

Common electrolyte problems

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Electrolyte disorders are among the most frequent and challenging problems facing the admitting physician and many have serious prognostic significance¹. Early and informed intervention is necessary, but the outcome may be disappointing. Hyponatraemia with serum sodium below 130 mmol/l occurs in 3–5% of hospital admissions² and death rates vary from 11–70%³. In patients with hypernatraemia with serum sodium above 150 mmol/l death rates have reached 42%, with significant debility among survivors⁴.

Basic physiology of salt and water handling

The kidneys handle sodium and water separately. Sodium handling is

influenced by sympathetic tone, aldosterone (amongst other stimuli) and diuretics acting on three major sites of sodium reabsorption. Sodium reabsorption takes place without reabsorption of water because the renal tubule is impermeable to water unless aquaporin-2 water channels are inserted into the luminal surface of the collecting duct tubules, allowing water to be reabsorbed in the medulla⁵. Vasopressin acts on V2 receptors to cause insertion of the aquaporin channels. The major stimuli to vasopressin release are:

- a rise in plasma osmolality
- effective or true hypovolaemia
- non-osmotic stimuli, including pain and nausea.

Hyponatraemia

Common causes of hyponatraemia are summarised in Table 1. The reference range for plasma sodium is 134–144 mmol/l. Sick patients commonly have hyponatraemia due to loss of intracellular osmolytes drawing water into the extracellular fluid. In the insulinopenic state, hyperglycaemia lowers serum sodium by 1.5 mmol/l for every 3.5 mmol/l increase in plasma glucose by translocating intracellular water⁶. This may be counterbalanced by glycosuria causing a water diuresis, and

conversely lead to severe hypernatraemia as in hyperosmolar non-ketotic coma.

Significant hyponatraemia, with a rapid fall to below 120 mmol/l, causes generalised encephalopathy leading to stupor, coma and death³. It arises from excess water and/or sodium loss and is sustained by an inability to elaborate dilute urine due to stimulation of AVP release by non-osmotic mechanisms.

Diagnostic evaluation

Clinical evaluation is directed towards an assessment of extracellular volume (Table 2) and the presence of thyroid, pituitary, adrenal, cardiac, hepatic or renal disease⁷. Peripheral oedema in cardiac failure and ascites in hepatic cirrhosis indicate sodium retention, but the effective circulating volume is reduced, stimulating AVP production^{8,9}.

Thiazide diuretics frequently cause hyponatraemia^{2,10}, particularly in elderly women who may respond by increased thirst and weight gain, with a fall in sodium to below 125 mmol/l within a few days. In an analogous way to beer drinkers' potomania, a high intake of sodium-free fluid and poor nutrition restrict urine output due to reduced osmolar load¹¹.

Syndrome of inappropriate antidiuresis

Diagnosis of the syndrome of inappropriate antidiuresis requires the presence of hypo-osmolar hyponatraemia with urine sodium above 40 mmol/l, a urine/plasma osmolality ratio above 1, and normal pituitary, adrenal and thyroid function¹². Elevated AVP persists in the face of low plasma osmolality due to ectopic release from tumours, non-osmotic stimuli such as pain, and many drugs (Table 3). Hyponatraemia after surgery follows infusion of hypotonic fluids, with oliguria produced by AVP release due to anaesthetics, pain, nausea and opiates. Hyponatraemia with cerebral oedema may develop rapidly, particularly in children¹³ and menstruating females¹⁴, possibly due to inhibition of brain volume regulation by oestrogen¹⁵.

Key Points

Management of plasma sodium and potassium abnormalities is a frequent challenge in all areas of medicine

Hyponatraemia and hypernatraemia are most commonly due to retention and loss of water, respectively

Hypokalaemia and hyperkalaemia are largely due to renal dysfunction which may be primary or iatrogenic

Clinical assessment of blood volume and the antecedent drug history are essential for diagnosis

Restoration of euvolaemia allows the normal kidney to correct electrolyte imbalance

Intracellular adaptation to changes in extracellular electrolyte content occur within 48 hours, thereafter over-rapid correction may worsen prognosis

KEY WORDS: CPD, electrolyte disorders, hyperkalaemia, hypernatraemia, hypokalaemia, hyponatraemia, potassium, sodium

Table 1. Common causes of hyponatraemia.

Hypovolaemic	Euvolaemic	Hypervolaemic
Gastrointestinal: vomiting, diarrhoea, fistulae, drains.	Spurious due to high triglyceride or protein	Cirrhosis
Burns	Sick cell syndrome	Cardiac failure
Pancreatitis	Hyperglycaemia or other osmotic agents	Nephrotic syndrome
Diuretics	Syndrome of inappropriate antidiuresis	Renal failure
Addison's disease	ACTH deficiency	
Salt wasting nephropathy	Diuretics	
Cerebral salt wasting		

ACTH = adrenocorticotrophic hormone.

Table 2. Clinical indicators of extracellular volume depletion.

Clinical indicators	Comments
Postural hypotension and tachycardia	Reliable bedside test
Reduced skin turgor, dry mucous membranes and sunken eyeballs	Signs of severe hypovolaemia only, difficult to assess in the elderly
Spot urinary sodium <20 mmol/l <i>Demonstrates renal sodium conservation</i>	Concealed in some renal diseases and by urinary sodium bicarbonate loss in metabolic alkalosis (eg vomiting)
Elevated urea/creatinine ratio <i>Reduced renal perfusion and tubular flow increases reabsorption of urea</i>	Also increased by gastrointestinal haemorrhage, steroids and catabolic metabolism

Treatment of hyponatraemia

During the first 48 hours of exposure to hyponatraemia, cell swelling is successfully counterbalanced by loss of intracellular potassium and organic osmolytes¹⁶. Reversal is a much slower process. In symptomatic hyponatraemia of more than 48 hours' duration rapid correction risks causing cell shrinkage and osmotic demyelination, with signs of central pontine myelinosis manifesting two days later. Hypertonic or isotonic saline should be used to correct hyponatraemia at a rate less than 0.5 mmol/l/h and not exceeding 10–12 mmol/l per 24 hours until symptoms subside^{16,17}. Hyponatraemia of acute onset requires rapid correction until symptoms heralding cerebral oedema disappear. Asymptomatic patients can be restricted to a litre of fluid a day.

In the future, measurement of urinary aquaporin-2 excretion reflecting the renal response to vasopressin may prove helpful in defining causes of hyponatraemia, and

specific oral V2 receptor antagonists may be useful in management⁹.

Hypernatraemia

Hypernatraemia (Table 4) is common in hospital patients, arising from water loss with inadequate replacement. Poor prognosis is related more to rapid correction than to the degree of hypernatraemia⁴.

Relative water deficiency is sustained, despite thirst, by lack of access to water in the young, the old and the infirm. Ability to concentrate urine may be reduced by osmotic diuresis (intravenous nutritional supplements, hyperglycaemia or other osmotic diuretics), loop diuretics, resolution of obstructive nephropathy or failure of arginine vasopressin (AVP) action. It is generally reduced in the elderly.

Hypernatraemia has been described following intrauterine saline for attempted abortion and oral ingestion in non-accidental salt poisoning in children¹⁸.

Treatment of hypernatraemia

Treatment of hypernatraemia follows similar principles to that of hyponatraemia, reducing serum sodium concentration at a maximal rate of 0.5 mmol/l/h and not more than 10 mmol/l per 24 hours with 0.45% sodium chloride (half normal saline) or 5% dextrose, and avoiding cerebral oedema. A helpful quantitative approach is contained in the article by Adrogué and Madias¹⁹.

Diabetes insipidus

Cranial diabetes insipidus (DI) is due to lack of AVP, which may be partial, and 50% of cases are idiopathic. Nephrogenic DI follows damage to the renal concentrating mechanism by drugs (eg lithium, amphotericin B, foscarnet), hypercalcaemia, nephrocalcinosis and Fanconi

Table 3. Drugs associated with the syndrome of inappropriate antidiuresis.

- Carbamazepine
- Thiazide diuretics
- All potassium-sparing diuretics, particularly amiloride
- Combinations (eg Moduretic (thiazide + potassium-sparing diuretic))
- Tricyclic antidepressants
- Selective serotonin reuptake inhibitors
- Antipsychotic: phenothiazines (provoke thirst), haloperidol
- Chlorpropamide
- 'Ecstasy' and related drugs
- Chemotherapy: vincristine, vinblastine, cyclophosphamide
- Bromocriptine

Table 4. Causes of hypernatraemia with predominant water loss.

- Inappropriate fluid replacement, nutritional supplementation
- Increased insensible loss: febrile illness
- Gastrointestinal loss: diarrhoea, colostomy, ileostomy
- Urinary loss: diuretics, osmotic diuresis, hypercalcaemia, diabetes mellitus
- Failure of urine concentration: diabetes insipidus

syndrome. Inherited DI has been attributed to defects in the V2 receptor and an autosomal dominant defect in the aquaporin-2 channel⁵. A calcium sensor located in the inner medullary collecting ducts regulates the tubular response to AVP, accounting for the polyuric response to hypercalcaemia and possibly for some inherited forms of DI. Placental vasopressinase may cause DI in late pregnancy. DDAVP resists inactivation and is therapeutic.

Potassium disorders

The glomerular filtration rate (GFR), urinary flow rate and renal tubular exchanges regulate renal potassium excretion.

Hypokalaemia

The reference range for plasma potassium is 3.5–5.0 mmol/l. Serum levels are about 0.5 mmol/l higher due to release of platelet potassium during clotting²⁰. Hypokalaemia (Table 5) arises with transcellular shifts, extrarenal (gastrointestinal) or renal loss. Alkalosis moves potassium into cells, leading to the development of kaliuria by inhibition of proximal resorption of bicarbonate, promoting potassium exchange in the distal tubule and increased distal tubular flow.

In normotensive young patients with unexplained hypokalaemia and raised bicarbonate, diuretic abuse, surreptitious vomiting and inherited tubulopathy should be considered²¹. Diuretic abuse is usually denied and must be screened for, but characteristically urinary chloride falls rapidly to low levels when the patient stops diuretics to attend the clinic. Urinary chloride will also be low in surreptitious vomiting and laxative abuse. The latter, also denied and requiring screening for, usually

causes hypokalaemic acidosis and must be distinguished from renal tubular acidosis.

Bartter's syndrome is caused by one of several mutations deactivating sodium and chloride reabsorption at precisely the same site of action as frusemide²², whereas in Gitelman's syndrome the mutations affect the same site of action as thiazide diuretics²³. Bartter's is rarely seen in adults, and predictably Gitelman's is associated with hypocalciuria. Hypertensive hypokalaemia with renal potassium wasting suggests mineralocorticoid excess²⁴.

Diagnostic evaluation

A careful drug and family history is essential. Raised plasma bicarbonate is a useful confirmatory test. Renal loss is suggested by urinary potassium above 15 mmol/l or above 25 mol/day provided that the patient is sodium replete. In hypertensive patients the aldosterone/renin ratio is a useful screening test for Conn's syndrome²⁵ and glucocorticoid remediable hyperaldosteronism. Low levels of both aldosterone and renin

suggest Cushing's syndrome or pseudo-hyperaldosteronism, for example lack of 11-beta hydroxysteroid dehydrogenase activity, liquorice abuse²⁶ and Liddle's syndrome (an activating mutation of the amiloride sensitive epithelial sodium channel²²).

Hyperkalaemia

Hyperkalaemia (Table 6) may be caused by transcellular shifts, reduced GFR or tubular dysfunction exacerbated by high potassium intake. Shifts occur in hyperchloraemic acidosis and some poisonings, but not in ketoacidosis or lactic acidosis where the anions readily enter cells.

Hyperkalaemia presents more frequently with aggressive treatment of heart failure combining angiotensin-converting enzyme inhibitors, angiotensin II antagonists, aldosterone antagonists²⁷ and beta-blockers. Drugs and other hyperkalaemic factors interact to cause serious hyperkalaemia, for example, potassium-sparing diuretics and non-steroidal anti-inflammatory drugs with salt substitutes and apple or other fruit juices which contain potassium. The elderly and diabetics are particularly vulnerable to superadded intercurrent illness reducing renal perfusion²⁸. Mineralocorticoid deficiency results from Addison's disease and hyporeninaemic hypoaldosteronism, common in analgesic nephropathy and diabetes mellitus. Aldosterone resistance

Table 5. Causes of hypokalaemia.

Transcellular shifts	Metabolic alkalosis, insulin, beta2-agonists, familial periodic paralysis
Gastrointestinal loss (extrarenal)	Diarrhoea, vomiting, drains, suction, laxatives
Renal loss	Drugs: loop and thiazide diuretics Increased distal tubular flow rates: osmotic diuresis (eg hyperglycaemia, parenteral or enteral nutrition), bicarbonaturia Resolving obstructive nephropathy Renal tubulopathy: proximal and distal renal tubular acidosis, Fanconi, Bartter's and Gitelman's syndromes Mineralocorticoid excess: Cushing's and Conn's syndromes Syndromes of apparent mineralocorticoid excess and liquorice abuse, Liddle's syndrome Secondary hyperaldosteronism due to cardiac and liver disease, malignant hypertension, renal artery stenosis

Table 6. Causes of hyperkalaemia.

Spurious	Delayed separation of red blood cells from serum, haemolysis, high platelet or white cell counts, drip arm contamination or wrong collecting tube (potassium EDTA)
Transcellular shifts	Insulin lack, metabolic acidosis, beta-blockers
Poisoning	Methanol, ethylene glycol, salicylate, barium
Hormone lack	Addison's disease, hyporeninaemic hypoaldosteronism
Drugs	Potassium-sparing diuretics: amiloride, triamterene, spironolactone, ACE inhibitors, angiotensin II antagonists, trimethoprim, heparin, cyclosporin, tacrolimus, NSAIDs
Dietary intake	Fruit juices, health foods, Noni juice, food supplements
Renal tubulopathy	Pseudohypoaldosteronism, eg ATN, post-obstructive nephropathy
Renal failure	Acute and chronic due to reduced GFR

ACE = angiotensin-converting enzyme; ATN = acute tubular necrosis; EDTA = ethylenediamine tetraacetic acid; GFR = glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drug.

results from an inherited renal tubule epithelial sodium channel defect (pseudohypoaldosteronism) or may follow obstructive nephropathy.

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