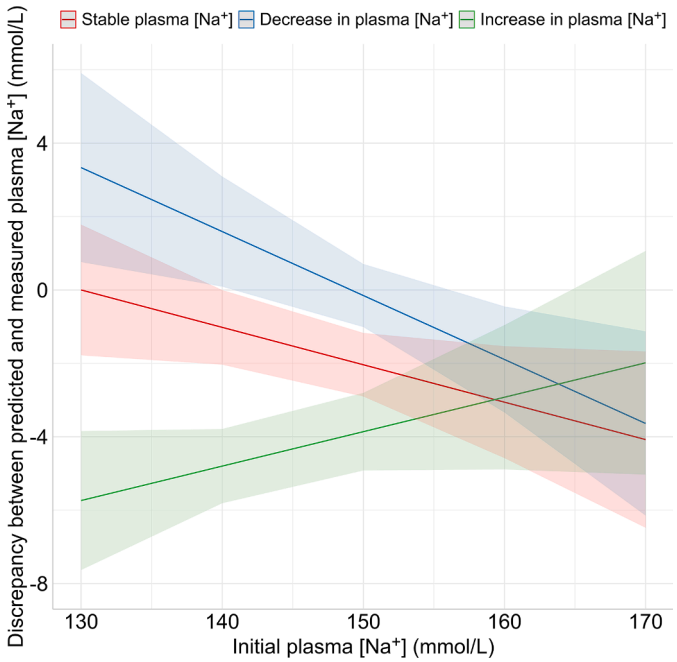

Fig. 1. Inaccuratenes when predicting plasma [Na^+]. The association between the discrepancy between predicted and measured plasma [Na^+] plotted against the two most important explanatory values: initial plasma [Na^+] and change in plasma [Na^+] following treatment. The red line represents the ICU observations during which plasma [Na^+] remained stable compared to the previous day, the blue line represents the ICU observations on which the plasma [Na^+] decreased ≥2 mmol/L, and the green line represents the ICU days on which the plasma [Na^+] increased ≥2 mmol/L. The shaded margin area represents the 95% confidence interval for each group.

The median discrepancy between predicted and measured plasma [Na^+] was higher in those with reduced eGFR (≤59 ml/min/m^2) compared to those with normal kidney function (>60 ml/min/1.73m^2; 3.41 mmol/L (1.63, 6.27) versus 2.91 mmol/L (1.39, 5.14), p=0.029). In patients with normal kidney function, plasma [Na^+] change and the interaction term between initial plasma [Na^+] and change in plasma [Na^+] were significantly associated with the discrepancy between predicted and measured plasma [Na^+]. In patients with reduced kidney function, we found significant associations between TBW, initial plasma [Na^+], change in plasma [Na^+], and the interaction term (Supplemental Table 5).

The median discrepancy between predicted and measured plasma [Na^+] was similar among both sexes (3.46 mmol/L (1.72, 5.99) versus 2.91 mmol/L (1.38, 5.19), p=0.19). In males, kidney function, TBW, initial plasma [Na^+] and change in plasma [Na^+] were associated with the discrepancy between predicted and measured plasma [Na^+], whereas in females, initial plasma [Na^+], change in plasma [Na^+] and the interaction between initial plasma [Na^+] and change in plasma [Na^+] were associated with the discrepancy (Supplemental Table 6).

4. Discussion

In this post-hoc analysis of ICU patients, we demonstrated that patient characteristics linked to tissue sodium accumulation are associated with the inaccurateness of plasma [Na^+] prediction. In particular, TBW, baseline plasma [Na^+] and the plasma [Na^+] change were consistently associated with the discrepancy between predicted and measured plasma [Na^+].

The Barsoum-Levine and the Nguyen-Kurtz formulas both

incorporate the fluid and cation balance. The Nguyen-Kurtz formula also takes the slope and intercept of the original Edelman equation into account. By doing so, it has been suggested to partially correct for tissue sodium accumulation [8]. The results of both formulas were very similar, except for eGFR, which was associated with the inaccurateness of the BL formula. We also found different explanatory variables for subgroups based on eGFR, suggesting that kidney function should be taken into account in future studies. The use of creatinine measurements to estimate kidney function in ICU patients is a limitation of this analysis [22,23].

We found that the initial plasma [Na^+] was associated with the discrepancy between predicted and measured plasma [Na^+]. This is in line with a previous study that demonstrated that the relation between exchangeable cations and TBW is different below and above a plasma [Na^+] of 133 mmol/L [21].

We observed that the direction of plasma [Na^+] change modulates the relationship between initial plasma [Na^+] and the discrepancy between predicted and measured plasma [Na^+], suggesting that the pathophysiology of an increase and decrease in plasma [Na^+] is different. This may be explained by sodium accumulation in tissues during periods with sodium excess or water shortage and sodium release from this compartment when total body sodium content is low or water is present in excess. This hypothesis is supported by a case report demonstrating high tissue sodium content during hypernatremia and normalization of tissue sodium content after infusion of hypotonic solutions [7]. In addition, two intervention studies in healthy volunteers demonstrated that sodium could disappear into a third compartment after hypertonic saline infusion and appear after drinking large amounts of water [9,10].

Our finding that TBW is associated with the inaccuracy of plasma [Na^+] prediction is consistent with a previous study demonstrating that body weight and oedema are modulators of the Edelman equation [21]. Additionally, a ^{23}Na-MRI study demonstrated that body weight, body mass index and total body overhydration were all associated with tissue sodium content [24].

We found that different patient characteristics explained the inaccuracy in males and females. This is in accordance with previous studies showing that males accumulate sodium mainly under their skin, whereas females accumulate most sodium in muscle tissue [25-27].

We found no association between age, blood pressure, plasma albumin, CRP and the discrepancy between predicted and measured plasma [Na^+]. This could be explained by our ICU population with often low blood pressure compared to the hypertensive subjects previously studied [16]. Similarly, CRP has been associated with tissue sodium content in various patient groups with chronic inflammation, whereas in our cohort, CRP was mainly driven by infection [28].

By using longitudinal data on plasma [Na^+] changes in ICU patients in one of the largest databases available, we were able to investigate both inter- and intra-individual factors that affect the prediction of plasma [Na^+] changes. We lacked data on faecal fluid and cation loss and measured TBW.

In conclusion, our post-hoc analysis suggests that the release and storage of sodium from tissue stores might contribute to the inaccuracy of plasma [Na^+] prediction in acutely ill patients. Future studies investigating the pathophysiology of hypo- and hypernatremia should include measurements of tissue sodium content. Such studies could improve the existing formulas for plasma [Na^+] prediction.

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Declaration of competing interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.07.032.

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