Title: Challenges in using fractional excretion of sodium in the assessment of salt poisoning

Running Head: FENa and salt poisoning

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Abstract

Aim: Hypernatraemia typically reflects dehydration, yet in rare instances may be caused by salt poisoning. Identifying these rare cases is a difficult challenge. Making the diagnosis of salt poisoning can have severe consequences, such as removal of the child from its home or even prison sentences for the implicated carer. It is therefore imperative to get the diagnosis right. Guidelines for the assessment of hypernatraemia emphasise the importance of the fractional excretion of sodium to distinguish between dehydration and salt poisoning, but no generally accepted cut-off value exists. Opinions about the diagnosis of salt poisoning in some cases consequently may differ. Here, we aim to highlight the challenges and stimulate discussion on how to improve the tools for the assessment of hypernatraemia.

Methods: Report of a case of unexplained hypernatraemia in which the treating paediatrician raised the suspicion of salt poisoning.

Results: Two consulted experts made opposing judgements about the aetiology of the observed hypernatraemia.

Conclusion: Clear diagnostic criteria for the diagnosis of salt poisoning are lacking and more data are needed for their establishment. Without this, victims may experience further harm and carers are at risk of devastating, yet potentially erroneous accusations.

Key notes:

Diagnosing salt poisoning is critical to protect children at risk, yet no clear criteria exist to unequivocally separate from a diagnosis of dehydration. The presented case of hypernatraemia demonstrates how interpretation of the same set of data by two experts led to opposing conclusions. Consequently, court cases of suspected salt poisoning may be decided by the personal opinion of the consulted expert rather than by generally accepted uniform diagnostic criteria.

Introduction

Salt poisoning is a serious and potentially fatal cause of hypernatraemia. Fortunately, it is also rare, with one study reporting the annual incidence of recognised deliberate salt poisoning as 1/10,000,000 children under 16 years of age (1). Of course, many cases may go unrecognised, so the true incidence may be substantially higher. Reasons for failure to recognise salt poisoning may include the fact that salt is an effective emetic and a history of vomiting usually suggests dehydration to the assessing clinician (2). Further, as paediatricians, we are trained to promote allyship between caregiver and medical team, whereas the diagnosis of salt poisoning requires suspicion of the ally.

The natural and instinctive response of any person ingesting a large amount of salt is to immediately spit it out and/or vomit. Moreover, the increase in plasma osmolality from any absorbed salt will trigger thirst, release of antidiuretic hormone (ADH) with consequent urinary concentration resulting in an increase in circulating volume, which, in turn stimulates salt diuresis by the kidneys. These protective factors of avoidance/emesis, thirst, water retention and salt diuresis usually prevent the development of severe hypernatraemia. Yet, patients without free access to water and/or with a stomach tube, that can be used to bypass the taste buds in the mouth are at increased risk and indeed, constitute the majority of case reports of salt poisoning (reviewed in (2)).

Once salt poisoning is suspected, the clinician should obtain urine samples to assess salt excretion by the kidneys (3). However, questions were raised about the diagnostic value of the absolute urine sodium concentration and a subsequent guideline from the Royal College of Paediatrics and Child Health emphasised the importance of calculating the fractional excretion of sodium (FENa) to distinguish between dehydration and salt poisoning (4, 5). Yet,

there are no clear and generally accepted cut off values for FENa and interpretation can therefore be controversial, as in the following example, based on a real case.

Case report and diagnostic assessment

A 12-months old boy was admitted with a history of lethargy, fever (single measurement of 38.7C), reduced feeding and vomiting for 4 days, as well as hard stools.

His past medical history was relevant for prematurity with low birth weight, a prolonged stay in intensive care and subsequent chronic lung disease. He received oxygen at home and received a milk feed (SMA High Energy, 900 ml/d) via nasogastric tube. He did not drink independently.

On examination, the absence of clinical signs of dehydration was noted. His heart rate was 129/min and blood pressure 114/58 mmHg. Capillary refill time was <2 seconds and temperature normal at 37.2 ^{0}C. The initial blood gas showed hypernatraemia with a sodium of 189 mmol/l. The possibility of salt poisoning was considered, and plasma, urine and gastric aspirate biochemistries were obtained (Table 1). Subsequently, he was treated with administration of an enteral rehydration fluid (Dioralyte) by nasogastric tube at a rate of 100 ml/kg/d and plasma sodium values normalised over the following 62 hours (Table 1).

Social services were contacted and the local authorities appointed an expert who determined that the hypernatraemia was purely due to dehydration and the child was definitely not salt poisoned. In contrast, a second expert, consulted by the clinical team, concluded that salt poisoning was a highly likely diagnosis. The opposing assessments of the two experts hinged primarily on different interpretations of the urinary sodium excretion and highlight potential difficulties in using FENa for the diagnosis of salt poisoning.

Salt poisoning: assessment

Key parameters in the assessment of hypernatraemia and whether this is due to too little water or too much salt are clinical examination and history, changes in body weight, fluid balance and the urinary salt excretion. In addition, sodium concentration in the stomach and feed, if available, can be important. Unfortunately, few of these signs and symptoms are definitive for making the diagnosis. Clinical signs are soft and often subjective, weight can be difficult to interpret because of the lack of a reference weight, or because of the use of different scales and fluid balance is often inaccurately documented. Moreover, the diagnoses of dehydration and salt poisoning are not mutually exclusive: as salt is an effective emetic, victims of salt poisoning may experience vomiting and thus can also be dehydrated (2). These difficulties were evident also in this case, as each expert felt that the available weight and fluid balance data were compatible with a diagnosis of dehydration or salt poisoning, respectively. Similarly, the sodium concentration in the gastric aspirate (161 mmol/l) was considered non-diagnostic by both experts: while it was higher than usual (<60 mmol/l), it was still below the concentration of sodium in the plasma (6).

A key factor in the distinction between dehydration and salt poisoning is the assessment of the renal response: with dehydration, the kidneys are expected to conserve salt to maintain volume homeostasis, whereas in salt poisoning the kidneys are expected to avidly excrete sodium. The UK guidelines propose to assess this via FENa, with a “high” FENa being indicative of salt poisoning (4). Yet, what constitutes a “normal”, “low” or “high” FENa?

A normal fractional excretion of sodium (FENa)

Typically, a FENa <1% is considered normal, yet, importantly, there are no published data on normal FENa in children. Rather, the 1% limit is based on the concept that in steady state,

sodium intake should equal sodium output. An average adult with a plasma sodium concentration of 140 mmol/l and a glomerular filtration rate (GFR) of 100 ml/min filters 14 mmol/min of sodium or ~20000 mmol/d. A high salt Western diet contains about 10 g of salt (molar weight 58.44 g), containing roughly 170 mmol of sodium. Thus, to maintain sodium balance the kidneys need to excrete 170 mmol or just under 1% of the filtered amount. Unfortunately, there are neither accepted reference ranges for FENa in dehydration nor with salt poisoning. There are case reports of salt poisoning with values well in excess of 5%, even as high as 21% , but this obviously does not exclude the possibility of lower values in salt poisoning (4). In this case, the measured FENa was between 1.4 and 1.5%. Indeed, in one report of a case of proven salt poisoning (the mother admitted to it), FENa was 2.0%, similar to the values observed in this case (5).

Nevertheless, in the opinion of the first expert, a FENa of 1.5% definitely excluded the possibility of salt poisoning.

But there are several aspects to consider in the interpretation of FENa:

FENa depends on glomerular filtration rate (GFR)

As detailed above, the normal FENa value is based on a high salt intake (~10 g/d) and a normal GFR of around 100 ml/min/1.73 m^2. If the same salt intake is maintained in a person with a GFR of 50 ml/min/1.73 m^2, then those 10 g of salt are equivalent to almost 2% of the filtered sodium load and consequently a FENa of 2% should be considered normal.

In this case, the creatinine on admission was 23 μmol/l and based on the height from 4 weeks before admission of 68 cm, the estimated GFR by the modified Schwartz formula would have been ~105 ml/min. However, he likely had abnormally low muscle mass and thus creatinine may overestimate GFR. In fact, during the admission, his creatinine dropped below 20 μmol/l,

so the true GFR at admission may have been lower than calculated. This complicates assessment of the FENa in this case.

FENa depends on sodium intake

As detailed above, the "normal" FENa of 1% reflects steady state with a high salt diet. Yet, this patient was on a milk feed with a low sodium content. The total amount of sodium from feed and medications (if all was tolerated) was calculated at 24 mmol/d. By history, he had been vomiting and feed volumes were reduced, so the actual total sodium intake would have been even substantially less than 24 mmol. Assuming a GFR of 100 ml/min/1.73m^2 and given his body surface area of 0.36 m^2 and sodium concentration of 189 mmol/l, he would be filtering ~5660 mmol of Na/d. An intake of 24 mmol represents 0.4% of this filtered load. Consequently, a FENa of 0.4% would be a reasonable first estimate for the expected FENa in steady state. Yet, if GFR was lower, he would filter less sodium and those 24 mmol would represent a higher percentage of the filtered load. Yet, even if his actual GFR was ~20% lower than estimated by the Schwartz formula, the expected FENa would still be only 0.5%. Moreover, by history, the ingested amount of sodium from regular feed and medications was likely considerably less than 24 mmol because of the vomiting and in dehydration, the kidneys are expected to avidly retain sodium, so 0.4% could actually be an overestimate of the expected FENa with pure dehydration. Nevertheless, the observed initial FENa of 1.5% was substantially higher than what would have been expected in steady state in this boy with a prescribed sodium intake of 24 mmol.

The absolute excretion of sodium may be a better diagnostic indicator for salt poisoning than FENa

Given these uncertainties in interpreting FENa it may be more useful to assess the total amount of sodium excreted. The urinary sodium concentration initially was 368 mmol/l (Table 1). The next urinary sodium measurement was obtained roughly a day later and returned with a concentration above the measurement threshold of 400 mmol/l. The documented urine volume in that time period was 256 ml and it is reasonable to assume that the average sodium concentration in those 256 ml was at least 368 mmol/l. Thus, he excreted approximately 100 mmol of sodium in the first ~24-h after admission, or roughly 13 mmol/kg/d. During that time, the documented intake was 890 ml of Dioralyte, which would have provided ~27 mmol of sodium. Consequently, he was in a strongly negative sodium balance after admission, which is the opposite of what would have been expected with pure dehydration. Thus, the high absolute salt excretion strongly suggested salt poisoning and this is what the second expert based his opinion on. But how is it possible that absolute salt excretion and FENa can suggest such opposing diagnoses?

In salt poisoning, the maximal FENa depends on the availability of water

The kidneys cannot excrete pure salt but need to dissolve it in water. Thus, to excrete a salt load, we need water and the physiologic response to salt ingestion is to drink. The fluid intake not only ameliorates the increase in the blood sodium concentration, but also provides the necessary volume for the kidneys to excrete the salt load. Yet, this key protective mechanism is impaired in subjects without access to free water. Consequently, children without access to free water, like this infant, are at highest risk of symptomatic salt poisoning: without additional water, the ability to excrete salt is limited by the urinary concentration ability. In this case, the urine sodium concentration at admission was 368 mmol/l, with an osmolality of 1017 mosm/kg, which likely reflected maximal urinary concentration at the time. This

indicated that sodium plus the accompanying anion constituted the vast majority (>70%) of solutes in the urine. As the kidneys also need to excrete other solutes, such as urea and potassium (plus accompanying anion), the observed sodium concentration likely reflected the upper limit of salt that could be contained in this highly concentrated urine and the observed FENa therefore was the maximum achievable under the conditions. Let's hypothesise a scenario, where the child had received 500 ml more fluid before admission, but otherwise had had the same plasma levels for sodium, osmolality and creatinine, and the same urine osmolalities. With 500 ml more water available for excretion, the urine volume would have been almost 3x larger (768 ml) and consequently, the urine concentrations of creatinine and the other waste products would have been about a third of the observed ones, allowing for a higher sodium concentration in the urine (~550 mmol/l), as urine concentration would still have been expected to be maximal (considering the observed plasma osmolality of 402 mosm/kg). The lower urine creatinine and the higher urine sodium levels would then have resulted in the calculation of a higher FENa value (~ 6.5%), that might have been more convincing for the diagnosis of salt poisoning. Obviously, this is a hypothetical scenario and with more fluids, plasma sodium probably would not have risen so much, but it nevertheless illustrates how much FENa in salt poisoning depends on the availability of water.

Discussion

Salt poisoning is an extremely rare occurrence and, as with almost all rare disorders, this creates challenges in the diagnosis. Diagnostic parameters, such as weight and fluid balance are often inaccurate in clinical reality, as discussed in this case. For this reason, emphasis has been placed on the assessment of the urinary sodium excretion, as this can be measured

accurately and easily expressed as FENa (4). Yet, unfortunately, an accurate measurement still does not provide an unequivocal diagnosis. A key problem in this case is the discrepancy between the large absolute sodium excretion (~13 mmol/kg/d) and the rather modest FENa of 1.5%. This case therefore raises important questions about interpreting FENa in hypernatraemia, mainly what level of FENa can reliably distinguish between dehydration and salt poisoning. Ideally, there would be a large database of cases with either diagnosis and their respective FENa values that could provide solid information on discriminating values and their sensitivity and specificity. Unfortunately, no such database exists. Most importantly, it would require a gold standard for the diagnosis of salt poisoning, so that cases were reliably stratified. But what would be that gold standard? Expert opinion? This can vary, as this case demonstrates. A judicial verdict in criminal cases? Judge and jury in such cases may mostly rely on the medical expert witness(es). Arguably, the only certain cases of deliberate salt poisoning are where solid forensic evidence has established salt poisoning, such as the identification of salt contamination in the feed and/or where a carer has admitted to the act. But the number of such cases in the literature are very few and may not have concomitant documentation of FENa. Less controversial are cases of accidental salt poisoning, where the cause is clearly established, such as in the Binghamton hospital disaster in 1962, where 14 infants were given a feed mistakenly made up with salt instead of sugar and suffered severe hypernatraemia (7). Unfortunately, no data on urinary sodium excretion in these infants was provided and presumably, it was not measured. Thus, in the current literature, there is insufficient data to clearly establish precise limits for FENa that would be specific for salt poisoning. Arguably, the key problem in this case was that dehydration and salt poisoning are not necessarily mutually exclusive. A salt contaminated feed could not only cause salt poisoning, but, as salt is an effective emetic, also dehydration, especially in a subject without

free access to water. Given the limit on the maximal FENa by the availability of water, we propose that the absolute sodium excretion may be more informative in such cases.

In the absence of solid discriminating data, the diagnosis of dehydration *vs.* salt poisoning currently rests mainly on appointed experts providing informed opinions, which, as seen here, can be diametrically opposed. Considering the legal consequences of a diagnosis of deliberate salt poisoning, such differences in expert opinion are extremely concerning: whether a child is taken from its home, or a carer found guilty and sentenced may depend in part or wholly on who the court happened to appoint as the medical expert in the case. Establishing clear diagnostic criteria is therefore imperative to support correct decision making. The UK guidelines from 2009 represented such an attempt and highlighted the limitations of using an absolute urinary sodium concentration for the distinction between hypernatraemic dehydration and salt poisoning and emphasised instead the use of FENa (4). However, a clear cut-off value for FENa to make the distinction was not and could not be established at the time. Unfortunately, now, more than a decade on, we have not made much progress. We need to publish cases we have been involved with, especially those where salt poisoning, be it accidental or deliberate, has been clearly established, and with as much data on urinary salt excretion and FENa as possible, so that we can learn from these cases and hopefully establish better criteria for the diagnosis in the future.

Statements

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List of abbreviations

ADH antidiuretic hormone

FENa fractional excretion of sodium

GFR glomerular filtration rate

Table 1: Pertinent clinical data

hours post admission [h]	0	3	6	12	24	36	62
Weight [kg]	7.26					7.5	7.38
Plasma Na [mmol/l]	189	189	186	173	164	158	142
K [mmol/l]	3.5	3.9	3.9		3.8	4.7	4.3
CL [mmol/l]	157	158	153		131	116	97
HCO_3^- [mmol/l]*	19	20	21		26	29	29
Urea [mmol/l]	3.9	7.1	5.4	4.2	4.7	2.9	3.5
Creatinine [umol/l]	23	24	28	20	<20	<20	26
Osmolality [mosm/kg]		402			335		
Venous pH	7.26	7.36	7.36		7.39	7.38	7.46
Urine Na [mmol/l]		368			>400		
Urine Creatinine [mmol/l]		3.1			3.6		
Urine K [mmol/l]		89					
Urine urea [mmol/l]		174					
Urine Osmolality [mosm/kg]		1017		1188	1185		
FENa [%]		1.5			1.4		
NG aspirate Na [mmol/l]		161					
Cumulative fluid input [ml]				580		1320	
Cumulative urine output [ml]		50		122	256	378	

Table 1: Pertinent data on weight, fluid balance, as well as plasma and urine biochemistries
Shown are pertinent data as available from presentation up to normalisation of plasma sodium 62 hours later.
*: HCO_3^- values are from the blood gas, i.e. calculated and not measured.

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