Pediatr Nephrol (1995) 9: 375–381

Pediatric Nephrology

Practical pediatric nephrology

The syndrome of inappropriate secretion of antidiuretic hormone

George B. Haycock

Department of Paediatrics, UMDS (Guy's Campus), 12th Floor, Guy's Tower, Guy's Hospital, St Thomas's Street, London SE1 9RT, UK

Received October 14, 1994; received in revised form October 24, 1994; accepted October 26, 1994

Abstract. The physiology of the release of antidiuretic hormone (ADH) from the posterior pituitary is briefly reviewed. The importance of both osmolar and non-osmolar stimuli is emphasised. Osmolar and non-osmolar factors usually reinforce each other; for example, hydropenia leads to hyperosmolality and hypovolaemia, both promoting ADH release, while hydration has the opposite effect. In disease, osmolar and non-osmolar factors may become dissociated leading to baroreceptor-mediated ADH release in the presence of hyponatraemia and hypo-osmolality. Examples include heart failure, glucocorticoid or thyroxine deficiency, hepatic cirrhosis and nephrotic syndrome with or without the superimposed effect of diuretics, i.e. conditions in which circulatory, and in particular effective arterial, volume is reduced. It is dangerous to label such conditions as 'inappropriate' secretion of ADH since the maintenance of circulating volume is at least as important a physiological requirement as the defence of tonicity. The syndrome of inappropriate secretion of ADH (SIADH) is uncommon in childhood and should only be diagnosed when physiological release of ADH in response to non-osmolar as well as osmolar factors has been excluded. Criteria for the correct identification of SIADH are discussed; the presence of continuing urinary sodium excretion in the presence of hyponatraemia and hypo-osmolality is essential to the diagnosis. SIADH in children is usually due to intracranial disease or injury. The mainstay of treatment is water restriction which reverses all the physiological abnormalities of the condition. Hypertonic saline is rarely indicated for the short-term control of neurological manifestations such as seizures. Drugs have little or no place in the treatment of SIADH in children. In many situations labelled as SIADH it is only the diagnosis that is inappropriate.

Key words: Antidiuretic hormone – Arginine vasopressin – Hyponatraemia – Sodium – Baroreceptors – Osmolality

Introduction

In 1957, Schwartz et al. [1] described two adult patients with carcinoma of the bronchus who developed persistent hyponatraemia and hypo-osmolality with urinary wasting of sodium and chloride that could not be corrected with oral or intravenous salt. They speculated that the cause was secretion of antidiuretic hormone (ADH) in amounts inappropriate to the prevailing low plasma osmolality. Ten years later, in a detailed review, Bartter and Schwartz [2] coined the term 'syndrome of inappropriate secretion of ADH' (SIADH). In the same paper they set out the criteria to be met before making the diagnosis; these criteria remain sound 27 years on and are discussed below.

Control of ADH secretion

Arginine vasopressin, the human ADH, is a cyclic nonaide similar in structure to oxytocin (Fig. 1). It is synthesised in the cell bodies of neurons in the supraoptic and paraventricular nuclei of the anterior hypothalamus and released into the blood from the axons of the same neurons, which terminate in the posterior pituitary (neurohypophysis). Its two major physiological actions are: (1) to increase the permeability of the collecting duct of the nephron to water, the *hydro-osmotic effect* and (2) to cause arteriolar vasoconstriction and a rise in arterial blood pressure, the *pressor effect*. The receptors that mediate the pressor and hydro-osmotic effects are designated V_1 and V_2, respectively; complementary DNA and messenger RNA for both have now been cloned and selective blocking compounds developed [3]. The ADH-dependent increase in tubule water permeability is due to insertion of water channels in apical membranes of collecting duct principal cells [4]. The hormone stimulates electrolyte transport in certain nephron segments [5] and increases the permeability of the inner medullary collecting duct to urea [6], processes that further enhance urinary concentration. Via V_2 receptors, ADH also facilitates haemostasis by effects

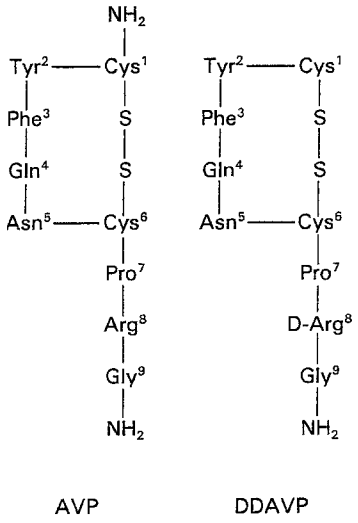

Fig. 1. The molecular structure of the human antidiuretic hormone, arginine vasopressin (*AVP*). The structure of the pharmacological analogue 1-deamino, 8-D-arginine vasopressin (*DDAVP*) is also shown

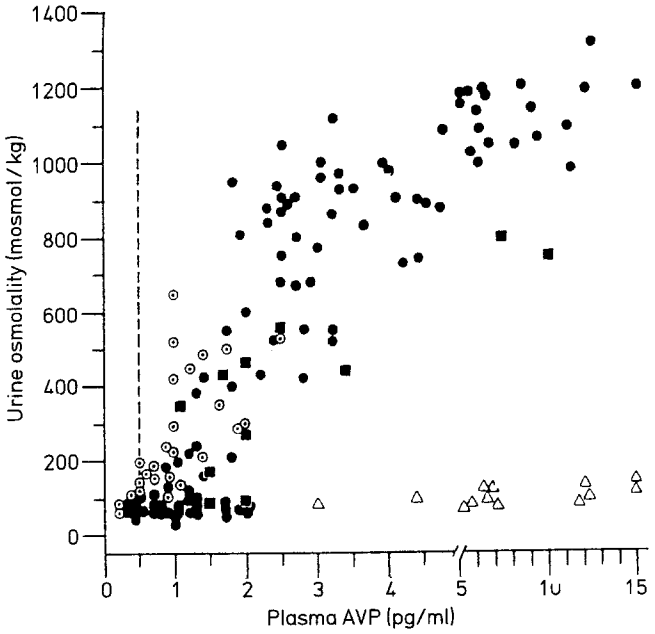

Fig. 2. The relationship of plasma AVP to urine osmolality in normal subjects (●, n = 23) and in patients with polyuria of diverse aetiologies (■, primary polydipsia, n = 2; △, nephrogenic diabetes insipidus, n = 2; ⊙, pituitary diabetes insipidus, n = 8). Reproduced from Robertson et al. [7] with permission

on megakaryocytes and factor VIII synthesis; these actions will not be discussed further in this article.

By its hydro-osmotic effect, ADH increases the osmotic concentration of urine. If renal function is normal, urinary osmolality (U_{OSM}) varies from a minimum of 40–50 mosmol/kg H_2O in the absence of detectable circulating ADH to a maximum of about 1,200 mosmol/kg H_2O at a plasma ADH concentration (P_{ADH}) of 5 pg/ml [7]. Between these limits the relationship between P_{ADH} and U_{OSM} is approximately linear (Fig. 2). Plasma concentrations higher than 5 pg/ml have no further effect on U_{OSM}.

The pressor effect of ADH comes into play at plasma concentrations higher than that necessary to produce maximally concentrated urine. The physiological role of this action has not been well defined in humans, but in experimental animals it appears to be one of the effectors that maintain central arterial blood pressure, and therefore perfusion of vital organs, in states of volume contraction or when [1] effective arterial volume is reduced, such as in heart failure [8] or hypotension induced by epidural anaesthesia [9].

Osmolar control of ADH release

Verney [10] showed that altering the tonicity of the blood in the carotid artery of a dog led to changes in urine flow rate, and inferred the existence of an ADH produced somewhere in the brain (probably the hypothalamus) that maintained extracellular fluid (ECF) osmolality within a narrow range by regulating the rate of urinary water excretion [11]. This brilliant insight was confirmed much later by direct measurement of P_{ADH}. The *osmoreceptor* that perceives changes in ECF osmolality is a group of specialised cells lying close to, but distinct from, the cells that synthesise ADH. The results of ablation experiments implicate the organum vasculosum of the lamina terminalis in dogs [12] and the subfornical organ in rats [13, 14]. The signal received is probably an osmotically induced change in the volume of the osmoreceptor cells themselves. It is important to note that it is the ECF concentration of only those solutes that do not readily diffuse into the cells that have this property. Thus, in most circumstances it is the ECF concentration of sodium chloride that is the principal determinant of osmotic ADH release. The osmoreceptor feedback loop operates at very high gain, a 2% increase in the controlling variable (plasma osmolality) being sufficient to cause the controlled variable (urine osmolality) to change from minimal to maximal. ADH is undetectable in plasma below an osmotic threshold of about 286 mosmol/kg H_2O in man [7] and about 290 in the rat [15], and rises in a linear fashion as P_{OSM} rises above this value (Fig. 3).

Non-osmolar control of ADH release

Verney [10] noted that stimuli other than changes in osmolality, such as a mild electric shock, could alter urine flow rate and concentration, and concluded that 'stress' might be another factor influencing ADH release. Later studies confirmed that hypovolaemia and hypotension caused P_{ADH} to rise [15], sometimes to levels much higher than that needed to produce maximally concentrated urine. The afferent component of this control system consists of baroreceptors located in the carotid sinuses, aortic arch,

[1]) Effective arterial volume is a hypothetical concept relating the fullness of the arterial (high pressure) compartment of the circulation to its holding capacity. Reduction in effective arterial volume may be due to hypovolaemia without change in capacity (e.g. haemorrhage) or to vasodilatation without change in volume (e.g. administration of hydralazine).

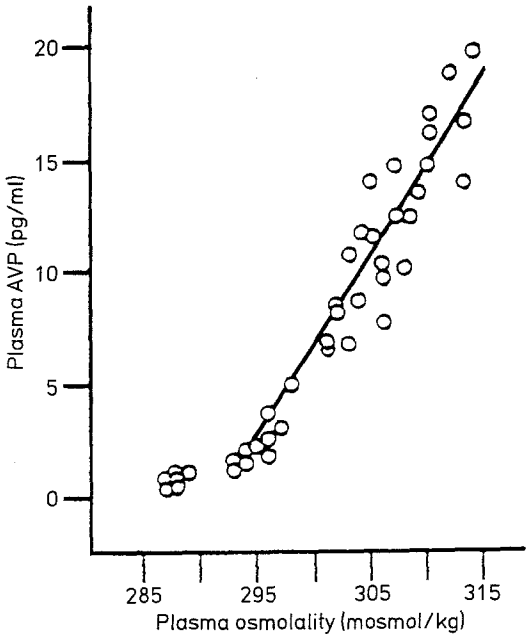

Fig. 3. The relationship of plasma AVP to isovolaemic changes in plasma osmolality in the rat, induced by the intraperitoneal injection of saline solutions of different osmolalities. Reproduced from Dunn et al. [15] with permission. $P_{AVP} = 0.83\ (P_{OSM} - 292)$, $r = 0.95$, $P < 0.001$

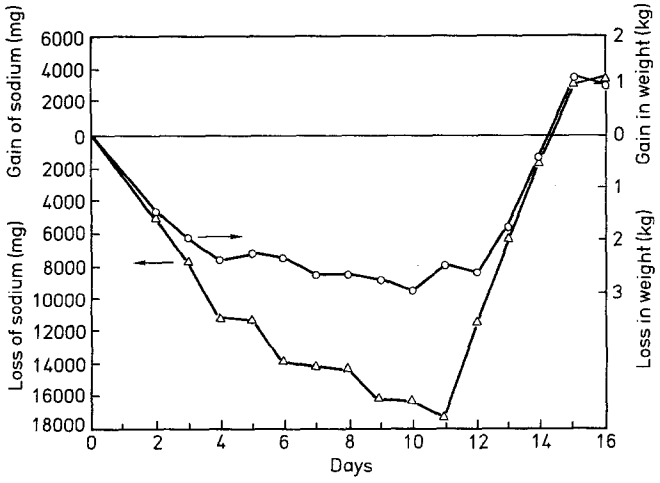

Fig. 5. Changes in body sodium content and body weight during 11 days of progressive salt depletion in three human volunteers. Salt depletion was accomplished by administration of a diet very low in salt and repeated thermally induced sweating. Free access to water was allowed throughout the experiment. Initially, salt loss in accompanied by proportionate water loss leading to extracellular fluid volume contraction. From the 3rd day weight is maintained despite continuing negative sodium balance, due to water retention presumably caused by baroreceptor-mediated AVP release. The weight scale and the sodium scale are so constructed that 1 kg in weight corresponds to 3,300 mg (140 mmol) sodium. Reproduced from McCance [19] with permission

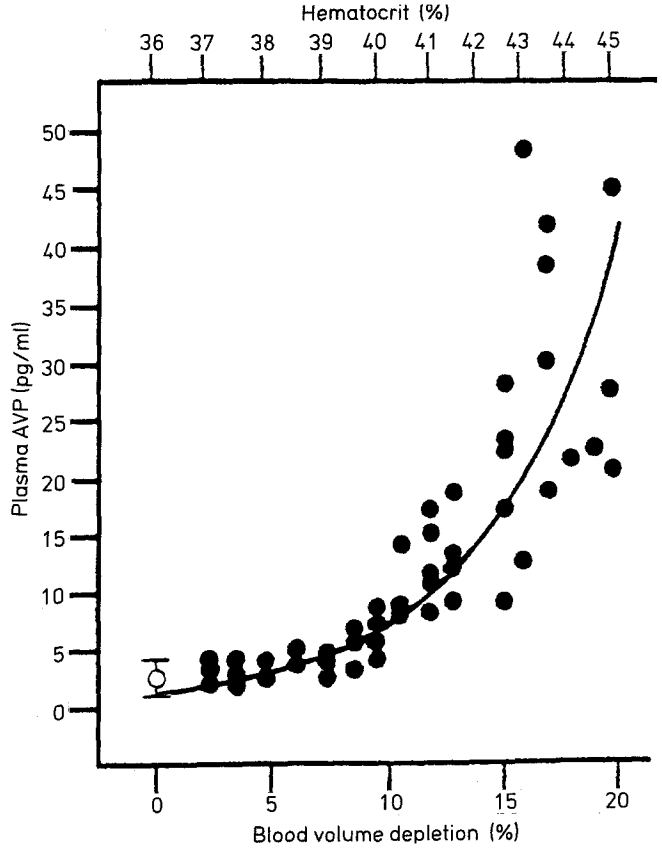

Fig. 4. The relationship of plasma AVP to isosmotic changes in blood volume in rats, induced by intraperitoneal injection of isotonic saline containing polyethylene glycol at concentrations of 100, 150, 200 or 250 mg/ml. Changes in blood volume were calculated from changes in haematocrit. Reproduced from Dunn et al. [15] with permission. $P_{AVP} = 1.3e^{-0.17\triangle \blacksquare vol}$, $r = 0.89$, $P < 0.001$

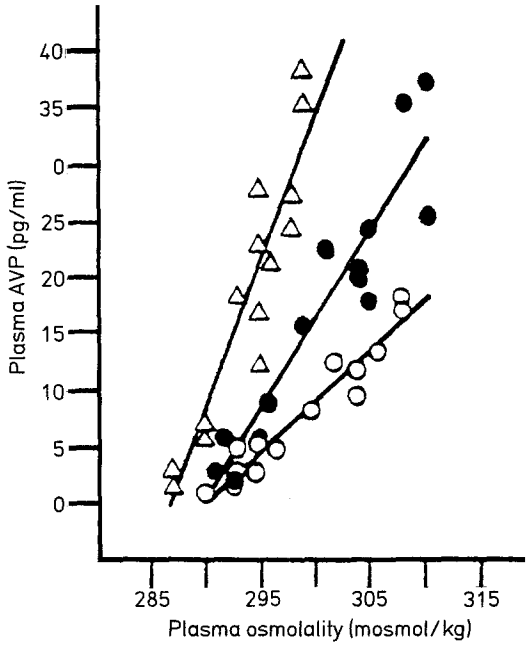

Fig. 6. The effect of hypovolaemia on the plasma AVP response to osmotic stimulation in rats. Osmolality and blood volume were manipulated simultaneously by intraperitoneal injection of saline solutions of different osmolalities with or without polyethylene glycol in varying concentrations. 'Small' and 'large' volume depletion refers to a reduction in blood volume of $6.3 \pm 1.6\%$ and $14.5 \pm 0.6\%$, respectively. ○, Controls, $P_{AVP} = 2.6\ (P_{OSM} = 287)$, $r = 0.93$, $P < 0.001$; ●, small volume depletion; $P_{AVP} = 1.6\ (P_{OSM} = 290)$, $r = 0.93$, $P < 0.001$; △, large volume depletion; $P_{AVP} = 0.91\ (P_{OSM} = 290)$, $r = 0.96$, $P < 0.001$. Reproduced from Dunn et al. [15] with permission

Table 1. Criteria for the diagnosis of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Plasma	– hyponatraemia – hypo-osmolality
Urine	– not maximally dilute[a] – contains sodium
Vascular volume	– normal or increased
Blood pressure	– normal
Renal function	– normal
Adrenal function	– normal
Thyroid function	– normal
Cardiac function	– normal

[a] The urine does *not* have to be more concentrated than the plasma

cardiac atria and great veins. The results of experiments involving carotid sinus denervation and bilateral cervical vagotomy [16–18] suggest strongly that baroreceptor stimulation is the main, if not the only, non-osmolar trigger for ADH release and accounts for impaired urinary dilution in several conditions known to be associated with P_{ADH} higher than would be expected from plasma osmolality alone. These include cardiac failure, glucocorticoid and thyroxine deficiency and some cases of cirrhosis of the liver and nephrotic syndrome. Under experimental conditions, the gain of the baroreceptor-mediated feedback system is much lower than that of the osmolar one, with plasma volume needing to be reduced by 8%–9% before a significant response is seen. When plasma volume falls beyond this point, however, the relationship between plasma volume and P_{ADH} is approximately exponential, and very high ADH concentrations are achieved with only small further reductions in volume (Fig. 4).

Interaction between osmolar and non-osmolar control of ADH release

Dehydration, the commonest naturally occurring disorder of water balance, leads to both hypernatraemia and volume contraction; osmolar and baroreceptor stimuli are therefore activated in parallel. Similarly, water repletion will normally inhibit both osmolar and baroreceptor stimulation of ADH release. When there is a change in either osmolality or volume without a corresponding change in the other variable, or when the two change in opposite directions, conflicting signals may arise. Because of the different gains and sensitivities of the two feedback loops, the osmotically mediated signal predominates when the volume change is relatively small ($<5\%–8\%$ of control values) but the baroreceptor-mediated response overrides the osmolar control system when volume contraction is marked. Put teleologically, osmoregulation takes second place to maintenance of central blood pressure in life-threatening volume contraction: dilutional hyponatraemia is preferable to death from circulatory failure. The operation of this mechanism is beautifully illustrated in an experiment performed in 1934 by McCance [19] (Fig. 5). In less extreme conditions, the threshold and slope of the relationship between P_{OSM} and P_{ADH} are continuously modulated by the level of baroreceptor activity (Fig. 6) [15].

Criteria for diagnosis of SIADH

SIADH should only be diagnosed when P_{ADH}, and therefore U_{OSM}, is inappropriately high as judged by *both* osmolar *and* non-osmolar criteria. The clinical features of the condition, as originally proposed by Bartter and Schwartz [2], are listed in Table 1. The hyponatraemia of mineralocorticoid deficiency, caused primarily by urinary salt wasting, is exaggerated by renal water retention secondary to both ADH release and an ADH-independent increase in the permeability of the collecting duct to water [20, 21]. Likewise, glucocorticoid deficiency causes renal water retention partly by causing ADH release [21, 22] and partly by a direct effect on the tubule [20]. The high ADH levels found in cardiac failure and hypothyroidism are probably baroreceptor mediated and respond to treatment of the causative condition. Urinary dilution is impaired in renal failure and in some tubular disorders, independent of ADH levels. The cerebral salt-wasting syndrome (CSWS), rarely recognised in children, may be underdiagnosed because it occurs in clinical situations in which SIADH may be seen, and shares some features with it (hyponatraemia and high urinary sodium concentration). However, CSWS is a polyuric state associated with gross urinary salt wasting and volume contraction, while SIADH is characterised by oliguria, volume expansion and mild, self-limiting salt loss. The two conditions should not be difficult to distinguish on clinical grounds. CSWS may be due to inappropriate secretion by the brain of atrial natriuretic peptide or the closely related brain natriuretic peptide [23].

Pathophysiology of SIADH

SIADH has been experimentally modelled in normal subjects by the administration of exogenous ADH [24]. The immediate response is water retention, leading to weight gain and hyponatraemia. Urinary sodium excretion increases despite the hyponatraemia and a period of negative sodium balance ensues. After a few days sodium excretion falls again to match dietary input and a new steady state is established, in which total body water is expanded, total body sodium is reduced and sodium excretion is responsive to changes in sodium input [25]. Total body cation is not reduced because potassium is retained. The same sequence of events is seen in 'natural' SIADH [1, 26].

The establishment of a new equilibrium results from the influence of factors other than ADH on sodium and water excretion. Aldosterone is suppressed by volume expansion during the initial phase of the condition but later rises again, perhaps in response to hyponatraemia, limiting sodium loss and restoring the capacity to regulate acid-base and potassium status [27]. The plasma concentration of atrial natriuretic peptide is increased, and recent evidence suggests that this is a major, and perhaps the predominant, factor in the natriuresis of SIADH [28, 29]. Similarly, ex-

Table 2. Malignant neoplasms associated with SIADH

Pulmonary
oat-cell carcinoma
epidermoid carcinoma
adenocarcinoma
mesothelioma
Gastrointestinal
duodenum
pancreas
stomach
Genitourinary
prostate
bladder
ureter
Other
Hodgkin's disease
adrenocortical carcinoma

Table 3. Intracranial causes of SIADH

Infectious
tuberculous meningitis
bacterial meningitis
herpes simplex encephalitis
brain abscess
Vascular
aneurysm
cerebrovascular disease
subarachnoid haemorrhage
cavernous sinus thrombosis
Neoplastic
Congenital malformations
Traumatic
Other
hydrocephalus
Guillain-Barré syndrome
status epilepticus
sarcoidosis

Table 4. Non-malignant pulmonary diseases and psychiatric conditions associated with SIADH

a) Pulmonary diseases:
tuberculosis
pneumonia
aspergillosis
empyema
chronic obstructive lung disease
positive pressure ventilation
b) Psychiatric disorders:
schizophrenia
compulsive water drinking

Causes of SIADH

Table 5. Drugs that cause renal water retention

(1) By promoting ADH release:
barbiturates
carbemazepine
clofibrate
colchicine
isoprenaline
nicotine
vincristine
(2) By potentiating the action of ADH:
chlorpropamide
cyclophosphamide
(3) By increasing nephron water permeability:
vasopressin (ADH)
1-deamino, 8-D-arginine vasopressin (DDAVP)
other vasopressin analogues
oxytocin
vasotocin
(4) By inhibiting prostaglandin synthesis:
salicylates
indomethacin
paracetamol
other non-steroidal anti-inflammatory drugs

ternal water balance is restored by a progressive increase in urine flow rate as weight increases. By definition, this cannot be the result of suppression of ADH. Several other processes are probably involved. Volume expansion, by increasing delivery to the distal nephron, reduces transit time through the collecting duct and limits the time available for osmotic water reabsorption. Increased vasa recta blood flow causes wash-out of medullary solute, diminishing the osmotic gradient for water reabsorption. There is evidence that the permeability of the collecting duct to water increases by a process independent of ADH [30, 31]. These compensatory factors that limit water retention are sufficiently powerful that oedema is rarely, if ever, seen in SIADH. Symptoms, when present, are due to hyponatraemia.

Since its original description in bronchial carcinoma, SIADH has been described as a complication of many other malignant neoplasms (Table 2). However, extracranial malignancy rarely or never causes the syndrome in children. Other major categories of disease in which SIADH has been described include intracranial causes (Table 3), non-neoplastic pulmonary diseases (Table 4) and psychiataric disorders (Table 4). Intracranial causes predominate in paediatric practice. Several drugs can induce inappropriate ADH release or cause water retention by other mechanisms (Table 5). A few 'idiopathic' cases have been reported in which no underlying disease could be identified.

Management of SIADH

The first step in management is to make the correct diagnosis. It is particularly important to differentiate between SIADH and conditions in which P_{ADH} is high as a result of

Table 6. Drugs that antagonise the effects of ADH on water excretion

Lithium carbonate	– causes tubular resistance to ADH – doesn't always work – has side effects
Demeclocycline	– impairs tubular generation of cAMP – interferes with effects of cAMP
Ethanol	– interferes with hypothalamic release of ADH – intoxicating does may be required – has side effects – unsuitable for use in children
Phenytoin (Dilantin)	– interferes with hypothalamic release of ADH – has been effective in limited experience
Vasopressin analogues	– block tubular ADH receptors – d(CH_2)$_5$ Tyr(Et)VAVP

baroreceptor stimulation (hypovolaemia, hypotension, cardiac failure, adrenal and thyroid deficiency), since these conditions require quite different treatment from SIADH. The most reliable differentiating feature is the urinary sodium excretion rate which is low in hypovolaemia and related conditions and high in SIADH (equal to or greater than intake). The condition underlying the SIADH should be treated if possible. However, the disease may be refractory to treatment and in any case it may be some time before a response is seen; symptomatic treatment should be instituted as soon as the diagnosis is made.

All the physiological abnormalities of SIADH are secondary to water retention: hyponatraemia, volume expansion and sodium depletion. Predictably, they are completely reversed by water restriction, which is the only treatment needed in the great majority of children. All but a very few paediatric cases of SIADH have a transient form of the condition, and water intake should be limited to the amount that keeps the plasma sodium concentration normal for as long as the underlying condition persists. Very occasionally, the plasma sodium is low enough to cause neurological symptoms and signs (usually seizures) even in patients whose underlying condition is not a neurological one. These patients usually have a sodium concentration below 120 mmol/l. In such cases it is appropriate partially to correct the hyponatraemia with 3% or 5% sodium chloride. This will only be transiently effective because of the renal salt wasting state characteristic of SIADH, and must be accompanied and followed by water restriction to control the condition more physiologically. Even in these rare cases care should be taken not to raise the plasma sodium concentration too rapidly or by too great an increment because of the risk of causing permanent brain damage (central pontine myelinolysis). The aetiology of this devastating condition is controversial, some experts holding the view that the cause is too rapid correction of hyponatraemia while others maintain that it is the severity of the original hyponatraemia. While doubt exists it is certainly prudent to give the smallest amount of hypertonic saline that reverses the neurological symptoms.

Chronic SIADH, of the kind that affects adults with carcinoma, rarely if ever occurs in the paediatric population. Even in patients with this variant, water restriction is the best and most physiological treatment but may be very difficult to achieve, particularly since some patients may have an associated abnormality of thirst. Several drugs antagonise the effect of ADH (Table 6) and some have a place in the management of chronic SIADH. Of these, demeclocycline (dimethylchlortetracycline) is probably the first choice, being more consistently effective and causing fewer side effects than lithium. Alcohol is not suitable for administration to children, experience with phenytoin is very limited, and the newer synthetic blocking analogues of ADH are as yet experimental. In practice, it is doubtful whether drug administration is ever indicated for SIADH in children.

References

1. Schwartz WB, Bennett W, Curelop S, Bartter FC (1957) A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 23: 529–542
2. Bartter FC, Schwartz WB (1967) The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med 42: 790–806
3. Hirai A, Uchida D, Yoshida S (1992) Vasopressin (ADH). Jpn J Clin Med 50: 2893–2900
4. Deen PM, Verdijk MA, Knoers NV, Wieringa B, Monnens LA, Os CH van, Oost BA van (1994) Requirement of human renal water channel aquaporin-2 for vasopressin dependent concentration of urine. Science 264: 92–95
5. Rouffignac C de, Corman B, Roinel N (1983) Stimulation by antidiuretic hormone of electrolyte tubular reabsorption in rat kidney. Am J Physiol 244: F156–F164
6. Knepper MA, Star RA (1990) The vasopressin-regulated urea transporter in renal inner medullary collecting ducts. Am J Physiol 259: F393–F401
7. Robertson GL, Mahr EA, Athar S, Sinha T (1973) Development and clinical application of a new method for the radioimmuno-y of arginine vasopressin in human plasma. J Clin Invest 52: 2340–2352
8. Arnolda L, McGrath BP, Johnston CI (1991) Vasopressin and angiotensin II contribute equally to the increased afterload in rabbits with heart failure. Cardiovasc Res 25: 68–72
9. Peters J, Schlaghecke R, Thouet H, Arndt JO (1990) Endogenous vasopressin supports blood pressure and prevents severe hypotension during epidural anesthesia in conscious dogs. Anesthesiology 73: 694–702
10. Verney EB (1947) The antidiuretic hormone and factors that determine its release. Proc R Soc Lond [Biol] 135: 25–106
11. Jewell PA, Verney EB (1957) An experimental attempt to determine the site of the neurohypophyseal osmoreceptors in the dog. Philos Trans R Soc Lond [Biol] 240: 197–324
12. Terry TN, Keil LC, Ramsay DJ (1982) Lesions of the organum vasculosum of the lamina terminalis (OVLT) attenuate osmotically-induced drinking and vasopressin secretion in the dog. Endocrinology 110: 1837–1839
13. Iovino M, Steardo L (1984) Vasopressin release to central and peripheral angiotensin II in rats with lesions of the subfornical organ. Brain Res 332: 365–368
14. Ferguson AV, Kasting NW (1986) Electrical stimulation in subfornical organ increases plasma vasopressin concentrations in the conscious rat. Am J Physiol 251: R425–R428
15. Dunn FL, Brennan TJ, Nelson AE, Robertson GL (1976) The role of blood osmolality and volume in regulating vasopressin secretion by the rat. J Clin Invest 52: 3212–3219
16. Berl T, Cadnapaphornchai P, Harbottle JA, Schrier RW (1974) Mechanism of suppression of vasopressin during alpha-adrenergic stimulation with norepinephrine. J Clin Invest 53: 219–227

17. Berl T, Cadnapaphornchai P, Harbottle JA, Schrier RW (1974) Mechanism of stimulation of vasopressin release during beta adrenergic stimulation with isoproterenol. J Clin Invest 53: 857–867
18. Anderson RJ, Cadnapaphornchai P, Harbottle JA, McDonald K, Schrier RW (1974) Mechanisms of effect of thoracic inferior vena cava constriction on renal water excretion. J Clin Invest 54: 1473–1479
19. McCance RA (1936) Experimental sodium chloride deficiency in man. Proc Roy Soc London [Biol] 119: 245–268
20. Schwartz MJ, Kokko JP (1980) Urinary concentrating defect of adrenal insufficiency. Permissive role of adrenal steroids on the hydroosmotic response across the rabbit cortical collecting tubule. J Clin Invest 66: 234–242
21. Ishikawa S-E, Schrier RW (1982) Effect of arginine vasopressin antagonist on renal water excretion in glucocorticoid and mineralocorticoid deficient rats. Kidney Int 22: 587–593
22. Linas SL, Berl T, Robertson GL, Aisenbrey GA, Schrier RW, Anderson RJ (1980) Role of vasopressin in the impaired water excretion of glucocorticoid deficiency. Kidney Int 18: 58–67
23. Ganong CA, Kappy MS (1993) Cerebral salt wasting in children. The need for recognition and treatment. Am J Dis Child 147: 167–169
24. Schrier RW, Bichet DG (1981) Osmotic and nonosmotic control of vasopressin release and the pathogenesis of impaired water excretion in adrenal, thyroid and edematous disorders. J Lab Clin Med 98: 1–15
25. Leaf A, Bartter FC, Santos RF, Wrong O (1953) Evidence in man that urinary electrolyte loss induced by Pitressin is a function of water retention. J Clin Invest 32: 868–878
26. Carter NW, Rector FC Jr, Seldin DW (1961) Hyponatremia in cerebral disease resulting from the inappropriate secretion of antidiuretic hormone. N Engl J Med 264: 67–72
27. Cohen JJ, Hulter HN, Smithline N, Melby JC, Schwartz WB (1976) The critical role of the adrenal gland in the renal regulation of acid-base equilibrium during chronic hypotonic expansion. J Clin Invest 58: 1201–1208
28. Mansogian C, Pandian M, Ehrlich L, Fisher D, Horton R (1988) Plasma atrial natriuretic hormone levels in patients with the syndrome of inappropriate antidiuretic hormone secretion. J Clin Endocrinol Metab 67: 571–575
29. Kamoi K, Ebe T, Kobayashi O, et al (1990) Atrial natriuretic peptide in patients with the syndrome of inappropriate antidiuretic hormone secretion and with diabetes insipidus. J Clin Endocrinol Metab 70: 1385–1390
30. Jaenike JR, Waterhouse C (1961) The renal response to sustained administration of vasopressin and water in man. J Clin Endocrinol 21: 231–242
31. Levinsky NG, Davidson DG, Berliner RW (1959) Changes in urine concentration during prolonged administration of vasopressin and water. Am J Physiol 196: 451–456

Literature abstract

Nephron (1994) 67: 73–81

IGF-I as an early indicator of malnutrition in patients with end-stage renal disease

Tsutomu Sanaka, Michitaka Shinobe, Minoru Ando, Naomi Hizuka, Hiroshi Kawaguchi, and Hiroshi Nihei

The present study was performed to clarify the possibility of IGF-I as an early indicator of malnutrition in patients with end-stage renal disease. Thirty-two patients (19 males, 13 females; mean age 49.6 ± 10.0 years) undergoing dialysis were enrolled in the study. Body weight, skinfold thickness, and midarm muscle circumferences (MAMCs) were measured for anthropometric nutritional indices. Blood samples were collected to measure the following endocrinological, biochemical and hematological indices: IGF-I, growth hormone, (GH), total protein, prealbumin, albumin, transferrin, hematocrit, and lymphocyte count. Nutritional indices were measured again 1 month later to calculate the percent difference among them. Moreover, 2 patients who showed a decrease in IGF-I and suffered from malnutritional complications, such as hypoproteinemia and emaciation, which could not be successfully treated by conventional therapies were selected in order to confirm the nutritional role of IGF-I mediated by recombinant human GH (r-hGH). The serum IGF-I concentration distribution ranged from 22 to 225 ng/ml. In 15 patients (10 males, 5 females), it fell from 22 to 82 ng/ml below the normal range. Partial correlation coefficient analysis demonstrated that baseline IGF-I and the percent difference of each the body weight, MAMC, prealbumin and albumin were highly significantly correlated ($r = 0.431$, 0.641, 0.624 and 0.348, respectively; $p = 0.014$, 0.001, 0.001 and 0.028, respectively). The percent difference of IGF-I did not correlate significantly with that of any other nutritional index during the 1-month observation without administration of r-hGH. However, the correction of serum IGF-I by the short-term administration of r-hGH obviously increased plasma protein and albumin, peripheral erythrocate and lymphocyte counts, and body weight. From these results, we conclude that IGF-I is a good indicator which may reflect the initiation of a malnutritional state in patients with chronic renal failure.