The Essentials of Calcium, Magnesium and Phosphate Metabolism: Part II. Disorders

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ABSTRACT

Objective: *To review the components of calcium, phosphate and magnesium metabolism that are relevant to the critically ill patient, in a two-part presentation.*

Data sources: *A review of articles reported on calcium, phosphate and magnesium disorders in the critically ill patient.*

Summary of review: *Abnormal calcium metabolism in the critically ill patient often presents with an alteration in plasma ionised calcium. The characteristic clinical features of an acute reduction in ionised plasma calcium include tetany, laryngospasm, paraesthesia, confusion, hallucinations, seizures and, rarely, hypotension all of which resolve with intravenous calcium administration. The clinical features of an acute increase in plasma ionised calcium include anorexia, nausea, vomiting, constipation, polyuria, weakness, lethargy, hypotonia and ectopic calcification and, depending on the aetiology, may require intravenous saline, frusemide, diphosphonate, glucocorticoid or calcitonin.*

Acute hypophosphataemia may present with paraesthasia, confusion, seizures, weakness, hypotension and heart failure and in the critically ill requires intravenous sodium or potassium phosphate. Hyperphosphataemia is often associated with renal failure and if severe usually presents with the clinical features of the associated hypocalcaemia.

The clinical features of hypomagnesaemia include confusion, delirium, seizures, weakness, cramps, tetany and tachyarrhythmias, all of which resolve with intravenous magnesium sulphate. Hypermagnesaemia is usually associated with excess magnesium administration in a patient with renal failure and if severe can cause areflexia, hypotonia, respiratory and cardiac arrest. Intravenous calcium chloride will rapidly reverse the cardiovascular abnormalities.

Conclusions: *Calcium, phosphate and magnesium functions are closely linked with abnormal plasma levels of these compounds often causing similar cardiovascular and neurological features.* (**Critical Care and Resuscitation 2002; 4: 307-315**)

Key words: Hypocalcaemia, hypercalcaemia, hypophosphataemia, hyperphosphataemia, hypomagnesaemia, hypermagnesaemia

In chronic critical illness increased bone reabsorption with hypercalcuria is common, although it may be associated with hypercalcaemia, hypocalcaemia or normocalcaemia.[1] The increased bone reabsorption may be caused by calcium deficiency, hyperparathyroidism or an abnormality of vitamin D metabolism but in general it is often thought to be caused by a prolonged elevation in the inflammatory cytokines (e.g. TNF-α and IL-6) associated with patient immobility.

Disorders of calcium metabolism

Hypocalcaemia

Hypocalcaemia is defined as a total plasma calcium less than 2.10 mmol/L (ionised plasma calcium < 1.15 mmol/L) and may be caused by a reduced ionised, or

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protein-bound calcium (Table 1). Hypocalcaemia caused by critical illness is usually multifactorial (e.g. impaired parathyroid hormone action or synthesis,[2] impaired Vitamin D action or synthesis[3]), although calcium loss due to increased tissue sequestration of calcium may be the predominant cause in patients with pancreatitis, septicaemia, burns or toxic shock.[4-8]

Table 1. Causes of hypocalcaemia

Factitious
- Sample contamination with EDTA

Normal plasma ionised with reduced total calcium
- Hypoalbuminaemia

Reduced plasma ionised with normal total calcium
- Respiratory alkalosis
- Citrate toxicity (e.g. massive transfusion)

Reduced plasma ionised and total calcium

a) *Decreased PTH activity*
- Hypoparathyroidism
  - Primary
  - Secondary (e.g. irradiation of neck, thyroidectomy, sepsis)
- Pseudohypoparathyroidism
- Hypomagnesaemia

b) *Vitamin D deficiency*
- Malabsorption of vitamin D (e.g. steatorrhoea) calcium (small bowel surgery)
- Vitamin D resistant rickets

c) *Excessive calcium loss*
- Rhabdomyolysis
- Pancreatitis
- Critical illness (e.g. burns, septicaemia, toxic shock)
- Frusemide and saline diuresis
- Malabsorption of calcium (e.g. small bowel surgery)
- Hyperphosphataemia
- Fluoride toxicity
- Oxalate poisoning

d) *Unknown mechanism*
- Hypermagnesaemia

In chronic critically ill patients who are hypocalcaemic and enterally fed, calcitriol administration (e.g. 0.25 μg/day orally or intravenously) will lower parathyroid hormone (PTH) levels but does not reduce the accelerated bone reabsorption which is reduced only by the co-administration of disodium pamidronate (e.g. 30 mg/day for three consecutive days).[9]

Clinical features. Tetany is the commonest symptom associated with an acute reduction in plasma ionised calcium and usually involves muscles of the extremities and larynx. The latter may lead to laryngospasm and asphyxia, whereas the former may be demonstrated by Chvostek's sign (i.e. contraction of the ipsilateral facial muscles by tapping over the facial nerve at the angle of the jaw) and Trousseau's sign (i.e. spasm of the muscles of the arm and hand which may be provoked by inflating a blood pressure cuff between systolic and diastolic pressures for 3 min).[10] As plasma proteins are more ionised when the extracellular fluid pH is increased (causing more protein anion to bind calcium),[11]acute hypocalcaemic tetany can occur with respiratory alkalosis (e.g. if $PaCO_2 < 21$ mmHg).[10] An acute reduction in plasma ionised calcium with tetany can also occur with hypomagnesaemia and with rapid correction of severe hypokalaemia.

Other clinical features associated with acute hypocalcaemia include paraesthesia (usually circumoral or fingertip tingling and burning), cramps, mental changes (e.g. hallucinations, confusion), areflexia, seizures and a decrease in cardiac output with hypotension. Chronic hypocalcaemia may present with cataracts, papilloedema, basal ganglia calcification, alopecia, coarse dry skin and areas of dermal candidiasis.

Investigations. Blood is taken to measure plasma ionised calcium, magnesium, phosphate and bicarbonate. Plasma PTH levels are < 3.0 pmol/L with hypoparathyroidism and are > 6.5 pmol/L in all secondary hyperparathyroid states (e.g. renal failure, vitamin D deficiency). Plasma vitamin D levels are measured if vitamin D deficiency is suspected. A spot urine hydroxyproline/creatinine index is high in patients who have increased bone reabsorption. An assessment of forearm mineral density will gauge whether bone formation is keeping up with any increased reabsorption.

Treatment. Acute hypocalcaemia is usually treated with intravenous calcium only if the patient is symptomatic. Calcium chloride 10%, 5 mL intravenously (i.e. 3.4 mmol of calcium) or 10 mL of calcium gluconate 10% (i.e. 2.23 mmol of calcium) may be administered over 3 - 5 min. If it is administered too rapidly it may cause an unpleasant flushing and nausea.

In cases of continuing symptomatic hypocalcaemia (e.g. postparathyroidectomy), intravenous calcium chloride 10%, 1 - 5 mL/hr (i.e. 0.7 - 3.5 mmol/hr) and monitoring plasma ionised calcium 4-hourly, to keep the plasma ionised calcium > 0.8 mmol/L, may be administered.[3]

Chronic hypocalcaemia due to hypoparathyroidism may require oral calcium supplements (2 - 4 g daily) and 0.25-1.0 μg of $1,25\ (OH)_2D_3$. The latter will produce an effect within 24 - 48 hr.

Hypercalcaemia

Hypercalcaemia is defined as a total plasma calcium level of greater than 2.55 mmol/L, and may be factitious (e.g. postprandial or caused by haemoconcentration; therefore the blood specimen should be fasting and free flowing), or due to an increased ionised calcium level (i.e. ionised plasma calcium > 1.30 mmol/L, Table 2).

Table 2. Causes of hypercalcaemia

Factitious
Immobility
Carcinoma
Primary (lymphoma, myeloma)
Secondary (breast, bronchogenic, renal)
Paget's disease
Hyperparathyroidism
Renal failure (tertiary hyperparathyroidism)
Recovery from acute renal failure
(particularly when associated with rhabdomyolysis)
Vitamin D toxicity
Vitamin A toxicity
Drugs (e.g. lithium, thiazides)
Granulomas
Sarcoidosis
Tuberculosis
Other (e.g. berylliosis, histoplasmosis)
Endocrine
Thyrotoxicosis
Addison's disease
Acromegaly
Phaeochromocytoma
Vasoactive intestinal polypeptide secreting tumour
Familial hypocalcuric hypercalcaemia

Clinical features. The characteristic clinical features of hypercalcaemia usually do not appear until the total plasma calcium is greater than 3.00 mmol/L (i.e. ionised plasma calcium > 1.50 mmol/L) and include anorexia, nausea, vomiting, constipation, polyuria (due to nephrogenic diabetes insipidus), polydipsia, pruritus, muscular weakness, lethargy, arthralgia, myalgia, hypotonia and ectopic calcification (e.g. band keratopathy, nephrocalcinosis). Mental disturbances of psychosis, apathy, somnolence, confusion, depression and rarely coma (i.e. hypercalcaemic crisis) usually only appear if the total plasma calcium is > 3.50 mmol/L (i.e. ionised plasma calcium > 1.70 mmol/L). Hypercalcaemia may also predispose the patient to peptic ulceration and pancreatitis.

Investigations. History and examination are performed (e.g. to detect the presence or absence of carcinoma). Blood is taken to measure plasma calcium (both total and ionised), magnesium, phosphate and bicarbonate. A low albumin (which may conceal the extent of hypercalcaemia if only total calcium levels are measured) and high bicarbonate levels are more common with carcinoma.[12] Plasma parathyroid hormone levels are $\leq$ 3.0 pmol/L in all nonhyperparathyroid causes of hypercalcaemia and $\geq$ 5.0 pmol/L in hyperparathyroid states. Plasma parathyroid hormone values between 3.0 - 5.0 pmol/L are equivocal and should be repeated after 4 - 8 weeks. Plasma vitamin D levels are measured if vitamin D toxicity is suspected, thyroid function tests are performed to exclude hyperthyroidism and a plasma electrophoretic pattern is measured to exclude paraproteinaemia with multiple myeloma.

While hyperchloraemic acidosis and low phosphate levels may be found with hyperparathyroidism, this is not a regular finding.[12,13] High plasma alkaline phosphatase and increased urinary hydroxyproline levels indicate a high bone turnover.

Treatment. This requires resuscitation (i.e. methods to provide an acute reduction in plasma ionised calcium particularly when a hypercalcaemic crisis exists) as well as management of the underlying disorder (e.g. management of carcinoma, hyperthyroidism and parathyroid adenoma). Parathyroidectomy is not indicated in all patients with primary hyperparathyroidism particularly if they are asymptomatic. It is usually performed only in patients who have any one of the following markers: age less than 50, plasma calcium greater than 2.99 mmol/L, hypercalcuria greater than 9.98 mmol/day, osteoporosis or osteitis fibrosis cystica (bone mineral densities > 2.5 SD below normal), renal calculi, neuromuscular disease (e.g. weakness, tiredness, malaise, depression, anxiety, failing memory) or reduced creatinine clearence.[14-17]

Intravenous fluids and a frusemide diuresis are commonly used to treat acute symptomatic hypercalcaemia. Initially, 2 L of fluid (1 L of 0.9% saline and 1 L of 5% dextrose) are administered to correct dehydration (which commonly occurs with hypercalcaemic nephrogenic diabetes insipidus). Frusemide (80 mg 2- to 4-hourly) is administered and the urine output is replaced with alternating 0.9% saline and 5% dextrose (commonly up to 6 L daily), monitoring plasma calcium, potassium, phosphate and magnesium. Renal calcium reabsorption is inhibited by saline solutions (expanding the extracellular fluid space and thereby inhibiting proximal tubule sodium and calcium reabsorption) and frusemide (inhibiting calcium reabsorption in the ascending loop of Henle). A significant fall in plasma calcium usually occurs during the first 4 hr and renal loss of calcium usually exceeds 25 mmol/day. This therapy is contraindicated in patients with cardiac failure or severe renal failure.

Recently, the diphosphonates (biphosphonates) have been used rather than saline and frusemide. These compounds act as analogues of pyrophosphate and interfere with growth and dissolution of hydroxyapatite crystals (although at therapeutic doses their predominant activity is to directly impair osteoclastic activity[18]). In patients with chronic hypercalcaemia disodium etidronate 400 mg may be given orally for 14 days. It is not given with meals as oral absorption (as with all diphosphonates) is poor (e.g. 1 - 10%). Disodium pamidronate is usually reserved for severe hypercalcaemia and is given as a single infusion of 60 - 90 mg over 8 hr[19] (60 mg if plasma calcium is between 3.0 and 3.38 mmol/L and 90 mg if plasma calcium is > 3.38 mmol/L).[20] The calcium level usually falls after 2 days (and is usually within normal limits after 7 days) and normocalcaemia often persists for up to one month.[20]

Other therapies include corticosteroids, which are beneficial in the management of hypercalcaemia due to sarcoidosis or vitamin D toxicity. They usually take 24 hr before the calcium level begins to fall. Calcitonin (4 U/kg subcutaneously 12-hourly) also produces a significant decline in plasma calcium within 2 hours. This may be useful in refractory hypercalcaemia associated with malignancy. However, after 2 days patients often become refractory to treatment, although the addition of a corticosteroid may prevent this calcitonin 'escape'. Gallium nitrate (200 mg/m^2 intravenously in 1 L of fluid daily for 5 days, which has a delayed effect, reaching its nadir 3 days after the completion of the infusion)[21] has also been used. However, it is nephrotoxic and is not administered in the presence of renal failure. Mithramycin (25 μg/kg i.v. over 4 - 8 hr) usually has an effect within 12 - 24 hr although its maximal effect may take 2 - 3 days. This agent is not used in patients who have overt renal or hepatic failure.[21] Octreotide has also been used successfully to treat hypercalcaemia associated with malignancy.[22]

Phosphate infusions are no longer recommended because soft tissue and renal calcification are common complications associated with this therapy.

Calcium disorders of chronic renal failure

In patients with chronic renal failure, a reduction in 1,25 $(OH)_2D_3$ levels and reduced phosphate excretion lead to hypocalcaemia and hyperphosphataemia. This chronically stimulates PTH secretion (i.e. secondary hyperparathyroidism) and may require a low-phosphate diet with oral phosphate-binders (e.g. calcium carbonate[23] or calcium acetate[24] taken with each meal) to maintain plasma phosphate at approximately 1.4 mmol/L. Supplemental oral calcium (which needs to be taken between meals to function as a calcium supplement rather than a phosphate binder[25]) and 1,25 $(OH)_2D_3$ (2 - 4 μg/day) to maintain plasma calcium levels in the high end of the normal range to maximally suppress PTH secretion, may also be required. If the PTH stimulation is prolonged then it may become autonomous (i.e. tertiary hyperparathyroidism) and parathyroidectomy may be warranted.

A dialysate calcium level of 1.25 mmol/L will not affect the calcium balance, whereas a dialysate calcium level of 1.75 mmol/L provides an influx of approximately 20 mmol of calcium per dialysis.

Disorders of phosphate metabolism

Hypophosphataemia

Hypophosphataemia is defined as a fasting plasma phosphate level of less than 0.8 mmol/L and may be caused by a decreased intake, increased excretion or intracellular redistribution (Table 3). Moderate hypophosphataemia exists if the phosphate level is between 0.32 and 0.80 mmol/L.[26] Severe hypophosphataemia exists when the plasma level is less than 0.32 mmol/L.[27] Plasma phosphate levels as low as 0.48 mmol/L may occur after a standard oral glucose tolerance test[28] or down to 0.32 mmol/L during hyperventilation.[29] Patients with hypophosphataemia may be asymptomatic, however symptoms often occur when the plasma phosphate is less than 0.32 mmol/L.[27,30]

Clinical features. The clinical features of hypophosphataemia are shown in Table 4.[30,31]

Investigations. In hypophosphataemic patients, in the absence of alkalosis, if the urinary phosphate is greater than 25 mmol/day, then excessive renal loss is occurring. If the urinary loss is less than 5 mmol/day, then there is no excess renal loss.[30] If hypophosphataemia is associated with hypercalcaemia, hyperparathyroidism should be considered.

Treatment. Hypophosphataemia should be differentiated from the hypophosphataemic syndrome. If hypophosphataemia is due to compartmental shift resulting from respiratory alkalosis, or catecholamine infusions (particularly in the asthmatic who may also have hypocapnia) then, even though phosphate levels may decrease to 0.4 mmol/L, treatment with phosphate may not be necessary. However, in the critically ill patient, generally the plasma phosphate level should be kept above 0.8 mmol/L, to ensure adequate respiratory, cardiac and intracellular function.

With severe hypophosphataemia, intravenous phosphate therapy is recommended at a rate of 2 - 6 mmol/hr (although up to 15 - 20 mmol/hr for 1 - 2 hr

Table 3. Causes of hypophosphataemia

Decreased intake
Reduced oral intake or absorption (e.g. antacids)
Increased renal loss
Hyperparathyroidism
Vitamin D deficiency
Vitamin D resistant rickets
Renal tubular acidosis
Haemodialysis (dialysate fluid loss)
Alcoholism (reduced intake and increased loss)
Redistribution
Alkalosis
Parenteral nutrition
Catecholamines
Treatment of diabetic ketoacidosis
Correction of chronic hypercapnia
Recovery of thermal injury
Insulin-like growth factor infusion

Table 4. Clinical features of hypophosphataemia

Haematological
Haemolytic anaemia
Decrease in red blood cell 2,3 DPG
Chemotaxis and phagocytosis abnormalities of neutrophils
Decrease in platelet aggregation
Neurological
Paraesthesia, neuropathy, ataxia, confusion, delirium, coma, seizures
Skeletal
Muscle weakness (resembling Guillain-Barré syndrome)
Hypoventilation
Rhabdomyolysis
Cardiac
Hypotension, cardiac failure
Renal
Renal tubular acidosis, hypermagnesuria, hypercalcuria
Bone
Osteomalacia

has been reported to be well tolerated in hypophosphataemic critically ill patients[32,33]), and up to 40-100 mmol/24 hr may be administered as sodium or potassium phosphate.[34-36] If an intravenous solution is administered as the dihydrogen salt, an equimolar amount of Na^+ or K^+ and 80% of the molar amount as H^+ is administered with the phosphate. If it is administered as the monohydrogen salt then twice the molar amounts of sodium or potassium are administered with the phosphate. If high concentrations of organic calcium and phosphate are administered together (depending on the pH, temperature and other constituents within the intravenous solution), calcium phosphate precipitation may occur, causing respiratory failure and even death.[37] To prevent this (and to prevent the administration of sodium or potassium in patients who do not require these ions), inorganic phosphate (e.g. glycerol phosphate[38] or glucose-1-phosphate[33]) can be administered intravenously, which does not precipitate with calcium and when infused is hydrolysed within the body to yeild free phosphate.

Hyperphosphataemia

Hyperphosphataemia in adults is defined as a plasma phosphate greater than 1.6 mmol/L and is usually caused by an increased intake or decreased excretion (Table 5).

Table 5. Causes of hyperphosphataemia

Factitious (e.g. haemolysis, sample separation delay)
Redistribution
Trauma
Rhabdomyolysis
Acidosis (keto and lactic)
Tumour lysis
Diphosphonate therapy
Positive phosphate balance
Acute phosphate administration
Phosphate enema
Excess intravenous administration
Vitamin D toxicity
Renal retention
Renal failure
Hypoparathyroidism
Pseudohypoparathyroidism
Acromegaly

Clinical features. The clinical features of acute hyperphosphataemia include the clinical effects of acute hypocalcaemia (e.g. seizures, tetany), acute tubular necrosis, and ectopic calcification (e.g. nephrocalcinosis, nephrolithiasis and band keratopathy). Ectopic calcification usually occurs when the product of total plasma calcium and phosphate, if measured in mmol/L, is greater than 6.

Treatment. Treatment may require haemodialysis, although hypertonic dextrose solutions to shift extracellular fluid phosphate into the intracellular

compartment may be effective. The phosphate-binders of calcium carbonate or calcium acetate to decrease gastrointestinal absorption of phosphate, are usually reserved for conditions of chronic hyperphosphataemia (e.g. chronic renal failure) and along with a low-phosphate diet are used to maintain the plasma phosphate at approximately 1.4 mmol/L.

Disorders of magnesium metabolism

Hypomagnesaemia

Hypomagnesaemia is defined as a plasma level of less than 0.7 mmol/L and is associated with a 24 hr urine magnesium of less than 1 mmol/L in the absence of abnormal renal magnesium losses. Hypomagnesae-mia may be caused by redistribution (e.g. alkalosis, excess catecholamine states - phaeochromocytoma, trauma, acute myocardial infarction, catecholamine infusions[39]) or magnesium depletion due to decreased intake or increased loss[40] (Table 6). While loop, osmotic and thiazide diuretics are associated with magnesium depletion, potassium sparing diuretics (spironolactone, amiloride and triamterene) are magnesium sparing and do not cause magnesium depletion. Carbonic anhydrase has little effect on magnesium balance.[41]

Clinical features. Clinical features due to hypomag-nesaemia are uncommon and tend only to occur when the plasma level is less than 0.5 mmol/L. They usually manifest as neurological, cardiovascular or metabolic disturbances (Table 7).[42,43] Hypomagnesaemia[43-45] and magnesium deficiency (as assessed by retention of an intravenous magnesium load) may occur in up to 65% of critically ill patients and is associated with an increase in mortality.[46,47]

Investigations. Total body magnesium depletion may exist in the presence of a normal total plasma mag-nesium level[48,49] and a normal ionised plasma magnesi-um level.[47] However, with magnesium deficiency, the renal loss is usually minimal (0.05 - 0.10 mmol/day). Furthermore, as the majority of an intravenous dose of magnesium is normally excreted in the urine in 24 hr, 30 mmol of magnesium chloride administered over 8 hr and a 24 hr collection of urine (commencing with the beginning of the magnesium infusion) can be used as an estimate of magnesium balance in patients with normal renal function. Normally, greater than 70% of the dose is excreted; if less than 70% is excreted, the patient has magnesium deficiency.[50]

Hypomagnesaemia may also cause hypocalcaemia (due to impaired synthesis and/or release of PTH and impaired peripheral action of PTH, which is not associated with hyperphosphataemia),[51] hypokalaemia (due to renal potassium loss caused by an impaired Na/K ATPase activity, impaired K-Na-Cl co-transport and increased efflux through potassium channels)[52,53] and type I RTA.[54]

Table 6. Causes of magnesium deficiency

Gastrointestinal disorders
Malabsorption syndromes
Starvation, malnutrition, liquid protein diets
Gastrointestinal tract fistulas
Short-bowel syndrome
Prolonged nasogastric suction
Diarrhoea
Pancreatitis
Parenteral nutrition
Alcoholism
Endocrine Disorders
Hyperparathyroidism
Hyperthyroidism
Conn's syndrome
Diabetes mellitus
Hyperaldosteronism (primary and secondary)
Renal losses
Renal tubular acidosis
Post-obstructive diuresis
Diuretic phase of acute tubular necrosis
Bartter's syndrome
Gitelman's syndrome
Drugs
Aminoglycosides
Carbenicillin, ticarcillin
Amphotericin B
Osmotic, thiazide and loop diuretic therapy
Cis-platinum
Cyclosporine

Treatment. Magnesium sulphate is the most widely available intravenous preparation and while intravenous salts of chloride and aspartate have also been used, it is the magnesium ion (and not its anion) that modulates the biological effects. Treatment of acute magnesium deficiency consists of intravenous magnesium sulphate, (0.15 mmol/kg for each 0.1 mmol/L the plasma magnesium is less than 0.7 mmol/L). This is usually given as a bolus of 10 mmol administered over 15 minutes (if it is administered too rapidly it may cause unpleasant flushing with nausea) followed by an infusion of 20 - 60 mmol during the next 24 hr. When normal plasma levels are achieved, 4 - 8 mmol of magnesium are administered daily. This dose should also be given to all critically ill patients with normal renal function.[43-45] If renal failure exists, the intravenous

dosages should be halved and the plasma magnesium levels closely monitored. Magnesium administration should cease if the plasma level is > 1.5 mmol/L. If mild or chronic magnesium deficiency exists, oral magnesium chloride may be administered.

Table 7. Clinical features of hypomagnesaemia

Neurological
Confusion, irritability, delirium, convulsions
Depression, psychosis
Ataxia, athetoid movements
Weakness, tremors, cramps, tetany
Trousseau and Chvostek signs
Wernicke's encephalopathy
Cardiovascular
Tachyarrhythmias (torsade de pointes)
Enhanced digoxin toxicity
Biochemical
Resistant
hypokalaemia
hypocalcaemia.
RTA
Keto acidosis
Lactic acidosis

Potassium and magnesium depletion often coexist, with more than 40% of hypokalaemic patients in one study revealing an associated hypomagnesaemia.[55] In hypokalaemic patients, magnesium may be repleted with potassium in a molar ratio of 1:8.[56] If hypomagnesaemia is not corrected, the associated hypocalcaemia and hypokalaemia are often resistant to therapy.[52]

Hypermagnesaemia

Hypermagnesaemia is defined as a plasma level greater than 1.0 mmol/L (although the therapeutic range for eclampsia ranges from 2.0 - 3.5 mmol/L).[57] In subjects with normal renal function, up to 200 mmol of Mg^{2+} may be excreted daily, thus large doses may be administered without toxicity.[44] Acidosis may increase the extracellular magnesium concentration due to redistribution,[58] and haemolysis may spuriously elevate the plasma magnesium level.[59]

Hypermagnesaemia is often caused by excessive administration of magnesium salts (cathartics or enemas) in the presence of renal failure.

Investigations. Hypermagnesaemia depresses plasma ionised and non-ionised calcium levels (but not phosphate levels) by a mechanism which is not yet clear.[60] Some have suggested that magnesium interferes with the synthesis or release of PTH;[61] however, others have reported high levels of PTH during magnesium-induced hypocalcaemia indicating that another mechanism may be responsible.[60]

Clinical features. The clinical features include drowsiness, hyporeflexia, coma, respiratory paralysis (excess magnesium suppresses the release of acetylcholine and blocks transmission at the neuro-muscular junction), hypotension, conduction defects of sinoatrial and atrioventricular nodal block and asystole. The ECG changes include a prolonged PR interval and widened QRS complex. These features are often dose related (Table 8).

Table 8. Dose related effects of hypermagnesaemia

Plasma level (mmol/L)	Clinical effects
0.7 - 1.0	Normal range
2.0 - 3.5	Therapeutic range for eclampsia
3.0 - 5.0	ECG changes
4.0 - 5.0	Areflexia
6.0 - 7.0	Respiratory arrest
10 - 12.5	Cardiac arrest

Treatment. Treatment of hypermagnesaemia is directed towards increasing excretion of the ion, which may require dialysis. Intravenous calcium chloride may be used to rapidly treat the cardiac conduction defects.[51]

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