Q J Med 1998; **91**:749–753

Treating the syndrome of inappropriate ADH secretion with isotonic saline

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Received 10 June 1998 and in revised form 17 August 1998

Summary

It has been widely accepted that there is little use for saline treatment in the syndrome of inappropriate secretion of ADH (SIADH). However, having observed that most SIADH patients increased their plasma sodium (PNa) after 2 l isotonic saline over 24 h, we investigated whether urine osmolality or the sum of urinary sodium and potassium (UNa + K) predicted this response, in 17 consecutive patients with chronic SIADH. The initial measure of urinary sodium plus potassium (UNa + K t_0) was weakly correlated to the change in PNa (DPNa) after infusion ($r = -0.51$; $p < 0.05$), while initial urine osmolality (UOSM t_0) was a much better predictor ($y = -0.024x + 12.90$; $r = -0.81$; $p < 0.001$). The lack of predictive value for UNa + K t_0 was probably because urine electrolyte concentrations were not maximal for the corresponding initial UOSM. This reflects differences in salt intake between the patients. The theoretical maximal value for UNa + K t_0 (*th max* UNa + K t_0) for a given UOSM t_0, was as good a predictor as UOSM t_0 (*th max* UNa + K vs. DPNa: $r = -0.81$; $p < 0.001$). A theoretical model describing the effect of 2 l isotonic saline infusion on DPNa as a function of UNa + K, produced values comparable to those observed in our patients. Only 6/17 patients, those with UOSM > 530 mOsm/kg, had their hyponatraemia aggravated by 2 l isotonic saline. Many SIADH patients have lower UOSM; in most such patients, 2 l of isotonic saline will improve PNa.

Introduction

In hyponatraemia related to SIADH, it has widely been accepted that isotonic saline infusion is useless, since electrolytes would be quickly excreted in the urine and water will be retained,[1,2] which could eventually worsen the hyponatraemia. In a mathematical approach to the effect of isotonic saline in SIADH, Rose proposed that to effectively raise the plasma sodium concentration, the osmolality of the administered fluid must exceed the latter in the urine.[2,3] However, in a previous study[4] we observed a mean increase in plasma sodium (PNa) in SIADH after 2 l isotonic saline from 124 to 127 mEq/l despite a mean initial urinary osmolality (UOSM) of 429 mosm/kg. This led us to study prospectively in 17 consecutive SIADH patients the influence of UOSM and urinary sodium and potassium upon the increase or decrease in plasma sodium (DPNa) after isotonic saline infusion.

Methods

We infused 2 l isotonic saline over 24 h in 17 consecutively-encountered hyponatraemic SIADH patients. They met the usual criteria for SIADH: hyponatraemia and corresponding hypo-osmolality accompanied by excessive natriuresis (urinary sodium > 50 mEq/l in all the patients[4]) and inappropriate high UOSM, absence of oedema, and normal renal, adrenal and thyroid function. Only patients with an initial plasma sodium in the range 115–130 mEq/l were included. None of them was sympto-

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matic. To study the effect of isotonic saline in SIADH, we included only patients with a stable antidiuresis. Patients in whom an increase in water intake was not associated with a worsening of the hyponataremia, because they were able to suppress ADH and to excrete large volumes of hypotonic urine, were not included. When treated by water restriction, such patients largely increased their urinary osmolalities, since increasing plasma sodium is associated with ADH stimulation. Although such patients with 'reset osmostat' are considered to be a subclass of SIADH,[5] we excluded them from our study. During the saline infusion, water restriction (<0.75 l/day) was continued as was food intake, which was maintained stable (70–120 mEq sodium/day) for at least 3 days before saline infusion. Just before starting the saline infusion (t_0) and after the infusion (t_{24}), sodium, potassium (measured by ion selective electrode; Hitachi 737, Boehringer Mannheim) and osmolality were measured on plasma samples and a urine spot collection. Within these 17 patients (11 men, 6 women, mean age 64 ± 13 years), we attempted to correlate DPNa to urinary Na plus K (UNa + K) and also to UOSM at t_0. Statistical analysis used means of correlation coefficients and Student's t-test.

Results

The infusion of 2 l isotonic saline was well tolerated by all of the 17 patients. They suffered from lung cancer ($n=6$), various other pulmonary diseases ($n=4$), cerebral traumatism ($n=2$), ovarian cancer ($n=1$), sarcoma ($n=1$), cortical atrophia ($n=1$), and idiopathic SIADH ($n=2$). None of the observed patients showed subarachnoid hemorrhage. The biochemical parameters of this group, at initial evaluation and after saline infusion, are shown in Table 1. When each patient was examined separately, a great DPNa range could be noted. However, in the group mean plasma sodium tended to increase slightly from 126 to 127 mEq/l, although mean urinary osmolality (502 mosm/kg H_2O) exceeded clearly the osmolality of the saline infusion (308 mosm/kg H_2O). All the patients were further treated by water restriction. Mean plasma sodium 24 h after the end of the isotonic saline infusion was at 128 mEq/l, a value non significantly different from that at t_{24}.

Table 1 Biochemical parameters at initial evaluation (t_0), and after 2l (t_{24}) isotonic saline in 17 SIADH patients

	t_0	t_{24}
Plasma		
Sodium (mEq/l)	126 ± 5	127 ± 6
Potassium (mEq/l)	4 ± 0.4	3.9 ± 0.5
Urinary		
UNa + K (mEq/l)	128 ± 61	163 ± 41
UOSM (mosm/kg)	502 ± 128	497 ± 113
UNa + K/UOSM	0.25 ± 0.1	0.33 ± 0.1

Data are means $\pm$ SD.

We wondered whether DPNa after 2 l isotonic saline could be predicted in an individual SIADH patient, and we tested first the predictive value of UNa + K t_0. The response to isotonic saline can not be accurately predicted from initial UNa + K t_0 (Figure 1), since these parameters are only weakly correlated ($r=-0.51$; $p<0.05$).

A much more interesting parameter in this prediction to saline is UOSM t_0. DPNa and UOSM t_0 are inversely correlated ($r=-0.81$; $p<0.001$): the lower the UOSM, the higher DPNa (Figure 1). From the linear regression, $y=-0.024x+12.90$, we

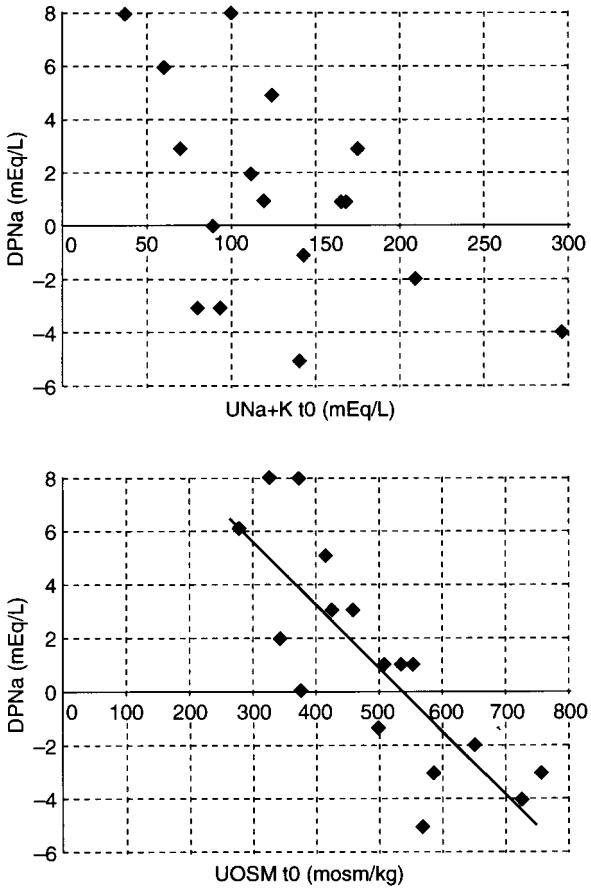

Figure 1. Upper panel, a weak correlation between the initial urinary sodium plus potassium (UNa + K t_0) value and the variation in plasma sodium (DPNa) after 2 l isotonic saline in 17 SIADH patients ($r=-0.51$; $p<0.05$). Lower panel, a significant correlation between the initial urine osmolality (UOSM t_0) and the variation in plasma sodium (DPNa) after 2 l isotonic saline in 17 SIADH patients following water restriction. ($y=-0.024x+12.90$; $r=-0.81$; $p<0.001$).

can estimate theoretically that only patients with UOSM > 538 mosm/kg have their hyponatraemia aggravated.

Why was UNa + K t_0 not useful in predicting the response to saline? Perhaps because in most patients, urine electrolyte concentrations were not at their maximal values for the corresponding UOSM, reflecting variable salt intake between the analysed SIADH patients. We postulated that urine electrolyte concentrations in SIADH patients after 2 l isotonic saline will have reached their maximal values for the corresponding UOSM. As expected, both UNa + K t_{24} and UOSM t_{24} were better correlated ($y = 0.27x + 29$; $r = 0.72$; $p < 0.01$) (Figure 2) than UNa + K t_0 and UOSM t_0 ($y = 0.28x - 10$; $r = 0.60$; $p < 0.01$). With the equation describing the correlation between UNa + K t_{24} and UOSM t_{24} ($y = 0.27x + 29$), we could predict which theoretical maximal value for UNa + K t_0 (*th max* UNa + K t_0) could be expected from a given UOSM t_0. Using this new parameter in the prediction of the response to saline, the correlation with DPNa reappeared ($y = -0.088x + 15.45$; $r = -0.81$; $p < 0.001$) (Figure 2) and was as reliable as the predictive value of UOSM t_0 ($r = -0.81$; $p < 0.001$). Only six of the 17 patients had worse hyponatraemia after isotonic saline infusion.

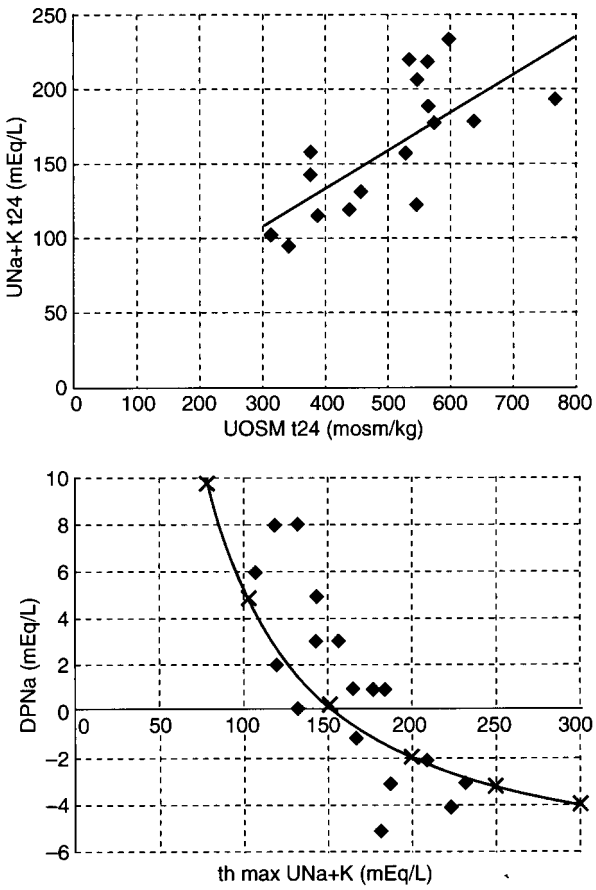

Figure 2. Upper panel, a significant correlation between the urinary sodium plus potassium values (UNa + K) t_{24} and the corresponding urinary osmolalities (UOSM) t_{24} obtained after 2 l isotonic saline over 24 h in 17 SIADH patients ($y = 0.27x + 29$; $r = 0.72$; $p < 0.01$). Lower panel, a significant correlation between the initial theoretical maximal urinary sodium + potassium values (*th max* UNa + K t_0) and the variation in plasma sodium (DPNa) in 17 SIADH patients (◆) ($y = -0.088x + 15.45$; $r = -0.81$; $p < 0.001$). To obtain the *th max* UNa + K for a given UOSM t_0, we used the relationship between UNa + K and UOSM after 2 l isotonic saline (see upper panel). The lower panel presents also a theoretical model of a hypothetical SIADH patient (x) after 2 l isotonic saline (see Table 2).

Discussion

There are reasons to suppose that saline can frequently be harmful in SIADH patients. It has been proposed that to effectively increase the plasma sodium by means of isotonic saline, the osmolality of the administered fluid must exceed urinary osmolality. Since the urine osmolality is usually > 300 mosm/kg in SIADH, there is essentially no reason for the use of isotonic saline in this disorder.[2,3] However, we observed that most of our SIADH patients increased their plasma sodium after 2 l isotonic saline, despite mean urinary osmolalities clearly exceeding the osmolality of the administered saline. Theoretically, our data show that only SIADH patients with UOSM > 538 mosm/kg aggravate their hyponatraemia, while SIADH patients with lower values are able to increase their plasma sodium concentration. Our observation that isotonic saline in SIADH patients is not harmful despite a UOSM higher than the osmolality of the infused saline, is related to the incapacity of the kidney to use only electrolytes to elaborate a given urine osmolality, which would leave no place for other osmolytes. When for instance UOSM = 310 mosm/kg, the maximal UNa + K value for this osmolality will not be 155 mEq/l, but rather about 110 mEq/l. Thus, we can expect that water-restricted SIADH patients will not have their hyponatraemia aggravated by isotonic saline as long as UNa + K does not exceed the sodium concentration of the infused fluid (154 mEq/l).

One could argue that in this mathematical approach, the correlation between UOSM t_0 and DPNa or between *th max* UNa + K t_0 and DPNa ought to be stronger, and the correlation coefficient near −1 instead of −0.81. One reason why not could be that it seems most likely that the solute load had not already been entirely excreted at t_{24}, since the saline had been infused over 24 h and

Table 2 Effect of 2 l isotonic saline administration in a theoretical SIADH patient with 30 l total body water, an initial PNa of 128 mEq/l and variable levels of antidiuresis, indirectly presented as the maximal UNa + K values for the corresponding urine osmolalities

UNa + K (mEq/l)	Water excreted for 2 l isotonic saline (l)	New TBW (l)	New PNa (mEq/l)	DPNa (mEq/l)
75	2 × 154/75 = 4.11	27.89	137.7	9.7
100	2 × 154/100 = 3.08	28.92	132.8	4.8
150	2 × 154/150 = 2.05	29.95	128.2	0.2
200	2 × 154/200 = 1.54	30.46	126.1	−1.9
250	2 × 154/250 = 1.23	30.77	124.8	−3.2
300	2 × 154/300 = 1.03	30.97	124	−4

Total Body Osmoles (TBO) = Total Body Water (TBW) × 2PNa (plasma sodium). After isotonic saline, TBO remain unchanged since the administered NaCl will be excreted.[1,2] New TBW = initial TBW + 2l − water excreted for 2l isotonic saline. New PNa = TBO/2 New TBW.

DPNa was determined just after the end of the infusion.

We also have to keep in mind that an attempt to predict saline responsiveness in SIADH is only reliable as far as there are no significant changes in antidiuresis and fluid intake, which was the case in our study group. Unfortunately, as precise water excretion in our patients was not measured, we can not present exact 'balance data', but the significant correlation between UOSM and DPNa after 2 l isotonic saline could probably be approached by a theoretical model. If we put forward the hypothesis of a SIADH patient with a body weight of 60 kg (corresponding to the mean body weight of our study group) and different levels of antidiuresis, who will receive 2 l isotonic saline over 24 h, and who will quickly excrete the whole sodium load in the urine, we can find a theoretical curviform relationship between DPNa and UNa + K (see Table 2 and Figure 2). The individual DPNa values for the corresponding *th max* UNa + K values observed in our patients, are close to this curve (Figure 2). It is also interesting to note from this curviform relationship, that even with a UNa + K value of 300 mEq/l, the corresponding decrease in PNa is expected to be limited to 4 mEq/l. The slight difference between the theoretical model and the real SIADH study group, could easily be explained by differences in sex, age and weight of the different patients, and by the assumption that the total amount of electrolytes is excreted in 24 h, as far as there is no ADH escape. In a recent report on the pathogenesis of postoperative hyponatraemia observed after infusion of large volume of near-isotonic saline (> 5 l/24 h), the mean UNa + K value was 294 mEq/l, corresponding to 36% of the concomitant UOSM (personal communication, M.L. Halperin) and the mean decrease in PNa only 4 mEq/l.[6] What are we to do with these findings in daily practice? In some patients, the depletional origin of the hyponatraemia is not always easy to recognize and they can be confounded on clinical and biochemical grounds with true SIADH.[4,7] Physicians sometimes need to try a therapeutical dose of isotonic saline. Our observation shows that a test infusion with isotonic saline is rarely hazardous in SIADH, and that it can be surprisingly efficient in some SIADH patients despite the absence of sodium depletion. Thus, the interpretation of a rise in PNa higher than 5 mEq/l after a 2 l isotonic saline infusion over a period of 24 h, needs to be viewed with caution. Although such responses are generally considered as evidence for depletional hyponatraemia,[7] they can also be observed in SIADH patients. They can however be differentiated from patients with depletional hyponatraemia by their high urinary salt excretion, since salt-depleted hyponatraemic patients conserve salt as long as hyponatraemia persists.

In conclusion, the response to isotonic saline in SIADH can be predicted from UOSM and also from UNa + K, but only when UNa + K is maximal for the corresponding UOSM. Our study was mostly performed in elderly patients, known to have a decreased urine concentrating ability and it is likely that in younger patients, 2 l isotonic saline would have more frequently caused a slight decrease in PNa.

Acknowledgements

This study was supported by a grant from the FONDS National de la recherche scientifique (FNRS) (1-5-198.97F)/(1-5-164.98F).

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