Water, Electrolyte, and Endocrine Homeostasis in Infants with Bronchiolitis[1]

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ABSTRACT. Twenty-two of 23 consecutive infants with bronchiolitis, 5.5 ± 3.5 mo of age, showed a 1.9 ± 1.4% increase in body weight, increased urinary osmolality of 737 ± 193 mmol/L with low plasma osmolality of 275 ± 4 mmol/L, and markedly elevated plasma antidiuretic hormone (ADH) levels of 114 ± 225 pg/mL. Increased ADH, which usually suppresses plasma renin activity, was associated with increased plasma renin activity of 11–55 ng angiotensin 1/mL/h (normal for age <10 ng angiotensin 1/mL/h). Hyperaldosteronism was evident from the low fractional excretion of sodium of 0.27 ± 0.2% and high fractional excretion of potassium of 21 ± 15%. Serum sodium concentrations were normal. All of the pathologic findings returned to normal when the bronchiolitis subsided. A control group of 10 infants with nonrespiratory febrile illness did not show any of the above abnormalities. Thus, bronchiolitis of infancy is characterized by both increased ADH secretion and hyperreninemia with secondary hyperaldosteronism, which induce water retention but counterbalance each other with respect to serum sodium. Increased ADH secretion as well as increased plasma renin activity are not "inappropriate," but rather suggest a response to the perception of hypovolemia by intrathoracic receptors. We therefore conclude that the clinical management of bronchiolitis requires close monitoring of body wt and plasma osmolality-urinary osmolality relationship; serum sodium levels may be misleading. (*Pediatr Res* 27: 204–209, 1990)

Abbreviations

ADH, antidiuretic hormone
SIADH, syndrome of inappropriate ADH secretion
PRA, plasma renin activity
FE, fractional excretion
Uosm, urinary osmolality
Posm, plasma osmolality
Ang, angiotensin

It has been our clinical impression that infants with severe bronchiolitis develop facial puffiness that lessens and disappears as the respiratory distress improves. The possibility that excess fluid retention causes this appearance has been reinforced by the observation that concomitant with the loss of facial puffiness, a reduction in body wt occurs. The association of (SIADH) has been described in severe pulmonary conditions in childhood (1–9) including bronchiolitis (4, 8).

Our study was undertaken to evaluate whether the elevated ADH and plasma renin levels are a common finding in bronchiolitis and represent a response to a perceived diminished intravascular volume.

MATERIALS AND METHODS

The subjects included in the study were all children of younger than 12 mo old and weighing more than 3.5 kg admitted to the pediatric department over a 3-mo period (December 1986 through February 1987) with a clinical diagnosis of bronchiolitis. None of the patients had a history of preceding chronic disease or was receiving medication. Inasmuch as no precise definition of acute bronchiolitis has been agreed upon in the literature, the diagnosis was based on the following clinical features (10): a history of preceding upper respiratory tract infection with an acute onset of illness, mild fever, dyspnea, tachypnea, chest retractions, wheezing, rhonchi with or without rales and evidence of hyperinflation of the chest, both clinical and radiologic. No attempt to define the specific viral etiology of the disease was made. A diagnostic agreement of two pediatricians was required for the patient to be included in the study.

On admission each patient underwent the following protocol: A thorough medical history and physical examination. A clinical symptom grading system as described by Wennergren *et al.* (11) was repeated every 6 h to assess semiquantitatively the evolution of the disease in each patient. Laboratory investigations included the following: chest x-ray, CBC, arterial blood gases, serum electrolytes, urea and creatinine, and plasma osmolality, PRA, and ADH levels. Every 8 h, wt was measured on an electronic scale, and urine was collected and analyzed for electrolytes, creatinine, and osmolality. All tests were repeated upon discharge. To ascertain that the abnormalities in fluid balance observed were indeed due to bronchiolitis and not to the stress of acute disease, 10 sick infants were examined for the same parameters listed above. These stressed control infants, age 3.5 ± 1.3 mo, had acute febrile disease with rectal temperature higher than 39.5°C without respiratory or gastrointestinal symptoms and no evidence of CNS infection. All the values from the control group were obtained on admission.

Oral fluid intake was unrestricted but in infants with marked respiratory distress and feeding difficulties intravenous fluids were administered. In these cases, a total of 100 mL/kg of dextrose 5% in NaCl 0.33% was administered daily. Oxygen through a tent was added if needed, to maintain the arterial oxygen tension between 70 and 90 torr.

Plasma ADH levels were determined by the radioimmunoassay method of Husain *et al.* (12). Blood samples for ADH were collected in heparinized tubes on ice, centrifuged immediately at −4°C, separated, and stored frozen with 0.1% acetic acid. Ex-

traction with acetone and delipidation of the extract with petroleum ether was performed and the samples were lyophilized and stored at −20°C until assayed. Recovery was 65 to 70% and assay sensitivity was 0.1 pg/mL with an intraassay coefficient of variation of 16.7% and an interassay coefficient of variation of 17.2%.

Plasma and urine osmolality were determined by freezing point depression using a Fiske OU osmometer that was calibrated daily with Accuref 300. We obtained an intraassay variation of 0.5 to 0.7% ($n = 15$), and the interassay variation was 0.3% (mean 280.1 mmol/kg; $n = 36$).

Two mL of blood for PRA were collected in ice chilled plastic tubes containing 10 mg EDTA. Plasma was immediately separated in a refrigerated centrifuge and kept stored at −20°C until assay. PRA was determined by angiotensin 1 generation at pH 6.0 with EDTA, dimercaprol (BAL), and 8-hydroxiquinoline as inhibitors of converting enzyme and angiotensinase activity and results expressed in ng Ang 1/mL/h. New England Nuclear commercial kit (New England Nuclear, Boston, MA), RIANEN, was used for the RIA. Intraassay coefficients of variation for PRA at concentrations of 0.1, 1.0, 4.0 ng Ang 1/mL/h were 7, 4, and 8%, respectively. Interassay values at 0.1, 2.0, and 4.0 ng Ang 1/mL/h concentrations were 10, 7, and 12%. The normal range of values used for the population under study was 1.5 to 10 ng Ang 1/mL/h, as recently published by Fiselier *et al.* (13).

Fractional excretions of sodium and potassium were calculated using the standard formula shown below:

$$FEsol\ (\%) = \frac{Usol*Scr}{Ucr*Ssol} *100$$

Where FEsol indicates fractional excretion of solute and U and S the respective concentrations of solute and creatinine (cr) in either urine or serum. The simultaneous urine and plasma osmolality value pairs obtained in each patient were plotted on a standard nomogram (14). Plasma osmolality values were also correlated to plasma ADH concentrations and analyzed graphically according to available published data (15–17). Parental informed consent was obtained in each case before inclusion in the study. Statistical analysis of the data was performed using the *t*-test for paired or nonpaired data as appropriate. Significance was indicated by $p \leq 0.05$.

RESULTS

Twenty-three patients, 16 boys and seven girls, comprised the cohort. Mean age was 5.5 ± 3.5 mo. The mean duration of symptoms before admission was 3.1 ± 1.9 days and that of dyspnea 1.5 ± 0.9 days. The mean dyspnea severity score on a scale of 0 to 6 was 3.65 ± 0.95 on admission. Arterial blood

gases drawn on room air showed a mean Po_2 of 71.3 ± 12.2 mm Hg (range 48–94 mm Hg), mean Pco_2 36 ± 6 mm Hg (27–54), and mean pH 7.36 ± 0.04 (7.29–7.42). Chest x-rays disclosed hyperinflation in all patients and small, usually unilateral infiltrates in six.

The relationship of urine osmolality to plasma osmolality, as depicted in Figure 1, shows that in 22 patients on admission, the Uosm-Posm values fell to the left of the nomogram lines. In all but four patients, Uosm-Posm values on discharge returned to within the nomogram lines. The mean Posm was 275.2 ± 4.1 mosm/L on admission and 283.8 ± 2.2 mosm/L on discharge ($p < 0.001$), compared to 284 ± 1.1 mosm/L in the stressed control patients. Patients' Uosm admission and discharge values were 737 ± 193 mosm/L and 396 ± 184 mosm/L, respectively ($p < 0.001$), compared to 444 ± 131.7 of the stressed controls.

Mean serum sodium levels were 136.8 ± 2.8 mEq/L and 140.2 ± 2.1 mEq/L on admission and discharge, respectively ($p < 0.01$), compared to 140.4 ± 1.7 mEq/L of the stressed control group (Fig. 2). Hb, hematocrit, serum urea, and creatinine values did not change significantly in any of the patients during hospitalization.

Wt change calculated as the difference between wt on admission and at discharge divided by wt on admission and multiplied by 100 to be expressed as a percentage, showed a mean decrease of 1.9 ± 1.4%. In only two patients, a wt increase was noted.

The relationships of plasma ADH levels to osmolality on admission and discharge are shown in Figure 3. The respective mean ADH values are 113.8 ± 224.8 ($n = 23$) and 1.9 ± 0.9 pg/
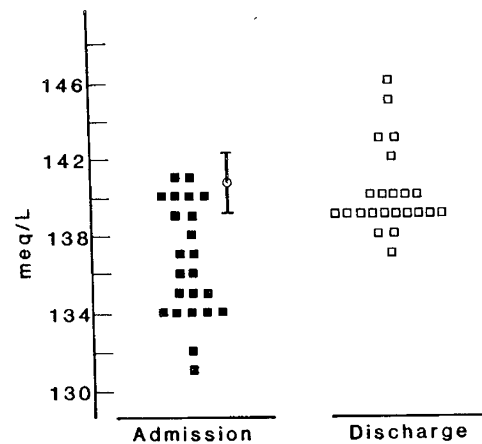

Fig. 2. Serum sodium levels in patients with bronchiolitis ($p < 0.01$). The mean ± SD of the stressed control patients is indicated by the *bar* on the admission side.
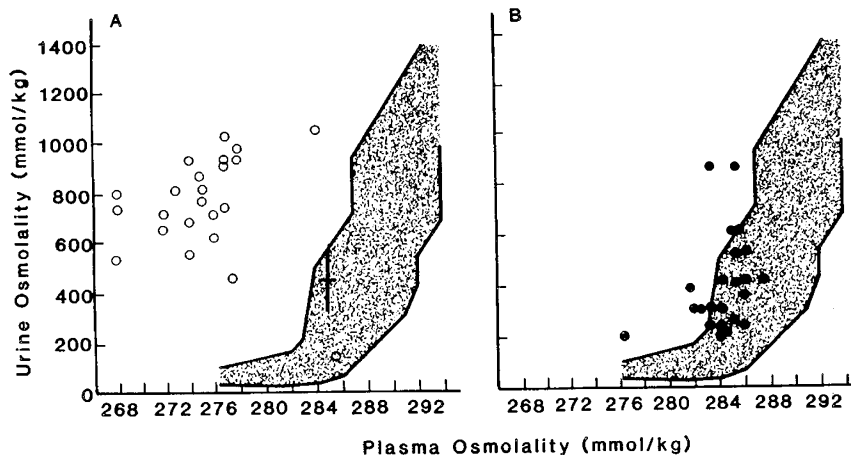

Plasma Osmolality (mmol/kg)

Fig. 1. Relationship of Uosm and Posm in 23 infants with bronchiolitis on admission (*open circles*) and discharge (*closed circles*) ($p < 0.001$). The mean ± SD of the stressed control patients is indicated by the cross in the shaded area of *A*.

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mL ($n = 15$) ($p < 0.001$). ADH values of the stressed control group were 1.0 ± 1.3 pg/mL. It was noteworthy that the only patient value within normal range on admission corresponded to the patient whose Uosm-Posm levels were within the nomogram lines in Figure 1.

Mean plasma renin activity levels on admission and discharge were 22.1 ± 13.8 and 9.1 ± 3.8 ng Ang 1/mL/h, respectively ($p < 0.025$). The PRA values of the stressed control infants were 10 ± 3.5 Ang 1/mL/h ($p < 0.0005$ compared to admission, $p > 0.05$ compared to discharge) (Fig. 4). The mean FENa and FEK on admission were calculated as 0.27 ± 0.2 and $21.6 \pm 14.7\%$, respectively. In all but four patients the FENa was found to be increased at discharge so that a mean value of $0.62 \pm 0.39\%$ was obtained. A reciprocal decrease of FEK to $8 \pm 4.3\%$ was found at discharge in all but two patients. The FENa/FEK ratios ($\times 10$) increased therefore from 0.16 ± 0.14 to 0.86 ± 0.52 ($p < 0.001$). FENa in the stress control infants was $0.43 \pm 0.18\%$ (mean $\pm$ SD). FEK was $4.9 \pm 0.2\%$. The mean ratio was 0.9 ± 0.3. Results of these admission fractional excretion values and their ratio in the control group were not statistically different from the discharge values of the bronchiolitis patients. The individual changes occurring in these parameters are shown in Figure 5.

Two illustrative cases are shown in Figure 6 that depict the concomitant changes observed throughout hospitalization in the clinical status, body wt, and urine osmolality.
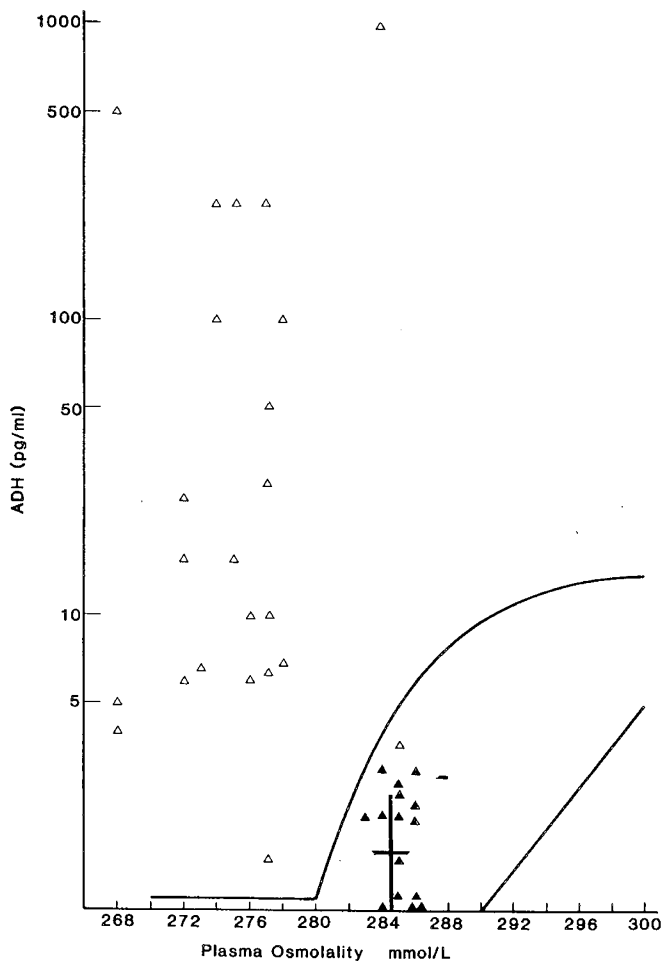

Fig. 4. PRA in patients with bronchiolitis ($p < 0.025$). The stressed control values are indicated as *dots* on the admission panel.

Fig. 3. Relationship of plasma ADH levels and plasma osmolality in infants with bronchiolitis on admission (*open triangles*) and discharge (*closed triangles*) ($p < 0.001$). The values for the stressed control infants are marked by the *cross* (mean $\pm$ SD).
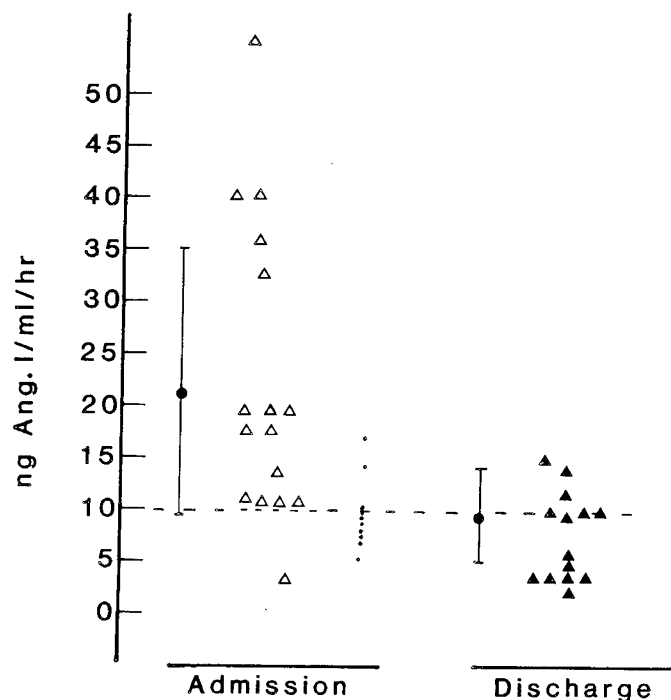
DISCUSSION

SIADH, as described by Schwartz *et al.* (18), implies in its classical clinical expression the presence of hyponatremia with continuing urinary sodium excretion, and inappropriately high urinary osmolality as related to plasma osmolality in the absence of renal or adrenal disease. The occurrence of SIADH in various pulmonary conditions including bronchiolitis, has been noted, and several pathophysiologic mechanisms may be involved (1-9). The incidence of SIADH, within a cohort of patients with bronchiolitis admitted consecutively during a seasonal epidemic, has not as yet been systematically studied. Our study was conducted to determine whether the perception of diminished intravascular volume during bronchiolitis is commonly associated with elevated plasma vasopressin and renin levels rather than incidental SIADH, as would be suggested by the occasional case reports in the literature (4, 8).

To evaluate this assumption, we used adult Posm-Uosm nomograms previously validated by us in infants and children (19) but not in newborns and premature infants (20). The high urine osmolality in the presence of low plasma osmolality observed on admission in all but one patient, together with the wt decrease observed on discharge in 21 of 23 patients, appear to confirm our hypothesis, as do the concomitant high ADH levels which revert to normal values on discharge (Fig. 3).

Our study group of infants, having recovered from bronchiolitis, had lower mean ADH levels than those in Rascher's study (21). This disparity cannot be explained exclusively on the grounds of different study populations or assay methods used. Further studies in this age group are needed to establish reliable reference values. Three mechanisms could have played a role in the causation of increased ADH observed in our patients. First, a vagal reflex stimulated by atrial baroreceptors triggered by decreased venous return. This is caused by the increased intrathoracic pressure associated with the increased work of breathing in bronchiolitis (22, 23). Hyperinflation caused by air trapping may, through the same mechanism, stimulate a similar ADH response (24). The second possible mechanism is hypoxemia,
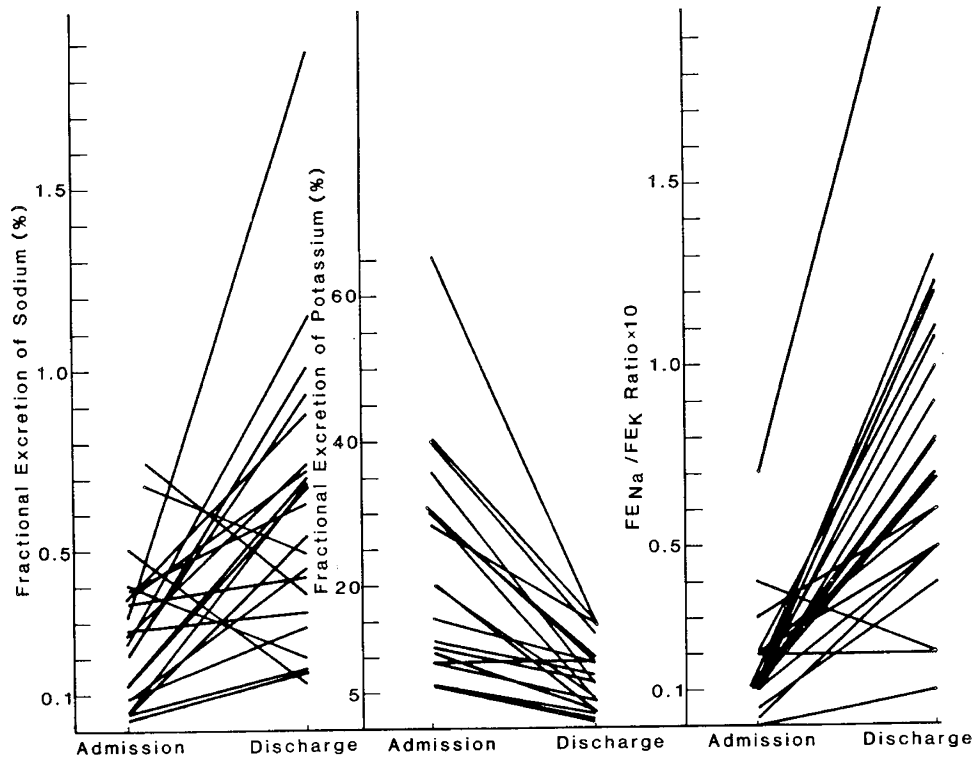
Fig. 5. Individual fractional excretions of FENa, FEK, and their ratio in infants with bronchiolitis. In the 10 stressed control infants FENa was 0.43 ± 0.18% (mean ± SD), FEK was 4.9 ± 0.2% and mean ratio 0.9 ± 0.3.
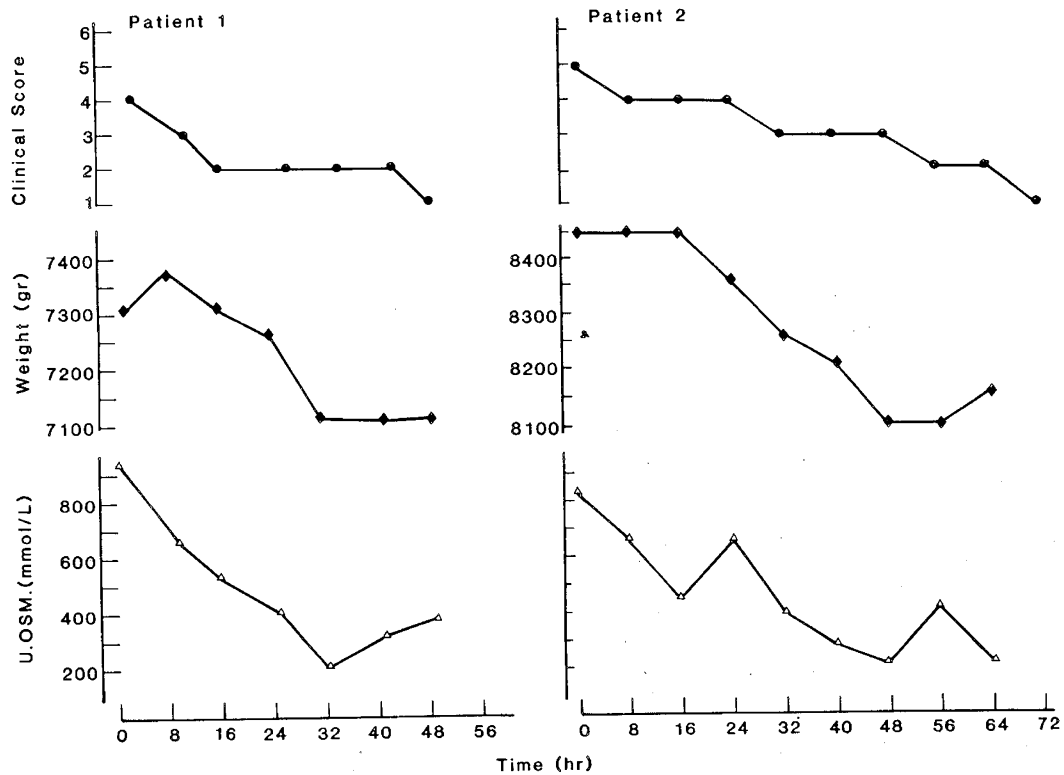

Fig. 6. Flow diagram of two illustrative cases of bronchiolitis with respect to clinical severity of respiratory distress, weight, and urinary osmolality.

which has been independently shown to induce ADH secretion (25–27). Finally, stress through central hypothalamic pathways may also play a role (23, 28). This latter mechanism may have been excluded by our findings in the control infants whose admission values were all comparable to the bronchiolitis group discharge values. it is, however, possible that the type or degree of stress caused by high fever may not be comparable to that associated with bronchiolitis.

PRA levels are expected to be low in the presence of high ADH because of increased plasma volume (29–32) and a direct inhibitory effect of ADH on renin secretion (33). The association of elevated PRA levels in patients with increased ADH seems to occur specifically in conditions resulting from increased intrathoracic pressure. The physiologic mechanisms by which PRA is elevated in bronchiolitis involve vagal reflexes similar to those described for ADH release in this clinical setting, *i.e.*, decreased venous return triggering atrial baroreceptors with ensuing stimulation of juxtaglomerular renin secretion through sympathetic pathways (32) and stress-associated PRA elevation (34, 35).

This hyperreninemia resulted in secondary hyperaldosteronism as evidenced by sodium retention (decreased FENa) and concomitant potassium diuresis (elevated FEK) as shown in Figure 5. This in turn could have contributed to further water retention and increase in the patients' body wt. The results of our study demonstrate two mechanisms operative in water retention in infants with bronchiolitis, *i.e.*, increased ADH and hyperreninemia and consequent hyperaldosteronism.

The recent observations by Dreyfus *et al.* (36), showing a marked decrease in free water clearance coincidental with increased plasma vasopressin in infectious pneumonia, probably reflect the same mechanisms, although PRA was not examined in their study.

Schwartz's original description of the syndrome of inappropriate ADH secretion requires that patients have an elevated urinary sodium excretion, or a normal or elevated fractional excretion of sodium as well as hyponatremia. Both of these findings were absent in our patients.

We hypothesize that the attempt to conserve salt and water is in fact appropriate to the clinical situation in which there is a perception, albeit erroneous, of hypovolemia. This in turn leads to activation of the mechanisms necessary to maintain volume. Thus, in the face of nonosmotic stimuli to vasopressin release in which there is activation of volume sensors, the urine will appear to be inappropriately concentrated but is consistent with the more pressing need to preserve intravascular volume. This is further buttressed by the finding of a parallel rise of PRA.

The concordant and similar directions in the change of vasopressin and plasma renin activity underscore the appropriate physiologic response demonstrated by the body to the perception that intravascular volume is contracted in lung disease involved with increased intrathoracic pressure. These two mechanisms have a masking effect on the serum sodium by virtue of their opposite influence on these levels. In SIADH, water retention and continuing natriuresis result in hyponatremia. In patients with bronchiolitis this seems to be counterbalanced by the hyperreninemic-hyperaldosteronism state inducing sodium retention. We assume that the relatively well-preserved serum sodium concentrations found in this elevated ADH setting were due to the accompanying secondary hyperaldosteronism.

Whether the dual response of ADH and PRA increase in bronchiolitis has any beneficial impact on the child with pulmonary disease, could perhaps be elucidated by studies in which vasopressin antagonists are administered in a similar clinical setting and noting the effect on the clinical course of the disease.

The possible effect of ANF was not investigated. The decreased filling of the right atrium caused by increased intrathoracic pressure and a resulting inhibition of ANF, may also have played a role in the sodium and fluid homeostasis of these patients.

In the management of infants with bronchiolitis the clinician may be misled by the normal serum sodium, but should be aware of the possibility of pending fluid overload. With this in mind, fluid intake should be carefully adjusted to the individual patient with this complex clinical condition, using the Uosm-Posm relationship together with close monitoring of body wt.

The observation by Tal *et al.* (37) showing that corticosteroid therapy had a beneficial effect on their bronchiolitis patients requires further investigation. Bearing in mind the fluid retention caused by both increased ADH and renin activity described by us, we share the reservations regarding use of corticosteroids in bronchiolitis in Skoner and Caliguri's recent review (38), and believe that caution should be exercised when using these fluid retaining hormones in this disease.

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