Interpretation of the Fractional Excretion of Sodium in the Absence of Acute Kidney Injury: A Cross-Sectional Study

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Keywords

Fractional excretion of sodium · Glomerular filtration rate · Sodium excretion · Renal tubular function

Abstract

Background/Aims: The fractional excretion of sodium (FeNa) may be helpful in establishing the cause of acute renal failure. This study was performed to determine the influence of the glomerular filtration rate (GFR), sodium intake, and tubular function on FeNa in children without renal failure. **Methods:** In this single institute cross-sectional study, 24-h-urine collections from patients (4–18 years of age, GFR >60 mL/min/1.73 m²) were used when considered reliable, and analyzed to determine sodium excretion, creatinine clearance and FeNa. The influence of tubular function was studied in 5 patients with generalized tubular dysfunction. **Results:** Based on data from 761 patients, a multiple regression formula was designed based on GFR and sodium excretion that predicted over 80% of the variation in FeNa ($R^2 = 0.824$, $p < 0.001$). Using this formula, the predicted FeNa was significantly lower than the measured FeNa in the children with tubular dysfunction. **Conclusion:** FeNa depends on GFR and sodium intake, and tubular function cannot be assessed

without possessing adequate knowledge on all factors. Therefore, no normal range or cut-off value for FeNa to assess tubular function can be given, and doing so is a misapplication of this equation.

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Introduction

The fractional excretion of sodium (FeNa) has been reported to be of value in determining the cause of acute kidney injury (AKI) [1, 2]. Nguyen et al. [3] described misapplications of commonly used kidney equations including FeNa and focused on the application and caveats of FeNa during AKI. In the absence of AKI, FeNa has been described to be influenced by daily sodium intake [4] and the glomerular filtration rate (GFR) [5].

It is unresolved whether FeNa can provide additional information, for instance, on tubular function, and which factors limit its use. Several papers have been published that describe FeNa as a marker of proximal tubular function without considering GFR or sodium intake [6, 7]. It may, however, be argued that as long as a nor-

mal serum level of sodium is maintained, renal sodium handling is functioning properly regardless of the level of FeNa.

In order to study the possible misapplication of FeNa, we addressed the function and interpretation of FeNa in the absence of AKI and determined the influence of GFR, sodium intake, and tubular (dys)function on FeNa, by analyzing 24-h-urine data from a cohort of children from our out-patient clinics.

Subjects and Methods

To study the influence of sodium excretion, as a marker of dietary sodium intake, and GFR (measured by 24 h urine creatinine clearance) on FeNa, we performed a cross-sectional study and analyzed the results of 24-h-urine collections from the database of the Department of Pediatric Nephrology of the VU University Medical Center that were collected from our out-patient clinics between 2002 and 2008.

A single 24-h-urine collection per patient was used when considered reliable. We considered the urine collection reliable when both the nurse and the parents considered it to be reliable and without any missing portions. Also, strict criteria had to be met, based on the age of the patient (over 4 years), the collection period (between 20 and 28 h), urinary creatinine excretion (between 88 and 265 μmol/kg/24 h [8]) and urine volume (between 300 and 2,000 mL/m²/24 h). Patients with documented diuretic use were excluded. Using this strict selection, a total of 761 out of 1,953 patients were selected, and the first reliable 24 h urine collections from these patients were used to calculate 24 h sodium excretion, cCreat and FeNa, using formula 1:

FeNa (%) = (Na_{urine} (mmol/L) × Creat_{serum} (μmol/L) / (Na_{serum} (mmol/L) × Creat_{urine} (mmol/L) × 1,000)) × 100% (1)

This formula helps in the calculation of FeNa using random but simultaneous blood and urine measurements without the necessity of urine collections. However, the rationale behind formula 1 is based on:

FeNa (%) = (Na_{24 h-excretion} / Na_{24 h-filtration}) × 100% (2a)

FeNa (%) = (Na_{24h-excretion} (mmol/day) / (Na_{serum} (mmol/L) × GFR (mL/min/1.73 m²) × 1.44 (×1,000 min/day) × BSA (m²)/1.73)) × 100% (2b)

Formula 2 shows that FeNa is expected to depend on both GFR and sodium excretion and thereby sodium intake. As a rule, GFR is corrected for body surface area (BSA) in pediatrics, but the amount of filtered sodium depends on the product of serum sodium and absolute or uncorrected GFR (hence, the factor [BSA/1.73] in formula 2b).

On the basis of predetermined cut-off levels of urinary sodium excretion, 4 groups were formed: group A with a sodium excretion of less than 50 mmol/day (<~3 g salt/day), group B with a sodium

Table 1. Demographic data

Number	761
Male, %	48.6
Age, years	9.32 (3.77)
Body surface area, m ²	1.12 (0.34)
Creatinine clearance, mL/min/1.73 m ²	99.1 (22.7)
Uncorrected creatinine clearance, mL/min	65.3 (27.9)
Serum sodium, mmol/L	139 (4.3)
FeNa, %	0.76 (0.45)
FeNa ≥1%, %	18.9
Sodium excretion, mmol/day	96.8 (70.0)

Data are presented as number, percentage, or mean (SD). FeNa, fractional excretion of sodium.

excretion of 50–100 mmol/day (~3–6 g salt/day), group C with a sodium excretion of 100–150 mmol/day (~6–9 g salt/day), and group D with a sodium excretion of over 150 mmol/day (>~9 g salt/day). Per group of sodium excretion, regression on the association between cCreat and FeNa was performed.

Creatinine was measured using the Jaffe method and sodium was measured using an ion selective electrode.

Statistical Analysis

Data is presented as mean (SD). Univariate linear regression and stepwise multiple regression were performed (probability of F to enter ≤0.050, probability of F to remove ≥0.10), and the regression coefficients are presented with R². Patients with missing data were excluded per analysis. SPSS version 11.0.1 (Windows, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A p value of <0.05 was considered to be statistically significant.

Results

Patient characteristics and results from the urine collections are presented in Table 1. Figure 1 shows the association between uncorrected cCreat and FeNa for the 4 categories of sodium intake. As can be seen in Table 2, for all four categories of sodium intake, a highly significant association was present between cCreat and FeNa with cCreat explaining 48–85% of the variation in FeNa. However, for each category of sodium intake, the numerical relation with cCreat is different and analysis of cCreat was not significantly related to FeNa (r² = 0.029) in a univariate model not taking urinary sodium excretion into account.

Performing univariate linear regression with the factors age (R² = 0.001, p = 0.47), weight (R² = 0.002, p = 0.18), height (R² = 0.002, p = 0.21), BSA (R² = 0.002, p = 0.20), uncorrected cCreat (R² = 0.017, p < 0.001), and so

Table 2. Regression analysis between uncorrected creatinine clearance (cCreat) and fractional excretion of sodium (FeNa) per category of sodium intake

Urinary sodium excretion, mmol/day	N	Regression formula	R ²	p value
0–50	137	FeNa = 1.00 – (0.016 * cCreat) + (0.000073 * cCreat ²)	0.485	<0.001
50–100	338	FeNa = 1.55 – (0.020 * cCreat) + (0.000085 * cCreat ²)	0.486	<0.001
100–150	183	FeNa = 2.37 – (0.029 * cCreat) + (0.00011 * cCreat ²)	0.855	<0.001
>150	102	FeNa = 4.46 – (0.056 * cCreat) + (0.00020 * cCreat ²)	0.478	<0.001
All	760	FeNa = 0.98 – (0.0044 * cCreat) + (0.000012 * cCreat ²)	0.029	ns

ns, not significant.

Table 3. Renal functional data of children with generalized tubular dysfunction

Urinary sodium excretion	Patient A*	Patient B	Patient C	Patient D	Patient E	Mean (SD)
Gender	Female	Male	Male	Male	Male	
Age, years	0.45	16.3	13.1	7.3	8.2	9.1 (6.1)
Diagnosis	Mito	TIN	TIN	Mito	NPH	
Creatinine clearance, mL/min/1.73 m ²	30.4	23.1	9.7	33.9	60.5	31.5 (18.7)
Uncorrected creatinine clearance, mL/min	5.1	23.0	8.2	15.0	23.4	14.9 (8.4)
FeNa, %	2.5	1.7	9.4	7.2	6.2	5.4 (3.2)
Estimated FeNa, %	0.9	1.0	1.8	2.0	2.5	1.6 (0.7)
Sodium excretion, mmol/24 h	24	75	161	209	290	152 (106)

Mito, mitochondriopathy; TIN, tubulo-interstitial nephritis; NPH, nephronophthisis; FeNa, fractional excretion of sodium. * 24-h urine collection performed by bladder catheterization.

Fig. 1. Association between the fractional excretion of sodium (FeNa) and uncorrected creatinine clearance per category of sodium intake.

dium excretion ($R^2 = 0.539$, $p < 0.001$), only the latter 2 were included in the stepwise multiple regression model that explained more than 80% of the variation in FeNa ($r^2 = 0.824$, $p < 0.001$):

$$\text{FeNa (\%)} = 0.77 + (0.0066 \cdot \text{Na excretion [mmol/day]}) - (0.0098 \cdot \text{cCreat}_{\text{uncorrected}} [\text{mL/min}]) \quad (3)$$

To evaluate the influence of tubular function on FeNa, 5 patients with generalized tubular dysfunction were identified in the study cohort (Table 3). Measured FeNa was significantly higher than the estimated FeNa based on formula 3 (mean difference 3.77 [95% CI 0.28–7.26], $p = 0.04$) illustrating that FeNa does reflect tubular (dys)function, but only after correction for GFR and sodium intake.

Discussion

Our data show that FeNa depends on GFR and sodium intake. The use of FeNa to evaluate tubular function can be made only after correction is carried out for these 2 factors, and therefore, no cut-off level to distinguish between a normal and abnormal tubular sodium handling can be provided. The cut-off level of 1% that is used in the literature [6, 7] is therefore not suitable unless pre-renal AKI is diagnosed [1, 2].

As the level of FeNa depends on several important factors (glomerular filtration, tubular function and sodium intake), it cannot be used to interpret one of these factors without considering the others. FeNa is useful for the classification of AKI, as pre-renal failure volume depletion causes a maximal stimulus for salt retention and hence a low FeNa. In other clinical situations, however, defining any single cut-off value for FeNa is unhelpful for the diagnosis of tubular dysfunction. FeNa could be used to this end if the two other determinants (i.e., GFR and total sodium intake) are known and taken into account as demonstrated by the analysis of 5 patients with documented tubular dysfunction. By comparing expected FeNa on the basis of urinary sodium excretion and cCreat using formula 3, a difference between the measured and predicted FeNa of more than 1% may be indicative of tubular dysfunction.

For practical reasons, it would be best to have a formula to predict FeNa solely on (an estimate of) GFR, as it would implicate that no urine collection is necessary. Unfortunately, the overall regression formula in Table 2 shows that such a formula would not be accurate, thereby restricting its value on forehand. Even when the analysis is limited to individuals with a sodium intake between 50 and 150 mmol/day, as sodium intake in children is expected to be in this range [9], still only 33% of the variation in FeNa would be predicted (data not shown), compared with 82% when both GFR and sodium excretion are used (formula 3). This shows that for a proper interpretation of FeNa, knowledge of both GFR and sodium excretion is indispensable.

Our study has several limitations. First, 24 h urine collections were used to calculate the sodium and creatinine excretion, which is known to be unreliable in many instances. In order to try and optimise the reliability, we used strict inclusion criteria based on history and creatinine excretion. As collection of 24 h urine is done routinely at our institution, families are very familiar with this technique. Also, although imprecise urine collection may have introduced higher variability in our analysis, it should have no systematic effect on the relation between

GFR and urine sodium excretion in our analysis, both of which depend on urine collection.

We have chosen to present both sodium excretion and GFR without correction for weight or BSA, which is the usual approach in adults. As both anthropometric parameters are physiologically linked, correction for weight or BSA would have yielded comparable results.

Another limitation is that selection of patients cannot be excluded, as the patients in our study are derived from a hospital-based series. Even though we have tried to exclude patients using diuretics, database data on drug use may very well have been incomplete, allowing for some patients using diuretics to be included. In our experience, however, most patients will have been referred to the outpatient clinic of our department before such treatment has been initiated, thereby minimizing the possible influence of drug use on our results. The selection steps that resulted in the 761 patients included in the current analysis did change the characteristics of the cohort. With the exclusion of patients younger than 4 years of age, the mean age of the included group (9.32 [SD 3.77] years) was higher than the entire cohort (6.22 [SD 5.37] years). More boys were in the entire cohort (56.7%) than in the cohort that was used for the current analysis (48.6%; Table 1). Both changes were to be expected due to the exclusion of patients below the age of 4 years, in which an overrepresentation of boys is anticipated.

Only a few patients diagnosed with generalized tubular dysfunction fulfilled the criteria for inclusion based on missing data. These low numbers do not provide enough statistical power to establish a precise threshold for the difference between measured and calculated FeNa that is indicative of tubular dysfunction. Furthermore, the GFR in these 5 patients was lower than the GFR in the cohort from which the estimation formula was derived.

In conclusion, besides tubular function, FeNa depends on GFR and sodium intake. Therefore, tubular function cannot be assessed without the knowledge of the other 2 factors. Still, FeNa is useful for the classification of acute renal failure.

Statement of Ethics

As this was a retrospective analysis of anonymous data, no ethical approval was required.

Disclosure Statement

The authors declare no conflicts of interest.

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