

Osmolar Disorders

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ABSTRACT

Objective: *To present a practical approach to the management of osmolar disorders by considering the mechanisms involved in their development.*

Data sources: *Articles and published peer-review abstracts on the mechanisms and management of disorders of plasma osmolality.*

Summary of review: *In health, plasma osmolality is determined largely by the concentration of sodium and its accompanying anion, and regulated by mechanisms that regulate body water. Water excess or deficiency causes hypo and hyper osmolality, respectively. Hyperosmolality may also be caused by an excess of body solutes, with the biochemical and clinical features depending on whether these compounds are impermeant (i.e. remain in the extracellular fluid) or permeant (i.e. are distributed throughout the total body water). Sodium metabolism is regulated by those mechanisms that regulate extracellular fluid volume. An increase (or decrease) in total body sodium is associated with retention (or excretion) of body water, an increase (or decrease) in the extracellular fluid (ECF) volume, and no change in plasma osmolality.*

The initial presentation of an osmolar disorder is usually with an abnormal plasma sodium, therefore management often focuses on treatment of hypo or hypernatraemia. However, treatment requires an estimation of all fluid and solute excesses and deficiencies, with the need or otherwise for prompt correction depending upon the nature of the disorder and time taken for it to develop.

Conclusions: *Osmolar disorders are associated with varying changes in total body fluid and solute. Consideration of these changes, using a body fluid compartment model, is useful in understanding the abnormalities present and to facilitate management. (Critical Care and Resuscitation 1999; 1: 45-54)*

Key words: Plasma osmolality, plasma tonicity, hyponatraemia, hypernatraemia, osmolar gap

Osmolality is a measure of the total number of particles of solute (e.g. ions, molecules) present in a given weight of solvent. Osmolarity, on the other hand, is a measure of the total number of particles of solute present in a given volume of solvent, and so (unlike osmolality) is dependent on the temperature of the solution. The osmotic effect of a substance in solution depends only on the number of particles dissolved (i.e. it is independent of the weight, electric charge, valence or chemical formula).

Properties of a solution that depend solely on the number of solute particles present are known as its colligative properties. Addition of a solute to a solvent results in changes in the four colligative properties of the solvent; its vapour pressure and freezing point are lowered, and its osmotic pressure and boiling point are increased. In an aqueous solution the osmolality is

commonly assessed by measuring the freezing point depression, using the fact that each mosmol/kg increase in osmolality is associated with a depression of the freezing point of the solvent, water, by 0.00186°C. This method is used because direct measurement of osmolality is difficult (due to the difficulty in obtaining a true semipermeable membrane), alteration in boiling point is inappropriate for solutions containing substances that are unstable at high temperatures, and measurement of vapour pressure is often inaccurate in the presence of volatile solutes (e.g. methanol, ethanol).¹

In solution, each mole of an unionized solute provides one osmole. As each molecule of sodium chloride in an ideal solution (e.g. extremely dilute solution) dissociates into two ions, sodium chloride contributes twice as many osmotically active particles as a non-ionized substance (e.g. glucose). Thus 1 mmol of

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sodium chloride in an ideal solution provides 2 mosmol. However, body fluids are not ideal solutions, and although the dissociation of the electrolyte compound may be complete, the number of particles to exert an osmotic effect is reduced due to ionic interaction.¹ For sodium chloride a factor of 1.86 makes allowance for the interaction of ions in concentrations that normally exist in plasma water;² accordingly, the osmolality of 0.9% saline (which contains 154 mmol of sodium/l and 154 mmol of chloride/l) is 286 mosmol/kg and not 308 mosmol/kg.

Plasma osmolality

In humans, the normal extremes of plasma osmolality are 280 and 295 mosm/kg (i.e. 287 ± 7 mosm/kg) although, in a given subject, the normal daily range is much narrower.³ Plasma osmolalities of 280 mosmol/kg suppress plasma ADH to levels low enough to permit maximum urinary dilution.⁴ Above this value an increase in ECF tonicity of about 1-2%, or a decrease in total body water of 1 to 2 litres, stimulates hypothalamic osmoreceptors, causing posterior pituitary release of antidiuretic hormone (ADH). Maximum plasma ADH levels are reached at an osmolality of 295 mosmol/kg (e.g. a loss of 2.2 litres of water in a 70 kg man),⁴ and further defense against a reduction in intracellular fluid (ICF) volume depends on the thirst mechanism, which is also influenced by the hypothalamic osmoreceptors.⁵

ADH acts on the collecting duct of the nephron by binding to the cell membrane V₂ vasopressin receptor, activating an adenylate cyclase present on the basolateral (not luminal) cell membrane and increasing intracellular cAMP. The increase in intracellular cAMP causes an increase in intracellular Ca²⁺ concentration, which in turn causes a calmodulin-dependent increase in permeability of the luminal side of the collecting-duct cell membrane to water and urea, due to the insertion of highly selective water channels (aquaporin 2, one of a family of six highly selective water channels) into the apical membrane.⁶ While the collecting ducts are impermeable to water in the absence of ADH, if the distal nephron flow is slow enough, the gradient between the hypotonic luminal fluid and the hypertonic medullary interstitium will allow moderately hypertonic urine to be formed, even in the absence of ADH. The main function of ADH is to prevent excessive dilution of urine, as the amount of water saved by not excreting a dilute urine (e.g. 18 litres/24h/70kg adult), is much greater than the amount of water saved by producing a maximally dilute urine (e.g. 1.5 litres/24h/70kg adult).

Plasma tonicity

Body fluid solutes are either permeant (i.e. they are

able to permeate throughout the ICF and ECF compartments) or impermeant (i.e. because of molecular size, electrical charge or active membrane pumps, they are distributed within the ECF only). Tonicity refers to the osmotic pressure generated by impermeant solutes. It may be calculated by measuring the plasma osmolality and reducing this value by the molar concentrations of permeant solutes (e.g., urea, ethanol) or by adding the molar concentrations of plasma sodium (and its accompanying anion), and glucose (although in the critically ill patient, other circulating impermeant solutes, e.g. sorbitol, fructose, mannitol should also be included).²

Hyperosmolar states have an increased plasma osmolality due to a decrease in total body water or an increase in body solutes.³ Hypertonic states, on the other hand, have an increased plasma osmolality due to an increase in impermeant solutes, which in turn leads to a reduction in ICF volume (due to the ECF/ICF osmotic difference, which shifts fluid from the ICF to the ECF compartment).³ This effect, if due to hypertonic substances not containing sodium (e.g. glucose or mannitol), is associated with a predictable reduction in the plasma sodium concentration. For example, in the presence of hyperglycaemia, for every 1 mmol/l rise in glucose (above a plasma glucose level of 5.6 mmol/l), the plasma sodium decreases by 0.288 mmol/l.⁷⁻¹⁰ The corrected sodium value (Na⁺c) in mmol/l, may be derived from the formula;

$$\text{Na}^+c = \text{Na}^+m + (\text{Gluc} - 5.6) \times 0.288$$

Where,

Na⁺c = Corrected plasma sodium (mmol/l)

Na⁺m = Measured plasma sodium (mmol/l)

Gluc = Measured plasma glucose (mmol/l)

Thus if a patient has a measured sodium of 131 mmol/l and a glucose of 73.5 mmol/l the 'corrected' sodium value (i.e. sodium concentration if the plasma glucose were normal) would be $131 + 67.9 \times 0.288 = 151$ mmol/l.

If hypertonic saline or sodium bicarbonate solutions are the cause of hypertonicity, the plasma sodium rises. The anticipated increase in plasma sodium may be calculated by multiplying the initial plasma sodium by the ratio of the increase in plasma osmolality. For example, in a 70 kg man who has a total body water of 60% and a plasma sodium and osmolality of 140 mmol/l and 286 mosmol/kg, respectively, the rise in plasma sodium due to the administration of 100 mmol (in 100 ml of water) of sodium bicarbonate (assuming no water or sodium is excreted and the sodium bicarbonate is completely dissociated i.e. discounting the interaction of

ions in plasma), may be calculated as follows:

Plasma osmolality	=	286 mosmol/kg,
Total body water	=	70 x 0.6,
	=	42 litres
Total body osmoles	=	42 x 286,
	=	12 012 mosmol.
After 100 mmol of sodium bicarbonate,		
Total body water	=	42 + 0.1,
	=	42.1 litres
Total body osmoles	=	12 012 + 200
	=	12 212 mosmol,
Plasma osmolality	=	12 212/42.1
	=	290 mosmol/kg,
Final plasma sodium	=	290/286 x 140,
	=	142 mmol/l.

As an approximation, the plasma sodium rises 1 mmol/l for every 40 mmol of sodium, which is administered without water (i.e. numerically the same amount of sodium in mmol as the patient's total body water).

Osmolar (osmolal) gap

In health, plasma osmolality is contributed to largely by sodium and its accompanying anion, glucose and urea, allowing for a reasonably accurate estimation of the plasma osmolality by the simple addition of the molar concentrations of these compounds. For example,

$$\text{Plasma osmolality} = 2 \times \text{Na}^+ + \text{glucose} + \text{urea}$$

where the plasma sodium, glucose and urea concentrations are measured in millimoles per litre¹¹. The doubling (rather than x 1.86) of plasma sodium concentration, offsets to some degree the effect that plasma normally contains 93% water and 7% solids. The plasma solids consist of 5.5% proteins, 1% salts and 0.5% lipids. If the solid phase is elevated significantly, for example, in hyperlipidaemia or hyperproteinaemia, then any instrument that requires a specific amount of plasma for dilution prior to analysis (e.g. flame emission spectrophotometer) will be effectively 'short sampled' by the percentage increase of solid phase, falsely lowering values for all compounds measured. This effect causes a 'pseudohyponatraemia' and is associated with a normal measured plasma osmolality.¹² Measurement of plasma

sodium by an ion-selective electrode is not affected by the volume of plasma 'solids' and therefore 'pseudohyponatraemia' will not occur when the plasma sodium is measured by this method.¹²

The osmolar gap is the difference between the measured osmolality and the calculated osmolality and is normally less than 10. The gap increases in conditions of 'factitious' hyponatraemia where plasma water is less than normal (e.g. if the method of measurement is 'short sampled' by the presence of a hyperlipidaemia or hyperproteinaemia), or in the presence of unmeasured osmotically active compounds such as ethanol, methanol, isopropyl alcohol, ethylene glycol, (although the sensitivity of the osmolar gap as a screen for alcohol toxicity is low),^{13,14} paraldehyde, ether, trichloroethylene, acetone, mannitol, glycerol, sorbitol, glycine (e.g. TURP syndrome) and fructose.¹¹ The osmolar gap is also elevated in patients with chronic renal failure¹⁵ and in keto and lactic acidosis,¹⁶ although the reasons for this are not entirely clear.

Osmolality may be measured in plasma or serum, as haemolysis does not alter osmolality. While the heparin in a plasma sample can artefactually elevate the osmolality by up to 0.6 mosmol/kg,¹⁷ in practice this is regarded as negligible.¹⁸ However, if a blood specimen is left standing for some time before the osmolality is measured, the formation of lactate may artefactually increase the osmolality by up to 8 mosmol/kg.¹⁷

In clinical practice, plasma osmolality is measured to determine whether total body water deviates from normal (e.g. hypo or hypo-osmolar states) or to detect (from an elevation in the osmolar gap) the presence of abnormal low-molecular weight substances in the blood.¹⁹

DISORDERS OF HYDRATION (water excess or deficiency)

Water is distributed throughout the ICF and ECF largely in response to osmolar gradients. The total body water, extracellular and intracellular compartments and total body osmoles may be represented diagrammatically (Figure 1).

As the ECF sodium (and its accompanying anion) and ICF potassium (and its accompanying anion) are largely responsible for the total body osmoles (approximately 12 000 mosmol), the total exchangeable

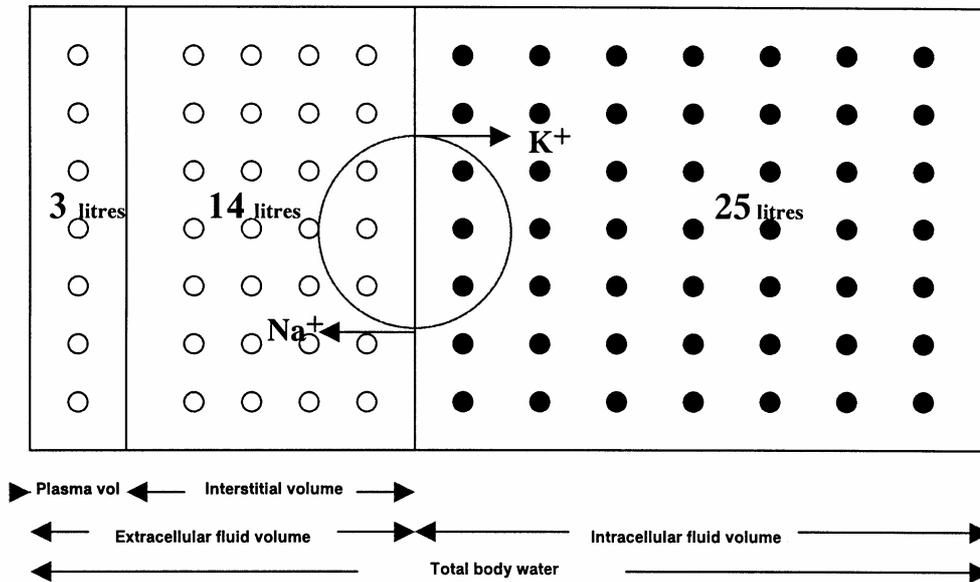


Figure 1. Body fluid compartment volumes with O representing extracellular sodium and ● representing intracellular potassium.

sodium and potassium (i.e. that which exchanges with isotopic tracer sodium or potassium within 24 h) for a 70 kg subject may be calculated as follows,

$$\begin{aligned} \text{Exchangeable sodium} &= \text{ECF volume} \times \text{plasma osmolality} \times 0.5 \\ &= 17 \times 286 \times 0.5 \\ &\approx 2\,500 \text{ mmol} \end{aligned}$$

$$\begin{aligned} \text{Exchangeable potassium} &= \text{ICF volume} \times \text{plasma osmolality} \times 0.5 \\ &= 25 \times 286 \times 0.5 \\ &\approx 3\,500 \text{ mmol} \end{aligned}$$

In health, the plasma sodium concentration is regulated by factors that alter water intake and excretion (i.e. plasma sodium concentration largely reflects water excess or deficiency), and not total body sodium. Total body sodium is regulated largely by factors that regulate effective extracellular volume. An increase or decrease in total body sodium is reflected by an increase or decrease in ECF volume (and therefore plasma volume), the clinical effects of which are predominantly cardiovascular in nature. For example, the clinical features of a reduction in total body sodium include postural hypotension, tachycardia, hypotension, a decrease in urine sodium excretion and reduction in urine output; and the clinical features of an increase in

total body sodium include, peripheral oedema, pulmonary oedema, ascites and pleural effusions.

The clinical effects of an increase or decrease in total body water are predominantly neurological in nature (i.e. alteration in consciousness). In conditions of water excess or deficiency (as plasma sodium concentration usually varies with the plasma osmolality) one may assess the amount of water excess or water deficiency by the formulae,

$$X = \text{TBW} \times \left(\frac{\text{Na}^+_n}{\text{Na}^+_m} - 1 \right)$$

Where,

- X = Water excess or deficiency (litres)
- TBW = Total body water (litres)
- Na⁺_n = Normal plasma sodium (mmol/l)
- Na⁺_m = Measured plasma sodium (mmol/l)

Water excess

In a 70 kg man, for every litre of excess water, the ECF increases, on average, by 400 ml and the ICF increases by 600 ml. The osmolality also decreases by approximately 6 mosmol/kg and the plasma sodium falls by approximately 3.0 mmol/l. If a 70 kg man with a total body water content 60% of total body weight has a plasma sodium of 125 mmol/l and normally has a

normal plasma sodium of 140 mmol/l, the water excess can be calculated to be $42 \times (140/125-1) = 5.04$ litres.

Hyponatraemia

In health the plasma sodium varies between 135 and 145 mmol/l. Hyponatraemia is defined as a plasma sodium less than 135 mmol/l and may be classified as isoosmolar, hyperosmolar (hypertonic) or hypoosmolar, depending upon the measured plasma osmolality. The common causes of hyponatraemia are listed in Table 1.

Table 1. Causes of Hyponatraemia

Isoosmolar	
	Pseudohyponatraemia
	Hyperlipidaemia
	Hyperproteinaemia
Hyperosmolar (Hypertonic)	
	Hyperglycaemia
	Mannitol, glycerol or sorbitol excess
Hypoosmolar	
<i>Water excess</i>	
	Syndrome of inappropriate antidiuretic hormone secretion
	Syndrome of inappropriate antidiuresis
	Psychogenic polydipsia, beer potomania
	Transurethral resection of the prostate syndrome
	Endometrial ablation
<i>Salt depletion</i>	
	Adrenocortical failure
	Diuretic excess
<i>Potassium depletion</i>	

Hypoosmolar hyponatraemia is often caused by an excess of total body water, from excessive hypotonic, or water generating intravenous fluids (i.e. 1.5% glycine (200 mosmol/kg), 0.45% saline (143 mosmol/kg) or 5% dextrose), particularly when administered rapidly or in the presence of high circulating levels of ADH (e.g. in the postoperative period); or excessive ingestion of water (e.g. psychogenic polydipsia, beer potomania).^{20,21} In psychogenic polydipsia, if the water intake exceeds the renal capacity to form dilute urine, water retention and hyponatraemia will occur.²² In health, a fluid intake up to 15-20 litres may be tolerated before water is retained. However, less water is needed to produce hyponatraemia in individuals in whom an increase in nonosmotic stimulation of ADH (e.g. hypovolaemia, hypotension, pain, nausea, and post operative stress),^{3,23,24} reduction in urinary osmotic excretion (e.g. patients with a reduced urea production), or a reduction

in renal capacity to respond to ADH, is also present. In psychogenic polydipsia the plasma osmolality exceeds urine osmolality.

Hyponatraemia may rarely be due to loss of exchangeable sodium or loss of exchangeable potassium.²⁵ In the latter two circumstances, a loss of approximately 40 mmol of sodium or potassium (i.e. numerically the same as the patient's total body water), without a change in total body water content, is required to lower the plasma sodium by 1 mmol/l (i.e. a loss of 400 mmol of sodium or potassium is required to decrease the plasma sodium by 10 mmol/l).

In clinical practice, hyponatraemia may be associated with an alteration in both total body water and total body sodium, therefore the ECF may be increased (hypervolaemia), decreased (hypovolaemia) or exhibit no change (isovolaemia).¹¹ The proposal that disease may cause a 'sick cell syndrome',^{26,27} causing the ECF sodium to leak into cells and produce hyponatraemia, is a misconception,²⁸ because it requires,

- a reciprocal leak of ICF osmolar particles out of the cell into the ECF (if the ECF sodium content is to decrease, otherwise water would follow the sodium into the cell and the ECF sodium concentration would remain the same), or
 - no reduction in osmolality, and therefore an increase in the osmolar gap,
- neither of which have been observed in patients with hyponatraemia.²⁹

Clinical features

Hypoosmolar hyponatraemia due to excess total body water, results in symptoms caused by cerebral water excess (i.e. cerebral oedema).³⁰ Normally, the brain partially adapts to the hypoosmolality within 24 h, reducing the cerebral water excess by losing or inactivating intracellular osmotically active solutes.³¹⁻³⁴

Acute hyponatraemia with cerebral oedema may require emergency treatment, whereas chronic hyponatraemia (with plasma sodium values well below 125 mmol/l), may be well tolerated due to cerebral osmotic compensation.³¹ The mortality associated with hyponatraemia usually relates to its rate of development rather than to its severity³⁵. Chronic hyponatraemia has a mortality of less than 10%³⁵, whereas a mortality up to 50% has been reported with acute hyponatraemia.³⁶

If the patient develops acute hyponatraemia (i.e. 3 days or less), then symptoms of headache, anorexia, nausea, weakness, lethargy, confusion, disorientation, blurred vision, muscle cramps, coma and seizures usually occur when the sodium concentration is less than 125 mmol/l (osmolality 260 mosmol/kg).^{31,32,37}

Diagnosis

Plasma osmolality, osmolar gap, and urinary sodium are measured. The urinary sodium is usually greater than 40 mmol/l and plasma urea is low when an excess total body water exists. In the rare case of salt depletion, the urinary sodium loss is usually less than 20 mmol/l, and the plasma urea and uric acid are high.¹¹

Chronic hyponatraemia is an epiphenomenon of disease; therefore, in these patients it is important to determine the underlying cause. For example, a chest X-ray, and chest and cerebral CT scans may be required to investigate the possibility of tumour induced syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Treatment

Chronic hyponatraemia (> 3 days duration). If the patient is asymptomatic and hyponatraemia has been present for greater than 3 days, fluid restriction and reversal of any precipitating factor is often all that is required.³⁸ Fluid should be restricted to less than 500 ml/day. The rate of correction for chronic hyponatraemia should be no greater than 12 mmol/l/day (0.5 mmol/l/h) and is continued only until the plasma sodium is 130 mmol/l.³⁷⁻⁴¹ If chronic fluid deprivation is difficult to maintain in patients with SIADH or syndrome of inappropriate antidiuresis (SIAD)³⁶ then, in patients with hyponatraemia and chronic cardiac failure, an ACE inhibitor (to inhibit both angiotensin II stimulation of thirst and ADH release) with frusemide may be of benefit.^{42,43} However, in these patients a direct ADH inhibitor may be of greater value.⁴⁴ Phenytoin has been used to reduce ADH release from the hypophysis in patients with SIADH and central nervous system disorders.⁴⁵ In other patients with SIADH, lithium and demeclocycline have been used.^{11,45}

With chronic hyponatraemia the brain is less able to tolerate rapid correction, and, when hypertonic saline is used, central pontine and extrapontine myelinolysis (i.e. the osmotic demyelination syndrome) has been reported.⁴¹ The lesions are characterized histologically by loss of myelin with sparing of neurons in the central pons (central pontine myelinolysis), internal capsule, basal ganglia, cerebellum and cerebrum. These lesions cause a variety of clinical features ranging from coma, flaccid quadriplegia, dysarthria, dysphagia, facial weakness, pseudobulbar palsy and ataxia, to minor behavioral changes without focal findings. The features are often delayed and appear typically 3 days after the hyponatraemia has been corrected⁴⁶ and may require MRI to confirm the diagnosis.⁴⁷

While an association with the osmotic demyelination syndrome (ODS) and correction of hyponatraemia has been reported experimentally,⁴⁰ a causal relationship

between it and the rapidity of correction of hyponatraemia has not been firmly established in clinical practice. In 170 cases of ODS, hyponatraemia occurred in only 28% of cases (most of whom were corrected slowly),⁴⁸ an observation which has been confirmed by others.⁴⁹ In one review, hypokalaemia was found to be a risk factor of ODS and it was proposed that correction of hypokalaemia should precede the correction of hyponatraemia in patients without severe neurological symptoms.⁵⁰

Acute hyponatraemia (< 3 days duration). This is often associated with inappropriate intravenous fluid administration, particularly in women, and in the postoperative period.⁵¹ The total water excess in adults ranges from 5-10 litres.

The rate of correction for acute hyponatraemia should be no greater than 2 mmol/l/h until the plasma sodium has increased to 120 mmol/l or by a maximum of 20 mmol/l during the first 24 h.^{33,52,53} This may be achieved initially by intravenous administration of hypertonic saline (50 - 70 mmol/h), which is not used to correct a saline deficit, but used as an easily measured hypertonic agent required to shift fluid from the ICF to the ECF (i.e. correct the problem of cerebral oedema). A spontaneously induced or frusemide-induced diuresis (e.g. urine output > 160 ml/h) is then needed to excrete the water excess.

When the plasma sodium has increased to 120 mmol/l, precautions should be taken to prevent the plasma sodium rising to greater than 130 mmol/l over the next 24 h.^{52,53} If the hyponatraemia presents with seizures then urgent correction of the cerebral oedema using 250 mmol of hypertonic sodium chloride over 10 min (50 ml of 29.2% saline which is equivalent to 500 ml of 20% mannitol) has been used, which immediately elevates the plasma sodium in adults by about 7 mmol/l.⁵⁴

The complications reported with the use of hypertonic saline include pulmonary oedema, cerebral haemorrhage and ODS. To reduce the incidence of pulmonary oedema, monitoring of central venous pressure or pulmonary arterial occlusion pressure, throughout saline administration, will allow an assessment of the increase in intravascular volume. Cerebral haemorrhage will only occur if there is an inappropriate administration of hypertonic saline in normonatraemic states.⁵⁵

There is still not uniform agreement that ODS is produced by a rapid correction of acute hyponatraemia.^{56,57} Nevertheless, it is believed that the increase in plasma sodium should be only up to 130 mmol/l, and that this value should be maintained for 24-48 h, in an attempt to reduce overcorrection and any likelihood of ODS occurring.

Transurethral resection of prostate (TURP) syndrome

The TURP syndrome consists of hyposmolar hyponatraemia, cardiovascular disturbances (e.g. hypertension, hypotension, bradycardia), an altered state of consciousness (e.g. agitation, confusion, nausea, vomiting, myoclonic and grand mal seizures) and (when glycine solutions are used) transient visual disturbances of blurred vision, blindness and fixed dilated pupils, associated with transurethral resection of the prostate (although a similar syndrome has also been described following endometrial ablation).^{58,59}

It may occur within 15 minutes or be delayed for up to 24 hours, postoperatively,⁶⁰ and is caused by an excess absorption of the irrigating fluid which contains 1.5% glycine with an osmolality of 200 mosmol/kg (although hyponatraemic syndromes have also been described when irrigating solutions containing 3% mannitol or 3% sorbitol have been used, both of which have an osmolality of 165 mosmol/kg). The addition of ethanol 1% to these solutions has allowed fluid absorption to be monitored by expired ethanol tests⁶¹. Symptomatology usually occurs when > 1 litre of 1.5% glycine or > 2 - 3 litres of 3% mannitol or sorbitol are absorbed.⁶²

The excess absorption of irrigating fluid causes an increase in total body water (which is often associated with only a small decrease in plasma osmolality), hyponatraemia (as glycine, sorbitol or mannitol reduces the sodium component of ECF osmolality), and an increase in the osmolar gap.⁶³⁻⁶⁵

When glycine is used, other features include hyperglycinaemia (up to 20 mmol/l - normal plasma glycine levels range from 0.15 to 0.3 mmol/l), hyperserinaemia (as serine is a major metabolite of glycine), hyperammonaemia (following deamination of glycine and serine), metabolic acidosis and hypocalcaemia (due to the toxic effects of the glycine metabolites, glyoxylic acid and oxalate). Because glycine is an inhibitory neurotransmitter (by blocking chloride channels)⁶⁶ and as it passes freely into the intracellular compartment, when glycine solutions are used, hyperglycinaemia may be more important in the pathophysiology of this disorder than a reduction in body fluid osmolality and cerebral oedema,⁶⁷ as cerebral oedema is often minimal in this condition.⁶⁸

Treatment is largely supportive with the management of any reduction in plasma osmolality being based on the measured plasma osmolality and not plasma sodium levels. If the measured osmolality is > 260 mosmol/kg and mild neurological abnormalities exist, if the patient is haemodynamically stable with normal renal function, close observation and reassurance (e.g. the visual disturbances are reversible and will last for less than 24

hours) are usually all that is needed. If the patient is hypotensive and bradycardic with severe and unresolving neurological abnormalities, haemodialysis may be warranted.⁶⁹ Hypertonic saline is only used if the measured osmolality is < 260 mosmol/kg and severe non-visual neurological abnormalities exist.

Water deficiency

In a 70 kg man, for every litre of water lost, 600 ml is lost from the ICF and 400 from the ECF. The osmolality increases by 7-8 mosmol/kg and the plasma sodium rises by 3.5-4.0 mmol/l. If a 70 kg man with a total body water content 60% of total body weight has a plasma sodium of 155 mmol/l and normally has a plasma sodium of 140 mmol/l, the water deficit can be calculated to be $42 \times (140/155-1) = -4.06$ litres.

Hypernatraemia

Hypernatraemia is defined as a plasma sodium greater than 145 mmol/l. It is always associated with hyperosmolality and may be caused by water depletion, excessive administration of sodium salts or a combination of both. The common causes of hypernatraemia are listed in table 2. The highest serum sodium recorded in a patient who survived is 209 mmol/l.⁷⁰

In water-depleted states, the thirst mechanism normally stimulates a conscious individual to imbibe water; thus water loss only produces hypernatraemia if the patient is unconscious or otherwise physically unable to drink. Excessive administration of sodium salts is a rare cause of hypernatraemia and usually only occurs as a result of a therapeutic misadventure.

Clinical features

Hypernatraemia is usually symptomatic if the plasma sodium is 155-160 mmol/l or greater (i.e. osmolality of 330 mosmol/kg or greater). This equates to a water depletion of 6 litres or greater in a 70 kg man.³¹ The clinical features include pyrexia, restlessness, weakness, irritability, drowsiness, lethargy, confusion, tremor, hyperreflexia, seizures, paralysis and coma.⁷¹

Treatment

If hypotension exists due to a reduction in intravascular fluid volume, then isotonic saline infusions are used to replace some of the intravascular volume and improve tissue perfusion before hypotonic solutions are used.

Treatment of pure water depletion consists of water administration and, in a conscious patient with normal gastrointestinal function, oral ingestion of water is encouraged. In the event that parenteral administration of fluid is required, 5% dextrose or hypotonic saline

solutions (e.g. 0.45% saline) are often used, as sterile water through a peripheral vein causes haemolysis.⁷² In rare cases, where saline and dextrose solutions are deemed inadvisable, central venous administration of sterile water have been used without causing haemolysis, and may be of benefit in such circumstances.⁷³

Table 2. Causes of Hypernatraemia

Water depletion

Extrarenal loss

Exposure

Gastrointestinal losses

Renal loss

Osmotic diuresis (urea, mannitol, glucose)

Diabetes insipidus

Neurogenic

Post traumatic, postoperative

Cerebral tumours

Meningitis, encephalitis

Fat embolism

Nephrogenic

Congenital

Hypercalcaemia, hypokalaemia

Lithium, amphotericin B

Renal diseases

Chronic pyelonephritis

Medullary sponge kidney

Polycystic kidney

Analgesic nephropathy

Post obstructive uropathy

Multiple myeloma, amyloid, sarcoid

Salt gain

Hypertonic saline or sodium bicarbonate

As the brain accommodates by accumulating 'idiogenic osmoles' during hypertonicity,^{31,33,74} rapid rehydration may give rise to cerebral oedema. The change in plasma osmolality should be no greater than 2 mosmol/kg/h.^{31,33} Recently, NMR spectroscopy of the brain has been used to assess the intracellular accumulation of the 'idiogenic osmoles' and may be used to guide the rate of correction in osmolality.⁷⁵ Treatment of hypernatraemia due to excess sodium consists of water and diuretic administration,⁷⁶ or when renal failure exists, dialysis.

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