OVERVIEW OF ELECTROLYTE ABNORMALITIES

(Na, K, Mg, PO_4)

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POTASSIUM

Normal intake 40-120meq/day; total body stores ~50meq/kg of which 98% is intracellular. Ratio of intra/extracellular Na and K^+ maintains resting membrane potential (rmp). Small changes in extracellular K^+ produce large changes in intra/extracellular ratio and thus changes in rmp. A fall in extracellular K^+ increases rmp making the cell less sensitive to excitation. Conversely a rise in extracellular K^+ increases excitability initially, however at very high K^+ levels the rmp may rise above the threshold potential preventing repolarisation after depolarisation.

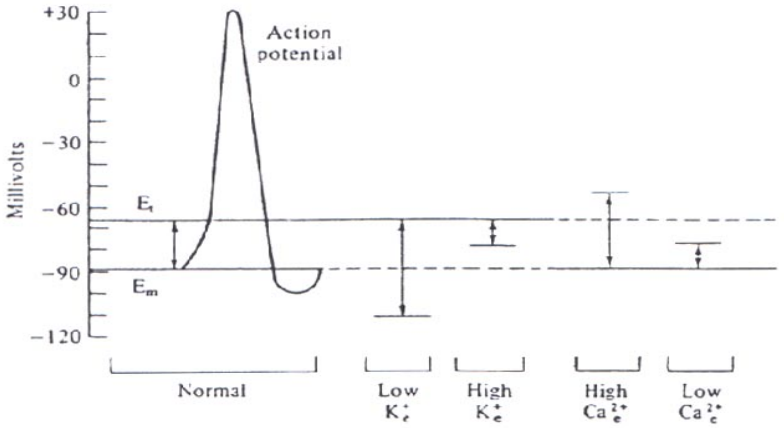


Figure 28-1 Relationship between the extracellular concentrations of K^+ ($[K^+]_e$) and Ca^{2+} ($[Ca^{2+}]_e$) and the resting (E_m) and threshold (E_t) potentials of normal skeletal muscle. The height of the arrows is equal to the difference between the resting and threshold potentials and represents the excitability of the cell membrane. An action potential is generated when there is sufficient depolarization to reach the threshold potential. This process can be affected by changes in the $[K^+]_e$ or $[Ca^{2+}]_e$ which influence the resting and threshold potentials, respectively. (*Adapted from Leaf, A, Cotran, R, Renal Pathophysiology, Oxford University Press, New York, 1976.*)

Large individual variations in the clinical effect of specific K^+ levels occur. This is probably due to the intra/extracellular ratio (not the absolute K^+ level). Thus transcellular shifts produce greater clinical effect than changes in total body K^+. The plasma calcium level and pH also modify the effect of a given K^+ level. Low calcium levels and acidic pH tend to worsen the clinical effect of hyperkalaemia by lowering the threshold potential and vice versa. Functional parameters such as ECG changes and muscle strength better reflect the consequences of K^+ regardless of the numeric level.

Transcellular movement of K^+ is tightly regulated to prevent sudden changes in the intra/extracellular ratio - this is controlled primarily by NaK ATPase, catecholamines, insulin, plasma K^+ levels and exercise. Potassium excretion is controlled by aldosterone, plasma K^+ and the distal tubular flow rate with a minimum daily renal loss of 15-25mmol/day.

HYPOKALAEMIA

Causes:

1. Decreased net intake
   - poor dietary intake (rare unless severe and prolonged)
   - clay ingestion

2. Intracellular shift
   - Alkalosis: H^+ and K^+ exchange across cell membrane to maintain normal pH. A pH increase of 0.1 causes a 0.2-0.4mmol/l fall in K^+. However many processes cause both H^+ and K^+ loss thus alkalosis with severe hypokalaemia
   - Increased insulin (Px of hyperglycaemia, sudden CHO load)
   - Increased β adrenergic activity (Px with β agonists)
   - Periodic paralysis: episodes precipitated by rest after exercise, CHO load and stress with sudden intracellular shift, resolves in 6-8 hours. Rare, autosomal dominant or acquired. Associated with thyrotoxicosis.
   - Hypothermia

3. Increased gastrointestinal losses
   - vomiting, gastric suction
   - diarrhoea
   - malabsorption
   - fistulae
   - chronic laxative abuse

4. Increased urinary losses
   - Loop and thiazide diuretics
   - Mineralocorticoid excess
     - primary hyperaldosteronism (Conns, hyperplasia esp 17α and 11β deficiency)
     - secondary hyperaldosteronism (CCF, cirrhosis, hypoproteinaemia, nephrotic syndrome)
     - hyperreninism (RAS, Bartters syndrome, JGM tumours)
     - Cushings syndrome and congenital adrenal hyperplasia
     - exogenous (licorice, aldosterone analogues)
   - Tubular disease: RTA (type 1 and 2), salt losing nephropathies
   - Drugs: amphotericin B, acetazolamide

5. Hypomagnesaemia: mechanism unclear but common concurrent finding with hypokalaemia and K^+ is refractory until Mg^+ corrected.

6. Barium poisoning

7. Pseudohypokalaemia: grossly elevated WCC shift K^+ intracellularly after collection if not processed rapidly.

Effects:

1. Muscle weakness. Initially low [K] increases rmp reducing cellular excitability causing weakness, usually seen at [K]<2.5mmol/l. At very low levels spontaneous depolarization may occur (cause unclear). Typical clinical picture of ascending weakness beginning in legs and eventually causing respiratory failure, rarely involving cranial nerves. May also have cramps, tetany, fasciculations, muscle tenderness and paralytic ileus.

2. Rhabdomyolysis. Local [K] controls skeletal muscle blood flow which increases with exercise. Decreased [K] decreases blood flow leading to ischaemic necrosis and rhabdomyolysis

3. Cardiac changes. Increased automaticity, delayed ventricular repolarisation and prolonged refractory period with an increased risk of reentrant arrhythmias. Clinical effects include AEBs, VEBs, sinus bradycardia, PAT, SVT, AV block, VT. Increased risk of significant arrhythmias if underlying IHD, LVH or digoxin therapy. ECG changes (sequentially): ST depression, decreased T wave height then inversion, U-waves (Purkinje repolarisation), prolonged QT and QU, increased P amplitude, prolonged PR , widening of QRS.

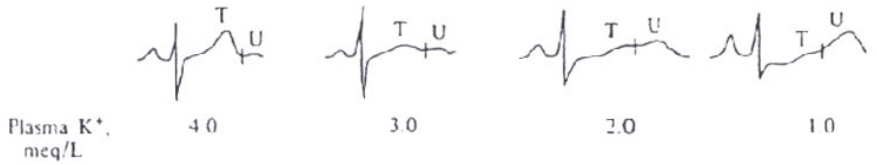


Figure 29-4 Electrocardiogram in hypokalemia. As the plasma K^+ concentration falls, the initial changes are ST segment depression, decreased amplitude of the T wave, and increased height of the U wave. With more severe hypokalemia, the P wave amplitude is increased, as is the duration of the QRS complex. The approximate relationship between these changes and the plasma K^+ concentration is indicated, although there is substantial interpatient variability. (*Adapted from Surawicz, B. Am Heart J. 73:814, 1967.*)

4. Renal effects. Impaired concentrating ability (polyuria/polydipsia), increased HCO_3 reabsorption leading to alkalosis and paradoxical aciduria, direct tubular necrosis (only with severe, prolonged depletion), increased renal ammonia production (may precipitate hepatic encephalopathy if underlying CLD).

5. Hyperglycaemia. Probably due to impaired insulin secretion and diminished insulin effect, most often seen with thiazide diuretics

Management:

Urgency of replacement depends on physiological effect (ECG changes and muscle strength). Difficult to assess total K^+ deficit, in general each mmol/l below 4.0 represents total body deficit of 200-400mmol assuming normal transcellular distribution. Serum levels may not accurately reflect the severity of hypokalaemia. Particularly in metabolic acidosis the acidaemia raises plasma [K] and masks the severity eg DKA.
Where possible replacement should be slow and oral if there is no clinical urgency. Comes as a variety of salts (Cl, HCO_3, PO_4, gluconate), KCl is advantageous because hypokalaemia is commonly associated with alkalosis and chloride depletion. Slow K contains 8 mmol KCl per tablet, Kayciel contains 15mmol KCl/20mls, Chlorvescent

14mmol K, 8mmol Cl per tablet. Slow release preparations tend to be better tolerated and are more palatable than solutions.

Infusion of 20mmol K raises [K] by ~0.25mmol/l, however concurrent changes in acid-base status may alter this, and regular sampling is required to determine the rate of change. The maximum intravenous infusion rate is 40mmol/hr, rates greater than 15mmol/hr require cardiac monitoring. Concentrations >60mmol/l should be given by central line because of local pain and venous sclerosis. In refractory hypokalaemia, concurrent hypomagnesaemia is common and needs to be corrected before [K] will respond.

HYPERKALAEMIA

Causes:

1. Increased intake
   - oral - must be large sudden load to cause significant change in [K]
   - intravenous - stored whole blood, rapid K infusion, part of medications

2. Transcellular shift (intra to extracellular)
   - metabolic acidosis
   - insulin deficiency and hyperglycaemia
   - tissue catabolism - trauma, massive haemolysis, burns, tumor lysis syndrome, rhabdomyolysis, vigorous physical exercise
   - β-blockade
   - digoxin toxicity - inhibition of NaK ATPase pump
   - periodic paralysis - hyperkalaemic form, autosomal dominant, precipitated by K ingestion or rest after exercise
   - suxamethonium

3. Decreased renal excretion
   - renal failure
   - hypoaldosteronism
     - Addisons disease
     - Hyporeninaemic hypoaldosteronism (type IV RTA), common in elderly diabetics
     - ACE inhibitors
     - Congenital adrenal hyperplasia - primarily 21 hydroxylase deficiency
     - Aldosterone antagonists
     - NSAIDs

4. Pseudohyperkalaemia
   - elevation occurs after blood is drawn, eg artifactual haemolysis, markedly increased WCC or platelets (plasma [K] normal but serum [K] elevated)

Effects:

1. Muscle weakness. Similar pattern to hypokalaemia with ascending paralysis, usually [K]>8.0mmol/l.

2. Cardiac effects. Characteristic sequential changes in ECG. Initially peaked narrow T wave +/- shortened QT (abnormally rapid repolarisation), typically [K]>6.0. Then AV block and diminution of P wave, [K] >8.0; widening of QRS [K]>9.0 (delayed depolarisation). Finally sine wave with broad QRS merging into the T wave followed by VF or asystole, [K]>10. However ECG changes are unpredictable and depend on acidemia, [Ca] and rapidity of elevation.

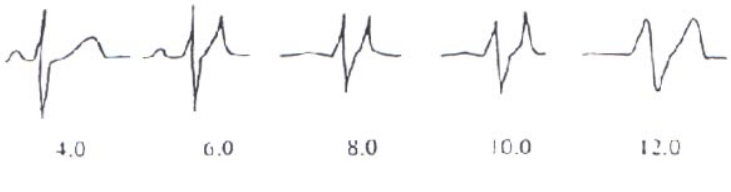


Figure 30-3 Electrocardiogram in hyperkalemia. The initial change is peaking and narrowing of the T wave with a short QT interval. With more severe hyperkalemia, widening of the QRS complex, decreased amplitude and eventual loss of the P wave, and a sine wave pattern as the QRS complex merges with the T wave may be seen. The approximate relationship between these changes and the plasma K^+ concentration is indicated, although there is a large interpatient variability. (*Adapted from Surawicz, B. Am Heart J. 73:814, 1967.*)

Management:

Urgency depends on presence of ECG changes and/or muscle weakness.

- Cardiac stabilisation. Calcium indicated if any ECG changes present other than minor T wave peaking, acts by raising (making less negative) the threshold potential and reducing membrane excitability. 10mls of 10% calcium gluconate (0.22mmol/ml) over 1-5 minutes, repeat in 5 minutes if ECG changes persist. Maximum 30-40ml , endpoint is normalisation of QRS and T. alternatively can use 10% $CaCl_2$ (0.7mmol/l) but causes more venous sclerosis, need large bore or central line.
- 15 units Actrapid with 50 mls 50% dextrose iv bolus. Insulin increases NaK ATPase activity, driving K^+ into cells. Lowers [K] by 1-2mmol/l, takes 1 hour to work, effect lasts 4-6 hours. Theoretically, if normal pancreatic function, dextrose bolus alone will stimulate adequate insulin release.
- $NaHCO_3$ 50-100mmol iv bolus. Alkalosis drives K^+ into cells in exchange for H^+. Effect within 30 minutes and lasts 2 or more hours. Contraindicated if fluid overloaded especially if poor renal function or concern re Na loading.
- β-agonists increase NaK ATPase activity. Salbutamol 0.5mg infused over 15 minutes lowers [K] 1-1.5mmol/l within 30 minutes. Alternatively continuous nebulised salbutamol can be used but with less predictable effect.
- Hypertonic saline rarely used in Australia but known to reverse ECG changes and reduce [K] by driving K into cells (?mechanism) and by a dilutional effect. 100-200mls 3% saline (50-100mmol) infused over 15 minutes, effect seen within 30 minutes.

- Dialysis indicated with severe hyperkalaemia unresponsive to other treatment especially in the context of renal failure, persistent acidosis or fluid overload. Haemodialysis more rapidly effective than peritoneal.
- Cation exchange resins increase K^+ excretion by taking up K^+ in the gut in exchange for other cations (usually Na), onset of action 1-2 hours, can be given orally or rectally. Resonium A 15g orally (30g rectally) reduces [K] by 0.5-2mmol/l.
- Diuresis with frusemide will increase potassium excretion but must correct hypovolaemia first. Dependent on intact renal function.

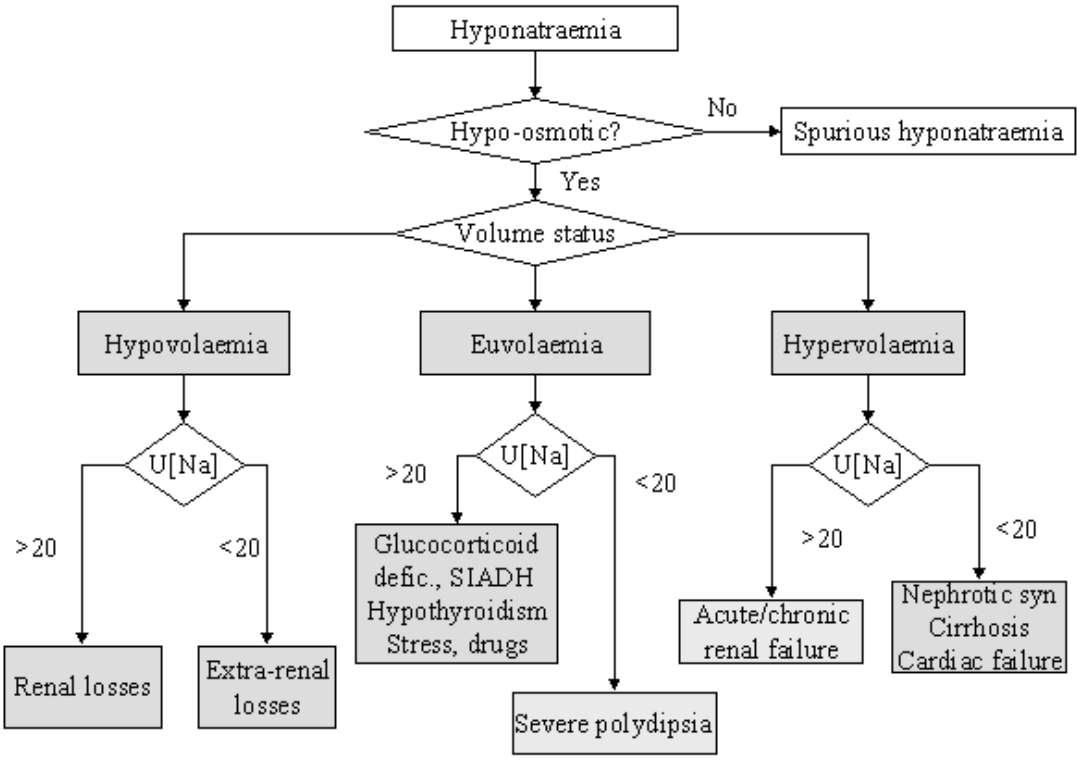
SODIUM

TBW constitutes 60% of lean body weight (slightly more in kids and less in elderly), 60% TBW is ICF and 40% ECF. Osmotic forces determine water distribution between these compartments and Na^+ is the major ECF osmolar solute. Total body Na^+ is ~50mmol/kg of which 98% is extracellular. In general changes in [Na] reflect changes in water balance, though occasionally there may be true changes in total body Na^+ balance. Osmoregulation is controlled by ADH and thirst which determine urine osmolality. Volume regulation is controlled by Na^+ excretion (via aldosterone, angiotensin and ANP).

HYPONATRAEMIA

Defined as <135mmol/l. Hyponatraemia usually reflects hypoosmolarity with net water movement into cells, unless there is abnormal solute accumulation (eg mannitol, glucose). Reduced renal water excretion is necessary to maintain hyponatraemia and may be due to renal failure, excess or increased sensitivity to ADH, or reduced distal urine flow. Clinical assessment of extracellular volume status and urinary excretion of sodium are used to determine the cause of hyponatraemia. Arterial volume depletion causes reabsorption of water and sodium. A urine Na^+<20mmol/l suggests effective volume depletion, >20mmol/l suggest euvolaemia, or renal disease with hypo or hypervolaemia. Urinary sodium measurement is unreliable when diuretics, osmotic loads (exogenous or endogenous), renal failure or severe metabolic alkalosis are present.

Causes:



Hyponatraemia with normal serum osmalality

This is true pseudohyponatraemia. Sodium is present only in the aqueous phase of serum and high lipid or paraprotein levels decrease the proportion of serum that is water. Laboratory techniques using flame photometry do not take into account changes in the aqueous portion of serum and measure the serum sodium as low when it is normal or high. This can be overcome by using a different assay technique which measures serum sodium directly (an ion-specific electrode). As calculated osmolarity will be low and measured osmolarity normal, there will be an elevated osmolar gap. Absence of this excludes the diagnosis.

Hyponatraemia with hyperosmolality (translocational hyponatraemia)

The presence of excess amounts of osmotically active substances such as glucose and mannitol causes water movement into the ECF leading to a dilutional lowering of the serum sodium. For hyperglycaemia, the true sodium can be estimated by (BSL-10)/3 + [Na].

Hyponatraemia with hypo-osmolarity

This is the most common cause of hyponatraemia and clinical assessment of the patient's fluid status is essential in determining the underlying cause.

a) Volume depleted

- Renal losses - urinary sodium >20mmol/l
  - Diuretics
  - Mineralocorticoid deficiency
  - Salt losing nephropathies
  - Osmotic diuresis

- Extrarenal losses - urinary sodium <20mmol/l
  - Vomiting
  - Diarrhoea
  - Sweat
  - Third space - burns, pancreatitis, bowel obstruction

b) Euvolaemic - urinary sodium >20mmol/l

- Hypothyroidism
- Adrenal insufficiency (pure glucocorticoid deficiency)
- Psychogenic polydipsia
- Physical/emotional stress
- SIADH - diagnostic criteria: urine osmolarity inappropriately high (>100mosmol/kg) with plasma osmolarity <280mosmol/kg; urinary sodium >20mmol/l; normovolaemia; normal cardiac, renal, hepatic, adrenal and thyroid function; and normal acid-base status.
  - CNS disorders: trauma, tumour, infection, haemorrhage, DTs, GBS and more
  - Pulmonary disease: acute and chronic infection, CAL, cystic fibrosis
  - Tumours: lung, pancreas, duodenum, lymphoma, thymoma
  - Drugs: narcotics, NSAIDs, vincristine, chlorpropamide, cyclophosphamide, MAOIs, phenothiazines, tricyclics, oxytocin, SSRIs, tricyclics

c) Hypervolaemic

- Urinary sodium <20mmol/l

  - Cardiac failure
  - Hepatic failure
  - Nephrotic syndrome

- Urinary sodium >20mmol/l
  - Acute renal failure
  - Chronic renal failure

Effects:

The signs and symptoms of true hyponatraemia (ie. hypoosmolar group) are due to intracellular movement of water into brain cells with subsequent raised intracranial pressure. Symptoms rarely occur unless [Na] <125mmol/l. CNS clinical effects include; headache, lethargy, confusion, delirium, seizures, hyporeflexia, positive Babinske reflex, focal neurological deficits, pseudobulbar palsy and brain herniation. Non-CNS effects include muscle cramps, rhabdomyolysis, anorexia and vomiting. The speed of development and the magnitude of hyponatraemia determine the severity of clinical signs.

Management:

The method and rapidity of correction are determined by the severity of the clinical signs and the patient's volume status. The correction of [Na] to prevent cerebral oedema, brain herniation and anoxic brain injury must be weighed against the risk of the osmotic demyelination syndrome.

The osmotic demyelination syndrome is used to describe delayed neurological deterioration following treatment of hyponatraemia leading to sudden brain shrinkage. Myelin disruption with axonal sparing is seen most commonly in the pons but can occur anywhere in the brain. The classical central pontine myelinolysis causes spastic quadraparesis, dysphasia and dysarthria. Patients most at risk are those with chronic hyponatraemia who undergo rapid correction of [Na]. Concurrent hypokalaemia, liver disease, malnutrition and burns all increase the risk of demyelination. The safe rate of correction is controversial but most authors agree on 12mmol/l maximal increase in the first 24 hours, though the rate of increase in the first few hours in a severely symptomatic patient may be up to 1-2mmol/l/hour initially. An increase in 4-6mmol/l from the initial level is usually enough to stop hyponatraemic convulsions, regardless of the initial [Na].

The sodium deficit can be calculated by total body water (ie body wt in kg x 0.6) x (desired [Na] - measured [Na]). Hypertonic (3%, 0.5mmol Na^+/ml) saline is indicated in the presence of seizures or coma with [Na]<120mmol/l. It should only be used until [Na]=120mmol/l, aiming to increase [Na] by 5mmol/l in the first 4-6 hours, and no more than 12mmol/l/24 hours.

Example: 70kg man, fitting, [Na] 107mmol/l. Initially aim to increase [Na] 5mmol in first 4 hours. 70x0.6x(112-107) = 210mmol Na = 420mls 3% saline over the first 4 hours = 105mls/hr. Then over next 20 hours aim for [Na] 119mmol/l, thus further 7mmol/l increase in next 20 hours = 70x0.6x7 = 294 mmol over 20 hours = 30mls/hr.

In the hypervolaemic group requiring hypertonic saline, a loop diuretic can be given concurrently to promote water excretion. Frusemide creates close to half isotonic urine and will remove more water than salt. Dialysis may be required in patients with renal failure and limited urine output. In the hypovolaemic and euvolaemic groups hypertonic saline alone or with concurrent maintenance/replacement fluids is used. Maintenance of [K] at normal levels probably reduces the risk of the osmotic demyelination syndrome.

In patients with less severe or no symptoms treatment is aimed at the underlying cause. In hypovolaemic patients replacement of ECF volume and restoration of organ perfusion is achieved by administration of normal saline. Although this group is at low risk for the osmotic demyelination syndrome, [Na] can increase very rapidly and 1/2 normal saline should be used if [Na] increases by more than 2mmol/hr. An estimate of the effect on serum sodium of infusion of a litre of any given infusate can be made form the formula:

$$\text{Change in [Na]} = (\text{infusate [Na]} - \text{serum [Na]})/(\text{TBW} + 1)$$

By determining the desired rate of increase in [Na], an appropriate infusate rate can be calculated for any given infusate using this formula.

In the hypervolaemic group water restriction and improvement in cardiac function are the mainstays of treatment. These patients are often difficult to treat because of high total body water and multiorgan dysfunction.

Euvolaemic hyponatraemic patients may also respond to water restriction. Treatment of underlying endocrine disease or correction of causative factors in SIADH is obviously indicated. In refractory SIADH demeclocycline or lithium can be used, both interfere with the effect of ADH on the collecting tubule.

HYPERNATRAEMIA

Hypernatraemia is an extracellular hyperosmolar state due to decreased water intake, water loss or, rarely, Na^+ retention. Defined as [Na] .150mmol/l. The usual defence mechanisms against hypernatraemia are thirst and ADH secretion. Even with absolute failure of ADH secretion a normal thirst mechanism will maintain [Na] near normal. Thus hypernatraemia is usually associated with diminished thirst mechanism and/or diminished access to water. This situation arises either in children unable to ask for water, or adults with altered mental status. In older adults there is diminished osmotic stimulation of thirst therefore this group is particularly at risk.

Causes:

1. Diminished water intake
    - Lack of environment water
    - Inability to communicate water need

2. Water loss in excess of sodium loss
    - Insensible losses - heat, fever, tachypnoea, burns, exercise
    - GIT losses - diarrhoea, vomiting, fistulae, NG drainage, cathartics (eg lactulose)
    - Renal loss
        - Central diabetes insipidus with failure of ADH secretion 2^o to head injury, neoplasia, hypoxic enecephalopathy, anorexia nervosa, CNS infection
        - Renal DI with reduced renal response to ADH many causes eg lithium, hypercalcaemia, hypokalaemia, amyloidosis, renal failure, sickle cell anaemia
        - Osmotic diuresis: glucose, mannitol
    - Hypothalamic disorders
        - Loss of osmoreceptor function
        - Primary hypodypsia

3. Sodium retention
    - Administration of $NaHCO_3$ or hypertonic sodium
    - Excess sodium ingestion

Urine osmolarity helps to diagnose the underlying cause and hydration status.
U_{osm}>700mmol/l = insufficient water intake or osmoreceptor defect.
U_{osm}<700 but >P_{osm} = partial DI, renal failure, loop diuretics, osmotic diuresis.
U_{osm}<P_{osm} = complete DI.

Effects:

In the alert patient intense thirst is the normal response to a 3-4mmol/l increase in [Na], therefore lack of thirst in an alert patient indicates a defect in the thirst mechanism. The predominant clinical effects are due to hyperosmolarity and cellular dehydration with cerebral dehydration causing lethargy, irritability, seizures and coma. Rapid increase in [Na] may cause sudden decrease in brain volume which can produce cerebral vein rupture and subarachnoid bleeding. Normalisation of brain

volume occurs over 24-48 hours, patients with chronic or slowly developing hypernatraemia may have minimal signs. As an underlying neurological defect may cause hypernatraemia it is often difficult to determine which is cause and effect. Permanent brain damage has been reported in 23% of patient with [Na]>160mmol/l.

Volume status can be normal, increased or decreased depending on the underlying cause, though the majority are dehydrated.

Management:

Rapid correction of [Na] can induce cerebral oedema, seizures, permanent neurological damage and death as brain volume suddenly increases. Therefore maximum rate of lowering should be 0.5mmol/l/hr. Initially, hypotension secondary to volume depletion should be corrected with normal saline to prevent rapid fall in [Na]. The majority of cases will be significantly water depleted, water deficit in patients with pure water deprivation can be calculate by:

TBW x ([Na]/140 - 1).

As a rough guide, each one litre of water deficit increases [Na] by 3-5 mmol/l. Once tissue perfusion is restored water should be replaced over 3 -4 days along with usual maintenance requirements. Water deficit can be replaced with ½ or normal saline if Na depletion is also likely (eg 2º to diarrhoea, vomiting or diuretics). If pure water loss is responsible (DI, insensible losses) D5W or 4%N/5 can be used. Calculated water deficits are only an estimate and frequent assessment of [Na] is necessary to prevent over-rapid lowering. The effect of a litre of any given infusate on serum sodium can be calculated by:

Change in [Na] = (infusate [Na] – serum [Na])/(TBW + 1)

By determining the desired rate of decrease in [Na] and the volume of fluid required over that 24 hour period, an appropriate infusate can be chosen using this formula.

Example: 60kg man with decreased LoC from nursing home. Clinically dehydrated but normotensive. Serum Na = 165mmol/l.

- Estimated water deficit = (60 x 0.6) x {(165/140) – 1} = 6.4 litres.
- Aim to replace water over 3 days plus maintenance fluid = 4 litres/24hours
- Aim to reduce [Na] by 10mmol/24hours, ie. each litre of fluid needs to reduce [Na] by 2.5mmol/l
- Applying above formula: 2.5 = (infusate [Na]-165)/37. Infusate of N/2 will be give correct rate of decrease. Normal saline would only reduce [Na] by 0.4mmol/l.

In central diabetes insipidus, drugs which mimic ADH (dDAVP, vasopressin) or enhance the action of ADH (chlorpropramide, carbamazepine) can be used. For renal DI, thiazide diuretics with a low salt, low protein diet can be used.

MAGNESIUM

Magnesium is an essential cofactor for over 300 enzymatic reactions. Less than 1% is in serum, where 1/3 is protein bound and 2/3 is in the active ionised form. Serum levels can therefore only be interpreted in the presence of an albumin level, and like other predominantly intracellular ions, the serum level poorly reflects total body stores. Short term magnesium homeostasis is controlled through changes in renal excretion, in the longer term small bowel absorption and bone metabolism are important.

HYPOMAGNESAEMIA

Hypomagnesaemia is frequently associated with potassium and calcium deficiencies, correction of Mg is usually required to correct the other deficiencies. High risk groups for Mg deficiency commonly present to EDs including those with chronic malabsorption, diabetes, renal failure, alcoholism and diuretic therapy.

Causes:

1. Decreased intake
    - severe malnutrition
    - prolonged iv fluids without Mg supplements

2. Decreased GI absorption
    - malabsorption syndromes
    - prolonged diarrhoea or NG suction
    - laxative abuse
    - alcoholism

3. Increased renal excretion
    - drugs - loop/thiazide diuretics, aminoglycosides, alcohol, cisplatinum
    - RTA
    - diuretic phase of ATN
    - post-obstructive diuresis
    - osmotic diuresis including glycosuria
    - hypercalcaemia
    - congenital

4. Endocrine disorders
    - hyperaldosteronism
    - hyperparathyroidism
    - hyperthyroidism
    - SIADH

5. Miscellaneous
    - ECF expansion (CCF, cirrhosis)

- pancreatitis
- extensive burns
- flouride poisoning

Effects:

1. Cardiovascular changes. Probably due to impairment of NaK pump. ECG changes include prolonged PR and QT, QRS widening, peaked or inverted T waves, U waves and a wide range of non-specific abnormalities. Arrhythmias including atrial tachycardias, SVT, VEBs, VT, torsade de pointes, VF have all been reported. Markedly increases digoxin toxicity.

2. Neuromuscular irritability similar to hypocalcaemia. Up to 1/3 of patients have concurrent hypocalcaemia but neuromuscular changes occur even with normal [Ca]. Signs include parasthaesia, tremor, tetany, positive Chovstek's and Trousseau's signs, choreoathetosis, weakness, cramps, hyperreflexia, convulsions, nystagmus, and dysarthria. Psychiatric manifestations such as apathy, depression, delirium, behavioural disturbance and psychosis all reported.

3. Metabolic effects include alkalosis, decreased K, Ca, Na, PO_4, and hypothermia.

Management:

Aimed at treatment of underlying cause and replacement of Mg as rapidly as clinically indicated. If [Mg]>0.5mmol/l and not symptomatic oral replacement is adequate. Intravenous $MgSO_4$ indicated for severe symptomatic hypomagnesaemia or in other clinical scenarios as discussed below. $MgSO_4$ 49.3% = 0.5g/ml = 2mmol/ml, should be diluted to 10% solution when given intravenously. For intravenous Mg replacement in symptomatic patients start with 4mmol/hr, as symptoms improve reduce to 20-30mmol/24hr. Commonly causes hypotension and vasodilatation, can also cause local pain and tissue necrosis and CNS depression with hyporeflexia. In an emergency $MgSO_4$ can be given as 8-10 mmol diluted to 10% as a slow iv push.

HYPERMAGNESAEMIA

Uncommon and usually a result of overvigorous therapy particularly in the presence of renal impairment. It may be precipitated by Mg containing cathartics in the presence of CRF. Clinical effects include nausea/vomiting, vasodilatation and hypotension, bradycardia, CNS depression, hyporeflexia, muscle weakness, respiratory failure.

Management:

Significant respiratory and CNS depression is seen at levels >5.0mmol/l. Intravenous calcium (5ml 10% $CaCl_2$) rapidly and transiently lowers [Mg] with reversal of heart block and respiratory depression, followed by saline diuresis with frusemide. Dialysis is indicated for severe persistent symptoms or persistent level >4.0mmol/l or renal failure.

MAGNESIUM AS A THERAPEUTIC AGENT

1. **Cardiac arrhythmias**. Mg increases RMP, prolongs AV conduction time and increases the refractory period.
   - Torsade de pointes, associated with a prolonged QT, is the major cardiac indication for Mg. Initial dose 8mmol as slow push then infusion of 12mmol over next hour. T de P with normal QT does not respond to magnesium.
   - Myocardial ischaemia: Several studies suggest that Mg infusion in the first 24 hours after AMI reduce the rate of arrhythmias and the mortality, even in the presence of normal [Mg]. Magnesium has been shown to rapidly relieve angina due to coronary artery spasm.
   - Digoxin toxicity is potentiated by Mg deficiency and Mg therapy has been used to treat digoxin induced arrhythmias. Pretreatment may prevent digoxin induced VF/VT. Can be used as an interim measure while finding Digibind, give 8mmol as a slow bolus.

2. **Alcohol withdrawal.** There is a correlation between the withdrawal syndrome and magnesium depletion. Several studies indicate Mg therapy may relieve many withdrawal symptoms and reduces benzodiazepine requirements.

3. **Preeclampsia and eclampsia.** Shown to reduce the incidence of seizures in preeclamptic patients with significant neurological signs (hyperreflexia with clonus, severe unrelenting headache, visual scotomata). Provides better seizure control in established eclampsia compared with phenytoin. Has mild hypotensive benefit but in Australia other measures (volume replacement, antihypertensives) used to control BP. Indication for Mg is also an indication for urgent delivery. Initial 6-8mmol bolus then 4mmol/hr or until suppression of reflexes.

4. **Asthma.** Theoretical benefit as a smooth muscle relaxant. Shown in some studies to be beneficial if given iv but possibly only in those with deficiency initially. Small study samples and at best only as adjunctive to usual therapy. Maximum benefit is in those with severe asthma, based on Cochrane meta-analysis.

PHOSPHATE

Virtually all blood phosphorus circulates as PO_4. Serum phosphate levels are controlled by multiple mechanisms including GI absorption, PTH, Vit D, calcitonin and renal excretion. 85%of total body phosphate is in bone, 14% in soft tissues, 1% in ECF with ~0.5% in blood. It is an essential component of many vital compounds including cAMP, ATP, NAD, 2,3-DPG, phospholipids and nucleic acids. Serum phosphate and calcium are inversely proportional to each other. The major factor affecting serum phosphate is transcellular shift, small percentage shifts can produce marked changes in serum levels.

HYPOPHOSPHATAEMIA

Acute hypophosphataemia can occur with normal or depleted phosphate stores. However, in the presence of normal body stores, serum levels usually return to normal rapidly. The major clinical effects of hypophosphataemia are seen in those with pre-existing depletion who then have rapid intracellular shift. At risk groups for phosphate depletion include the chronically malnourished (starvation or malabsorption), alcoholics and diabetic ketoacidotics.

Causes:

1. Intracellular shift (most common acute cause)
    - glucose loading (oral or i.v.) increases the consumption of phosphorylated intermediaries of glycolysis and stimulates the release of insulin. Rapid refeeding in the starved patient can induce are precipitous fall in serum phosphate on day 2-5 after institution of feeds as phosphate rapidly moves into cells on a background of phosphate depletion.
    - insulin (exogenous or endogenous) directly shifts phosphate intracellularly.
    - hyperventilation induces alkalosis which stimulates phosphofructokinase activity which enhances glycolysis. Usually transient, commonly seen in ED.

2. GI losses
    - malabsorption
    - PO_4 binding antacids (containing Al, Ca, Mg)
    - Vit D deficiency
    - diminished intake (must be severe and prolonged, usually associated with increased losses)

3. Renal losses
    - PTH excess
    - diuretics
    - glucocorticoids
    - renal tubule disorders (Fanconis, post ATN, post transplant, post obstruction)
    - hypomagnesaemia
    - hypokalaemia

Effects:

Mostly mediated through acute ATP and 2,3-DPG deficiency causing failure of adequate oxygen carriage and delivery. As stated before clinical effects are mostly

seen in those with underlying phosphate deficiency who undergo rapid intracellular shifts, commonly following carbohydrate loading (the refeeding syndrome).

1. Neuromuscular. A wide range of signs reported including delirium, coma, parasthaesthia, areflexic paralysis, GB-like syndrome, diffuse sensory loss, cranial nerve palsies, seizures, rhabdomyolysis.

2. Haematological.
   - RBC - (L) shift of dissociation curve, reduced membrane deformability, haemolysis, spherocytosis, reduced lifespan.
   - WBC - reduced phagocytic, chemotactic and bactericidal activity.
   - Platelets - thrombocytopenia and poor clot retraction.

3. Cardiac. Reduced contractility +/- overt CCF, dysrhythmias, cardiac arrest.

4. Respiratory failure secondary to muscle weakness.

Management:

Recognition of at risk patients and early phosphate replacement in ED is essential. Start with 0.5mmol/kg/24hours (normal daily requirement) and monitor closely. Can give up to 5mmol/hr if necessary. Significant clinical effect usually seen when phosphate <0.5mmol/l. KH_2PO_4 contains 10mmol of potassium and phosphate in each 10ml 10% ampoule. Oral supplementation is not effective in severe hypophosphataemia.

HYPERPHOSPHATAEMIA

Rarely an acute problem, but mild elevation a common chronic problem.

Causes:

1. Extracellular shift
   - severe haemolytic anaemia
   - rhabdomyolosis
   - tumour lysis
   - hyperthyroidism (increased bony rsorption, decreased renal excretion)
   - diphosphonate therapy

2. Reduced renal excretion

   - renal failure
   - hypoparathyroidism
   - acromegaly
   - tumour calcinosis (~50 reported cases in past 90 years!)

3. Excess phosphate

   - phosphate enemas (Fleet)
   - phosphate laxatives
   - iv phosphate (especially in renal failure)

Effects:

Most effects are due to reciprocal fall in calcium (except in severe thyrotoxicosis), with signs of acute hypocalcaemia. Metastatic calcification in soft tissues occasionally seen. Acute renal failure is frequently coexistent as many disorders which produce hyperphosphataemia also cause ARF. Phosphate may have a direct nephrotoxic effect via intratubular crystalline deposition.

Management:

Chronic hyperphosphataemia requires use of phosphate binding resins (eg AlOH). Management of acute hyperphosphataemia involves rehydration and urinary alkalinisation to maximise renal excretion, treatment of hypocalcaemia, dialysis for renal failure.

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