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Hypouricemia in Neonates with Syndrome of Inappropriate Secretion of Antidiuretic Hormone

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ABSTRACT. A prospective study of serum levels of uric acid in 23 hyponatremic neonates was performed. Infants on diuretic medications or with renal failure were excluded. The infants were separated into two groups: group I consisted of 11 neonates with clinical evidence of syndrome of inappropriate secretion of antidiuretic hormone (SIADH), (mean ± SD serum sodium 127 ± 1.36 mEq/liter). Group II included 12 infants with hyponatremia (mean serum sodium 128 ± 1.10 mEq/liter) associated with decreased effective vascular volume manifest by a fractional sodium excretion <1%. The groups were similar for gestational and postnatal ages, birth weight, clinical conditions, and concurrent use of drugs. The serum urate concentation in neonates with SIADH was 2.46 ± 0.54 mg/dl; serum urate concentration in group II infants was 8.49 ± 2.45 mg/dL ($p < 0.001$). Water restriction in the group I infants with SIADH resulted in a rise in mean serum urate concentration ($p < 0.001$). Fractional excretion of urate was elevated during hyponatremia in the group I infants (to 78 ± 0.13%) and fell to 51 ± 0.08% after correction ($p < 0.001$). In group I infants, a direct correlation was found between fractional excretion of urate and sodium ($r = 0.7667$, $p < 0.001$). These results indicate that hypouricemia is common in infants with suspected SIADH and seems to be due to increased urate clearance secondary to volume expansion. (*Pediatr Res* 19: 424–427, 1985)

Abbreviations

SIADH, syndrome of inappropriate secretion of antidiuretic hormone
FE_{Na}, fractional sodium excretion
SUr, serum urate concentration
FE_{Ur}, fractional urate excretion
ECFV, extracellular fluid volume
AVP, arginine vasopressin
C_{Cr}, creatinine clearance

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The diagnosis of SIADH in neonates and its differentiation from other common causes of hyponatremia is often difficult (1–6). In the syndrome of SIADH, dilution of body fluids occurs because of the inability of the kidney to excrete free water appropriately. Total body sodium content is normal or only moderately decreased; intravascular volume is slightly increased (7, 8). In most other hyponatremic syndromes there is either a marked increase (as in edematous states) or a marked decrease in total body sodium (as in true hypovolemia). In these latter conditions, excretion of water by the kidney may be impaired as a result of the decrease in effective intravascular volume (9). This in turn may cause decreased delivery of glomerular filtrate to distal nephron sites of dilution (10) or may initiate a nonosmolar stimulus to pituitary antidiuretic hormone release (9).

The present study was conducted to test the hypothesis that the "effective intravascular volume" is a potent modulator of renal urate clearance by the kidney and that SUr might reflect changes in effective volume (11–13).

PATENTS AND METHODS

Twenty-three newborn infants with postnatal ages ranging from 2 to 7 days were evaluated because of hyponatremia (serum sodium concentration < 130 mEq/liter) and hypoosmolality of body fluids (serum osmolality <270 mOsmol/kg) of 1 to 3 days duration. Patients with evidence of renal insufficiency (abnormal urinary sediment, serum concentration of creatinine of greater than 1 mg/dl) were excluded from study. Also excluded were

patients who had received diuretic agents. No patient had undergone a radiologic dye study. The patients were separated into two groups. Group I included 11 patients with probable SIADH with a mean gestational age of 34 wk and mean birth weight of 1935 g. Group II contained the remaining 12 patients with hyponatremia with a mean gestational age of 34.5 wk and a mean birth weight of 1870 g.

The presumptive diagnosis of SIADH was based on the following criteria: hypoosmolality of body fluids (as defined above), urinary osmolality of >300 mOsmol/kg, absence of edema or clinical signs of volume depletion, normal creatinine clearance, and absence of clinical evidence of endocrine deficiency (7, 8). Sepsis, pulmonary, and/or central nervous system abnormalities were present in all group I patients, and all required assisted ventilation. Of the 12 group II patients, eight had clinical signs of sodium depletion, usually due to gastrointestinal loss, and four manifested congestive heart failure with sodium overload and edema. All patients in group II had prerenal azotemia, with FE_{Na} of <1% suggesting decreased effective intravascular volume (14). The associated clinical conditions in group II included respiratory distress syndrome, sepsis, necrotizing enterocolitis, and intracranial bleeding. Most patients in this group required assisted ventilation (nine of 12).

Group I and II patients were similar with regard to concurrent use of medications and none had been given a hypouricemic agent. Fluid intake in each patient prior to the diagnosis of hyponatremia was 120 to 150 ml/kg/day and was adjusted to maintain a urine production rate of >3 ml/kg/h. Sodium intake was 3 mEq/kg/day.

Accurately timed 4- to 6-h urine samples were collected from each infant using a plastic urine bag. An arterialized capillary blood specimen (1 ml) was obtained during the urine collection and the serum was separated by rapid centrifugation (3000 rpm × 5 min) at room temperature. Each urine and serum sample was frozen at −20° C after collections were completed. Creatinine content of serum and urine was measured with a Beckman Creatinine Analyzer. Sodium was measured by flame photometry and uric acid with an iron reduction method. Filtered urate was calculated as the product of SUr and glomerular filtration rate (GFR). GFR was measured by endogenous C_{Cr}. FE_{Ur}, FE_{Na}, and free water clearance (C_{H2O}) were derived from the following formulas:

$$FE_{Ur} = C_{Ur}/C_{Cr} \times 100$$
$$FE_{Na} = C_{Na}/C_{Cr} \times 100$$
$$C_{H_2O} = V - C_{Osmol}$$

where C_{Ur} = urate clearance, C_{Na} = sodium clearance; and C_{Osmol} = osmolar clearance. All clearance studies were carried out during the period of hyponatremia.

Mean values in the two groups were compared using Student's two-tailed t test (15). Values are recorded as mean and SD. The study was approved by the University of Illinois Health Sciences Center Institutional Review Committee on Human Research.

RESULTS

The mean serum sodium concentration in the group I SIADH newborns was 127 ± 0.36 mEq/liter, a value similar to that in the group II infants (serum sodium = 128 ± 1.10 mEq/liter).

Figure 1 shows the individual SUr in the two groups of patients. The mean SUr in the infants with SIADH was 2.64 ± 0.54 mg/dl. In group II patients, the mean value was 8.49 ± 2.45 mg/dl ($p < 0.001$). The absolute SUr was <3.1 mg/dl in all 11 neonates with SIADH, whereas all patients with other causes of hyponatremia had values of 4 mg/dl or more.

To determine whether the relative hypouricemia in the SIADH infants was more closely related to the underlying disease or to the hyponatremia, SUr was assessed after correction of the hyponatremia by water restriction. For this purpose, daily maintenance fluid intake was restricted 50% over a period of 24 to 48 h. The mean SUr in these patients rose from 2.46 ± 0.54 to 4.95 ± 0.86 mg/dl ($p < 0.001$) after correction of hyponatremia. Moreover, as shown in Figure 2, the change in serum urate was consistent and occurred in every patient as serum osmolality was restored to normal.

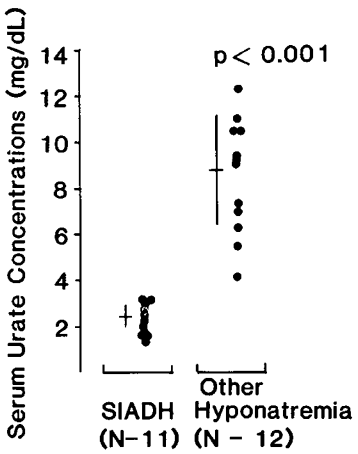

Fig. 1. Serum urate concentrations are compared in newborns with presumptive SIADH and those with decreased effective vascular volume. Mean values ± SD are given by *horizontal* and *vertical lines*, respectively, number of patients are given in *parentheses*.

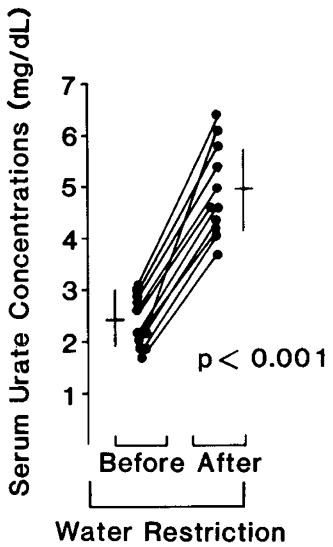

Fig. 2. Serum urate concentrations are compared before and after water restriction in infants with a presumptive diagnosis of SIADH. Mean values ± SD are given by *horizontal* and *vertical lines*, respectively, number of patients are given in *parentheses*.

To examine the pathophysiology of hypouricemia in SIADH, creatinine, urate, and free water clearance studies were performed before and after water restriction in the group I infants. Table 1 summarizes the results. Urate clearance (2.31 ± 0.68 ml/min), FE_{Na} (4.25 ± 0.67%), and FE_{Ur} (78 ± 0.3%) were elevated at the time of hyponatremia but fell significantly with restoration of normal plasma osmolality by water restriction (1.46 ± 0.36 ml/min, 2.5 ± 0.29%, and 51 ± 0.08%, respectively, each $p < 0.001$). As shown in Figure 3, the change in FE_{Ur} was consistent and occurred in every patient as hypoosmolality was corrected. In all studies, there was a direct and significant correlation between FE_{Ur} and FE_{Na} ($r = 0.7667$, $p < 0.001$, Fig. 4).

DISCUSSION

The criteria for a presumptive clinical diagnosis of SIADH include hyponatremia and hypoosmolality of body fluids with

Table 1. *Summary of clearance studies in 11 neonates with the SIADH (mean ± SD)**

	Fluid restriction		
	Before	After	*p*
Wt (g)	1935 ± 18	1863 ± 11	<0.05
SNa (mEq/liter)	127 ± 1.36	136 ± 1.05	<0.05
SOsm (mOsmol/kg)	262 ± 2.28	276 ± 2.77	<0.01
SUr (mg/dl)	2.46 ± 0.54	4.95 ± 0.86	<0.001
V (ml/min)	0.07 ± 0.01	0.04 ± 0.01	<0.01
UOsm (mOsmol/kg)	328 ± 5.31	676 ± 13.8	<0.01
C_{Cr} (ml/min)	2.99 ± 1.01	2.93 ± 1.01	NS
F.Ur (mg/min)	7.25 ± 3.08	14.23 ± 4.77	<0.001
C_{Ur} (ml/min)	2.31 ± 0.68	1.46 ± 0.36	<0.001
FE_{Ur} (%)	78 ± 1.30	51 ± 0.08	<0.001
FE_{Na} (%)	4.25 ± 0.67	2.57 ± 0.29	<0.001
C_{H_2O} (ml/min)	−0.01	−0.05	<0.05

* Abbreviations: SNa, serum sodium; SOsm, serum osmolality; V, urine flow; UOsm, urine osmolality; F.Ur, filtered load of urate; C_{Ur}, urate clearance; C_{H_2O}, free water clearance.

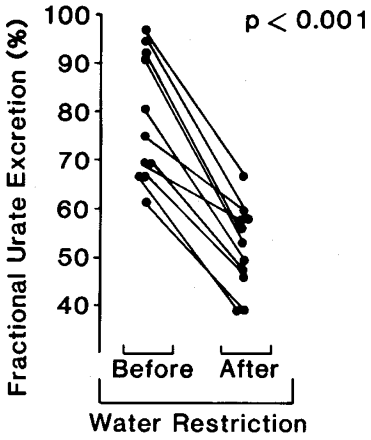

Fig. 3. Fractional urate excretion is compared before and after water restriction in the presumptive SIADH patients. Mean values ± SD are given by *horizontal* and *vertical lines*, respectively, number of patients are given in *parentheses*.

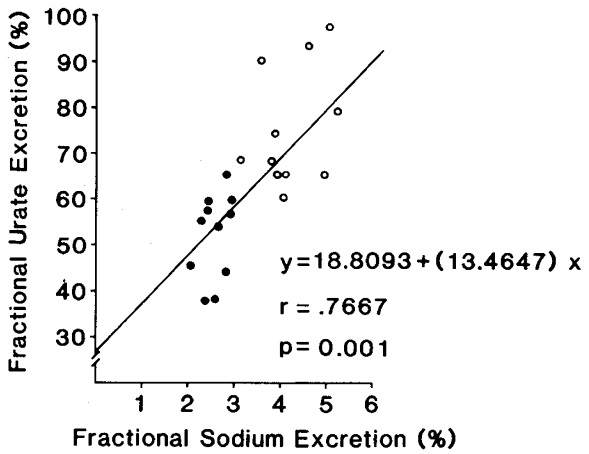

Fig. 4. Correlation betwen fractional urate excretion and fractional sodium excretion in neonates with presumptive SIADH, before (○) and after (●) water restriction.

simultaneous inappropriate osmolality of urine, which contains appreciable amounts of sodium, in a patient who shows no signs of hypovolemia and has normal renal and adrenal functions (7, 8). In the present study, group I infants met these diagnostic criteria. Plasma or urine AVP concentrations were not measured in these patients; thus, the diagnosis was not definitive (6, 16, 17).

Alterations of ECFV previously have been demonstrated to lead to changes in net tubular reabsorption of urate (11, 13). Urate is thought to be nearly completely filtered at the glomerulus. In the renal tubule urate is reabsorbed and secreted by relatively specific tubular transport processes (18); the amount of urate finally excreted in the urine appears to depend on the balance between tubular secretion and postsecretory reabsorption (11, 19, 20). Renal tubular urate transport is sensitive to many influences including the serum concentration of urate, changes in ECFV (12, 13), and age-related maturation of renal function during the early days of life (21). Expansion of ECFV increases urate clearance by inhibiting tubular reabsorption (12, 13); contraction of ECFV decreases the urate clearance, probably by enhancing tubular reabsorption. SUr, in turn, reflects the changes in urate clearance (12, 13).

In SIADH, there is usually some degree of volume expansion which leads to an increased clearance of urate and hypouricemia (22). This can be corrected by restriction of fluid intake and amelioration of volume expansion (23). The results of the present study are consistent with this hypothesis. The SUr in newborn infants is slightly higher than the values reported for children and adults (24–26). In normal infants, SUr increases from a mean value of 6.0 mg/dl in cord blood to 7.0 mg/dl at 24 h (26). Prolonged labor and respiratory distress tend to be associated with even higher SUr concentrations in the neonate (26). This relative hyperuricemia is thought to be the result of increase urate production; uric acid excretion does not appear to be limited by the immaturity of the neonatal kidney (26, 28, 29). In neonates, the mean FE_{Ur} is nearly three time the upper normal adult limit (28). Values as high as 70% are observed at 29 to 31 wk gestation; the mean value at term is 38% (29). The high FE_{Ur} during the neonatal period reflects increased tubular secretion, decreased tubular reabsorption, or both (28, 29).

The finding of low SUr in virtually every neonate with SIADH in our study is consistent with observations in adults with this syndrome (22, 23). The highest SUr in the present SIADH infants was 3.1 mg/dl. In sharp contrast, all hyponatremic patients in group II had SUr >4.0 mg/dl. Thus the two groups could be distinguished on the basis of SUr. The hypouricemia in the infants with SIADH could not have been merely a result of dilution since SUr values rose 100% during water restriction, whereas the serum concentrations of sodium increased only 5%.

Hypouricemia in SIADH may be caused by decreased urate production, increased urinary excretion of urate, or both. Although 24-h urinary excretion of urate was not measured in our patients, FE_{Ur} was high in every patient with the syndrome, a finding that probably excludes decreased production as a cause of hypouricemia. An increased filtered load of urate cannot explain the high FE_{Ur} in our babies with SIADH because the calculated amount of uric acid filtered at the glomerulus during water restriction was inversely related to FE_{Ur} (Table 1). Moreover, the clearance of urate was increased in the SIADH infants. This clearly is a secondary consequence of the water-expanded state since serum urate rose and urate clearance returned to normal after restoration of normal serum osmolality by water restriction. The correlation between FE_{Ur} and FE_{Na} in our subjects (Fig. 4) is consistent with this interpretation and indicates that net urate reabsorption is influenced by the state of hydration of the ECFV.

It is unlikely that a direct action of AVP on renal transport of urate is responsible for the increased clearance of urate in the SIADH patients. AVP, in the absence of volume expansion, has been shown to decrease urate clearance (30). Further, it has been demonstrated that AVP promotes the reabsorption of urate across the toad bladder (31). Thus our results suggest that hypouricemia is common in newborns with SIADH. The hypouricemia in such infants seem to be due to increased urate clearance

secondary to volume expansion. Although the coexistence of hypouricemia and hyponatremia may provide a helpful clue favoring the diagnosis of SIADH, other possibilities must be considered. The combination may occur, for example, in hereditary renal tubular disorders, such as Wilson disease, Hartnup disease (32), Fanconi syndrome, and severe liver disease (27, 33).

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