HYPONATREMIA

by

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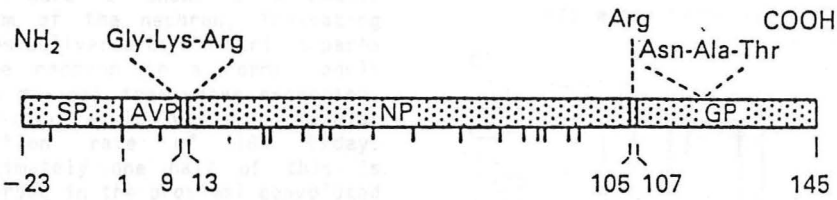
PREPROVASOPRESSIN



Department of Internal Medicine
Medical Grand Rounds
December 13, 1990

Hyponatremia is an important fluid and electrolyte disorder because of its high incidence and because it has marked effects on neurologic function. Anderson et al (1985) prospectively evaluated the incidence of hyponatremia in a hospital population. Because plasma sodiums were not measured in all patients, the estimated prevalence was a minimum estimate. These studies found that 2.5% of hospitalized patients were hyponatremic. In addition, these studies found that 2/3 of hyponatremia in these patients was hospital acquired. In examining the mortality as a function of plasma sodium concentration, Anderson et al found that patients with normal plasma sodium concentrations had a mortality of 0.2%. Among patients with plasma sodium concentration <130 mEq/L, mortality was 11.2%, and among patients with plasma sodium concentration <120 mEq/L, mortality was 25%. We will discuss later the significance of this high mortality rate in hyponatremic patients.

PHYSIOLOGY OF RENAL WATER EXCRETION

Hyponatremia is generally associated with a hyposmolar state. In this review the term hyponatremia will generally refer to hyposmolar hyponatremia. The mechanism responsible for prevention of hyponatremia and hyposmolality is renal water excretion. In all hyponatremic patients, water intake exceeds renal water excretion. Thus, **ALL HYPONATREMIA IS DILUTIONAL.** Changes in sodium balance will not in and of themselves lead to hyponatremia. Sodium loss from the body may transiently lower plasma osmolality. This, however, will be corrected rapidly by renal water excretion unless the mechanisms which regulate renal water excretion are abnormal. Thus, an understanding of the mechanisms of renal water excretion is an integral component of understanding hyponatremia.

Figure 1 shows a schematic diagram of the nephron, indicating volumes delivered to the various parts of the nephron in a normal adult during maximal free water excretion. An average adult has a glomerular filtration rate of 180 L/day. Approximately one half of this is reabsorbed in the proximal convoluted tubule leading to a distal delivery of 90 L/day. There is further salt and water absorption in the proximal straight tubule and the thin descending limb which leads to a distal delivery to the tip of the loop of Henle of approximately 36 L/day. The tip of the loop of Henle is the beginning of the diluting segment. Up until this point, the nephron has a high water permeability. From the tip of the loop of Henle until the beginning of the collecting duct, the nephron is impermeable to water as indicated by the broad lines in Figure 1. Here absorption of solute from the tubule lumen leads to dilution of the tubular fluid. Thus, this segment of the nephron is frequently referred to as the diluting segment. The last part of the nephron, the collecting duct, indicated by the dashed lines in Figure 1, has a

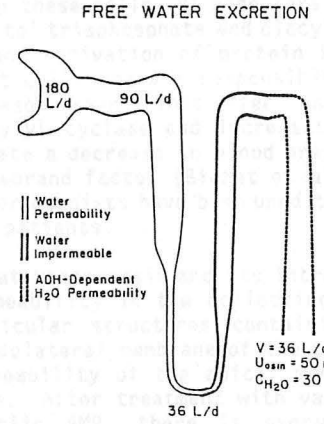


Figure 1

variable water permeability depending on the levels of antidiuretic hormone or vasopressin. In the absence of antidiuretic hormone, this segment is relatively impermeable to water and the volume of urine is equal to the volume of fluid delivered to the tip of the loop of Henle. In the presence of high concentrations of antidiuretic hormone, the collecting duct will be highly permeable to water. In this setting, the high osmolality in the medullary interstitium will cause reabsorption of most of the tubular fluid leading to urine low in volume and high in osmolality.

Based on this analysis, excretion of water by the kidney is dependent on three factors. First, there must be adequate delivery of filtrate to the tip of the loop of Henle. Second, solute absorption in the ascending limb and the distal nephron must be normal so that the tubular fluid will be diluted. Lastly, arginine vasopressin (AVP) levels must be low in the plasma. Of these three requirements for water excretion, the one which is probably most important in the genesis of hyponatremia is the failure to suppress AVP levels. In many conditions, decreased delivery of filtrate to the tip of the loop of Henle also contributes. Defective solute absorption in the ascending limb and distal nephron is probably only relevant to hyponatremia seen with chloriuretic diuretics.

Arginine Vasopressin

Because of its overwhelming importance in hyponatremia, we will first discuss the physiology of arginine vasopressin. Vasopressin exerts its effects on cells through two receptors, V1 and V2. V1 receptors are present in smooth muscle cells and cause vasoconstriction. In these cells, V1 receptors activate phospholipase C leading to increases in inositol trisphosphate and diacylglycerol with secondary increases in cell calcium and activation of protein kinase C. V2 receptors are present on collecting duct cells and are responsible for the increase in water permeability induced by vasopressin. This effect is mediated by G protein dependent activation of adenylyl cyclase and increases in cell cyclic AMP. In addition, V2 receptors mediate a decrease in blood pressure and the secretion of factor VIIIc and von Willebrand factor (Bichet et al, 1988). Because of these latter responses, V2 receptor agonists have been used to improve coagulation responses in certain groups of patients.

There is now accumulating evidence that vasopressin and its intracellular messenger, cyclic AMP, increase water permeability in the collecting duct by causing exocytotic insertion of tubulovesicular structures containing water channels. The water permeability of the basolateral membrane of the collecting duct is always very high. The water permeability of the apical membrane is extremely low in the absence of vasopressin. After treatment with vasopressin or with other agents which increase cyclic AMP, there is exocytosis of tubulovesicular structures. These structures contain a water channel which endows high water permeability on the vesicles and after exocytosis on the apical membrane.

Figure 2 shows the structure of arginine vasopressin as well as two related peptides. Arginine vasopressin is a nonapeptide with a disulfide bond connecting cystines 1 and 6, and an amide group on glycine 9. As can be seen in Figure 2, oxytocin, a hormone with related activities, is very similar in structure and differs only at two amino acid sites. Desamino-D-arginine-8-vasopressin (dDAVP)

is an analog of vasopressin which is a more potent agonist of V2 receptors and a less potent agonist of V1 receptors. This compound differs from AVP in that the N-terminal amino group has been removed and a d-arginine substitutes for an l-arginine.

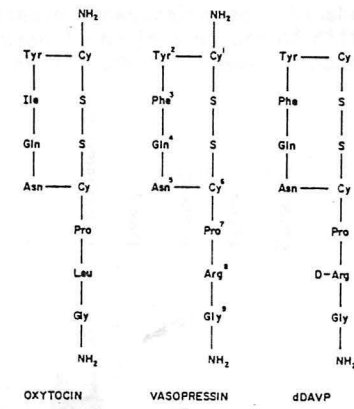
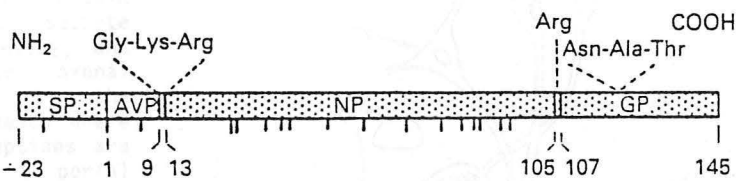


Figure 2

The cDNA encoding the bovine arginine vasopressin precursor has been cloned and sequenced (Land et al, 1982), and the structural organization of the gene defined (Schmale et al, 1983). As shown in Figure 3, the messenger RNA encodes a preprovasopressin molecule which includes three peptides and a signal sequence for protein secretion (Schmale et al, 1987). The three peptides are arginine vasopressin, neurophysin II, and a glycoprotein. The neurophysin II functions as a carrier protein for AVP in the secretory granule. The neurophysins form 1:1 complexes with AVP in a pH-dependent manner such that the complex exists in the acid secretory vesicle and dissociates in extracellular fluid. The function of the glycoprotein is not yet resolved, but

PREPROVASOPRESSIN



Schmale et al. Kidney Int 32:S8, 1987

Figure 3

the fact that its sequence is highly conserved across different animal species suggests that it serves an important role. Nagy et al (1988) have suggested that the glycoprotein serves as a prolactin releasing factor.

After synthesis as a preprohormone, the signal peptide is removed leaving the prohormone. Provasopressin is then cleaved to three separate peptides, and the carboxyterminal amino acid of AVP is amidated. The human vasopressin and oxytocin genes are both located on chromosome 20 in close proximity to each other

and were formed by gene duplication from a single ancestral gene. As shown in Figure 4, the mRNA for the AVP precursor has been found in a number of different tissues by northern blot analysis (Schmale et al, 1987). mRNA abundance is clearly greatest in the hypothalamus. Of great interest, the hypothalamic AVP mRNA is 720 bases long while the AVP mRNA from other tissues is 620 bases long. This different length is due to a longer poly A tail in the hypothalamic mRNA. This will be further discussed below.

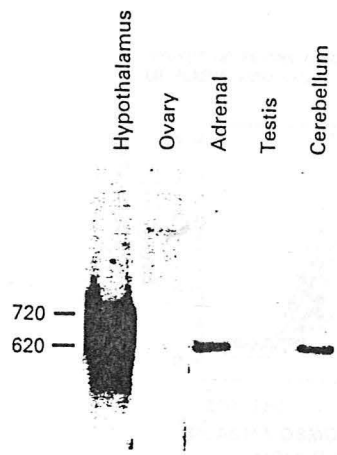


Figure 4

Figure 5 shows the relevant neuroanatomy of the AVP system. AVP is synthesized in three hypothalamic nuclei. These are the supraoptic nucleus, the paraventricular nucleus, and the suprachiasmatic nucleus. Neurons in the supraoptic nucleus and magnocellular neurons in the paraventricular nucleus are involved in the response to hypertonicity and volume depletion (see below), and send axons to the neurohypophysis for vasopressin secretion. Parvocellular neurons in the paraventricular nucleus secrete hypothalamic releasing factors, in certain circumstances secrete AVP (see below), and send their axonal projections to the median eminence where secreted peptides are carried by a portal circulation to the adenohypophysis. Neurons in the suprachiasmatic nucleus send their axons to the third ventricle and are responsible for AVP concentrations in the cerebrospinal fluid. The suprachiasmatic nucleus is the only AVP-containing nucleus which receives projections from the optic nerve, and

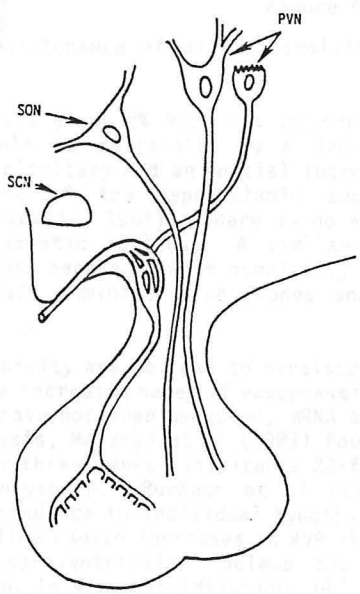
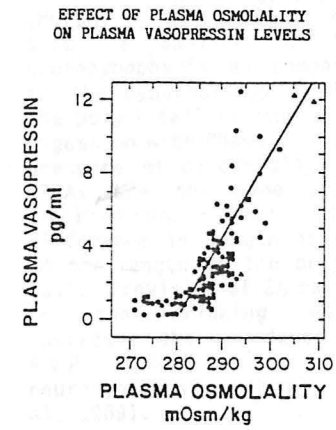


Figure 5

bilateral lesions of the suprachiasmatic nuclei eliminate nocturnal and circadian rhythms in drinking behavior and locomotor activity (Stephan and Zucker, 1972). Polyadenylate tail length of the vasopressin mRNA in the suprachiasmatic nucleus changes during the daily cycle (Robinson et al, 1988). No such circadian rhythm of AVP polyadenylate tail length is seen in the supraoptic or paraventricular nuclei.

Regulation of Vasopressin Secretion

Dunn et al (1973) have examined the effect of increases in plasma osmolality on plasma levels of AVP. These results, summarized in Figure 6 (Robertson and Berl, 1986), show the sensitive relationship between osmolality and vasopressin. At plasma osmolalities below the threshold for vasopressin secretion shown here as approximately 280 mOsm/kg, AVP levels are not detectable in the plasma. Once plasma osmolality exceeds the threshold for vasopressin secretion, there is an extremely sensitive linear relationship between these two variables. Thus, very small increases in plasma osmolality lead to measurable changes in plasma vasopressin levels. This extremely sensitive regulation of vasopressin by osmolality is responsible for the maintenance of plasma osmolality within a normal range.



Robertson and Berl. The Kidney, p. 385, 1986

Figure 6

Figure 7 shows that when rats are given 2% NaCl for drinking water, the increase in plasma vasopressin levels is associated by a decrease in the vasopressin content of the posterior pituitary and an initial increase and then decrease in the vasopressin content of the hypothalamic supraoptic and paraventricular nuclei (Zerbe and Palkovile, 1984). There is no effect on the vasopressin content of the suprachiasmatic nucleus. A similar decrease in neurohypophyseal vasopressin content has been seen when osmolality is increased either by water deprivation or by NaCl administration (Jones and Pickering, 1969).

If chronic increases in hypertonicity are to lead to persistent increases in vasopressin secretion, there must be increased rates of vasopressin synthesis. While rates of vasopressin synthesis have not been measured, mRNA abundance has been measured. By northern blot analysis, Majzoud et al (1983) found that rats given 2% saline for drinking water for three weeks exhibited a 20-fold increase in mRNA abundance for AVP and for oxytocin. Burbach et al (1984) used S1 nuclease protection to analyze mRNA abundance in individual hypothalamic nuclei and found that 14 days of 2% normal saline caused increases in AVP mRNA abundance in the supraoptic nucleus and the paraventricular nucleus but not in the suprachiasmatic nucleus. Similarly, by in situ hybridization, Uhl et al (1985) demonstrated increased AVP mRNA in the supraoptic and paraventricular nuclei of

EFFECT OF 2% NaCl DRINKING WATER
ON VASOPRESSIN CONTENT

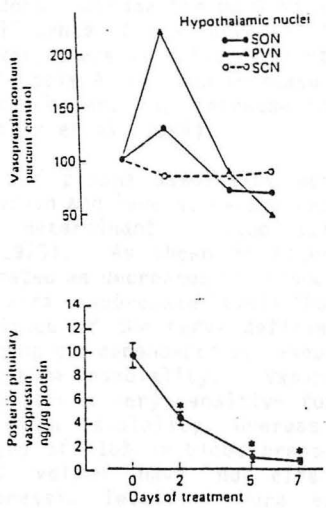


Figure 7

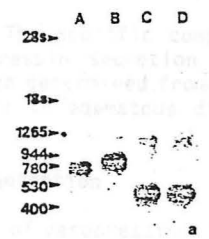
Zerbe and Palkovile, Neuroendocrinology 38: 285, 1984

dehydrated rats.

AVP mRNA has also been found in the pituitary, but is only found in the neurohypophysis and is absent in the adenohypophysis (Murphy et al, 1989). mRNA size is smaller in the neurohypophysis as compared to the hypothalamus. When the poly A tail is removed by digestion with RNase H in the presence of oligo-(dT), the mRNAs are the same size, indicating that the difference in length is due to the length of the poly A tail. Provision of 2% saline in the drinking water increases the abundance of AVP mRNA in the neurohypophysis (Murphy et al, 1989).

As noted above, hypothalamic vasopressin mRNA has an unusually long poly A tail. In addition to regulating mRNA abundance, it has been found that hypertonicity regulates the length of the poly A tail (Zingg et al, 1988; Carrazana et al, 1988; Carter and Murphy, 1989). Hypertonicity generated by either depriving water or placing 2% saline in place of drinking water causes an increase in the size of the AVP mRNA. Figure 8 shows an example of this where AVP mRNA from the hypothalamus of water deprived rats (lane B) is greater in size and more abundant than the mRNA from control animals (lane A). If the poly A tail is removed by digestion with RNase H in the presence of oligo (dT), the resulting mRNAs are similar in size (lanes C and D, control and water deprived, respectively). Thus, these studies demonstrate that the length of the poly A tail increases from approximately 200-250 bases in controls to 330-400 bases in hypertonic animals. A similar effect of hypertonicity on the length of the oxytocin mRNA was found, but there was no effect on somatostatin mRNA length (Carrazana et al, 1988). Water

EFFECT OF 72 HR WATER DEPRIVATION
ON VASOPRESSIN mRNA ABUNDANCE AND SIZE



Carrazana et al. Molec Cell Biol 8:2267,

Figure 8

deprivation has been shown to increase the size as well as the abundance of AVP mRNA in the supraoptic nucleus (Carter and Murphy, 1990). Interestingly, water deprivation has no effect on AVP mRNA abundance in the suprachiasmatic nucleus, but does increase the mRNA size in the segment (Carter and Murphy, 1990). The significance of the increased length of the poly A tail is presently unclear. However, there is evidence in other systems which suggests that increased length of the poly A tail can increase messenger RNA stability, secondarily increasing abundance, and can increase the efficiency of translation (Brawerman, 1987; Palatnik et al, 1984).

If plasma osmolality were the only determinant of plasma vasopressin secretion and levels, hyponatremia would be a far less common disorder. A second major determinant of vasopressin levels is effective arterial volume (Dunn et al, 1973). As shown in Figure 9, decreases in effective arterial volume, indicated as decreases in volume or blood pressure, are associated with increases in plasma vasopressin levels (Robertson and Berl, 1986). It should be noted that the shape of the curve defining this dependency is very different than that defining the dependence of vasopressin on plasma osmolality. Vasopressin levels are a very sensitive function of plasma osmolality, whereas small changes of <10% in blood pressure or blood volume have no effect on vasopressin levels. More extreme decreases in volume or pressure then lead to potent stimulation of vasopressin secretion. Teleologically, this system can be viewed as an emergency mechanism to defend blood pressure. Thus, small decreases in blood volume and blood pressure will cause the body to retain NaCl which will raise osmolality and lead to water retention. However, if NaCl is not available and if blood pressure and volume are becoming drastically low (down 10%), the body seems to make a decision that defense of blood pressure is more important than defense of osmolality and vasopressin is secreted. The specific compartment whose volume is sensed in order to determine vasopressin secretion in this setting is the effective arterial volume. This has been determined from studies examining urinary concentration and vasopressin levels in edematous disorders (see below).

REGULATION OF PLASMA VASOPRESSIN

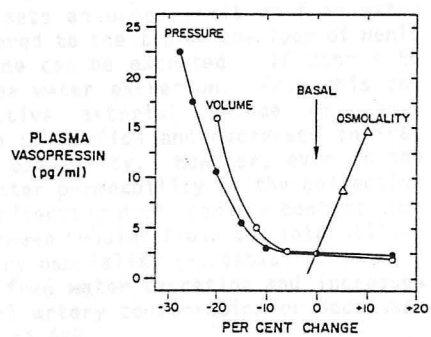


Figure 9
Robertson and Berl, The Kidney, p. 385, 1986

Vasopressin-Independent Urinary Concentration

Urinary concentration can increase in the absence of vasopressin. The most common circumstance in which this occurs is that of decreased effective arterial volume. The first studies which showed this were the classic experiments of Berliner and Davidson (1957). In these studies dogs received massive amounts of water such that urinary osmolality was <100 mOsm/L. The renal artery of one of the kidneys was then constricted. In response to this constriction, urinary

osmolality rose in the ipsilateral kidney but remained low in the contralateral kidney. The low urinary osmolality of the contralateral kidney confirmed that vasopressin secretion was suppressed. Thus, increased urinary concentration in the ipsilateral kidney was secondary to renal artery constriction and occurred in the absence of vasopressin. In these studies, urinary osmolality increased to >200 mOsm/L and could actually rise above 300 mOsm/L.

Similar results have been found in a series of studies from Valtin and colleagues (Edwards et al, 1980; Edwards and LaRochelle, 1984: Gellai et al, 1979) in which it was demonstrated that decreases in volume could cause urinary concentration in Brattleboro rats. Brattleboro rats have congenital diabetes insipidus which is due to deletion of a single nucleotide in the gene for preprovasopressin. These animals secrete no vasopressin. Thus, once again, the presence of urinary concentration in these animals upon volume depletion demonstrates urinary concentration in the absence of vasopressin.

An explanation of how renal vasoconstriction or decreases in effective arterial volume can decrease free water excretion and increase urinary osmolality can be offered using Figure 1. Volume contraction leads to decreases in glomerular filtration rate, increases in proximal tubule NaCl absorption, and increases in thin descending limb water absorption. All of these lead to a decrease in volume delivery to the tip of the loop of Henle. The volume delivered to the tip of the loop of Henle sets an upper limit on free water excretion. Thus, if only 6 liters are delivered to the tip of the loop of Henle per day, then a maximum of 6 liters of urine can be excreted. If Uosm = 50 mOsm/L, then 5 L of this will represent free water excretion. From this one would predict that decreases in effective arterial volume or renal vasoconstriction would lead to decreases in urine flow and decreases in free water excretion but would not affect urine osmolality. However, even in the complete absence of AVP there is a finite water permeability of the collecting duct. Thus, as flow rates slow down in the collecting duct, and the contact time available for equilibration of osmolality between tubular fluid and interstitium increases, water absorption occurs and urinary osmolality increases. This most likely is the explanation for decreases in free water excretion and increases in urine osmolality in the presence of renal artery constriction or decreases in effective arterial volume in the absence of AVP.

ETIOLOGIES OF HYPONATREMIA

As stated above, all hyponatremia is dilutional. Thus, the presence of hypotonic hyponatremia implies that water intake exceeds the ability of the kidney to excrete water. In unusual circumstances, this can occur when the kidney's ability to excrete free water is intact. However, because a normal kidney can excrete 20-30 L of water/day, the presence of hyponatremia with normal renal water excretion implies that the patient is drinking >20-30 L water/day. This condition is referred to as primary polydipsia. While primary polydipsia is a common condition which frequently leads to polyuria and polydipsia, it is an uncommon cause of hyponatremia.

In the absence of primary polydipsia, hyponatremia is always associated with decreased renal water excretion and a urine that is inappropriately concentrated. It is important to note that in the presence of hyponatremia urine should be maximally dilute and any osmolality higher than this is inappropriate.

A number of clinical conditions lead to hyponatremia by limiting renal free water excretion. These conditions can generally be divided according to the extracellular fluid volume.

As described above, any condition which leads to a decreased effective arterial volume will cause increases in vasopressin levels and decreases in distal delivery of filtrate, both of which will limit free water excretion and lead to increases in urine osmolality. In addition, although not discussed above, a decreased effective arterial volume will increase thirst. These specific conditions can be divided into those in which total extracellular volume is decreased, such as diuretics, osmotic diuresis, mineralocorticoid deficiency, salt losing nephropathy, vomiting, and diarrhea, and into edematous conditions such as congestive heart failure, cirrhosis, nephrosis, and third space volume losses. In the latter conditions extracellular fluid volume is increased while effective arterial volume is decreased. From the standpoint of AVP regulation and renal regulation, the body responds to effective arterial volume and does not seem to recognize the state of the extracellular fluid volume. While there are volume receptors in the venous circulation, these clearly are overridden by effective arterial volume.

In a number of conditions, hyponatremia is associated with a normal volume state. In these conditions effective arterial volume is normal and increased levels of AVP cannot be attributed to decreases in effective arterial volume or to increases in tonicity. These conditions include the syndrome of inappropriate ADH secretion (SIADH), glucocorticoid deficiency, hypothyroidism, drugs, and stress.

PATHOGENESIS OF HYPONATREMIA

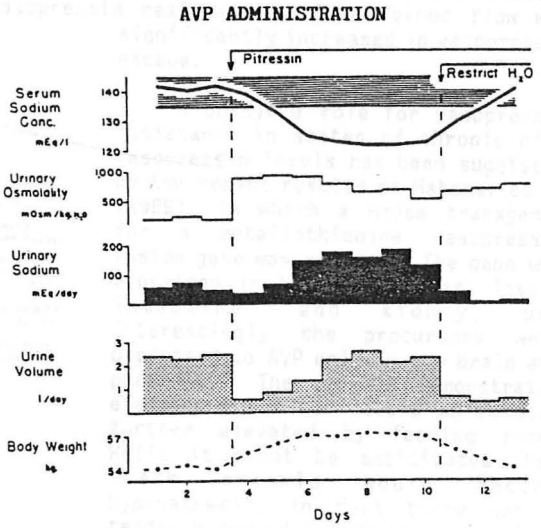
Decreased Effective Arterial Volume

As discussed above, hyponatremia is almost always associated with a defect in renal water excretion. In the conditions associated with decreased effective arterial volume, either associated with decreased or increased extracellular fluid volume, AVP secretion is increased in response to the low effective arterial volume. High AVP levels have been measured by radioimmunoassay in hyponatremic patients with congestive heart failure (Riegger et al, 1982; Szatalowicz et al, 1981). In addition, in a rat model of congestive heart failure secondary to myocardial infarction, blood pressure was decreased, plasma AVP was increased, and hypothalamic AVP mRNA was increased (Kim et al, 1990). Increased vasopressin levels have also been measured in humans and rats with cirrhosis (Bichet et al, 1982a; Bichet et al, 1982b; Linas et al, 1981). Lastly, high AVP levels have been found in human subjects with nephrotic syndrome (Usberti et al, 1984).

In addition to increases in AVP secretion, decreases in effective arterial volume lead to decreases in delivery of filtrate to the tip of the loop of Henle (Anderson et al, 1974; Anderson et al, 1976). This occurs because of a decrease in GFR, an increase in proximal tubular solute and volume absorption, and an increase in thin descending limb volume absorption. In addition, decreases in effective arterial volume lead to increases in thirst which further predispose to hyponatremia.

Euvolemic Hyponatremia
Syndrome of Inappropriate ADH Secretion (SIADH)

The syndrome of inappropriate ADH is caused by three general groups of diseases: cancers, pulmonary disease, and central nervous system disease. To understand the mechanisms of hyponatremia in SIADH it is useful to examine the effects of AVP administration. Figure 10 shows the results of administering vasopressin (Pitressin) plus water to human subjects. As can be seen, vasopressin administration leads to an increase in urine osmolality, a decrease in urine volume, an increase in body weight, an increase in urinary sodium excretion, and a decrease in serum sodium. While the natriuresis was once believed to be a direct effect of vasopressin, it is now known that the natriuresis occurs secondary to an increase in extracellular fluid volume as evidenced by the increase in body weight. If vasopressin is given without water, urine osmolality still increases, but body weight does not increase, extracellular fluid volume does not increase, and there is no natriuresis (Leaf et al, 1953). This can be seen in Figure 10 where continued administration of vasopressin, but with water restriction, leads to a decrease in body weight and a decrease in urinary sodium excretion.



Robertson and Berl. The Kidney p. 385, 1986

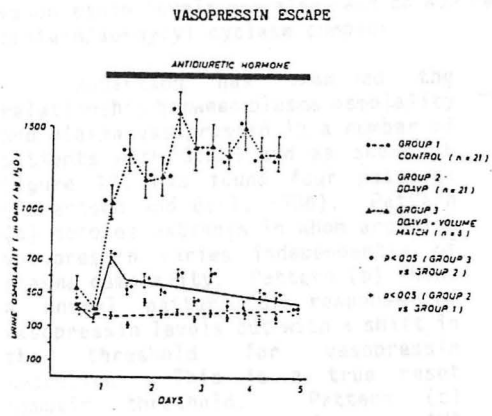
Figure 10

Also of note in Figure 10 is the fact that net water retention by the body is not relentless. On day 6, the serum sodium starts to plateau, and urine osmolality starts to drift downward. In some patients with SIADH, this behavior has been proposed to be attributable to a reset osmotic threshold for AVP secretion such that AVP secretion is turned off but at a lower than normal serum sodium concentration (see below). This is clearly not the case in the experiment in Figure 10 since AVP administration was continued throughout.

This "vasopressin escape" has been found to be due to overhydration and volume expansion. If water retention is prevented, chronic vasopressin administration does not lead to "escape" (Chan, 1973; Gross et al, 1983). Figure 11 shows the results of experiments which demonstrate this. When conscious rats are administered DDAVP chronically, urine osmolality increases to approximately 700 mOsm/kg, and then gradually decreases to control levels. If water administration is set to equal urine output such that there is no net water retention and no volume expansion, there is no escape; urine osmolality increases

to values between 1000 and 1500 mOsm/kg. Thus, in these studies, water retention rather than high vasopressin levels is responsible for vasopressin escape.

Gross et al (1983) also examined the mechanism by which water retention caused vasopressin resistance. There was no effect on baseline, vasopressin-stimulated or fluoride-stimulated adenylyl cyclase activity in renal medulla or in dissected collecting tubules. Medullary solute concentration was not decreased, eliminating medullary washout as a cause. Urinary PGE_2 excretion was increased. Since PGE_2 opposes the effect of ADH, this could contribute to vasopressin resistance. This, however, is not the only factor as indomethacin only transiently ameliorated vasopressin resistance. Renal blood flow was significantly increased in vasopressin escape.



Gross et al, Circ Res 53:794, 1983.

Figure 11

A possible role for vasopressin resistance in states of chronic high vasopressin levels has been suggested by the recent results of Habener et al (1989), in which a mouse transgenic for a metallothionine vasopressin fusion gene was created. The gene was expressed in brain, pancreas, liver, intestine, and kidney, but interestingly the precursors were processed to AVP only in the brain and pancreas. The animals demonstrated elevated serum AVP levels which were further elevated by feeding zinc. While it might be anticipated that these animals would become hyponatremic, in fact there was a tendency toward hypernatremia. Since AVP levels were high, this suggested

TABLE 1
MOUSE TRANSGENIC FOR METALLOTHIONEIN-VASOPRESSIN FUSION GENE: NEPHROGENIC DIABETES INSIPIDUS

	cAMP Production (fm/20 min)	
	Control	Transgenic
10^{-9} M Vasopressin	1182 ± 38	702 ± 24
100 μM Forskolin	5847 ± 133	5575 ± 77

Habener et al. J Biol Chem 264:18844, 1989.

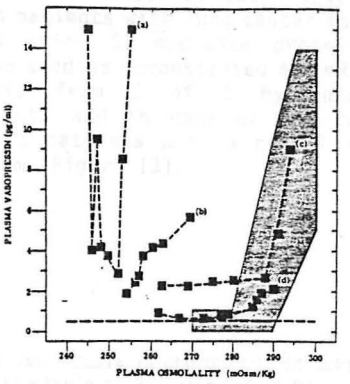
the presence of nephrogenic diabetes insipidus. Table 1 shows results of measurements of cyclic AMP production by renal medullary membranes from control and transgenic mice. As can be seen, 10^{-9} M vasopressin generated decreased cyclic AMP production in the transgenic mice suggesting some form of vasopressin resistance. Interestingly, forskolin, a direct activator of adenylyl cyclase had similar effects on cyclic AMP generation in control and transgenic

membranes. Thus, it appears that there is some down regulation in these mice, either of the receptor or of the receptor/G protein/adenylyl cyclase coupling. A similar mechanism may occur in patients with chronically high vasopressin levels.

Thus, chronic increases in plasma vasopressin cause "vasopressin escape." This escape is due to net water retention and volume expansion, which secondarily increases renal blood flow and renal PGE_2 production. The increased renal blood flow may lead to inhibition of proximal salt and water absorption with secondarily increased distal delivery of filtrate. It is then possible that increased distal delivery prevents osmotic equilibration in the collecting duct, even in the presence of vasopressin. In certain settings, chronically elevated vasopressin levels may also lead to AVP resistance at the level of the receptor/G protein/adenylyl cyclase complex.

Robertson has examined the relationship between plasma osmolality and plasma vasopressin in a number of patients with SIADH and as shown in Figure 12, has found four patterns (Robertson and Berl, 1986). Pattern (a) denotes patients in whom arginine vasopressin varies independently of plasma osmolality. Pattern (b) shows a normal pattern of response of vasopressin levels but with a shift in the threshold for vasopressin secretion. This is a true reset osmotic threshold. Pattern (c) represents patients who increase AVP with increases in plasma osmolality normally, but cannot completely suppress AVP release. Pattern (d) represents patients who appear to have a normal relationship between plasma osmolality and vasopressin, yet have the syndrome of SIADH. These latter patients may have another hormone being secreted or may have an alternative mechanism of urinary concentration. In 25 patients with SIADH, Robertson found pattern a in 6, pattern b in 9, pattern c in 8, and pattern D in 2 patients. The patterns did not appear to correlate with any specific etiologies. Thus, patients with bronchogenic carcinoma were found in all four groups.

PATTERNS OF AVP SECRETION IN SIADH



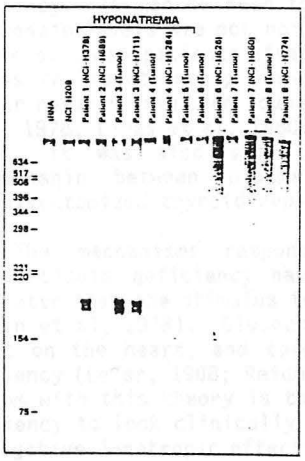
Robertson and Berl. The Kidney, p. 385, 1986

Figure 12

The source of the abnormal vasopressin secretion in SIADH has not been resolved. It has been presumed although not established that in SIADH associated with central nervous system disorders, vasopressin secretion is from the hypothalamus. The high incidence of SIADH in numerous different pulmonary diseases raises the question of whether lung tissue is able to secrete AVP, or whether pulmonary diseases are uniquely able to activate baroreceptors which would secondarily increase hypothalamic AVP secretion.

With cancers, vasopressin could be synthesized and secreted from the tumors or could once again be secreted from the hypothalamus. A number of studies have found antidiuretic hormone activity in tumor extracts (Amatruda et al, 1963;

AVP$_{mRNA}$ IN LUNG CANCER: S-1 NUCLEASE PROTECTION



Bliss et al. J Natl Cancer Inst 82:305, 1990.

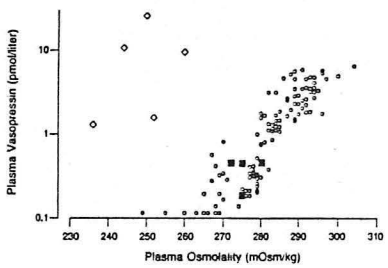
Figure 13

Bower et al, 1964; Vorherr et al, 1968). Vorherr et al found that tumor tissue from 5 of 10 lung tumor patients with SIADH was positive by bioassay for ADH. In addition, these investigators found that the tissue was positive for arginine vasopressin by immunoassay. George et al (1972) demonstrated in vitro vasopressin synthesis by tissue slices from a bronchogenic lung cancer. More recently, it has been demonstrated that a small cell lung cancer cell line, H378, produced significant quantities of preproAVP (Sausville et al, 1985). Bliss et al (1990) screened a number of tumor specimens from patients with lung cancer for AVP mRNA using S1 nuclease protection. These studies demonstrated AVP mRNA in tumors from 2 of 5 hyponatremic patients and in none of the tumors from 3 patients with a normal serum sodium (Figure 13).

Glucocorticoid Deficiency

Patients with glucocorticoid deficiency develop hyponatremia. It is important to separate this condition from that of mineralocorticoid deficiency and combined mineralocorticoid-glucocorticoid deficiency. In patients with mineralocorticoid deficiency, extracellular fluid volume and effective arterial volume are low. This leads to baroreceptor stimulation of vasopressin secretion and to decreased distal delivery of filtrate to the diluting segments of the nephron. In isolated glucocorticoid deficiency, the patients are euvolemic. While it is possible to develop isolated glucocorticoid deficiency with adrenal disease, most adrenal diseases cause loss of mineralocorticoid and glucocorticoid function. Thus, glucocorticoid deficiency in the absence of mineralocorticoid deficiency is usually due to pituitary disease. Figure 14 shows the relationship

PLASMA VASOPRESSIN IN GLUCOCORTICOID DEFICIENCY
(Controls o; Patients before ◇; and after ■ hydrocortisone Therapy)



Oelkers. N Engl J Med 321:492, 1989.

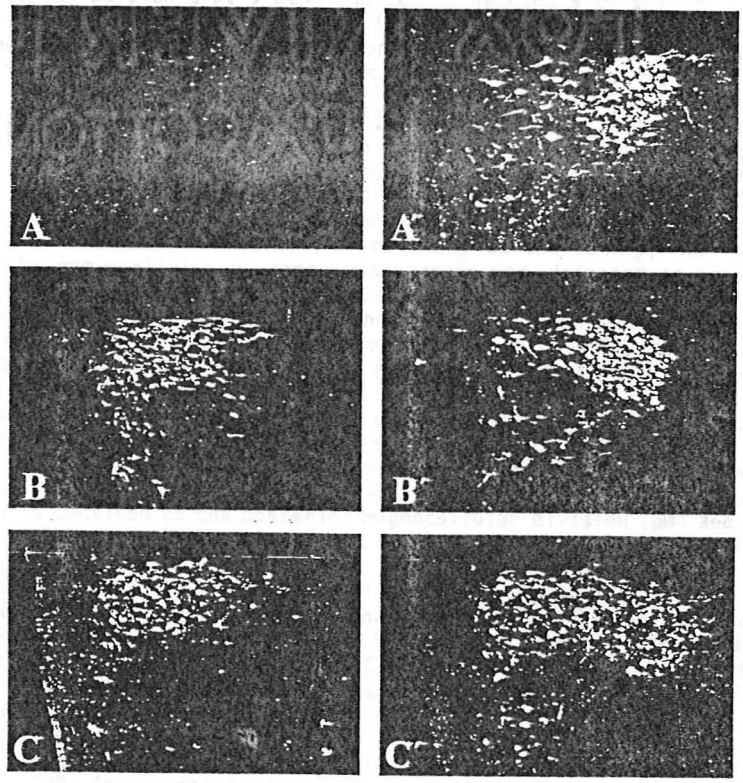
Figure 14

between plasma vasopressin and plasma osmolality in patients with glucocorticoid deficiency (Oelkers, 1989). The open circles show results from normal control subjects. The open diamonds show results in 5 patients with glucocorticoid deficiency. It can be seen that for any given level of low plasma osmolality vasopressin levels are not normally suppressed. The solid squares show results in four of these patients after hydrocortisone therapy. Hydrocortisone therapy returns the relationship between vasopressin and plasma osmolality to normal. Similar results have been found in glucocorticoid deficient dogs and rats (Boykin et al, 1978; Linas et al, 1980; Mandell et al, 1980). In the studies of Mandell et al, it was also shown that glucocorticoid replacement returned the relationship between plasma osmolality and vasopressin to normal in hypophysectomized thyroid repleted rats.

The mechanisms responsible for abnormal vasopressin secretion in glucocorticoid deficiency have received much attention. Initially, it was postulated that the stimulus to vasopressin secretion was hemodynamic in origin (Boykin et al, 1978). Glucocorticoids are known to have a positive ionotropic effect on the heart, and cardiac performance is subnormal in glucocorticoid deficiency (Lefer, 1968; Reidenberg et al, 1963; Lefer et al, 1968). The major problem with this theory is that one would expect patients with glucocorticoid deficiency to look clinically like patients with congestive heart failure. If the negative ionotropic effect is sufficient to increase vasopressin release it should also be sufficient to lead to the other manifestations of decreased cardiac output. However, patients with glucocorticoid deficiency appear euvolemic.

Vasopressin is able to cause the release of adrenocorticotropin from the adenohypophysis (Rivier and Vale, 1983a; Rivier and Vale, 1983b; Liu et al, 1990). This effect is independent of the presence of corticotropin releasing factor (CRF), but is synergistic with CRF. CRF is synthesized in the paraventricular nucleus of the hypothalamus and then is carried by axon terminals to the medial eminence where it is secreted into the hypothalamo-hypophyseal portal circulation. Although CRF and AVP are both synthesized in the paraventricular nucleus, the neurons responsible for their secretion are different under control conditions.

IMMUNOCYTOCHEMICAL LOCALIZATION OF CRF (LEFT)
AND AVP (RIGHT): A, control; B, colchicine; C, ADX



Sawchenko et al. PNAS 81:1883, 1984.

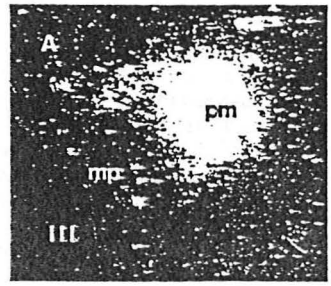
Figure 15

Figure 15 illustrates this point (Sawchenko et al,1984). The three figures on the left illustrate sections of the paraventricular nucleus stained immunocytochemically with antibodies against CRF, while the three figures on the right demonstrate the similar sections stained with antibodies against AVP. In the figures labelled A, control brains are stained. It can be seen that there is staining of magnocellular neurons with antibodies against AVP but there is little positive staining for CRF. The figures shown in B are from animals treated with colchicine. Colchicine, by interrupting microtubular function, prevents the transport of synthesized peptides to their nerve terminals. In this setting, it can be seen once again that the magnocellular neurons contain AVP, and now it can be seen that a separate set of neurons with smaller cell bodies (parvocellular neurons) contain CRF. In this setting, it is unusual to find a neuron which stains positive for CRF and AVP. The figure shown in part C are from animals which have been adrenalectomized. In this setting CRF is far more abundant such that it can be visualized without colchicine treatment. In addition, on the right figure it can be seen that AVP is now present in the parvocellular neurons as well as in the magnocellular neurons. In this setting, >70% of CRF positive cells are vasopressin positive (Sawchenko et al, 1984). Similar results were found by Kiss et al (1984). In control animals, vasopressin labelling in the paraventricular nucleus was confined to magnocellular neurons, and CRF was difficult to detect. Following adrenalectomy, CRF was easily detected in parvocellular neurons, vasopressin was detected in parvocellular neurons, and vasopressin and CRF were colocalized to the same neurons. These investigators also demonstrated that the effects of adrenalectomy were reversed by treating rats with glucocorticoid but not mineralocorticoids. In addition, they demonstrated that dehydrating the animals did not reproduce these effects.

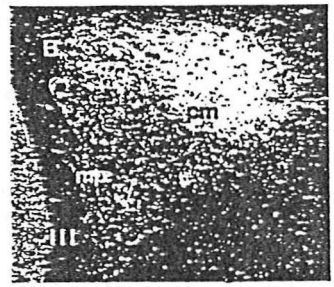
Similar results have been found using in situ hybridization to localize the AVP mRNA (Wolfson et al, 1985; Davis et al, 1986). These results are shown in Figure 16 where sections of the paraventricular nucleus are stained with a probe for AVP mRNA. Figure 16A shows sections from control animals where labelling is confined to the posterior magnocellular division (pm) and is absent in the medial parvocellular subdivision (mp). In sections from adrenalectomized animals (Figure 16B), AVP mRNA is also localizable in the medial parvocellular distribution. In Figure 16C where tissue is obtained from adrenalectomized animals treated with dexamethasone, once again, labelling is confined to the magnocellular subdivision. It has also been demonstrated by these investigators that neurons which are positive for CRF protein are positive for AVP mRNA. These studies found no effect of adrenalectomy on the distribution of AVP mRNA in the supraoptic nucleus.

These results can be best interpreted by referring to Figure 5. Normally, AVP is synthesized in the magnocellular subdivisions of the paraventricular nucleus and the supraoptic nucleus where it is carried by the axons to the neurohypophysis for systemic secretion. These are the neurons which mediate the response of AVP to changes in plasma osmolality. The parvocellular neurons of the paraventricular nucleus whose axons terminate in the medial eminence are also capable of AVP synthesis and secretion, as well as CRF synthesis and secretion. Under control conditions, AVP synthesis and secretion by these neurons is not detectable. However, following adrenalectomy these neurons increase CRF production and develop detectable AVP mRNA and peptide production. Both CRF and AVP are then secreted into the portal blood system and are delivered to the adenohypophysis where they synergistically stimulate ACTH

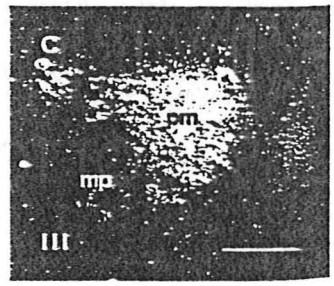
LOCALIZATION OF AVP mRNA
BY IN SITU HYBRIDIZATION:
CONTROL



LOCALIZATION OF AVP mRNA
BY IN SITU HYBRIDIZATION:
ADX



LOCALIZATION OF AVP mRNA
BY IN SITU HYBRIDIZATION:
ADX + DEXAMETHASONE



Davis et al. PNAS 83:1145, 1986.

Figure 16A, B, C

production. While AVP production in this setting contributes to normal glucocorticoid regulation, high levels of AVP secretion by these neurons lead to an increase in plasma AVP levels which causes hyponatremia.

In addition to high AVP levels, AVP-independent mechanisms lead to increases in urinary osmolality in glucocorticoid deficiency. Green et al (1970) found that glucocorticoid deficient rats demonstrated an increase in the minimum urinary osmolality achieved during water loading. In order to examine the role of vasopressin-independent mechanisms in this process, they examined the effect of glucocorticoid deficiency in Brattleboro rats. These rats have congenital diabetes insipidus and have no circulating vasopressin. In spite of the absence of vasopressin, these rats do increase urinary osmolality and decrease free water excretion in response to glucocorticoid deficiency. Similar results were found by Linas et al (1980) using a similar model. In addition, Ishikawa and Schrier (1982) found that V2 receptor antagonists were able to improve the diluting defect in the glucocorticoid deficient rat, but did not totally eliminate the defect.

All of these studies imply that in the absence of vasopressin or of vasopressin effect, glucocorticoid deficiency can still increase urinary osmolality and decrease the ability of the kidneys to excrete water. This finding agrees with the clinical observation that patients with diabetes insipidus appear to improve clinically when they develop coexistent anterior pituitary insufficiency, and treatment of these patients with glucocorticoids appears to worsen the diabetes insipidus (Martin, 1969). Thus, in the patient with diabetes insipidus free water excretion will be extremely large. When simultaneous glucocorticoid

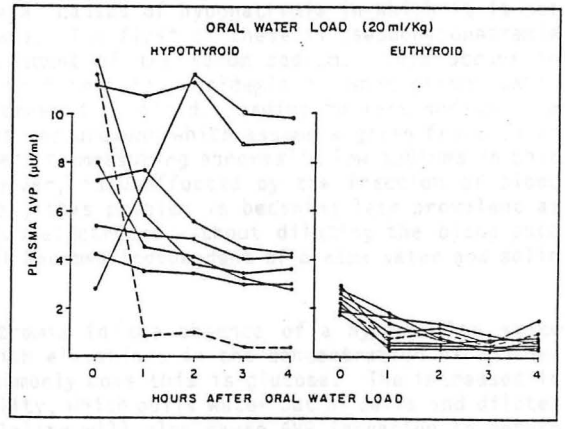
deficiency develops free water excretion decreases. The fact that this can occur in patients with diabetes insipidus confirms an AVP-independent effect.

The nature of this AVP-independent effect has not been elucidated. Schwartz and Kokko (1980) dissected cortical collecting tubules from glucocorticoid deficient rabbits and demonstrated no abnormality in AVP-independent water permeability. Thus, the most likely explanation is that distal delivery of filtrate to the diluting segment is abnormally low in glucocorticoid deficiency. As referred to above, these patients have decreased cardiac output and this may trigger a decrease in GFR, an increase in proximal tubular volume absorption and an increase in thin descending limb volume absorption. However, as pointed out above, these patients do not clinically appear to have a decreased effective arterial volume raising some concern about this explanation.

Hypothyroidism

Hyponatremia is seen in patients who are severely hypothyroid (Skowsky and Kikuchi, 1978). Once again, the inability to excrete free water appears to be related to both increases in plasma vasopressin levels and to AVP independent mechanisms. Figure 17 shows the response of plasma AVP to an oral water load. On the left is the response in hypothyroid patients, and on the right is the response in the same patients after being made euthyroid. It can be seen that most of the patients (solid lines) failed to suppress AVP appropriately, while one patient (dashed line) did suppress AVP appropriately. The defect was corrected by thyroid replacement. Emmanouel et al (1974) examined free water excretion in normal and Brattleboro rats. In these studies he found that hypothyroidism impaired free water excretion in both control and Brattleboro rats. Once again, the impairment of water excretion in Brattleboro rats suggests an AVP-independent mechanism.

PLASMA AVP LEVELS FOLLOWING A WATER LOAD
IN UNTREATED HYPOTHYROID AND TREATED
EUTHYROID PATIENTS



Skowsky and Kikuchi. Am J Med 64:613, 1978.

Figure 17

Drugs

Although many drugs have the ability to impair free water excretion, only a few of them are clinically significant causes of euvolemic hyponatremia. The drug which most commonly causes hyponatremia is chlorpropamide (Weissman et al, 1971). Numerous studies have shown that chlorpropamide works at the level of the collecting tubule enhancing the renal response to AVP. It has been suggested that this may be due to inhibition of prostaglandin synthesis (Zusman et al, 1977). There is no

evidence that chlorpropamide increases vasopressin secretion.

Another class of drugs which works to enhance the effects of vasopressin at the level of the collecting duct are the nonsteroidal antiinflammatory drugs. These drugs inhibit prostaglandin synthesis, and prostaglandins have been shown to oppose the effects of ADH. These drugs have no effect on vasopressin secretion. Interestingly, nonsteroidal antiinflammatory drugs, in spite of the prediction that they would cause hyponatremia, have never been found to cause hyponatremia in normal individuals. They will, however, predispose to hyponatremia in individuals who have other mechanisms driving vasopressin secretion such as patients with SIADH, patients with edematous disorders, or patients who are volume depleted.

Carbamazepine or tegretol is also a common cause of hyponatremia, although the mechanism is unclear. Cytoxan and vincristine can also cause hyponatremia when given in large amounts during chemotherapy.

A number of antipsychotic drugs have been postulated to cause hyponatremia. This list includes drugs from numerous classes. Since psychosis itself can cause hyponatremia, it is not presently clear whether the drugs also contribute.

CLINICAL APPROACH TO THE HYPONATREMIC PATIENT

Step One: Plasma Osmolality

The clinical approach to the hyponatremic patient involves three steps. In the first step, the question is asked, "Is the hyponatremia representative of a hypoosmolar state?" If osmolality is normal, hyponatremia is of no clinical significance. There are two general causes of hyponatremia in which it is not associated with a hypoosmolar state. The first of these is pseudohyponatremia which involves an abnormal measurement of the serum sodium. This occurs in patients with hyperglobulinemia or hypertriglyceridemia in whom plasma water relative to plasma solids, is decreased in blood, leading to less sodium in a given volume of blood. Methods of measurement which assume a given fraction of blood being plasma water are subject to measuring abnormally low sodiums in this setting. Plasma osmolality, however, is unaffected by the fraction of blood which is plasma water. In general, this problem is becoming less prevalent as many laboratories are using sodium electrodes without diluting the blood such that the plasma sodium measurement becomes independent of plasma water and solid contents.

The other cause of hyponatremia in the absence of a hypoosmolar state involves true hyponatremia but with elevations in the concentration of another osmole. The osmole which most commonly does this is glucose. The increases in plasma glucose raise serum osmolality, which pulls water out of cells and dilutes the serum sodium. The high osmolality will also cause AVP secretion to return plasma osmolality to normal. This will further lower the serum sodium. The net result is a normal plasma osmolality but a low serum sodium. None of these conditions involve abnormalities of osmolar regulation and none of these conditions need to be worked up further from the standpoint of osmolality.

The clinical approach to considering these conditions is to measure the plasma osmolality. In general, hyperglobulinemia sufficient to cause pseudohyponatremia is rare and occurs only in Waldenstrom's macroglobulinemia.

Triglycerides must be in the thousands to cause this condition and are most commonly seen in diabetics. Thus, the most common setting of hyponatremia associated with a normal osmolality will be in the diabetic patient combining hyperglycemia and hypertriglyceridemia. If a patient is not diabetic and has a normal serum glucose, it is probably safe to not measure plasma osmolality and to proceed on to the second step.

Step Two: Urinary Osmolality

In step two, the question is asked whether the kidney's ability to dilute the urine is intact. This is tested by measuring a urine osmolality. In general, because the normal kidney is able to excrete 20-30 liters of water per day, it is difficult to become hyponatremic with an intact diluting mechanism. However, this can occur in a few patients with primary polydipsia. Primary polydipsia is a common disorder which usually causes polyuria and polydipsia but does not lead to hyponatremia. In a few rare patients where water ingestion exceeds the kidney's ability to excrete water, hyponatremia evolves. These patients should have a urine osmolality <100 mOsm/L. More frequently, when hyponatremia occurs with primary polydipsia, there is also a coexistent diluting defect.

Thus, in step two one can measure a urine osmolality to examine whether the urine is appropriately dilute. A low urine osmolality associated with hyponatremia suggests primary polydipsia. As this condition is not subtle, a routine urine osmolality is probably not necessary in hyponatremia. The vast majority of patients will have a urine osmolality inappropriately elevated, namely >100 mOsm/L, and will lead the physician to step three in the work-up.

Step Three: Effective Arterial Volume

In most patients with hyponatremia, the urine is appropriately concentrated. At this step the most useful approach is to define whether effective arterial volume is decreased. This is because most of the causes of hyponatremia do so via a decrease in effective arterial volume which causes baroreceptor stimulation of AVP secretion and leads to decreased distal delivery of filtrate to the tip of the loop of Henle. Figure 18 summarizes the causes of hyponatremia according to their effective arterial volume and according to their extracellular fluid volume. If effective arterial volume is low extracellular fluid volume can be low in the volume depleted patient or can be high in the edematous patient. If effective arterial volume is normal, one is dealing with the euvolemic causes of hyponatremia. The clinical determination of effective arterial volume is usually straightforward. On physical examination the best index of effective arterial volume is the pulse and blood pressure. The most sensitive index is a postural change in the pulse. Postural changes in the pulse occur with a 10% decrease in blood volume, which coincides with the decrease in blood volume required for baroreceptor-mediated AVP secretion (see Figure 9). Thus, most patients with hyponatremia due to a decreased effective arterial volume will have a postural change in their pulse.

Urinary electrolytes are also extremely useful in the assessment of effective arterial volume. Patients with a low effective arterial volume will tend to have a low urinary sodium, low urinary chloride, and low fractional excretions of sodium and chloride in the urine. Patients with euvolemic

CLINICAL APPROACH TO HYPONATREMIA

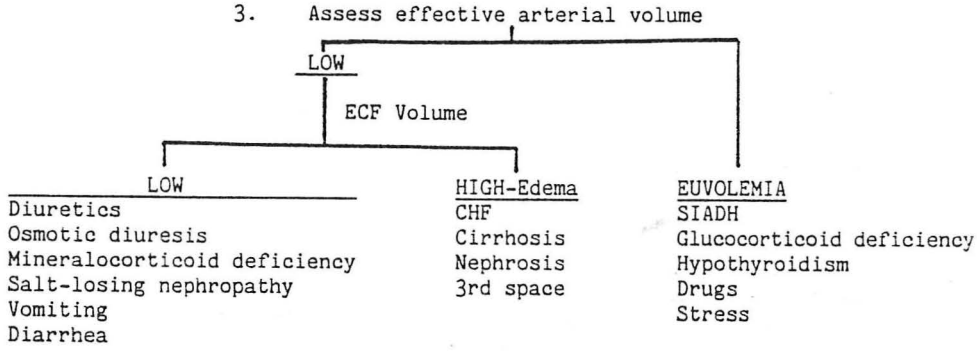


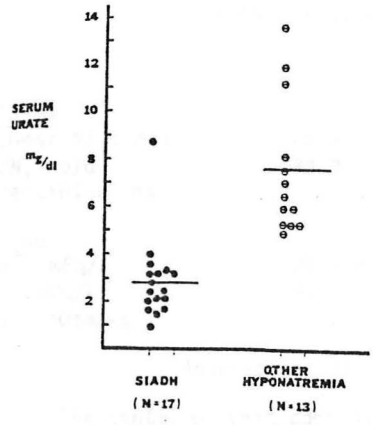
Figure 18

hyponatremia, however, will be in balance and will excrete sodium and chloride at rates that reflect dietary intake of sodium and chloride. Thus, generally they have urinary sodium and chlorides >20 mEq/L and fractional excretions of these electrolytes >1%.

Plasma composition can also be used to assess effective arterial volume. The blood urea nitrogen (BUN) is particularly sensitive to effective arterial volume. In patients with normal serum creatinines, a high BUN suggests a low effective arterial volume and a low BUN suggests a high effective arterial volume. The plasma uric acid can also be used as a sensitive index of effective arterial volume (Beck, 1979; DeCaux et al, 1980). Figure 19 shows the values for serum urate in patients with SIADH and patients with other causes of hyponatremia. As can be seen by the open circles, in patients with low effective arterial volume, serum urate levels tend to be elevated. In patients with SIADH serum urate is not only not elevated but is actually depressed. This is due to the fact that these patients are volume expanded although it is clinically difficult to detect the degree of volume expansion. Figure 20 shows the results of water restriction in patients with SIADH on the serum urate. When these patients are water restricted, expansion of the effective arterial volume is corrected and serum urate rises. Thus, the low serum urate levels are simply a reflection of the water induced volume expansion.

Anderson et al (1985) compared laboratory parameters in patients with hypovolemic, edematous, and euvolemic hyponatremia (Table 2). It can be seen that the lowest serum sodium value, the serum creatinine, the urine K, and the urine osmolality were of no use in distinguishing these conditions. The BUN was elevated in hypovolemic and edematous patients and was in the normal range in euvolemic patients. Urinary sodium was on the low side in hypovolemic and

SERUM URATE IN HYPONATREMIA



Beck. N Engl J Med 301:528, 1979.

Figure 19

patients with abnormalities in urate metabolism may have changes in uric acid which do not reflect effective arterial volume. However, taken together as a group, with all these parameters it is usually relatively straightforward to define the effective arterial volume. The definition of whether one is dealing with a hypovolemic, edematous, or euvolemic patient usually leads to the correct diagnosis. In addition, as will be described below, the treatment of the patient with hyponatremia is dependent on their classification into one of these three categories.

TREATMENT OF THE HYPONATREMIC PATIENT

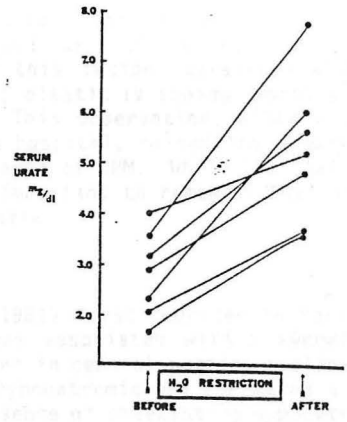
Acute Treatment

In considering the acute treatment of the patient, there are two issues which must be addressed. First, it must be determined whether the patient has hyponatremic, edematous, or euvolemic hyponatremia. Second, the physician must determine whether he/she is to correct the hyponatremia slowly or rapidly. This latter question has been a source of much controversy, and we will therefore review the evidence

edematous patients and was high in euvolemic patients.

In summary, by assessing the patient for postural changes in the pulse and blood pressure, by the urinary electrolytes, and by BUN and plasma urate, the physician is usually able to define the effective arterial volume. It is important to remember that any one of these parameters may mislead the physician. Thus, patients with autonomic neuropathy may not have postural changes in the pulse when volume depleted or may have postural changes in the blood pressure when euvolemic. Patients with Addison's Disease, renal salt wasting or diuretic ingestion may have high urine sodium and chloride excretion rates while volume contracted. Patients with poor protein intake or with significant liver disease may have low BUNs while volume contracted and

SERUM URATE IN HYPONATREMIA



Beck. N Engl J Med 301:528, 1979.

Figure 20

in favor of slow or rapid correction.

TABLE 2
LABORATORY DATA IN PATIENTS WITH HYPONATREMIA

	Hypovolemic	Edematous	Euvolemic
Plasma			
Lowest Na^+, mEq/L	125.4 ± 0.7	126.2 ± 0.5	125.1 ± 0.5
BUN, mg/dl	22.9 ± 2.5	30.3 ± 4.1	13.9 ± 1.1
Creatinine, mg/dl	1.3 ± 0.1	1.4 ± 0.1	0.9 ± 0.1
Urine			
Na^+, mEq/L	24.0 ± 3.7	19.3 ± 3.3	70.7 ± 3.8
K^+, mEq/L	47.4 ± 4.8	44.9 ± 4.5	40.8 ± 2.6
Osm, mOsm/kg	441 ± 47	453 ± 48	423 ± 24

Anderson et al. Ann Intern Med 102:164, 1985.

The center of this controversy is a lesion of the central nervous system, central pontine myelinolysis, frequently referred to as CPM. CPM was first described by Adams et al (1959) as a brain lesion of alcoholic and malnourished patients. The lesion involves axonal demyelination with infiltration by glial cells in the pons. Axons are spared. Lesions are generally symmetrical. In spite of its name, lesions can also involve tracks outside the pons, typically at areas where gray and white matter are near each other. Although originally a diagnosis made at autopsy, the diagnosis of CPM is now reliably made using magnetic resonance imaging. Clinically, patients develop quadriparesis, swallowing dysfunction, inability to speak, and pseudobulbar palsy.

It has been noted by Messert et al (1979) that in spite of extensive autopsy studies done during the 19th century and early 20th century, the lesion was not reported until 1959. The onset of this lesion correlates with the "plastic revolution," the free availability of plastic IV tubing, which allowed more liberal use of intravenous infusions. This observation, along with the observation that patients develop CPM in the hospital, raised the question of whether treatment with IV solutions was the cause of CPM. While the lesion has now been associated with hyponatremia, it is important to remember that not all patients with CPM have histories of hyponatremia.

Animal Studies

Kleinschmidt-DeMasters and Norenberg (1981) first reported in rats that hyponatremia followed by rapid correction was associated with a symmetrical demyelination of the brain similar to that seen in central pontine myelinolysis in humans. There was no demyelination when hyponatremia was corrected slowly, or when hypertonic saline was given in the absence of preexisting hyponatremia. Ayus et al (1985) found similar results. Careful histologic studies of the rat lesion showed its similarity to the human lesion (Kleinschmidt-DeMasters and Norenberg, 1982).

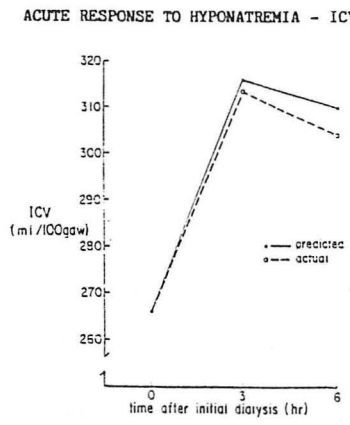
TABLE 3
INCIDENCE OF MYELINOLYSIS IN DOGS

	%
Uncorrected ↓Na	0
HS infusion	0
↓Na → H_2O restriction	17
↓Na → HS	50
One day rise in Na	
≥15 mEq/L	71
<15 mEq/L	0
Two day rise in Na	
≥20 mEq/L	80
<20 mEq/L	0

Laureno. Ann Neurology 13:232, 1983.

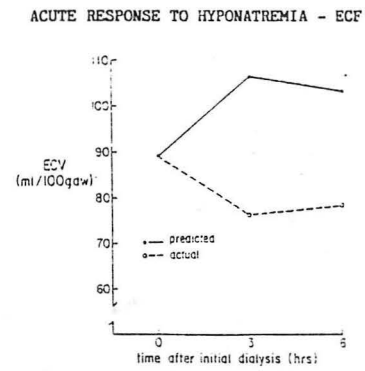
Laureno (1983) examined the incidence of myelinolysis in dogs with uncorrected or corrected hyponatremia (Na<120). Table 3 shows his results. In patients with uncorrected hyponatremia, no myelinolysis was seen. If hypertonic saline was given to normal dogs, no myelinolysis was seen. However, in dogs that had been made hyponatremic, correction of the serum sodium with water restriction or hypertonic saline caused myelinolysis, with myelinolysis occurring more frequently with hypertonic saline. When the incidence of myelinolysis was compared as a function of the rate of rise in serum sodium, it was found that myelinolysis was not seen in any dogs in whom the rise in serum sodium was less than 15 mEq/L during the first day, and there was a 71% incidence if the rise in serum sodium was greater than 15 mEq/L in one day. If the rise in serum sodium was greater than 20 mEq/L in two days there was an 80% incidence of myelinolysis while there was a 0% incidence in dogs in which the rise in serum sodium was less than 20 mEq/L in two days. These studies, as well as those of Kleinschmidt-DeMasters and Norenberg and Ayus et al, conclusively showed that it is the correction rather than hyponatremia per se that causes the myelinolysis. This result has now been confirmed in numerous studies in animals. In addition, it should be noted that it is not the method of correction but rather the rate of rise in serum sodium that causes the myelinolysis. Thus, even with water restriction, some dogs developed myelinolysis when the sodium corrected rapidly. Ayus et al (1985; 1989) has correlated the incidence of CPM with whether Na is rapidly corrected to subnormal (low incidence) or normal or supernormal values (high incidence). They have argued that the important variable is how far the serum sodium is corrected in the first 24 hours rather than the rate of correction in the first few hours. However, this is not supported by other studies, and the distinction seems of little importance.

In order to further understand how the correction of hyponatremia could lead to central pontine myelinolysis, it is useful to consider the response of the brain to acute and chronic hyponatremia. In acute hyponatremia achieved rapidly by peritoneal dialysis with hypotonic fluids in rats, brain volume does not increase as would be predicted for osmotic equilibration (Melton and Nattie, 1983). Thus, based on the degree of hyponatremia one can predict how much water would move into the brain in order to achieve osmotic equilibration. If one then



Melton and Nattie. Amer J Physiol 244:R724, 1983.

Figure 21A



Melton and Nattie. Amer J Physiol 244:R724, 1983.

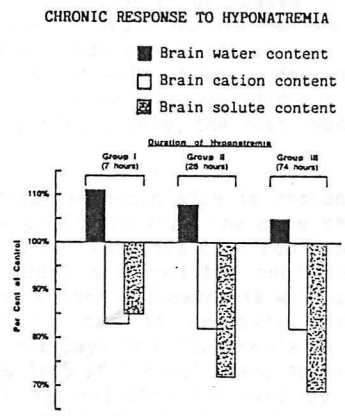
Figure 21B

measures brain water one can calculate that the increase is smaller than would be predicted. In these studies, the investigators then measured intracellular and extracellular brain volume. As shown in Figure 21, intracellular volume actually did increase as would be predicted for osmotic equilibration, but extracellular volume actually decreased (Melton and Nattie, 1983). These studies suggest that water shifting into brain cells leads to an increase in pressure which drives extracellular fluid out of the brain. This finding is confirmed by the observation that newborn puppies whose fontanelles have not closed and thus can tolerate the increase in brain water without increasing pressure, do not lower their extracellular fluid volume in response to acute hyponatremia, and in fact increase extracellular fluid volume as predicted for the degree of hyponatremia (Nattie and Edwards, 1981). If one measures brain electrolytes during this acute period, it is found that brain sodium and chloride content are decreased, but it is important to realize that this is extracellular sodium and chloride that are decreased (Melton and Nattie, 1983; Melton et al, 1987). This loss of extracellular NaCl and water is likely into the cerebrospinal fluid (Hochwald et al, 1976; Pullen et al, 1987).

Sterns et al (1989) examined brain water and solute content in hyponatremia of various durations in rats. As can be seen in Figure 22, hyponatremia of 7 hours duration led to an 11% increase in brain water content. This increase, however, was less than would be predicted for simple osmotic equilibration. The lesser increase in brain volume was due to a 17% decrease in brain solute content. This decrease in brain solute content was mostly attributable to a decrease in brain cation content, and the cation which decreased was sodium. Thus, the results at 7 hours are similar to the results of Melton and Nattie (1983) and Melton et al (1987) described above where acute defense of brain volume occurs by loss of extracellular volume from the brain.

At 25 hours of hyponatremia, brain water content decreases as compared to 7 hours representing a defense of brain volume. This is now due to a further decrease in brain solute content with no further change in brain cation content.

At 74 hours, brain water content further decreases, associated with a further decrease in brain solute content. In the chronic phase of hyponatremia, brain cation content remains stable. This, however, reflects a decrease in brain potassium with an increase in brain sodium back toward control values (Verbalis and Drutarosky, 1988). Thus, with chronic hyponatremia the brain extrudes K from the intracellular compartment. The loss of brain water and the return of brain pressures to normal allows extracellular fluid with sodium to return. The net result is that brain electrolytes remain stably low.

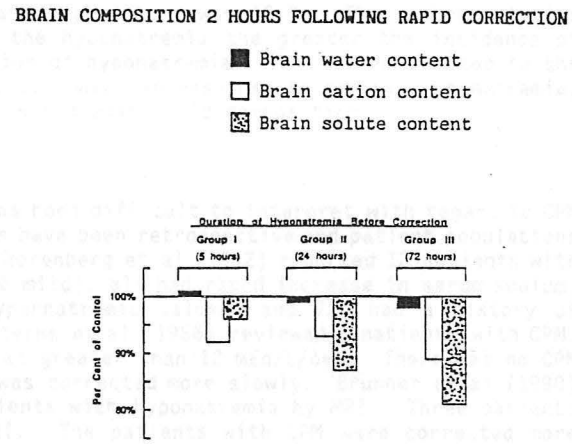


Sterns et al. Kidney Int 35:69, 1989.

Figure 22

As can be seen in Figure 22, chronic hyponatremia leads to a decrease in noncation solutes within the brain. The nature of these solutes, which have been called idiogenic osmoles, has not been elucidated. However, it has been demonstrated that brain amino acid content, especially taurine, decreases in this setting (Thurston and Hauhart, 1987).

Figure 23 shows the response to rapid correction of hyponatremia within 2 hours in the study of Sterns et al (1989). If hyponatremia was present for only 5 hours, brain water content returned to normal, associated with insignificant changes in brain solute content. If hyponatremia persists for 24 hours, there is a small decrease in brain water content upon rapid correction. This is due to a persistent decrease in brain solute content, partially attributable to a decrease in brain cation content, but also attributable to a decrease in idiogenic osmoles. When hyponatremia is rapidly corrected after 72 hours of chronic hyponatremia, there is a significant decrease in brain water content which is associated with a greater decrease in brain solute content. Thus, the more chronic the hyponatremia prior to rapid correction, the lower the brain



Sterns et al. Kidney Int 35:69, 1989.

Figure 23

solute content. Because the brain is not able to rapidly correct this brain solute deficit, rapid correction of hyponatremia can lead to decreases in brain volume. While part of the persistent decrease in brain solute is due to a decrease in cation, there is also a component due to idiogenic osmoles. Thurston and Hauhart (1987) showed that three days of hyponatremia caused a decrease in amino acid concentration and rapid correction of the hyponatremia did not allow brain amino acid content to return to normal. Quantitatively, the most important amino acid in these studies was taurine.

Based on the above results, if the decrease in brain size is responsible for central pontine myelinolysis, it would be predicted that the more chronic the hyponatremia the greater the incidence of CPM. This has been confirmed in two animal studies. Illowsky and Laureno (1987) examined the incidence of myelinolysis in hyponatremic rabbits. Prolonged severe hyponatremia with plasma sodiums less than 122 caused weakness but no paresis or paralysis and myelinolysis was observed in 0 of 8 rabbits. Three days of hyponatremia followed by rapid correction caused paresis or paralysis in 5 of 7 rabbits and documented myelinolysis in 3 of 7 rabbits. One day of hyponatremia followed by rapid correction caused paresis or paralysis in only 4 of 12 rabbits, and interestingly, none of 13 brain specimens showed evidence of CPM. Norenberg and Papendick (1984) rapidly corrected hyponatremia in rats and examined the degree of myelinolysis. Lesions were graded by a pathologic score where the higher the score the more severe the myelinolysis. In comparing rabbits whose hyponatremia was present for 1 or 3 days prior to correction, the level of the hyponatremia was similar and the rate of rise in serum sodium, 21 mEq/7 hours, was similar in both groups. However, in animals that were hyponatremic for 1 day prior to rapid correction the pathologic score was 3.9, while in animals that were hyponatremic for 3 days the pathologic score was 10.0. Thus, these studies suggest that the more chronic the hyponatremia the greater the incidence of myelinolysis with rapid correction of hyponatremia. This may be related to the chronic adaptations which the brain makes in response to chronic hyponatremia, such as decreases in brain cation and amino acid composition.

Human Studies

The clinical literature has been difficult to interpret with regard to CPM due to the fact that most studies have been retrospective and patient populations have been biased by selection. Norenberg et al (1982) reported 12 patients with CPM. All had hyponatremia (some mild), all had rapid increase in serum sodium, 11 of 12 were corrected to hypernatremic values, and 75% had a history of alcoholism or liver disease. Sterns et al (1986) reviewed 8 patients with CPM. All had hyponatremia corrected at greater than 12 mEq/L/day. There was no CPM in patients whose hyponatremia was corrected more slowly. Brunner et al (1990) prospectively evaluated 13 patients with hyponatremia by MRI. Three patients developed CPM detectable by MRI. The patients with CPM were corrected more rapidly, but also had a greater degree of hyponatremia.

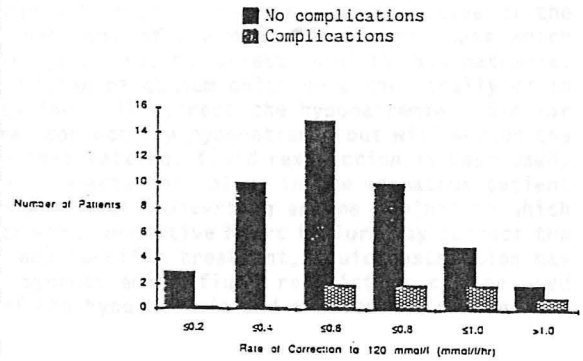
Ayus et al (1987) prospectively evaluated 33 patients with symptomatic hyponatremia who were corrected rapidly, but were not overcorrected, and none developed CPM. The problem with this study is the absence of a good control group.

Perhaps the most convincing clinical study is that of Sterns (1987).

Sixty-four consecutive presentations of hyponatremia with Na<110 were reviewed. Five patients died, one from CPM and 4 without neurologic problems from an unrelated disease. Neurologic sequelae occurred in none of 10 patients with acute hyponatremia, and in 7 of 54 patients with chronic hyponatremia. Figure 24 shows the incidence of neurologic complications as a function of the rate of correction of the serum Na. The incidence of neurologic complications increased in patients with more rapid correction of hyponatremia.

Baran and Hutchinson (1984) have questioned the danger of acute symptomatic hyponatremia. They prospectively studied 78 patients with sodium less than 128 mEq/L. Forty-six percent of patients had neurologic symptoms, but in most patients these were related to the underlying disorder rather than to the hyponatremia. Mortality was 64% in patients with CNS symptoms unrelated to hyponatremia. In patients with CNS symptoms due to hyponatremia, mortality was 9%, and was not different from a 10% mortality occurring in patients with no CNS symptoms. Thus, these investigators have argued that mortality in hyponatremia is attributable to the underlying disease which causes the hyponatremia, rather than the hyponatremia per se.

NEUROLOGIC COMPLICATIONS AS A FUNCTION OF THE RATE OF CORRECTION OF HYPONATREMIA



Sterns, Ann Int Med 107:656, 1987.

Figure 24

Acute Management of the Hyponatremic Patient

Based on the above discussion, the therapeutic approach to hyponatremia is based on the duration of the lesion. If hyponatremia is acute, it should be corrected rapidly. Acute hyponatremia is usually iatrogenic as it is unusual for patients to ingest water rapidly enough to develop acute symptomatic hyponatremia. The one exception to this is primary polydipsia where patients can drink enormous amounts of water and rapidly lower their serum sodium. One clue to the presence of acute hyponatremia is that it is symptomatic. In this setting, symptoms are due to cerebral edema because the brain has not had time to decrease its solute content. While symptoms can be severe with acute hyponatremia, this is not associated with central pontine myelinolysis. Because brain solutes have not decreased at this stage, the serum sodium can be corrected rapidly which should return brain size to normal and improve the patient's condition. Thus, acute hyponatremia is frequently symptomatic and should be corrected rapidly.

Chronic hyponatremia, which is clearly more common, is generally asymptomatic. Because hyponatremia has been generated slowly, the brain has

adapted to the hyponatremia by decreasing brain osmoles. Thus, brain size is normal. In this setting, rapid correction of hyponatremia can cause central pontine myelinolysis. Thus, slow correction is recommended.

Occasionally, a patient presents with symptomatic hyponatremia, and is thought to have a chronic hyponatremia, or the duration of the hyponatremia is uncertain. In this setting, the presence of symptoms suggests cerebral edema, but the chronicity raises the concern that rapid correction could cause CPM. In this setting, one should rapidly raise serum Na by 10% (Berl, 1990). As the increment in brain volume is unlikely to be greater than 10%, this should correct cerebral edema. Hyponatremia can then be further corrected more slowly.

The approach for slow correction is fairly straightforward. In general, fluid restriction will lead to correction of hyponatremia irrespective of the cause of the hyponatremia. In addition, if one can correct the cause which generated the hyponatremia this will also lead to correction of the hyponatremia. Thus, in hypovolemic patients provision of sodium chloride either orally or in the form of intravenous normal saline will correct the hyponatremia. Similar treatment of edematous patients may correct the hyponatremia but will worsen the edema and may not be advised. In this setting, fluid restriction is best used. Any maneuver which increases effective arterial volume in the edematous patient will also correct the hyponatremia. Thus, converting enzyme inhibitors which improve cardiac output in patients with congestive heart failure may correct the hyponatremia. In the absence of any specific treatment, fluid restriction may be most prudent. In euvolemic hyponatremia, fluid restriction can be used pending definition of the cause of the hyponatremia and institution of specific treatment.

Rapid correction is generally achieved with hypertonic saline. In the hypovolemic patient, hypertonic saline can be given alone. This will correct the serum sodium and correct the volume deficit. In edematous patients, hypertonic saline can also rapidly correct the hyponatremia. Furosemide is frequently given with hypertonic saline in edematous patients in order to prevent massive volume overload. In the euvolemic patient, hypertonic saline and furosemide are the treatment of choice for rapid correction (Hautman et al, 1973). The net result of this treatment is that sodium balance remains normal with sodium intake in the form of hypertonic saline equalling sodium output in the urine. However, in the presence of furosemide, urine osmolality is fixed at approximately 300 mOsm/L and the excretion of large amounts of sodium will obligate a large water excretion in the kidney. In the infusion, there is minimal water. Thus, the net result of this treatment is removal of marked amounts of water from the body.

The specific rate at which symptomatic hyponatremia should be corrected depends on the patient. In general correction rates should be less than 2.5 mEq/L/hr and less than 20 mEq/L/day. Under no circumstance should serum sodium be corrected to hypernatremic levels. If the patient is seizing, one would probably correct serum sodium as fast as possible within the above limits. If there is uncertainty about the duration of hyponatremia, if the hyponatremia is chronic, or if the patient is predisposed to central pontine myelinolysis (alcoholism, malnutrition, chronic disease), the physician may choose to correct the hyponatremia more slowly.

It is important to remember that many factors contribute to the correction of hyponatremia other than those instituted by the physician. The most important of these is renal free water excretion. Thus, if the cause of decreased renal water excretion is corrected, the kidneys will correct the hyponatremia very rapidly. In patients with primary polydipsia who stop drinking, the kidneys will correct hyponatremia rapidly. In addition, as hyponatremia corrects, intracellular idiogenic osmoles are regenerated which further increases osmolality. Lastly, insensible losses continue.

Thus, it is important to follow the serum sodium as you treat the patient, irrespective of whether you plan slow or rapid correction. Based on the serum sodium concentration, the treatment plans should be modified. In some cases free water may have to be administered to slow the rate of correction. Patients treated with fluid restriction have developed CPM.

Chronic Management

After the acute treatment of hyponatremia, it is sometimes necessary to address the chronic prevention of hyponatremia. The best approach is to correct the initial cause, such as correcting the volume deficit, improving cardiac or liver function, replacing a hormone deficit, stopping a drug, or curing a tumor, or CNS or pulmonary lesion. In cases where this is not possible, fluid restriction can be used to control the serum sodium. In patients with euvolemic hyponatremia fluid restriction is relatively easier because patients do not have a hypovolemic-driven drive for thirst. However, in patients with hypovolemic or edematous disorders, there is a continuous drive to thirst and fluid restriction may be more intolerable. Demeclocycline has been used in patients with SIADH to create a nephrogenic diabetes insipidus (Forrest et al, 1978; Cherrill et al, 1975). Demeclocycline inhibits cyclic AMP generation and protein kinase A in collecting duct cells and thus prevents the effect of ADH (Dousa and Wilson, 1974). Demeclocycline has not been tried extensively in edematous patients. It is not tolerated well in patients with liver disease because its normal route of metabolism is the liver. However, it may prove useful in patients with hyponatremia from intractable congestive heart failure.

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