Martindale: The Extra Pharmacopoeia 32th ed.

下册

Electrolytes

Electrolytes are used to correct disturbances in fluid and electrolyte homoeostasis or acid-base balance and to re-establish osmotic equilibrium of specific ions. The osmotic effects of solutions may be expressed in terms of osmolality which is defined as the 'molal' concentration in moles (or osmoles) per kg of solvent, or in terms of osmolarity which is the 'molar' concentration in moles (or osmoles) per litre of solution. In clinical practice, solute concentrations are measured per litre of solution and are expressed as millimoles (mmol) per litre or sometimes as milliequivalents (mEq) per litre. Milliequivalents are converted to millimoles by dividing by the valency of the ion. Positively charged ions are known as *cations* and include calcium, magnesium, potassium, and sodium ions. Negatively charged ions are known as *anions* and include bicarbonate, chloride, and phosphate ions. The ions principally involved in fluid and electrolyte homoeostasis and acid-base balance are sodium, chloride, bicarbonate, and potassium. Calcium, phosphate, and magnesium have a central role in the formation of bone mineral.

Acid-base Balance

Within the body, acid is mostly produced during cellular respiration in the form of carbon dioxide. Small amounts of various non-volatile acids are generated via metabolism, including lactic acid, uric acid, keto acids and some inorganic acids such as sulphuric and phosphoric acids. However, for normal tissue function, the pH of the body needs to be held within a narrow range. The pH of arterial blood is normally maintained between about 7.38 and 7.42 by means of compensatory respiratory, renal, and buffering mechanisms.

The most important buffer system in the extracellular fluid is the bicarbonate-carbonic acid system. Bicarbonate and hydrogen ions are in equilibrium with carbonic acid which is in turn in equilibrium with carbon dioxide in the body fluid, as expressed by:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

A normal plasma-bicarbonate concentration in adults is in the range of 20 to 30 mmol per litre and arterial partial pressure of carbon dioxide (P_aCO_2) is normally 4.7 to 5.7 kPa (31 to 43 mmHg).

Ultimately, excess acid must be removed from the body and base regenerated. P_aCO_2 is under respiratory control with carbon dioxide being excreted by the lungs. Plasma-bicarbonate concentrations are regulated by the kidneys, where bicarbonate is actively regenerated or reabsorbed. Organic acids such as lactic acid may be eliminated by metabolism; and other non-volatile acids, such as the inorganic acids of phosphate and sulphate, are excreted via the kidneys with simultaneous regeneration of bicarbonate.

The relationship between plasma pH, P_aCO_2, and bicarbonate is defined by the Henderson-Hasselbalch equation which is used to assess acid-base balance. For clinical purposes, this equation becomes

$$pH = pK_{CO_2} + \log\left(\frac{C_{HCO_3}}{\alpha \times P_aCO_2}\right)$$

where pH is the plasma pH, pK_{CO_2} is the carbonic acid dissociation constant (6.1), C_{HCO_3} is the plasma-bicarbonate concentration, α is a value representing carbon dioxide solubility, and P_aCO_2 is the arterial partial pressure of carbon dioxide. Disorders of acid-base balance may be due to a change in plasma-bicarbonate concentrations (metabolic) or to a change in P_aCO_2 (respiratory), although mixed disorders do occur.

The 4 major acid-base disturbances are:
- metabolic acidosis caused by a decrease in the plasma-bicarbonate concentration
- metabolic alkalosis caused by an increase in the plasma-bicarbonate concentration
- respiratory acidosis caused by hypoventilation and a raised P_aCO_2
- respiratory alkalosis caused by hyperventilation and a reduced P_aCO_2.

A further measure that may provide useful information in the assessment of metabolic acidosis is the plasma anion gap. This is the difference in ionic charge between the principal plasma cation (sodium) and anions (chloride and bicarbonate), and provides an estimation of unmeasured serum anions, which include inorganic and organic acids.

Metabolic acidosis. Metabolic acidosis, characterised by a low plasma-bicarbonate concentration and a tendency towards a fall in arterial pH, is the most frequent acid-base abnormality.

Metabolic acidosis with a normal anion gap is usually caused by excessive losses of bicarbonate from the gastro-intestinal tract (as in severe diarrhoeas) or failure of the kidneys to reabsorb or regenerate adequate bicarbonate (as in the renal tubular acidoses). Ingestion of acidifying salts such as ammonium chloride, which generate hydrochloric acid, can also result in this type of acidosis. Metabolic acidosis characterised by an increased anion gap is often due to a reduction in the renal excretion of inorganic acids such as phosphates and sulphates as in renal failure (uraemic acidosis), or to the net accumulation of organic acids as, for example, in lactic acidosis or diabetic ketoacidosis.

Metabolic acidosis is diagnosed and monitored by measurement of serum electrolytes, arterial pH, and P_aCO_2. There is often hyperventilation with reduced cardiac function, constriction of peripheral veins, inhibition of the hepatic metabolism of lactate, and impairment of consciousness.

The main aim of **treatment** is to manage any underlying disorder, and in some cases this will be sufficient to enable the body's homoeostatic mechanisms to correct the acid-base imbalance. The advantages of more active treatment of the acidosis must be balanced against the risks, including over-alkalinisation, and in consequence such therapy tends to be reserved for more persistent or severe cases.

The usual alkalinising agent is sodium bicarbonate. It may be given by mouth to replace bicarbonate losses in various chronic metabolic acidoses such as uraemic acidosis or renal tubular acidosis. Potassium bicarbonate may be preferred if the acidosis is associated with potassium deficiency. Potassium citrate and sodium citrate have also been used. More severe and acute cases (particularly where arterial pH is below 7.1) may require intravenous sodium bicarbonate therapy. Intravenous sodium bicarbonate has a role in acute metabolic acidoses attributable to severe renal failure, severe secretory diarrhoeas, and renal tubular acidosis. Although hypertonic solutions have been used, for example, in patients with circulatory overload, roughly isotonic bicarbonate solutions are otherwise preferred; arterial pH and plasma bicarbonate should be raised a little at a time and the patient's response monitored.

Although the role of bicarbonate is accepted in the forms of metabolic acidosis mentioned, its use in the treatment of metabolic acidosis with concomitant tissue hypoxia, particularly lactic acidosis, is controversial.[1,2] The administration of bicarbonate generates carbon dioxide which, if not appropriately eliminated, due to poor tissue perfusion or impaired ventilation or both, diffuses rapidly into the cells exacerbating intracellular acidosis. In addition, in metabolic acidosis associated with organic acids such as lactic acid, there is a risk of over-alkalinisation due to the metabolism of the acid after correction of the arterial pH.

For similar reasons, the use of sodium bicarbonate in advanced cardiac life support is no longer routine, although current guidelines permit consideration of its use to correct acidosis if the resuscitation effort is prolonged (see p.779).

The role of bicarbonate in the management of diabetic ketoacidosis is also limited, although it may be appropriate in certain situations—see p.316.

Because of concerns about the effects of bicarbonate other agents have been investigated for the treatment of metabolic acidosis, including trometamol (THAM) and sodium dichloroacetate.[1,2] Alkalinising agents that have to be metabolised to bicarbonate before they have an effect, such as sodium lactate, are not generally used as many patients with acute acidosis have impaired metabolic activity, particularly of lactate.

Peritoneal dialysis, haemodialysis, or haemofiltration is required for refractory metabolic acidosis associated with acute renal failure (p.1152).

1. Arieff AI. Indications for use of bicarbonate in patients with metabolic acidosis. *Br J Anaesth* 1991; **67:** 165–77.
2. Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med* 1998; **338:** 26–34. Correction. *ibid.* 1999; **340:** 247.

Metabolic alkalosis. Metabolic alkalosis with an increased plasma-bicarbonate concentration and a sustained elevation in arterial pH results from excessive renal reabsorption and/or regeneration of bicarbonate. It is commonly seen with volume contraction (chloride depletion), potassium depletion, or mineralocorticoid excess, and may occur with excessive alkali intake as in the milk-alkali syndrome. If the metabolic alkalosis is severe, cardiac arrhythmias and hypoventilation may develop and there can be symptoms of concomitant hypokalaemia such as muscle weakness.

Treatment is generally aimed at the underlying disturbances.[1] Correcting volume depletion by administration of a chloride salt often obviates the need for other treatment; sodium chloride is normally used. However, potassium chloride may also be required if there is potassium depletion, particularly if this is severe. Rarely, direct acidification by the administration of ammonium chloride, dilute hydrochloric acid, or acidifying salts such as lysine hydrochloride or arginine hydrochloride may be required if the alkalosis is severe.

1. Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med* 1998; **338:** 107–11.

Calcium Homoeostasis

The adult body contains about 1.2 kg of calcium, of which approximately 99% is incorporated into the skeleton where its primary role is structural. The remaining 1% is found in body tissues and fluids and is essential for normal nerve conduction, muscle activity, and blood coagulation.

The concentration of calcium in plasma is normally kept within a narrow range (total calcium about 2.15 to 2.60 mmol per litre) by homoeostatic mechanisms involving parathyroid hormone, calcitonin, and vitamin D. Normally about 47% of calcium in plasma is in the ionised physiologically active form (giving a usual range of about 1.00 to 1.25 mmol per litre), about 6% is complexed with anions such as phosphate or citrate, and the remainder is bound to

proteins, principally albumin. If the plasma-albumin concentration is raised (as in dehydration) or reduced (as is common in malignancy) it will affect the proportion of ionised calcium. Thus, the total plasma-calcium concentration is commonly adjusted for plasma albumin.

Hypercalcaemia. Hypercalcaemia, an increase in plasma-calcium concentration above the normal range, is most commonly due to primary hyperparathyroidism or malignant disease.[1,2] Rare causes of hypercalcaemia include vitamin D intoxication, granulomatous diseases such as sarcoidosis, prolonged immobility, acute renal failure, thiazide diuretics, and excess calcium carbonate ingestion (milk-alkali syndrome).[1]

Mild asymptomatic hypercalcaemia is often associated with a plasma-concentration elevated above the normal but below 3.00 mmol per litre. Severe symptomatic hypercalcaemia is broadly correlated with a plasma-calcium concentration of more than 3.50 mmol per litre.

Symptoms of hypercalcaemia include thirst, polyuria, anorexia, constipation, muscle weakness, fatigue, and confusion. In severe cases, there may be nausea and vomiting; cardiac arrhythmias may develop but are rare. Extreme hypercalcaemia may result in coma and death. Chronic hypercalcaemia can lead to interstitial nephritis and calcium renal calculi.

Mild asymptomatic hypercalcaemia does not require specific **treatment** and is best corrected by increasing oral fluid intake and treating any identified underlying disease. Patients with severe hypercalcaemia and/or significant symptoms require immediate therapy to reduce plasma-calcium concentrations independent of the cause.[2,3] The first step is rehydration with intravenous sodium chloride 0.9% to restore the intravascular volume and to promote calcium diuresis. Frusemide or other loop diuretics may assist in promoting the renal excretion of calcium but only in the presence of adequate volume expansion and control of other electrolyte losses. Large doses, for example 80 to 100 mg of frusemide administered intravenously every one to two hours, may be required. Thiazide diuretics should be avoided as they increase the renal tubular reabsorption of calcium. Peritoneal dialysis or haemodialysis with calcium-free dialysate should be considered in patients with renal failure for whom urinary excretion of calcium is inadequate. In life-threatening hypercalcaemia, more specific immediate therapy is generally required in addition to saline.[2,3] Calcitonins are likely to be first choice in this situation as they have a rapid onset of action. However, their effect is moderate and generally short-lived, and drugs with a more sustained effect may also be required. Most experience has been gained in the treatment of hypercalcaemia of malignancy (see below) using drugs that inhibit bone resorption such as bisphosphonates. Corticosteroids have been used to prolong the efficacy of calcitonin. Intravenous phosphates have been used to rapidly lower plasma-calcium concentrations but can cause soft tissue calcification resulting in serious adverse effects such as irreversible renal damage and hypotension, and are best avoided. Another drug that has been used for the emergency treatment of hypercalcaemia is trisodium edetate.

Choice of subsequent therapy is likely to depend on the specific cause.

1. Boyle I, Ralston S. Treatment of hypercalcaemia. *Prescribers' J* 1990; **30:** 180–6.
2. Bushinsky DA, Monk RD. Calcium. *Lancet* 1998; **352:** 306–11.
3. Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992; **326:** 1196–1203.

HYPERCALCAEMIA OF MALIGNANCY. About 10% of patients with cancer develop hypercalcaemia of malignancy, which is typically severe and progressive.[1-4] The condition is generally thought to be due to either the production of parathyroid hormone-related protein by a tumour (humoral hypercalcaemia of malignancy) or to the release of bone-resorbing factors (osteoclast-activating factors), which include cytokines such as tumour necrosis factor, growth factors, and interleukin-1, from the site of bone metastases (local osteolytic hypercalcaemia of malignancy). Humoral hypercalcaemia is frequently associated with squamous cell carcinomas of the lung and head and neck whereas local osteolytic hypercalcaemia tends to occur with breast cancer or myeloma.[2,5]

The bisphosphonate pamidronate has been widely used and is considered by many to be the drug of choice[1-5] for **treating** hypercalcaemia once the patient has been adequately rehydrated (see above). It is given as a single dose, adjusted according to initial plasma-calcium concentrations, by slow intravenous infusion and although it may be 24 to 48 hours before calcium concentrations start to decrease, the effects can last for 20 to 30 days: regular infusions at intervals of 2 to 3 weeks can be given to maintain normocalcaemia. Clodronate has also been given, administered by intravenous infusion and then by mouth or by intermittent infusion. Etidronate, administered by intravenous infusion on 3 successive days, has been found to reduce hypercalcaemia but has been reported to be less effective than pamidronate[6] and to have a shorter duration of action. Subsequent oral therapy with daily doses of etidronate can prolong the period of normocalcaemia but may cause osteomalacia. There is some evidence that the bisphosphonates may be less effective for humoral than for osteolytic hypercalcaemia.[7]

Plicamycin, a cytotoxic antibiotic with particular activity against osteoclasts, has been used to obtain a rapid (within 24 hours) and sustained reduction in plasma-calcium concentrations in severe hypercalcaemia. However, it is highly toxic and safer drugs such as the bisphosphonates and calcitonins are generally preferred. Gallium nitrate also inhibits bone resorption; initial studies in patients with hypercalcaemia associated with malignancy have indicated beneficial effects but clinical experience is limited; again, the bisphosphonates are likely to be preferred.[3,4]

Corticosteroids are useful in hypercalcaemia associated with steroid-sensitive haematological malignancies such as lymphoma or myeloma. In addition they may be useful to overcome renal tubular resistance to calcitonin[8] (see above) but otherwise are not usually effective.[9] There have been individual reports of beneficial results using somatostatin analogues such as octreotide for the treatment of hypercalcaemia of malignancy.

1. Anonymous. Treating cancer-associated hypercalcaemia. *Drug Ther Bull* 1990; **28:** 85–7.
2. Hall TG, Schaiff RAB. Update on the medical treatment of hypercalcemia of malignancy. *Clin Pharm* 1993; **12:** 117–25.
3. Chisholm MA, *et al.* Acute management of cancer-related hypercalcemia. *Ann Pharmacother* 1996; **30:** 507–13.
4. Watters J, *et al.* The management of malignant hypercalcaemia. *Drugs* 1996; **52:** 837–48.
5. Mundy GR, Guise TA. Hypercalcemia of malignancy. *Am J Med* 1997; **103:** 134–45.
6. Ralston SH, *et al.* Comparison of three intravenous bisphosphonates in cancer-associated hypercalcaemia. *Lancet* 1989; **ii:** 1180–82.
7. Gurney H, *et al.* Parathyroid hormone-related protein and response to pamidronate in tumour-induced hypercalcaemia. *Lancet* 1993; **341:** 1611–13.
8. Hosking DJ, *et al.* Potentiation of calcitonin by corticosteroids during the treatment of the hypercalcaemia of malignancy. *Eur J Clin Pharmacol* 1990; **38:** 37–41.
9. Percival RC, *et al.* Role of glucocorticoids in management of malignant hypercalcaemia. *Br Med J* 1984; **389:** 287.

HYPERPARATHYROIDISM. Excess secretion of parathyroid hormone in primary hyperparathyroidism is characterised by hypercalcaemia, which is most frequently asymptomatic, and by hypophosphataemia. Oral phosphates have been used to control hypercalcaemia, and oral bisphosphonates are being investigated. However, in the long term, hypercalcaemia associated with primary hyperparathyroidism appears to be best managed by parathyroidectomy (p.733). Symptomatic hypocalcaemia may occur after surgery, requiring short-term treatment with calcium supplements and vitamin D.

VITAMIN D-MEDIATED HYPERCALCAEMIA. Hypercalcaemia can occur because of increased gastro-intestinal absorption of calcium mediated by the active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (calcitriol).[1] This may be a feature of diseases associated with increased vitamin D sensitivity or increased vitamin D production, or may occur due to excess vitamin D administration. For example, granulomatous diseases such as sarcoidosis (p.1028) are associated with unregulated production of 1,25-dihydroxycholecalciferol. Hypercalcaemia due to vitamin D administration is most commonly seen in patients with renal failure receiving vitamin D analogues such as ergocalciferol (p.1367).

Treatment of severe hypercalcaemia requires prompt rehydration regardless of the cause (see above). Where hypercalcaemia is due to vitamin D administration, the vitamin D analogue should be discontinued until normocalcaemia is achieved. Corticosteroids effectively reduce gastro-intestinal absorption of calcium, and these may be used intravenously as adjuncts to rehydration in severe hypercalcaemia, and orally for milder hypercalcaemia or longer term therapy. Oral sodium cellulose phosphate, which binds calcium in the gastro-intestinal tract, and a low-calcium diet may also be considered. Oral chloroquine phosphate has been used in hypercalcaemia associated with sarcoidosis.

1. Adams JS. Vitamin D metabolite-mediated hypercalcemia. *Endocrinol Metab Clin North Am* 1989; **18:** 765–78.

Hypocalcaemia. Hypocalcaemia, a decrease in plasma-calcium concentration below the normal range, may be due to impaired or reduced absorption of calcium from the gastro-intestinal tract as with vitamin D deficiency disorders (see Osteomalacia, p.730) and chronic renal failure (see Renal Osteodystrophy, p.732). Alternatively, it may be due to deficient parathyroid hormone secretion and/or action as in hypoparathyroidism (p.733) and hypomagnesaemia (see below). Excessive phosphate administration is also a cause of hypocalcaemia (see below). Rarely, hypocalcaemia may follow repeated infusions of citrate ions, for example, during transfusions utilising citrated blood, as the citrate complexes with the calcium ion. Respiratory alkalosis due to hyperventilation can also lead to depression of ionised plasma-calcium concentrations.

Where symptoms of hypocalcaemia occur, they are typically associated with increased neuromuscular excitability; paraesthesias can occur and in more severe cases, carpopedal spasm, muscle cramps, tetany, and convulsions may develop.[1-3] Other symptoms include ECG changes and mental disturbances such as irritability and depression. Prolonged hypocalcaemia can lead to dental defects, cataract formation, and in children can result in mental retardation.

In patients with hypocalcaemia due to an underlying disease, long-term management should be aimed at **treating** this disease. Vitamin D supplements are widely used to enhance calcium absorption and correct vitamin D deficiency disorders and hypoparathyroidism. Oral supplements of calcium salts are often also given. Acute hypocalcaemia or hypocalcaemic tetany require emergency treatment with calcium salts administered intravenously.

1. Lebowitz MR, Moses AM. Hypocalcemia. *Semin Nephrol* 1992; **12:** 146–58.
2. Reber PM, Heath H. Hypocalcemic emergencies. *Med Clin North Am* 1995; **79:** 93–106.
3. Bushinsky DA, Monk RD. Calcium. *Lancet* 1998; **352:** 306–11.

Magnesium Homoeostasis

Magnesium is an essential body cation which is involved in numerous enzymatic reactions and physiological processes including energy transfer and storage, skeletal development, nerve conduction, and muscle contraction. Over half of the magnesium in the body is found in bone, about 40% is present in muscle and soft tissue, and only about 1% is present in the extracellular fluid. A normal concentration for magnesium in plasma is from about 0.7 to 1.0 mmol per litre.

Magnesium homoeostasis appears to be primarily regulated by the kidney where magnesium is extensively reabsorbed. Bone may act as a magnesium reservoir to reduce plasma-magnesium fluctuations. Magnesium is actively absorbed from the gastro-intestinal tract and this is enhanced to some extent by 1,25-dihydroxycholecalciferol (calcitriol).

Hypermagnesaemia. Hypermagnesaemia is an increase in the plasma concentration of magnesium above the normal range, as may follow excessive parenteral administration of salts such as magnesium sulphate. Hypermagnesaemia due to oral magnesium intake is uncommon as the kidneys are able to excrete a relatively large magnesium load. However, it may occur in patients with impaired renal function taking large amounts of magnesium, for example, in antacids or laxatives.

Symptoms of hypermagnesaemia include nausea, vomiting, CNS and respiratory depression, hyporeflexia, muscle weakness, and cardiovascular effects including

peripheral vasodilatation, hypotension, bradycardia, and cardiac arrest.

Treatment of mild hypermagnesaemia is usually limited to restricting magnesium intake. In severe hypermagnesaemia, ventilatory and circulatory support may be required. Slow intravenous administration of 10 to 20 mL of calcium gluconate 10% is recommended to reverse the effects on cardiovascular and respiratory systems. If renal function is normal, adequate fluids should be given to promote renal magnesium clearance. This may be increased by the use of frusemide. Haemodialysis using a magnesium-free dialysis solution effectively removes magnesium, and this may be necessary in patients with renal impairment, or for whom other methods prove ineffective.

Hypomagnesaemia. Hypomagnesaemia, a plasma-magnesium concentration below the normal range, may result from a reduced magnesium intake as in dietary deficiency or malabsorption syndromes. Alternatively, it may be due to excessive magnesium loss either via the kidney because of inadequate reabsorption or more often from the gut, for example, during chronic diarrhoea. Drugs that may cause renal magnesium wasting include aminoglycosides, cisplatin (p.514), and diuretics.

Hypomagnesaemia is closely associated with other electrolyte disturbances, especially hypocalcaemia (see above) and hypokalaemia (see below), and rarely occurs alone. Specific symptoms are therefore difficult to determine but may include anorexia, nausea, weakness, neuromuscular dysfunction such as tetany, tremor, and muscle fasciculations, and rarely seizures. Cardiac arrhythmias may occur, but the relative contribution of hypomagnesaemia and hypokalaemia to these is uncertain.

Magnesium salts can be given by mouth for the **treatment** of chronic or asymptomatic magnesium deficiency.[1,2] Parenteral therapy may be preferred in patients with poor gastro-intestinal absorption of magnesium or who are unable to tolerate oral supplements (usually because they cause diarrhoea); magnesium sulphate can be given by intravenous or intramuscular injection. In acute symptomatic hypomagnesaemia, rapid replacement therapy with intravenous magnesium salts may be necessary. Renal function and plasma-magnesium concentrations should be monitored.

1. Whang R, *et al.* Magnesium homeostasis and clinical disorders of magnesium deficiency. *Ann Pharmacother* 1994; **28:** 220–6.
2. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. *Lancet* 1998; **352:** 391–6.

Phosphate Homoeostasis

Phosphate is an essential bone mineral; about 80% of phosphorus in an adult body is incorporated into the skeleton as a calcium salt where it is required to give rigidity. The remainder is present in the soft tissues and is involved in several metabolic and enzymatic reactions including energy storage and transfer.

Phosphate exists in body fluids mainly as the divalent HPO_4^{2-} ion (about 80%) or monovalent $H_2PO_4^-$ ion (about 20%). Phosphate measurements are usually expressed as inorganic phosphorus to avoid confusion with the anion content. A normal range for phosphorus in plasma in adults is about 0.85 to 1.45 mmol per litre, but as only a small proportion of body phosphate is found in the extracellular fluid, plasma-phosphorus levels may not always reflect total body stores or predict replacement needs.

Phosphate concentrations in plasma are primarily regulated by renal excretion; parathyroid hormone reduces the renal tubular reabsorption of phosphate. Intestinal absorption of phosphate is enhanced by the vitamin D metabolite, 1,25-hydroxycholecalciferol.

Hyperphosphataemia. Hyperphosphataemia, an abnormally raised plasma-phosphorus concentration, is usually associated with renal failure and may lead to renal osteodystrophy (p.732). Hyperphosphataemia may also be a consequence of release of phosphate from cells; this may occur in conditions of cell breakdown such as in haemolysis or rhabdomyolysis, during chemotherapy when it may be part of the tumour lysis syndrome, or as a result of acidoses. Hypoparathyroidism may also lead to hyperphosphataemia due to decreased levels of parathyroid hormone (see p.733). Other causes include excessive phosphate administration during treatment of hypophosphataemia, overuse of phosphate enemas or oral phosphate bowel preparations, and excessive vitamin D intake.

Hyperphosphataemic symptoms include those of associated hypocalcaemia (see above). Complexation with calcium may lead to metastatic calcification.

The **treatment** of hyperphosphataemia[1] usually involves control of the relevant underlying condition, and the use of low-phosphate diets, and if necessary oral phosphate-binding agents, such as calcium acetate or carbonate or aluminium hydroxide. Haemodialysis has been used to correct hyperphosphataemia due to oral phosphate administration in renal failure.

1. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. *Lancet* 1998; **352:** 391–6.

Hypophosphataemia. Hypophosphataemia, a reduction in plasma-phosphorus concentrations below the normal range, may be due to insufficient absorption of phosphate or increased renal clearance as in primary hyperparathyroidism, vitamin D deficiency, or X-linked familial hypophosphataemia. An increased cell uptake of phosphate can also result in hypophosphataemia, as for example, in chronic respiratory alkalosis and related disorders including alcoholism, hepatic failure, and septicaemia. As phosphate is widely available in most foods, dietary deficiency is rare though it may occur in infants of low birth-weight fed exclusively on human breast milk (p.1160). The absorption of phosphate from the gastro-intestinal tract can be reduced if phosphate-binding antacids are taken in large amounts.

Hypophosphataemia is usually asymptomatic but clinical symptoms become apparent when plasma-phosphorus concentrations fall below 0.3 mmol per litre.[1-3] Symptoms include neuromuscular dysfunction such as muscle weakness and paraesthesias, convulsions, cardiomyopathy, respiratory failure, and haematological abnormalities. Prolonged hypophosphataemia can result in rickets or osteomalacia (p.730).

Treatment of hypophosphataemia primarily involves correction of any underlying disease. Milk or oral phosphate supplements may be appropriate if a phosphate deficiency is identified or in certain disorders such as X-linked hypophosphataemic rickets. Intravenous phosphate administration may be required for severe hypophosphataemia, but this should be used cautiously to avoid hypocalcaemia and metastatic calcification.[2,3] Consideration should be given to correcting concomitant electrolyte disturbances such as hypomagnesaemia.

1. Larner AJ. Clinical applicability of inorganic phosphate measurements. *Br J Hosp Med* 1992; **48:** 748–53.
2. Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; **7:** 123–8.
3. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. *Lancet* 1998; **352:** 391–6.

Potassium Homoeostasis

Potassium is predominantly an intracellular cation, primarily found in muscle; only about 2% is present in the extracellular fluid. It is essential for numerous metabolic and physiological processes including nerve conduction, muscle contraction, and acid-base regulation. A normal concentration of potassium in plasma is about 3.5 to 5.0 mmol per litre, but factors influencing transfer between intracellular and extracellular fluids such as acid-base disturbances can distort the relationship between plasma concentrations and total body stores. The body content of potassium is primarily regulated by renal glomerular filtration and tubular secretion. Aldosterone enhances the renal secretion of potassium and several other factors such as sodium excretion, dietary potassium intake, and plasma pH can modulate the excretion of potassium by the kidney. Insulin, beta$_2$ agonists, and aldosterone, and increases in plasma pH, can promote the cellular uptake of potassium. The passage of potassium into the cells and retention against the concentration gradient requires active transport via the Na^+/K^+ ATPase enzyme.

Hyperkalaemia. Hyperkalaemia, an abnormally raised plasma-potassium concentration, can occur if the potassium intake is increased, if the renal excretion decreases as in renal failure or adrenocortical insufficiency, or if there is a sudden efflux of potassium from the intracellular stores, for example, in acidosis or cell destruction due to tissue trauma, burns, haemolysis, or rhabdomyolysis. Hyperkalaemia may also be induced by drugs such as the potassium-sparing diuretics or ACE inhibitors. Usually the renal mechanisms for potassium excretion adapt readily to an increased potassium load and hyperkalaemia due to increased dietary intake is rare unless renal function is also impaired.

Hyperkalaemia predominantly results in disruption of cardiac function, but skeletal muscle function may also be affected. Symptoms include ECG abnormalities, ventricular arrhythmias, cardiac arrest, and also neuromuscular dysfunction such as muscle weakness and paralysis.[1-4]

Treatment involves the administration of calcium to counteract the negative effects of hyperkalaemia on cardiac excitability, the use of agents such as insulin or sodium bicarbonate to promote the transfer of potassium from the extracellular to the intracellar fluid compartment, and enhanced potassium excretion with exchange resins or dialysis.[1-4] The methods employed depend largely on the severity of the hyperkalaemia and critically, any associated ECG changes. Hyperkalaemia associated with a plasma concentration of potassium above 6.0 to 7.0 mmol per litre or with ECG changes is usually considered a medical emergency.

If cardiac manifestations of hyperkalaemia are present, then first-line therapy should be with a calcium salt administered intravenously; 10 to 30 mL of calcium gluconate 10% may be given by slow intravenous injection, the dosage being titrated and adjusted based on ECG improvement.

Calcium will not, however, reduce the plasma-potassium concentration. In moderate to severe hyperkalaemia, insulin, together with glucose to prevent hypoglycaemia, may be given intravenously in order to reduce the potassium concentration by stimulating the uptake of potassium by cells. Insulin is administered as a rapid-acting soluble insulin and typical doses are 5 to 15 units with 50 mL of glucose 50% given slowly over 5 to 15 minutes. Doses may need to be repeated as necessary. Alternatively or additionally, sodium bicarbonate may be employed to correct acidosis and promote cellular uptake of potassium; usual doses are in the order of 50 to 100 mL of a 4.2% solution (equivalent to 25 to 50 mmol) given intravenously.

The beta$_2$ agonist, salbutamol, administered intravenously or by a nebuliser, has also been found to enhance the cellular uptake of potassium and reduce plasma-potassium concentrations.[1,3,5,6] However, some clinicians prefer to avoid beta$_2$ agonists because of fears that large doses may induce cardiac arrhythmias.[7]

After the plasma-potassium concentration has been reduced in the immediate term by enhancing cellular potassium uptake, treatments are often required that will remove excess potassium from the body over the longer term. Cation exchange resins such as calcium or sodium polystyrene sulphonate can be given orally or rectally and, after about 1 to 2 hours, will begin to remove potassium from the body. Haemodialysis removes potassium from the body very effectively and is particularly useful in patients with acute renal failure, hypervolaemia, hypernatraemia, or severe hyperkalaemia. Peritoneal dialysis is effective in some patients.

1. Anonymous. Hyperkalaemia—silent and deadly. *Lancet* 1989; **i:** 1240.
2. Saxena K. Clinical features and management of poisoning due to potassium chloride. *Med Toxicol Adverse Drug Exp* 1989; **4:** 429–43.
3. Anonymous. Potassium disorders and cardiac arrhythmias. *Drug Ther Bull* 1991; **29:** 73–5.
4. Vaughan RS. Potassium in the perioperative period. *Br J Anaesth* 1991; **67:** 194–200.
5. Allon M, *et al.* Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; **110:** 426–9.
6. McClure RJ, *et al.* Treatment of hyperkalaemia using intravenous and nebulised salbutamol. *Arch Dis Child* 1994; **70:** 126–8.
7. Halperin ML, Kamel KS. Potassium. *Lancet* 1998; **352:** 135–40.

HYPERKALAEMIC PERIODIC PARALYSIS. Hyperkalaemic periodic paralysis is an inherited disorder in which sudden increases in plasma-potassium concentrations cause muscle paralysis. An acute attack may require in-

intravenous calcium gluconate and insulin with glucose (see above). Inhalation of a beta$_2$ agonist such as salbutamol has been used to treat or abort attacks.[1] Diuretics such as acetazolamide or the thiazides are used prophylactically to reduce the frequency of attacks.

1. Wang P, Clausen T. Treatment of attacks in hyperkalaemic familial periodic paralysis by inhalation of salbutamol. *Lancet* 1976; i: 221–3.

Hypokalaemia. Chronic hypokalaemia, a prolonged reduction of the plasma concentration of potassium, usually indicates a reduction in total body potassium. It may result from an inadequate intake, or gastrointestinal losses, for example in patients with secretory diarrhoeas, or from excessive renal losses as in hyperaldosteronism, Cushing's syndrome, or chronic metabolic alkalosis. Thiazides or loop diuretics increase urinary-potassium losses. Other drugs, notably corticosteroids and some antibacterials such as gentamicin, also have this effect. Hypokalaemia can also be caused by an increased cellular uptake of potassium rather than excess body losses. This may occur with drugs such as beta$_2$ agonists or xanthines, during insulin therapy, acute alkalosis, or possibly be induced by catecholamines after myocardial infarction. Hypokalaemia secondary to hypomagnesaemia can occur (see above).

Hypokalaemia results in neuromuscular disturbances ranging from muscle weakness to paralysis and respiratory insufficiency and can also cause rhabdomyolysis, ECG abnormalities, and ileus. Chronic hypokalaemia may lead to renal tubular damage (hypokalaemic nephropathy). Hypokalaemia increases the risk of digoxin toxicity.

Treatment involves correcting any underlying disorder and replacement therapy with potassium salts. Oral potassium supplements are generally preferred but in severe hypokalaemia associated with cardiac arrhythmias, paralysis or diabetic ketoacidosis, parenteral therapy may be necessary. Potassium salts, usually potassium chloride, may be given by intravenous infusion but must be administered slowly to avoid causing hyperkalaemia and associated cardiac toxicity; plasma-potassium concentrations should be closely monitored and ECG monitoring may be required. The choice of salt for oral potassium replacement depends on co-existing acid-base and electrolyte disturbances. Potassium chloride is generally the drug of choice for the treatment of hypokalaemia in patients with metabolic alkalosis with hypochloraemia, whereas a salt such as the bicarbonate may be preferred in patients with hyperchloraemic acidosis as in some renal tubular acidoses. Hypokalaemia secondary to hypomagnesaemia requires magnesium replacement therapy.

References.

1. Anonymous. Potassium disorders and cardiac arrhythmias. *Drug Ther Bull* 1991; **29:** 73–5.
2. Vaughan RS. Potassium in the perioperative period. *Br J Anaesth* 1991; **67:** 194–200.
3. Halperin ML, Kamel KS. Potassium. *Lancet* 1998; **352:** 135–40.
4. Gennari FJ. Hypokalemia. *N Engl J Med* 1998; **339:** 451–8.

BARTTER'S SYNDROME. Bartter's syndrome is thought to result from an inherited defect in the thick ascending limb of the loop of Henle. Patients exhibit hyperplasia of the juxtaglomerular cells, hypokalaemia and metabolic alkalosis, and excess aldosterone, prostaglandin, and renin production. Symptoms are primarily those of the hypokalaemia, including muscle weakness; polyuria and enuresis, and growth retardation in children, can occur. In contrast to other hyperreninaemic states, patients do not have hypertension or oedema.

Treatment rarely completely corrects hypokalaemia. Potassium supplementation may be given, while a cyclo-oxygenase inhibitor such as indomethacin,[1,2] or an ACE inhibitor such as captopril,[3,4] can produce benefit. Spironolactone and propranolol have also been tried.[4] Magnesium sulphate may be given by depot injection if there is hypomagnesaemia.[4]

1. Littlewood JM, *et al.* Treatment of childhood Bartter's syndrome with indomethacin. *Lancet* 1976; **ii:** 795.
2. Sechi LA, *et al.* Abnormalities of erythrocyte sodium transport systems in Bartter's syndrome. *Am J Nephrol* 1992; **12;** 137–43.
3. Jest P, *et al.* Angiotensin-converting enzyme inhibition as a therapeutic principle in Bartter's syndrome. *Eur J Clin Pharmacol* 1991; **41:** 303–5.
4. Crowe P, *et al.* Bartter's syndrome in two generations of an Irish family. *Postgrad Med J* 1993; **69:** 791–6.

DIURETIC-INDUCED HYPOKALAEMIA. Reduced potassium concentrations may result from the use of potassium-losing diuretics, particularly thiazides and loop diuretics. Clinically significant hypokalaemia is unlikely at the doses used in hypertension and the routine use of potassium supplements is no longer recommended. However, the concomitant administration of a potassium-sparing diuretic such as amiloride or, less usually, a potassium supplement may be necessary in patients at risk of hypokalaemia (see also p.885).

HYPOKALAEMIC PERIODIC PARALYSIS. Hypokalaemic periodic paralysis is an inherited disorder in which episodes of paralysis appear to be associated with a shift in potassium from the extracellular to the intracellular fluid resulting in hypokalaemia. Therapy has included the use of potassium supplements; acetazolamide has been found to reduce the frequency and severity of attacks.[1]

1. Griggs RC, *et al.* Acetazolamide treatment of hypokalemic periodic paralysis: prevention of attacks and improvement of persistent weakness. *Ann Intern Med* 1970; **73:** 39–48.

Sodium Homoeostasis

Sodium is the principal cation in the extracellular fluid and is responsible for the maintenance of the extracellular fluid volume and osmolality. In addition, sodium is also involved in nerve conduction, muscle contraction, acid-base balance, and cell nutrient uptake. A normal concentration of sodium in plasma would be expected to be within 135 to 145 mmol per litre.

Sodium homoeostasis is complex and closely associated with fluid balance. The osmolality and volume of the extracellular fluid are tightly regulated. Small changes in osmolality (plasma-sodium concentrations) are corrected by alteration of extracellular volume. This balance of plasma osmolality is achieved by the secretion or suppression of antidiuretic hormone (ADH; vasopressin), which primarily controls water excretion by the kidney. A tendency towards hyponatraemia suppresses ADH secretion and promotes renal loss of water; an increase in ADH secretion increases water reabsorption by the renal distal tubules. Changes in extracellular volume will also affect ADH release independently of osmolality. In addition, changes in extracellular volume result in modulation of the renal excretion of sodium.

Total body sodium content is regulated by renal sodium excretion, which can vary widely depending on dietary intake. Various mechanisms are involved in controlling renal sodium excretion including the renin-angiotensin system, glomerular filtration rate, and natriuretic factors. A reduction in extracellular fluid volume leads to the production of angiotensin II which stimulates the secretion of aldosterone. Aldosterone promotes the reabsorption of sodium ions by the distal tubules. There may be significant effects on sodium homoeostasis if adrenal insufficiency or mineralocorticoid excess disturb this mechanism.

Hypernatraemia. Hypernatraemia is an abnormal rise in the plasma-sodium concentration with a simultaneous rise in plasma osmolality. It is generally associated with volume depletion when water intake is less than water losses through renal or extrarenal routes. The causes include impaired thirst, as in coma or essential hypernatraemia, osmotic diuresis (solute diuresis), as in diabetic ketoacidosis or after mannitol administration, and excessive water losses, either from the kidney, as in diabetes insipidus, or extrarenally, for example, because of excessive sweating or diarrhoea.

Hypernatraemia can also occur following excessive oral sodium intake (but this is uncommon) and after inappropriate use of intravenous sodium chloride.

The clinical manifestations of hypernatraemia are caused by the effect of increased plasma osmolality on the brain and include somnolence, confusion, respiratory paralysis, and coma. CNS symptoms are more severe when hypernatraemia develops rapidly. In the presence of volume depletion, other symptoms such as hypotension, tachycardia, and various symptoms of circulatory insufficiency may occur concomitantly. A high volume of dilute urine is seen in patients with abnormal renal water conservation, whereas a low volume of concentrated urine is expected in patients with impaired thirst or excessive extrarenal water loss.

Treatment of hypernatraemia usually requires water replacement and oral administration of water may be sufficient for some patients. In more severe conditions, glucose 5% may be administered by slow intravenous infusion. Alternatively, some recommend the use of sodium chloride 0.9%. Care is required as too rapid correction can induce cerebral oedema, particularly in chronic conditions.

If the total body sodium is too high, loop diuretics may be used to increase sodium excretion with fluid losses being replaced by an infusion of glucose 5% and potassium chloride. It has also been suggested that dialysis may be necessary if there is significant renal impairment, if the patient is moribund, or if the serum-sodium concentration is greater than 200 mmol per litre.

For the treatment of hypernatraemia associated with some specific causes see diabetes insipidus (p.1237), diabetic ketoacidosis (p.316), and sodium chloride overdose (p.1162).

Hyponatraemia. Hyponatraemia, an abnormal fall in the plasma-sodium concentration, usually with a simultaneous fall in the plasma osmolality, is a frequent electrolyte disturbance that occurs with many different diseases including heart failure, cirrhosis, adrenocortical insufficiency, hyperglycaemia, and AIDS.

The kidney is able to conserve sodium and sodium depletion due to low salt intake is rare. Sodium depletion may occur if there are abnormal losses, either from the gut as a consequence of repeated diarrhoea and/or vomiting or from the kidney, for example, due to various renal disorders or the overuse of diuretics (p.886).

The most common cause of hyponatraemia is dilution. This may result from excessive fluid intake, for example, due to the ingestion of large volumes of water as in patients with primary polydipsia (psychogenic polydipsia). More frequently, however, it is a result of reduced water excretion, for example in impaired renal function or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) which is discussed on p.1241. Postoperative hyponatraemia is a frequent complication which may be exacerbated by the inappropriate intravenous administration of hypotonic, or even isotonic,[1] fluids.

Hyponatraemia due to sodium depletion in the presence of volume contraction may cause postural hypotension and circulatory insufficiency. Dilutional hyponatraemia can be asymptomatic but headache, confusion, nausea, vomiting, somnolence, and weakness may occur. If severe, cerebral oedema is present, and respiratory arrest, convulsions, and coma may ensue. CNS symptoms are more common when the condition is acute.

Therapy is guided by the rate of development and degree of hyponatraemia, accompanying symptoms, and the state of water balance, and should also take into account the underlying cause. Mild asymptomatic hyponatraemia does not usually require specific therapy. Chronic mild to moderate sodium depletion, such as occurs in salt-losing bowel or renal disease, may be treated with oral sodium chloride supplements while ensuring adequate fluid intake.

When there is substantial volume depletion, volume replacement is necessary and intravenous sodium chloride 0.9% is often used.

Chronic dilutional hyponatraemia, which is often asymptomatic, can generally be managed by correcting the underlying disease; water restriction may also be necessary and drugs that interfere with the action of ADH such as demeclocycline or lithium carbonate may be useful in SIADH.[2,3] Frusemide plus oral sodium chloride supplements have also been used (p.1241).

Acute symptomatic hyponatraemia (water intoxication) is generally associated with plasma-sodium concentrations below 120 mmol per litre and requires more aggressive therapy. This involves the intravenous administration of hypertonic or isotonic sodium chloride, often in conjunction with a loop diuretic such as frusemide, especially if fluid overload is likely to be a problem.[2,3] The aim is to render the patient asymptomatic with a plasma-sodium concentration of 120 to 130 mmol per litre; the plasma-sodium concentration should not be corrected to normal values nor should hy-

pernatraemia be allowed to develop.[2,3] Plasma-sodium concentrations and the total-body-water volume should be monitored throughout.

A rare neurological syndrome known as central pontine myelinolysis (osmotic demyelination) has been associated with the over-rapid correction of symptomatic hyponatraemia, particularly if the condition is well established, and it has been recommended that the plasma-sodium concentration should be increased at a rate not exceeding 0.5 mmol per litre per hour[4,5] in these patients, though the best correction rate is debatable.[3,6] Some have suggested an initial prompt increase in plasma sodium of about 10% or 10 mmol per litre, followed by correction at a rate not exceeding 1.0 to 1.5 mmol per litre per hour or 15 mmol per litre per 24 hours.[7] However, the association of hyponatraemia with central pontine myelinolysis is controversial and some authorities do not consider the rate of correction to be a factor in hyponatraemic brain injury.[3]

1. Steele A, *et al.* Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. *Ann Intern Med* 1997; **126:** 20–5.
2. Swales JD. Management of hyponatraemia. *Br J Anaesth* 1991; **67:** 146–53.
3. Arieff AI. Management of hyponatraemia. *Br Med J* 1993; **307:** 305–8.
4. Cluitmans FHM, Meinders AE. Management of severe hyponatremia : rapid or slow correction? *Am J Med* 1990; **88:** 161–6.
5. Laureno R, Karp BI. Myelinolysis after correction of hyponatremia. *Ann Intern Med* 1997; **126:** 57–62.
6. Stems RH. The treatment of hyponatremia: first, do no harm. *Am J Med* 1990; **88:** 557–60.
7. Kumar S, Berl T. Sodium. *Lancet* 1998; **352:** 220–8.

Dialysis Solutions (3276-x)

Pharmacopoeias. In *Eur.* (see p.viii), which includes separate monographs for solutions for haemodialysis, haemofiltration, and peritoneal dialysis.

Dialysis and filtration solutions are solutions of electrolytes formulated in concentrations similar to those of extracellular fluid or plasma. They always contain sodium and chloride and bicarbonate or a bicarbonate precursor. In addition, they often contain calcium and magnesium, and rarely potassium. Glucose may be added as an osmotic agent. These solutions allow the removal of water and metabolites and the replacement of electrolytes.

In *haemodialysis*, the exchange of ions between the solution and the patient's blood is made across a semi-permeable membrane, primarily by diffusion. Excess fluid is removed by ultrafiltration achieved by a pressure gradient. Membranes are either derived from cellulose (e.g. cuprophane) or are synthetic. Bicarbonate rather than a bicarbonate precursor is increasingly preferred as the bicarbonate source in haemodialysis since the problems of precipitation of calcium and magnesium have been overcome by changes in dialysis technique. Acetate is still used in some dialysers, but is thought to have vasodilatory and cardiodepressant actions, and may not be converted to bicarbonate fast enough for high-flux haemodialysis or in patients with liver disease. Haemodialysis solutions are provided in a sterile concentrated form for dilution with water before use; this water need not be sterile.

In *peritoneal dialysis*, the exchange is made across the membranes of the peritoneal cavity primarily by diffusion. Excess fluid is removed by ultrafiltration achieved by the use of osmotic agents such as glucose. The problems of calcium bicarbonate precipitation have not yet been overcome, and lactate is generally used as the bicarbonate precursor. Peritoneal dialysis solutions must be sterile and apyrogenic.

In *haemofiltration*, blood is filtered rather than dialysed. Metabolites are removed by convective transport, and excess water by hydrostatic ultrafiltration. Fluid and electrolytes are replaced by direct intravenous infusion of haemofiltration solution. Most haemofiltration solutions use acetate as the bicarbonate source. Haemofiltration solutions must be sterile and apyrogenic.

References.
1. Carlsen DB, Wild ST. Grams to milliequivalents: a concise guide to adjusting hemodialysate composition. *Adv Renal Replacement Ther* 1996; **3:** 261–5.
2. Zucchelli P, Santoro A. How to achieve optimal correction of acidosis in end-stage renal failure patients. *Blood Purif* 1995; **13:** 375–84.
3. Passlick-Deetjen J, Kirchgessner J. Bicarbonate: the alternative buffer for peritoneal dialysis. *Perit Dial Int* 1996; **16** (suppl 1): S109–S113.
4. Pastan S, Bailey J. Dialysis therapy. *N Engl J Med* 1998; **338:** 1428–37.

Adverse Effects

Adverse effects occurring during *haemodialysis* include nausea, vomiting, hypotension, muscle cramps, and air embolus. Effects related to vascular access include infection, thrombosis, and haemorrhage. Adverse effects occurring during *haemofiltration* are similar to those for haemodialysis.

The most common adverse effects associated with *peritoneal dialysis* include peritonitis, hernias, hyperglycaemia, protein malnutrition, and catheter complications.

Long-term complications in dialysed patients, some of which may relate to renal failure itself, include haemodialysis-related amyloidosis, acquired cystic kidney disease, and accelerated atherosclerosis. Dialysis dementia is a special hazard of aluminium overload. Long-term peritoneal dialysis results in progressive structural changes to the peritoneal membrane ultimately resulting in dialysis failure.

Aluminium overload. Accumulation of aluminium in patients on dialysis may result in dialysis dementia, anaemia, and aluminium-related bone disease (see also p.1547). Sources of aluminium include the water used for preparation of dialysis fluids and aluminium-containing phosphate binders used in treating renal osteodystrophy (p.732). It is therefore important that water used for the preparation of dialysis fluids has a low aluminium concentration; Ph. Eur. specifies a limit of aluminium of 10 μg per litre. Non-aluminium-containing phosphate binders such as calcium acetate or calcium carbonate may be preferred for long-term therapy. Aluminium overload in patients on dialysis has been treated with desferrioxamine (p.977).

Copper toxicity. Liver and haematological toxicity has occurred as a result of absorption of copper from dialysis fluids (p.1338).

Haemodialysis-induced cramp. Muscle cramps commonly occur during haemodialysis procedures, and are often associated with hypotension as a result of inappropriate volume removal. In addition, they may be exacerbated by cellulose-derived membranes or the use of acetate as a bicarbonate precursor. Sodium chloride tablets (p.1163), intravenous sodium chloride 0.9%, intravenous hypertonic glucose (p.1344), and quinine (p.442) have been used in the prevention or treatment of haemodialysis-induced cramp.

Hypersensitivity. The use of ethylene oxide for the disinfection of dialysis equipment has been associated with severe, sometimes fatal, anaphylactic reactions (p.1113).

Infections. Patients undergoing haemodialysis are at risk of infections from microbial contamination of dialysis fluid, and from inadequate care of vascular access sites. Maximum microbial counts and limits for endotoxins have been specified for water used in dialysis fluids. Bicarbonate-based dialysis solutions are more susceptible to microbial growth than acetate-based solutions.

Peritonitis is common in patients receiving peritoneal dialysis. The risk of infection may be minimised by using disconnect systems, good aseptic technique, and by good care of catheters. Treatment of bacterial peritonitis requires intraperitoneal administration of antibacterials, which are usually added to the dialysis fluid. Guidelines for treating peritonitis in patients on continuous ambulatory peritoneal dialysis have been published (see p.136).

Dialysis equipment should be regularly disinfected with agents such as formaldehyde (p.1114) or ethylene oxide (p.1113), but for mention of ethylene oxide anaphylactoid reactions, see p.1113.

Metabolic complications. The high concentrations of glucose in peritoneal dialysis solutions required to form an osmotic gradient can lead to weight gain, hyperglycaemia, hyperlipidaemia, and increased protein loss. Alternative osmotic agents such as icodextrin (p.1339) and amino acid-based solutions are being investigated.

Precautions

Peritoneal dialysis is not appropriate for patients with abdominal sepsis, previous abdominal surgery, or severe inflammatory bowel disease.

Haemodialysis should be used with caution in patients with unstable cardiovascular disease or active bleeding. During haemodialysis and haemofiltration, heparin (p.882) or epoprostenol (p.1418) are required to prevent clotting of the blood in the extracorporeal circuit.

Dialysis solutions should be warmed to body temperature with dry heat because wet heat carries a risk of microbial contamination.

Interactions

The effects of dialysis and filtration procedures on drug concentrations in the body can be complex. Because of the differences between the dialysis techniques, more drug may be removed by one technique than another. In general, drugs of low molecular weight, high water solubility, low volume of distribution, low protein binding, and high renal clearance are most extensively removed by dialysis. For example, aminoglycosides are extensively removed by dialysis procedures, and extra doses may be needed to replace losses, usually guided by serum-drug concentrations. Specific drug dosage adjustments for dialysis procedures may be employed where these are known. For drugs where the effect of dialysis is unknown, it is usual to give maintenance doses after dialysis. The ability of dialysis to remove some drugs has been used in the treatment of overdosage (see below).

Dialysis-induced changes in fluids and electrolytes have the potential to alter the effects of some drugs. For example, hypokalaemia predisposes to digoxin toxicity.

In patients undergoing peritoneal dialysis, drugs such as insulin and antibacterials may be added to the dialysis fluid. Consideration should be given to the possibility of adsorption of drugs onto the PVC bags.

References.
1. Aronson JK. The principles of prescribing in renal failure. *Prescribers' J* 1992; **32:** 220–31.
2. Bennett WM, *et al. Drug Prescribing in renal failure: dosing guidelines for adults.* 3rd ed. Philadelphia: American College of Physicians, 1994.
3. Cotterill S. Antimicrobial prescribing in patients on haemofiltration. *J Antimicrob Chemother* 1995; **36:** 773–80.

Uses and Administration

Dialysis and filtration procedures are used as part of renal replacement therapy in renal failure to correct electrolyte imbalance, correct fluid overload, and remove metabolites. They also have a limited role in the treatment of overdosage and poisoning. There are a number of techniques, and the choice between them will depend in part on the condition to be treated, the clinical state of the patient, patient preference, and availability. The two main techniques are haemodialysis and peritoneal dialysis, and a third less frequently used technique is haemofiltration.

Haemodialysis is more efficient than peritoneal dialysis at clearing small molecules such as urea, whereas peritoneal dialysis may be better at clearing larger molecules. Haemodialysis is considered to be less physiological than peritoneal dialysis as it involves periods of high clearance spaced between periods of no clearance.

Haemodialysis is usually performed intermittently, often 3 times a week, a typical session taking 3 to 5 hours. More recently high-flux dialysers have been developed which have reduced the time required for dialysis sessions. Haemodialysis is usually carried out in a dialysis centre, and less commonly at home.

Peritoneal dialysis may be performed continuously or intermittently. Continuous ambulatory peritoneal dialysis (CAPD) is the most commonly used technique. Patients remain mobile, except during ex-

changes, and can carry out the procedure themselves. There is always dialysis solution in the peritoneal cavity, and this is drained and replaced 3 to 5 times a day. Continuous cycle peritoneal dialysis (CCPD) is similar, except that exchanges are carried out automatically overnight, and patients do not have to carry out any exchanges during the day. Intermittent peritoneal dialysis (IPD) requires the patient to be connected to a dialysis machine for 12 to 24 hours 2 to 4 times a week. During this time, dialysis solution is pumped into and out of the peritoneal cavity, with a dwell time of about 10 to 20 minutes.

Haemofiltration is usually performed as a continuous technique and, as it is not portable, its principal use is in intensive care units. It may also be used intermittently as an adjunct to haemodialysis in patients with excess fluid weight gain. Continuous arteriovenous or venovenous haemodiafiltration (CAVHD or CVVHD) combines dialysis and filtration by perfusing the filtrate side of the haemofiltration membrane with peritoneal dialysis fluid.

Assessing serum concentrations of urea or creatinine before the next dialysis session is not a good measure of the adequacy of the dialysis, therefore various other measures have been developed including the urea reduction ratio and urea kinetic modelling. The use of such measures is more established for haemodialysis than for peritoneal dialysis.

Acute renal failure. Acute renal failure is characterised by a rapid decline in kidney function, and has a variety of causes.[1-3] It is often classified by origin as *prerenal* (e.g. due to hypovolaemia such as that associated with shock, burns, or dehydration; congestive heart failure; or renal artery obstruction), *renal* (such as acute tubular necrosis or interstitial nephritis of various causes, including nephrotoxic drugs and infections), or *postrenal* (acute urinary tract obstruction). The prognosis depends on the underlying disease, which should be identified and treated if possible, but the mortality may still be as high as 60%, particularly in patients who become oliguric, and after surgery or trauma. Management is essentially supportive in the hope that renal function will recover. Complications of acute renal failure include extracellular volume overload and hyponatraemia, hyperkalaemia, metabolic acidosis, hyperphosphataemia and hypocalcaemia. Those complications requiring urgent treatment, often including the use of dialysis, are severe hyperkalaemia (p.1149), pulmonary oedema, pericarditis, and severe metabolic acidosis (p.1147). The use of dialysis before clinical signs of uraemia is a matter of debate since it does not appear to hasten recovery *per se*,[1] but all save the shortest episodes of acute renal failure will require some form of renal replacement therapy with dialysis or filtration. Intermittent haemodialysis and peritoneal dialysis are both used, but the newer haemofiltration techniques have theoretical advantages in terms of volume control and cardiovascular stability, and are increasingly preferred.[2,4,5]

Numerous drugs have been tried in attempts to attenuate renal injury or hasten recovery in patients with acute tubular necrosis due to ischaemia or nephrotoxins.[1] These include drugs to increase renal blood flow (e.g. low-dose dopamine, atrial natriuretic peptide, or prostaglandins), drugs to increase urine flow and protect the epithelial cells (mannitol and loop diuretics, calcium channel blockers), or the use of chelating agents or antidotes against specific nephrotoxins. Consistent clinical benefit has not, however, been demonstrated.

Acute renal failure is reversible in about 95% of patients who survive the complications. A few patients who survive acute renal failure will require long-term dialysis or renal transplantation (p.499).

1. Brady HR, Singer GG. Acute renal failure. *Lancet* 1995; **346:** 1533–40.
2. Morgan AG. The management of acute renal failure. *Br J Hosp Med* 1996; **55:** 167–70.
3. Evans JHC. Acute renal failure in children. *Br J Hosp Med* 1994; **52:** 159–61.
4. McCarthy JT. Renal replacement therapy in acute renal failure. *Curr Opin Nephrol Hypertens* 1996; **5:** 480–4.
5. Joy MS, *et al.* A primer on continuous renal replacement therapy for critically ill patients. *Ann Pharmacother* 1998; **32:** 362–75.

Chronic renal failure. Chronic renal failure is the irreversible, usually progressive, loss of renal function that eventually results in end-stage renal disease (ESRD) and the need for renal replacement therapy (dialysis or renal transplantation). The rate of decline in renal function is generally constant for each patient and is usually monitored by measuring serum-creatinine concentrations as an indirect index of the glomerular filtration rate (GFR). In its early stages when the patient is asymptomatic, progressive loss of renal function is described as diminished renal reserve or chronic renal insufficiency. When the limits of renal reserve have been exceeded and symptoms become apparent, it is termed chronic renal failure or overt renal failure. When renal function is diminished to such an extent that life is no longer sustainable (GFR less than 5 mL per minute), the condition is termed ESRD or uraemia. Many diseases can lead to ESRD, the most common being diabetes (p.315), glomerulonephritis (p.1021), and hypertension (p.788).

The management of patients with chronic renal failure prior to ESRD involves measures to conserve renal function and compensate for renal insufficiency. Methods to slow the progression of renal failure include the treatment of hypertension, reduction of proteinuria with dietary protein restriction (p.1331) or in some cases ACE inhibitors (p.809), or both, and the reduction of hyperlipidaemia (p.1265). Anaemia (p.719) and renal osteodystrophy (p.732) often require active treatment. Nephrotoxic drugs, including NSAIDs, should be avoided.

The choice between haemodialysis, peritoneal dialysis, and organ transplantation is considered, and the patient prepared, before it is actually required. In patients for whom transplantation is the preferred option, dialysis may still be required while waiting for a kidney. Kidney transplantation is discussed on p.499. There are differences between countries in the choice of dialysis technique for patients with ESRD. For example, in-centre haemodialysis is used in about 80% of patients in the USA, whereas CAPD is used in over 50% of patients in the UK. Overall survival appears to be similar between the 2 techniques, but more patients on CAPD will eventually require haemodialysis.

Unlike renal transplant patients, dialysis patients still require replacement therapy with hormones that are usually produced by the kidney. Thus, recombinant erythropoietin (p.718) and hydroxylated vitamin D analogues (p.1368) are commonly administered.

References.

1. Klahr S. Chronic renal failure: management. *Lancet* 1991; **338:** 423–7.
2. NIH. Morbidity and mortality of dialysis. *NIH Consens Statement* 1993; **11:** 1–33.
3. The Renal Association. *Treatment of adult patients with renal failure: recommended standards and audit measures*. London: Royal College of Physicians of London, 1995.
4. Steinman TI. Kidney protection: how to prevent or delay chronic renal failure. *Geriatrics* 1996; **51:** 28–35.
5. Friedman AL. Etiology, pathophysiology, diagnosis, and management of chronic renal failure in children. *Curr Opin Pediatr* 1996; **8:** 148–51.
6. Gokal R, Mallick N. Continuous ambulatory peritoneal dialysis. *Prescribers' J* 1992; **32:** 251–6.
7. Walker R. General management of end stage renal disease. *Br Med J* 1997; **315:** 1429–32.

Electrolyte disturbances. Haemodialysis with magnesium-free dialysis solution has been used to remove magnesium from the body in severe hypermagnesaemia (p.1148). Similarly, haemodialysis, and sometimes peritoneal dialysis, has been used in treating hypercalcaemia (p.1148), hyperkalaemia (p.1149), hypernatraemia (p.1150), and hyperphosphataemia (p.1149).

Overdosage and poisoning. Haemodialysis, or less often peritoneal dialysis, can be used to remove some substances from the body after overdosage or poisoning. Substances most readily removed have a low molecular weight, low volume of distribution, low protein binding, high water solubility, and high renal clearance. Examples of agents for which haemodialysis may have a role in the treatment of severe overdosage include alcohol (p.1099), methyl alcohol (p.1379), lithium (p.292), and salicylates such as aspirin (p.16). Dialysis may be particularly important when poisoning with these agents is complicated by renal failure.

Preparations

Ph. Eur.: Solutions for Haemodialysis; Solutions for Haemofiltration; Solutions for Peritoneal Dialysis.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Aust.:*** Acetat-Haemodialyse; Dianeal; HAMFL; Hamofiltrasol; Peritofundin; ***Austral.:*** Dianeal; ***Fr.:*** Dialysol Acide; Dialysol Bicarbonate; Dialytan H; DPCA 2; ***Ital.:*** Nutrineal PD2; ***Spain:*** CAPD; Dialisol; Dianeal; DPCA†; Nutrineal PD4; Sol Dial Perit†; ***Swed.:*** Altracart II; BiCart; Bicbag; Biorenal; Biosol A; Biosol B; Dianeal; Diasol†; Dicalys 11; Duolys A; Duolys B; Extraneal; Gambrolys; Gambrosol; Haemovex; Hemofiltrasol; Hemofiltrationslosning 401; Lockolys; Nutrineal PD4; Peritolys med glukos†; Schiwalys Hemofiltration; Spectralys Hemofiltration 05, 23†; Spectralys Hemofiltration 19, 20†; Sterilys B 84†; ***Switz.:*** Clear-Flex Formula; Dianeal; DPCA; Gambrosol; HF; Nutrineal PD4; ***UK:*** Dialaflex Solutions†; Diambulate Solutions†; Dianeal; Difusor†; Nutrineal PD4; ***USA:*** Dialyte; Dianeal†; Inpersol†.

Oral Rehydration Solutions (3277-r)

Oral rehydration solutions have 4 main constituents:

- electrolytes—typically sodium chloride and potassium chloride
- a bicarbonate source to correct or prevent metabolic acidosis, such as sodium bicarbonate or sodium citrate
- water to replace fluid losses
- a carbohydrate source to maximise absorption of fluid and electrolytes—typically glucose, although cereal-based formulations have also been tried.

They are most commonly available as oral powders (oral rehydration salts) that are reconstituted with water before use, but effervescent tablets and ready-to-use oral solutions are also available.

The composition of oral rehydration solutions varies, particularly in sodium content. For example, in the UK the sodium content of oral rehydration solutions ranges from 50 to 60 mmol per litre, whereas the WHO formulation contains 90 mmol of sodium per litre. High sodium concentrations may be particularly appropriate for secretory diarrhoeas such as cholera. For discussion of modified formulations of oral rehydration solutions in the treatment of diarrhoea, including the use of cereal-based and low osmolarity preparations, see oral rehydration therapy under Diarrhoea on p.1168.

Adverse Effects

Vomiting can occur after administration of oral rehydration solution, and may be an indication that it was administered too quickly. If vomiting occurs, administration should be halted for 10 minutes then resumed in smaller, more frequent, amounts.

The risk of hypernatraemia or overhydration after administration of oral rehydration solutions is low in patients with normal renal function. Overdosage of oral rehydration solutions in patients with renal impairment may lead to hypernatraemia and hyperkalaemia.

Precautions

Oral rehydration salts or effervescent tablets should be reconstituted only with water and at the volume stated. Fresh drinking water is generally appropriate, but freshly boiled and cooled water is preferred when the solution is for infants or when drinking water is not available. The solution should not be boiled after it is prepared. Other ingredients such as sugar should not be added. Unused solution should be stored in a refrigerator and discarded 24 hours after preparation.

Oral rehydration solutions are not appropriate for patients with gastro-intestinal obstruction, oliguric or anuric renal failure, or when parenteral rehydration therapy is indicated as in severe dehydration or intractable vomiting.

Uses and Administration

Oral rehydration solutions are used for oral replacement of electrolytes and fluids in patients with dehydration, particularly that associated with acute diarrhoea of various aetiologies (p.1168).

The dosage of oral rehydration solutions should be tailored to the individual based on body-weight and the stage and severity of the condition. The initial aim of treatment is to rehydrate the patient, and, subsequently, to maintain hydration by replacing any further losses due to continuing diarrhoea and vomiting and normal losses from respiration, sweating, and urination.

For adults, 200 to 400 mL of oral rehydration solution for every loose motion has been suggested. The dosage for children is 200 mL for every loose motion, and for infants is 1 to 1.5 times their usual feed

volume. Normal feeding can continue after the initial fluid deficit has been corrected. Breast feeding should continue between administrations of oral rehydration solution.

Preparations

BP 1998: Oral Rehydration Salts;
USP 23: Oral Rehydration Salts;
WHO/UNICEF: Oral Rehydration Salts.

Proprietary Preparations (details are given in Part 3)

Aust.: Elodrink†; Elotrans; Eloverlan†; Milupa GES; Normhydral†; Normolyt; Oralpadon; *Austral.:* Gastrolyte; Gastrolyte-R; Repalyte; *Canad.:* Gastrolyte; Lytren; Lytren RHS; Pedialyte; Rehydralyte; *Fr.:* Adiaril; Alhydrate; Caril; Carogil; Gallialite†; GES 45; Lytren; *Ger.:* D-Iso; Elotrans; Isolyt; Oralpadon; Saltadol; Santalyt; *Irl.:* Dioralyte; Electrolade†; Elotrans†; Rapolyte; Rehidrat; *Ital.:* Alhydrate; Amidral†; Dicodral; Medidral†; Milupa GES; Pedialyte; Reidrax; Sodioral; Soluzione Darrow; *Neth.:* Dioralyte; *Norw.:* Gem; *S.Afr.:* Darrow-Liq; Darrowped; Electrona; Electropak; Enterolyte; Hemapep†; Hydrol; Kaostatex; Medipect†; Pectolin†; Pectrolyte; Rehidrat; Resalt; Scriptolyte; *Spain:* Bebesales; Didrica; Huberlitren; Oral Rehidr Sal Farmasur; Oralesper; Reemplazante Intesti; Sueroral; Sueroral Hiposodico; *Switz.:* Elotrans; GES 45; Normolytoral; Oralpadon; Servidrat†; *UK:* Diocalm Replenish; Dioralyte; Dioralyte Relief; Dycol†; Electrolade; Gluco-lyte†; Rapolyte†; Rehidrat; *USA:* Infalyte; Kao Lectrolyte; Naturalyte; Pedialyte; Rehydralyte; Resol.

Bicarbonate (3269-r)

Bicarbonate is an alkalinising agent administered as bicarbonate-containing salts (sodium or potassium bicarbonate) or bicarbonate-producing salts (acetate, citrate, or lactate salts). Allowance should be made for the effect of the cation. Bicarbonate-producing or bicarbonate-containing solutions have been reported to be **incompatible** with a wide range of drugs. In many cases this incompatibility is a function of the alkaline nature of the bicarbonate solution. Precipitation of insoluble carbonates may occur as may production of gaseous carbon dioxide when the bicarbonate ion is reduced by acidic solutions.

Potassium Bicarbonate (1178-h)

501; Kalii Hydrogenocarbonas; Monopotassium Carbonate; Potassium Hydrogen Carbonate.

$KHCO_3$ = 100.1.

CAS — 298-14-6.

Pharmacopoeias. In *Eur.* (see p.viii), *Pol.*, and *US.*

Colourless, odourless, transparent prisms or white granular powder. Each g of potassium bicarbonate represents approximately 10 mmol of potassium and of bicarbonate. Potassium bicarbonate 2.56 g is approximately equivalent to 1 g of potassium.

Freely **soluble** in water; practically insoluble in alcohol. It is gradually converted to potassium carbonate on heating. The pH of a 5% solution in water is not more than 8.6.

Potassium Citrate (1180-t)

E332; Kalii Citras; Tripotassium Citrate. Tripotassium 2-hydroxypropane-1,2,3-tricarboxylate monohydrate.

$C_6H_5K_3O_7.H_2O$ = 324.4.

CAS — 866-84-2 (anhydrous potassium citrate); 6100-05-6 (potassium citrate monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, and *US.*

Transparent, odourless, hygroscopic crystals or a white granular powder. It is deliquescent in moist air.

Each g of potassium citrate (anhydrous) represents approximately 9.8 mmol of potassium and 3.26 mmol of citrate. Each g of potassium citrate (monohydrate) represents approximately 9.3 mmol of potassium and 3.08 mmol of citrate. Potassium citrate (monohydrate) 2.77 g is approximately equivalent to 1 g of potassium.

Soluble 1 in 1 of water and 1 in 2.5 of glycerol; practically insoluble in alcohol. **Store** in airtight containers.

Sodium Acetate (1189-v)

262; Natrii Acetas; Natrium Aceticum.

$CH_3.CO_2Na.3H_2O$ = 136.1.

CAS — 127-09-3 (anhydrous sodium acetate); 6131-90-4 (sodium acetate trihydrate).

Pharmacopoeias. In *Eur.* (see p.viii), *Jpn*, *Pol.*, and *US.*

US also allows the anhydrous form.

Colourless transparent crystals or a white granular crystalline powder or white flakes, odourless or with a slight odour of acetic acid. It effloresces in warm dry air.

Each g of sodium acetate (anhydrous) represents approximately 12.2 mmol of sodium and of acetate. Each g of sodium acetate (trihydrate) represents approximately 7.3 mmol of sodium and of acetate. Sodium acetate (anhydrous) 3.57g is approximately equivalent to 1g of sodium. Sodium acetate (trihydrate) 5.92g is approximately equivalent to 1 g of sodium.

Soluble 1 in 0.8 of water, 1 in 0.6 of boiling water, and 1 in 19 of alcohol. A 5% solution in water has a pH of 7.5 to 9.0. **Store** in airtight containers.

Sodium Acid Citrate (1192-d)

Disodium Hydrogen Citrate; E331; Natrium Citricum Acidum.

$C_6H_6Na_2O_7.1\frac{1}{2}H_2O$ = 263.1.

CAS — 144-33-2.

Pharmacopoeias. In *Br.*

A white odourless or almost odourless powder. Each g of sodium acid citrate (sesquihydrate) represents approximately 7.6 mmol of sodium and 3.8 mmol of citrate. Sodium acid citrate (sesquihydrate) 5.72g is approximately equivalent to 1 g of sodium.

Freely **soluble** in water; practically insoluble in alcohol. A 3% solution in water has a pH of 4.9 to 5.2.

Sodium Bicarbonate (1190-r)

500; Baking Soda; Monosodium Carbonate; Natrii Bicarbonas; Natrii Hydrogenocarbonas; Sal de Vichy; Sodium Acid Carbonate; Sodium Hydrogen Carbonate.

$NaHCO_3$ = 84.01.

CAS — 144-55-8.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, *Jpn*, *Pol.*, and *US.*

A white crystalline powder. Each g of sodium bicarbonate (anhydrous) represents approximately 11.9 mmol of sodium and of bicarbonate. Sodium bicarbonate 3.65 g is approximately equivalent to 1 g of sodium. When heated or in moist air it decomposes, and is converted progressively into sodium carbonate.

Soluble 1 in 12 of water; practically insoluble in alcohol. A solution in water is alkaline to litmus; alkalinity increases on standing, agitation, or heating.

Sodium Citrate (1193-n)

E331; Natrii Citras; Trisodium Citrate. Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate.

$C_6H_5Na_3O_7.2H_2O$ = 294.1.

CAS — 68-04-2 (anhydrous sodium citrate); 6132-04-3 (sodium citrate dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, *Jpn*, and *Pol. Int.* and *US* specify anhydrous or dihydrate.

White granular crystals or crystalline powder; slightly deliquescent in moist air.

Each g of sodium citrate (anhydrous) represents approximately 11.6 mmol of sodium and 3.9 mmol of citrate. Each g of sodium citrate (dihydrate) represents approximately 10.2 mmol of sodium and 3.4 mmol of citrate. Sodium citrate (anhydrous) 3.74g is approximately equivalent to 1g of sodium. Sodium citrate (dihydrate) 4.26g is approximately equivalent to 1g of sodium.

Soluble 1 in 1.5 of water and 1 in 0.6 of boiling water; practically insoluble in alcohol. Sterilised solutions when stored may cause separation of particles from glass containers and solutions containing such particles must not be used. **Store** in airtight containers.

Sodium Lactate (1194-h)

E325. Sodium 2-hydroxypropionate.

$C_3H_5NaO_3$ = 112.1.

CAS — 72-17-3.

Pharmacopoeias. Chin., *Eur.* (see p.viii), and *US* include preparations of sodium lactate.

Each g of sodium lactate (anhydrous) represents approximately 8.9 mmol of sodium and of lactate. Sodium lactate (anhydrous) 4.88 g is approximately equivalent to 1 g of sodium.

Sodium Lactate Solution (Ph. Eur.) is a clear, colourless, slightly syrupy liquid; **miscible** with water and with alcohol. It has a pH of 6.5 to 9.0. Sodium Lactate Solution (USP) is a similar preparation, with a pH between 5.0 and 9.0. It should be **stored** in airtight containers.

Adverse Effects and Treatment

Excessive administration of bicarbonate or other compounds that are metabolised to form the bicarbonate anion may lead to hypokalaemia and metabolic alkalosis, especially in patients with impaired renal function. Symptoms may include mood changes, tiredness, shortness of breath, muscle weakness, and irregular heartbeat. Muscle hypertonicity, twitching, and tetany may develop especially in hypocalcaemic patients. Treatment of metabolic alkalosis associated with bicarbonate overdose consists mainly of appropriate correction of fluid and electrolyte balance. Replacement of calcium, chloride, and potassium ions may be of particular importance.

Excessive doses of *sodium salts* may also lead to sodium overloading and hyperosmolality (p.1162). Administration of sodium bicarbonate by mouth can cause stomach cramps, belching, and flatulence. Extravasation of irritant hypertonic sodium bicarbonate solutions resulting in tissue necrosis at the injection site has been reported following intravenous administration.

Excessive doses of *potassium salts* may lead to hyperkalaemia (p.1161). Oral administration of potassium salts can cause gastro-intestinal adverse effects, and tablet formulations may cause contact irritation due to high local concentrations of potassium.

Excessive oral administration of *citrate salts* may have a laxative effect.

Effects on the gastro-intestinal tract. In addition to minor gastro-intestinal effects (see above), spontaneous rupture of the stomach, although an exceedingly rare event, has been reported on several occasions following ingestion of sodium bicarbonate. The bicarbonate was believed to have resulted in the rapid production of enough carbon dioxide to rupture a stomach already distended with food.[1]

1. Mastrangelo MR, Moore EW. Spontaneous rupture of the stomach in a healthy adult man after sodium bicarbonate ingestion. *Ann Intern Med* 1984; **101:** 649.

Effects on mental state. Lactate infusions have been reported to induce feelings of anxiety, especially in patients with anxiety states, and have been used as a pharmacological model in the evaluation of mechanisms involved in clinical anxiety.[1] There has also been a report[2] of a patient receiving oral lactate (as calcium lactate) who was suffering from panic disorder associated with agoraphobia; when lactate was discontinued, the patient reported a reduction in panic intensity without a decrease in the frequency of attacks.

1. Lader M, Bruce M. States of anxiety and their induction by drugs. *Br J Clin Pharmacol* 1986; **22:** 251–61.
2. Robinson D, *et al.*. Possible oral lactate exacerbation of panic disorder. *Ann Pharmacother* 1995; **29:** 539–40.

Epileptogenic effect. Alkalosis may precipitate seizures; however, absence seizures have also been reported to be associated with sodium bicarbonate administration in a child in whom the serum pH was normal.[1]

1. Reif S, *et al.*. Absence seizures associated with bicarbonate therapy and normal serum pH. *JAMA* 1989; **262:** 1328–9.

Precautions

It is generally recommended that bicarbonate, or agents that form the bicarbonate anion after metabolism, should not be administered to patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria. During treatment of acidosis, frequent monitoring of serum-electrolyte concentrations and acid-base status is essential.

Sodium-containing salts should be administered extremely cautiously to patients with heart failure, oedema, renal impairment, hypertension, eclampsia, or aldosteronism (see Sodium, p.1162).

Potassium-containing salts should be administered with considerable care to patients with renal or adrenocortical insufficiency, cardiac disease, or other conditions that may predispose to hyperkalaemia (see Potassium, p.1161).

Abuse. High doses of bicarbonate have been taken by athletes to enhance performance in endurance sports by buffering hydrogen ions produced in conjunction with lactic acid.[1] Bicarbonates have also been used to alkalinise the urine and prolong the half-life of basic drugs, notably sympathomimetics and stimulants, thereby avoiding detection; however, such a practice may enhance toxicity.

1. Kennedy M. Drugs and athletes—an update. *Adverse Drug React Bull* 1994; (Dec): 639–42.

Interactions

Alkalinisation of the urine by bicarbonate or bicarbonate precursors leads to increased renal clearance of acidic drugs such as salicylates and barbiturates. Conversely, urinary alkalinisation prolongs the half-life of basic drugs and may result in toxicity (see also under Abuse, above).

The concomitant use of *potassium-containing salts* with drugs that increase serum-potassium concen-

trations such as ACE inhibitors and potassium-sparing diuretics should generally be avoided (p.1161). *Citrate salts* taken by mouth can enhance the absorption of aluminium from the gastro-intestinal tract (see p.1177 under Aluminium Hydroxide). Patients with impaired renal function are particularly susceptible to aluminium accumulation and citrate-containing oral preparations, including many effervescent or dispersible tablets, are best avoided by patients with renal failure taking aluminium-containing compounds.

Pharmacokinetics

Administration of bicarbonate, such as sodium bicarbonate, by mouth causes neutralisation of gastric acid with the production of carbon dioxide. Bicarbonate not involved in that reaction is absorbed and in the absence of a deficit of bicarbonate in the plasma, bicarbonate ions are excreted in the urine, which is rendered alkaline, and there is an accompanying diuresis.

Acetates such as potassium acetate and sodium acetate, citrates such as potassium citrate, sodium acid citrate, and sodium citrate, and lactates such as sodium lactate are metabolised, after absorption, to bicarbonate.

Uses and Administration

Bicarbonate-providing salts are alkalinising agents used for a variety of purposes including the correction of metabolic acidosis, alkalinisation of the urine, and use as antacids.

When an alkalinising agent is indicated for treating acute or chronic **metabolic acidosis** (p.1147), the usual agent used is sodium bicarbonate. In conditions when acute metabolic acidosis is associated with tissue hypoxia, such as *cardiac arrest* and *lactic acidosis*, the role of alkalinising agents such as sodium bicarbonate is controversial (see p.1147, and for guidelines on advanced cardiac life support, p.779). Sodium lactate has been given as an alternative to sodium bicarbonate in acute metabolic acidosis, but is no longer recommended because of the risk of precipitating lactic acidosis. In *chronic hyperchloraemic acidosis* associated with potassium deficiency, potassium bicarbonate may be preferred to sodium bicarbonate. The citrate salts of potassium or sodium have also been used as alternatives to sodium bicarbonate in treating chronic metabolic acidosis resulting from *renal disorders*. Sodium bicarbonate, lactate and acetate, and potassium acetate are used as bicarbonate sources in *dialysis fluids* (p.1151).

The dose of bicarbonate required for the treatment of acidotic states must be calculated on an individual basis, and is dependent on the acid-base balance and electrolyte status of the patient. In the treatment of moderate acidosis bicarbonate has been given by mouth and doses providing 57 mmol (4.8 g sodium bicarbonate) or more daily may be required. In acute acidosis, sodium bicarbonate has been given intravenously by continuous infusion usually with a 1.26% (150 mmol per litre) solution or by slow intravenous injection of a stronger (hypertonic) solution of up to 8.4% (1000 mmol per litre) sodium bicarbonate (but see the discussion on metabolic acidosis, p.1147). For the correction of acidosis during advanced cardiac life support procedures, doses of 50 mmol of sodium bicarbonate (50 mL of an 8.4% solution) may be given intravenously to adults. Frequent monitoring of serum-electrolyte concentrations and acid-base status is essential during treatment of acidosis.

Sodium bicarbonate may be employed in the management of **hyperkalaemia** (p.1149) to promote the intracellular uptake of potassium and correct associated acidosis.

Sodium bicarbonate, sodium citrate, and potassium citrate cause **alkalinisation of the urine**. They may therefore be given to relieve discomfort in mild *urinary-tract infections* (p.149) and to prevent the development of uric acid renal calculi in the initial stages of *uricosuric* therapy for hyperuricaemia in chronic gout (for example, see Probenecid, p.394). In both cases, they are administered with a liberal fluid intake, usually by mouth, in divided doses of up to about 10 g daily. Sodium bicarbonate has also been used with a diuretic in the treatment of *acute poisoning* from weakly acidic drugs such as phenobarbitone and salicylates to enhance their excretion, but this process, which is known as 'forced alkaline diuresis', is generally no longer recommended.

When administered by mouth, sodium bicarbonate and potassium bicarbonate neutralise acid secretions in the gastro-intestinal tract and sodium bicarbonate in particular is therefore frequently included in **antacid** preparations (p.1167). To relieve *dyspepsia* doses of about 1 to 5 g of sodium bicarbonate in water have been taken when required. Sodium citrate has been widely employed as a 'clear' (non-particulate) antacid, usually with an H_2-receptor antagonist, for the *prophylaxis of acid aspiration* associated with anaesthesia (p.1168). Sodium bicarbonate is also used in various preparations for *double-contrast radiography* where production of gas (carbon dioxide) in the gastro-intestinal tract is necessary. Similarly, solutions containing sodium bicarbonate or citrate have been used to treat acute *oesophageal impaction* (p.1174).

Sodium bicarbonate and sodium or potassium citrate are used as buffering or alkalinising agents in *pharmaceutical formulation*. Sodium bicarbonate and anhydrous sodium citrate are used in effervescent tablet formulations.

Individual salts also have **other specific uses**. A 5% solution of sodium bicarbonate can be administered as ear drops to soften and remove *ear wax*. Sodium bicarbonate injection has been used to treat *extravasation of anthracycline antineoplastics* (p.474) although as mentioned in Adverse Effects, above, hypertonic solutions may themselves cause necrosis.

Sodium citrate has anti-clotting properties and is employed, as sodium acid citrate, with other agents in solutions for the anticoagulation and preservation of blood for *transfusion* purposes. Similarly, sodium citrate 3% irrigation may be useful for the dissolution of *blood clots in the bladder* as an alternative to sodium chloride 0.9%. Enemas containing sodium citrate are given rectally as *osmotic laxatives*. Sodium citrate is also a common ingredient in *cough* mixtures.

Eye disorders. Sodium citrate eye drops have been employed in the management of certain ocular injuries. It has been suggested that corneal epithelial defects due to chemical weapon injuries and lasting for more than one week or those accompanied by limbal ischaemia require intensive topical therapy with eye drops of sodium citrate 10% and of potassium ascorbate 10%. Such therapy is said to prevent late corneal melting and to permit the continuation of local corticosteroid therapy as necessary.[1] The two types of eye drops are given in alternate doses and are believed to act by mopping up free oxygen radicals after chemical burns.[2]

Sodium bicarbonate is also used in the management of blepharitis, an inflammation of the margin of the eyelids that may be caused by a variety of conditions. It may be allergic in nature or associated with seborrhoea of the scalp. Infection of the eyelids can produce ulcerative blepharitis, a condition characterised by the formation of yellow crusts which may glue the eyelashes together. Parasites occasionally cause blepharitis. The condition is first treated by cleaning the eyes and eyelids with sodium bicarbonate solution or a suitable bland eye lotion; simple eye ointment or diluted baby shampoo can also be used to soften crusts to aid removal. If an infection is present suitable antibiotic eye drops or ointment may be used once the crusts have been removed (p.122). Long-term management consists of daily cleansing of the lid margins with a bland eye lotion.

1. Wright P. Injuries due to chemical weapons. *Br Med J* 1991; **302:** 239.
2. Anonymous. Citrate/ascorbate eye-drops for chemical weapons injuries. *Pharm J* 1991; **246:** 145.

Osteoporosis. Potassium bicarbonate administered by mouth in a dose of 1 to 2 mmol per kg body-weight daily for 18 days in 18 postmenopausal women was found to improve calcium and phosphorus balance, reduce bone resorption and increase its formation.[1] However, elderly subjects with renal impairment might be at risk of hyperkalaemia with the doses used and long-term studies would be required before this emerged as an effective treatment or preventative strategy for postmenopausal osteoporosis (p.731).[2]

1. Sebastian A, *et al.* Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994; **330:** 1776–81.
2. Sebastian A, Morris RC. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994; **331:** 279.

Renal calculi. Citrate forms soluble complexes with calcium, thereby reducing urinary saturation of stone-forming calcium salts. Potassium citrate has a hypocalciuric effect when given by mouth, probably due to enhanced renal calcium absorption. Urinary calcium excretion is unaffected by sodium citrate, since the alkali-mediated hypocalciuric effect is offset by a sodium-linked calciuresis.[1] An uncontrolled study has demonstrated that potassium citrate may be beneficial in reducing the rate of stone formation in patients with hypocitraturia.[2] As mentioned in Uses above, sodium bicarbonate or sodium or potassium citrate may also be employed for their alkalinising action, as an adjunct to a liberal fluid intake, to prevent development of uric acid renal calculi during uricosuric therapy.

Other causes of renal calculi and their treatment are discussed on p.888.

Urinary alkalinisation with sodium bicarbonate, sodium citrate, or potassium citrate may be useful in the management of cystine stone formation in patients with cystinuria (p.991).

1. Anonymous. Citrate for calcium nephrolithiasis. *Lancet* 1986; **i:** 955.
2. Pak CYC, Fuller C. Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate. *Ann Intern Med* 1986; **104:** 33–7.

Preparations

BP 1998: Alkaline Gentian Mixture; Aromatic Magnesium Carbonate Mixture; Compound Magnesium Trisilicate Oral Powder; Compound Sodium Bicarbonate Tablets *(Soda Mint Tablets)*; Compound Sodium Chloride Mouthwash; Kaolin and Morphine Mixture; Kaolin Mixture; Magnesium Trisilicate Mixture; Potassium Citrate Mixture; Sodium Bicarbonate Ear Drops; Sodium Bicarbonate Eye Lotion; Sodium Bicarbonate Intravenous Infusion; Sodium Citrate Eye Drops; Sodium Citrate Irrigation Solution; Sodium Citrate Tablets; Sodium Lactate Intravenous Infusion;
BPC 1968: Effervescent Potassium Tablets;
Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USP 23: Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Anticoagulant Sodium Citrate Solution; Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension; Modified Lactated Ringer's and Dextrose Injection; Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride for Effervescent Oral Solution; Potassium Bicarbonate Effervescent Tablets for Oral Solution; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution; Potassium Citrate And Citric Acid Oral Solution; Potassium Citrate Extended-release Tablets; Potassium Gluconate and Potassium Citrate Oral Solution; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution; Sodium Acetate Injection; Sodium Acetate Solution; Sodium Bicarbonate Injection; Sodium Bicarbonate Oral Powder; Sodium Bicarbonate Tablets; Sodium Citrate and Citric Acid Oral Solution; Sodium Lactate Injection; Sodium Lactate Solution; Tricitrates Oral Solution; Trikates Oral Solution.

Proprietary Preparations (details are given in Part 3)

Aust.: Bullrich Salz; ***Austral.:*** Citralka†; Sodibic; ***Canad.:*** Brioschi; Eno; K-Lyte; Polycitra-K; ***Fr.:*** Soludial; ***Ger.:*** Alkala T; Kalitrans; Kohlensaurebad Bastian; Natron†; Nephrotrans; ***Irl.:*** Cystopurin; ***Ital.:*** Citrosodina; Kation; ***Norw.:*** Kajos; ***S.Afr.:*** Nitrocit; ***Spain:*** Acalka; Plurisalina; ***Swed.:*** Kajos; ***Switz.:*** Nephrotrans; ***UK:*** Cymalon; Cystemme; Cystitis Treatment†; Cystocalm; Cystoleve; Cystopurin; Urisal†; ***USA:*** Bell/ans; Citra pH; K-Lyte; Neut; Urocit-K.

Multi-ingredient: numerous preparations are listed in Part 3.

Calcium (1151-j)

Ca = 40.078.

Calcium is a cation administered as various calcium-containing salts. Calcium salts have been reported to be **incompatible** with a wide range of drugs. Complexes may form resulting in the formation of a precipitate.

Calcium Acetate (1152-z)

E263.

$C_4H_6CaO_4$ = 158.2.

CAS — 62-54-4.

Pharmacopoeias. In *Br.* and *US.*

A white, odourless or almost odourless, hygroscopic crystalline powder. Each g of calcium acetate (anhydrous) represents approximately 6.3 mmol of calcium. Calcium acetate (anhydrous) 3.95 g is approximately equivalent to 1 g of calcium.

Freely **soluble** in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in acetone and in dehydrated alcohol. The BP states that a 5% solution in water has a pH of 7.2 to 8.2 and the USP states that a 5% solution in water has a pH of 6.3 to 9.6. **Store** in airtight containers.

Calcium Chloride (1154-k)

509; Calcii Chloridum; Calcium Chloratum; Calcium Chloride Dihydrate; Cloreto de Cálcio; Cloruro de Calcio.

$CaCl_2.2H_2O$ = 147.0.

CAS — 10043-52-4 (anhydrous calcium chloride); 7774-34-7 (calcium chloride hexahydrate); 10035-04-8 (calcium chloride dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Jpn*, and *US.*

Eur. also specifies the hexahydrate. *Pol.* only specifies the hexahydrate.

The dihydrate occurs as a white, hygroscopic, odourless, crystalline powder or granules. Each g of calcium chloride (dihydrate) represents approximately 6.8 mmol of calcium and 13.6 mmol of chloride. Calcium chloride (dihydrate) 3.67 g is approximately equivalent to 1 g of calcium.

Ph. Eur. **solubilities** are: freely soluble in water; soluble in alcohol. USP solubilities are: soluble 1 in 0.7 of water, 1 in 0.2 of boiling water, 1 in 4 of alcohol, and 1 in 2 of boiling alcohol. A 5% solution in water has a pH of 4.5 to 9.2. **Store** in airtight containers.

The hexahydrate is a white crystalline mass or colourless crystals. It melts above about 29°. Very **soluble** in water; freely soluble in alcohol. Each g of calcium chloride (hexahydrate) represents approximately 4.56 mmol of calcium and 9.13 mmol of chloride. Calcium chloride (hexahydrate) 5.47 g is approximately equivalent to 1 g of calcium.

Calcium Citrate (3275-t)

Tricalcium Citrate. Tricalcium 2-hydroxypropane-1,2,3-tricarboxylate tetrahydrate.

$C_{12}H_{10}Ca_3O_{14}.4H_2O$ = 570.5.

CAS — 5785-44-4.

Pharmacopoeias. In *Aust.* and *US.*

A white, odourless, crystalline powder. Each g of calcium citrate (tetrahydrate) represents approximately 5.3 mmol of calcium and 3.5 mmol of citrate. Calcium citrate (tetrahydrate) 4.74 g is approximately equivalent to 1 g of calcium.

Slightly **soluble** in water; practically insoluble in alcohol; freely soluble in diluted 3N hydrochloric acid and in diluted 2N nitric acid.

Calcium Glubionate (1156-t)

Calcium Glubionate *(USAN, rINN).*

Calcium Gluconate Lactobionate Monohydrate; Calcium Gluconogalactogluconate Monohydrate. Calcium D-gluconate lactobionate monohydrate.

$(C_{12}H_{21}O_{12})_2C_6H_{11}O_7)Ca.H_2O$ = 610.5.

CAS — 31959-85-0 (anhydrous calcium glubionate); 12569-38-9 (calcium glubionate monohydrate).

Pharmacopoeias. US includes Calcium Glubionate Syrup.

Each g of calcium glubionate (monohydrate) represents approximately 1.6 mmol of calcium. Calcium glubionate (monohydrate) 15.2 g is approximately equivalent to 1 g of calcium.

Calcium Gluceptate (1157-x)

Calcium Glucoheptonate *(pINN).*

$C_{14}H_{26}CaO_{16}$ = 490.4.

CAS — 17140-60-2 (anhydrous calcium gluceptate); 29039-00-7 (anhydrous calcium gluceptate).

Pharmacopoeias. In *Fr.*, and *US* which allows anhydrous or with varying amounts of water of hydration.

Calcium gluceptate is the calcium salt of the alpha-epimer of glucoheptonic acid or is a mixture of the alpha- and beta-epimers. A white to faintly yellow amorphous powder. It is stable in air, but the hydrous forms may lose part of their water of hydration on standing. Each g of calcium gluceptate (anhydrous) represents approximately 2 mmol of calcium. Calcium gluceptate (anhydrous) 12.2 g is approximately equivalent to 1 g of calcium.

Freely **soluble** in water; practically insoluble in alcohol and in many other organic solvents. A 10% solution in water has a pH of 6 to 8.

Calcium Gluconate (1158-r)

578; Calcii Gluconas; Calcium Glyconate. Calcium D-gluconate monohydrate.

$C_{12}H_{22}CaO_{14}.H_2O$ = 448.4.

CAS — 299-28-5 (anhydrous calcium gluconate); 18016-24-5 (calcium gluconate monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, *Jpn*, and *Pol.* Also in *US* as the anhydrous or the monohydrate form.

Calcium borogluconate is included in *Aust.* and as an injection in *BP(Vet).*

A white, odourless, crystalline or granular powder. Each g of calcium gluconate (monohydrate) represents approximately 2.2 mmol of calcium. Calcium gluconate (monohydrate) 11.2 g is approximately equivalent to 1 g of calcium.

Soluble 1 in 30 of water and 1 in 5 of boiling water; practically insoluble in alcohol.

Calcium Glycerophosphate (1931-t)

Calcii Glycerophosphas; Calcium Glycerinophosphate.

$C_3H_7CaO_6P(+xH_2O)$ = 210.1.

CAS — 27214-00-2 (anhydrous calcium glycerophosphate).

Pharmacopoeias. In *Eur.* (see p.viii).

A white hygroscopic powder. Sparingly **soluble** in water; practically insoluble in alcohol. It loses not more than 12% of its weight on drying. Each g of calcium glycerophosphate (anhydrous) represents approximately 4.8 mmol of calcium. Calcium glycerophosphate (anhydrous) 5.24 g is approximately equivalent to 1 g of calcium.

Calcium Lactate (1160-z)

Calcii Lactas; E327. Calcium 2-hydroxypropionate.

$C_6H_{10}CaO_6.xH_2O$ = 218.2 (anhydrous); 308.3 (pentahydrate); 272.3 (trihydrate).

CAS — 814-80-2 (anhydrous calcium lactate); 41372-22-9 (hydrated calcium lactate); 5743-47-5 (calcium lactate pentahydrate); 63690-56-2 (calcium lactate pentahydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Jpn*, *Pol.*, and *US.*

Eur. has separate monographs for the pentahydrate and the trihydrate. *Port.* also includes the hexahydrate. *US* allows anhydrous or hydrous forms.

A white or almost white, practically odourless, crystalline or granular powder. Each g of calcium lactate (trihydrate) represents approximately 3.7 mmol of calcium. Each g of calcium lactate (pentahydrate) represents approximately 3.2 mmol of calcium. Calcium lactate (pentahydrate) 7.7 g and calcium lactate (trihydrate) 6.8 g are approximately equivalent to 1 g of calcium.

Soluble 1 in 20 of water; freely soluble in boiling water; very slightly soluble, or practically insoluble in alcohol. The pentahydrate effloresces on exposure to air and becomes anhydrous when heated at 120°. **Store** in airtight containers.

Calcium Lactate Gluconate (16157-q)

$Ca_5(C_3H_5O_3)_6.(C_6H_{11}O_7)_4.2H_2O$ = 1551.4.

Each g of calcium lactate gluconate (dihydrate) represents approximately 3.2 mmol of calcium. Calcium lactate gluconate (dihydrate) 7.74 g is approximately equivalent to 1 g of calcium.

Calcium Lactobionate (16158-p)

Calcium Lactobionate Dihydrate. Calcium 4-*O*-β-D-galactopyranosyl-D-gluconate dihydrate.

$C_{24}H_{42}CaO_{24}.2H_2O$ = 790.7.

CAS — 110638-68-1.

Pharmacopoeias. In *US.*

Each g of calcium lactobionate (dihydrate) represents approximately 1.3 mmol of calcium. Calcium lactobionate (dihydrate) 19.7 g is approximately equivalent to 1 g of calcium.

A 5% solution in water has a pH of 5.4 to 7.4.

Calcium Laevulinate (1161-c)

Calcii Levulinas; Calcium Laevulate; Calcium Levulinate; Lévulinate Calcique. Calcium 4-oxovalerate dihydrate.

$C_{10}H_{14}CaO_6.2H_2O$ = 306.3.

CAS — 591-64-0 (anhydrous calcium laevulinate); 5743-49-7 (calcium laevulinate dihydrate).

Pharmacopoeias. In *Eur.* (see p.viii) and *US.*

A white crystalline or amorphous powder with a faint odour suggestive of burnt sugar. Each g of calcium laevulinate (dihydrate) represents approximately 3.3 mmol of calcium. Calcium laevulinate (dihydrate) 7.64 g is approximately equivalent to 1 g of calcium.

Freely **soluble** in water; slightly soluble or very slightly soluble in alcohol; practically insoluble in chloroform and in ether. The USP states that a 10% solution in water has a pH of 7.0 to 8.5; Ph. Eur. requires a pH of 6.8 to 7.8.

Calcium Hydrogen Phosphate (1159-f)

Calcii et Hydrogenii Phosphas; Calcii Hydrogenophosphas; Calcium Hydrophosphoricum; Calcium Monohydrogen Phosphate; Dibasic Calcium Phosphate; Dicalcium Orthophosphate; Dicalcium Phosphate; E341. Calcium hydrogen orthophosphate dihydrate.

$CaHPO_4.2H_2O$ = 172.1.

CAS — 7757-93-9 (anhydrous calcium hydrogen phosphate); 7789-77-7 (calcium hydrogen phosphate dihydrate).

Pharmacopoeias. In *Eur.* (see p.viii), *Jpn*, *Pol.*, and *US*, which include specifications for the anhydrous substance, the dihydrate form, or both.

A white, odourless, crystalline powder. Each g of calcium hydrogen phosphate (dihydrate) represents approximately 5.8 mmol of calcium and of phosphate. Calcium hydrogen phosphate (dihydrate) 4.29 g is approximately equivalent to 1 g of calcium. Practically **insoluble** in cold water and in alcohol; dissolves in dilute hydrochloric and nitric acids.

Calcium Phosphate (1162-k)

Calcium Orthophosphate; Fosfato Tricalcico; Phosphate Tertiaire de Calcium; Precipitated Calcium Phosphate; Tribasic Calcium Phosphate; Tricalcii Phosphas; Tricalcium Phosphate.

CAS — 7758-87-4 ($Ca_3(PO_4)_2$); 12167-74-7 ($Ca_5(OH)(PO_4)_3$).

Pharmacopoeias. In *Eur.* (see p.viii) and *Pol.* Also in *USNF.*

A white or almost white, odourless, amorphous powder. Calcium phosphate is not a clearly defined chemical entity but is a mixture of calcium phosphates that has been most frequently described as tricalcium diorthophosphate, $Ca_3(PO_4)_2$ (=310.2), or calcium hydroxide phosphate, $Ca_5(OH)(PO_4)_3$ (=502.3). Ph. Eur. specifies that it consists of a mixture of calcium phosphates and contains 35 to 40% of Ca. The USNF specifies that it consists of a variable mixture of calcium phosphates having the approximate composition $10CaO.3P_2O_5.H_2O$ (=1004.6) and contains 34 to 40% of Ca.

Practically **insoluble** in water and in alcohol. It dissolves in dilute mineral acids.

Calcium Pidolate (12511-d)

Calcium Pidolate *(pINNM).*

Calcium Pyroglutamate. Calcium 5-oxopyrrolidine-2-carboxylate.

$Ca(C_5H_6NO_3)_2$ = 296.3.

CAS — 31377-05-6.

Each g of calcium pidolate (anhydrous) represents approximately 3.4 mmol of calcium. Calcium pidolate (anhydrous) 7.39 g is approximately equivalent to 1 g of calcium.

Calcium Sodium Lactate (1164-t)

$2C_3H_5NaO_3.(C_3H_5O_3)_2Ca.4H_2O$ = 514.4.

Pharmacopoeias. In *Br.*

A white deliquescent powder or granules with a slight characteristic odour. Each g of calcium sodium lactate (tetrahydrate) represents approximately 1.9 mmol of calcium and 3.9 mmol of sodium and of lactate. Calcium sodium lactate (tetrahydrate) 12.8 g is approximately equivalent to 1 g of calcium.

Soluble in water and in boiling alcohol; practically insoluble in ether.

Adverse Effects and Treatment

Administration of some calcium salts by mouth can cause gastro-intestinal irritation; calcium chloride is generally considered to be the most irritant of the commonly used calcium salts.

Injection of calcium salts can also produce irritation and in particular intramuscular or subcutaneous injection can cause local reactions including sloughing or necrosis of the skin; solutions of calcium chloride are extremely irritant and should not be injected intramuscularly or subcutaneously. Soft-tissue calcification has also followed the use of calcium salts parenterally.

Excessive amounts of calcium salts may lead to hypercalcaemia. This complication is usually associated with the parenteral route of administration, but can occur after oral administration, usually in pa-

tients with renal failure or who are taking vitamin D concurrently. Symptoms of hypercalcaemia may include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, mental disturbances, polydipsia, polyuria, nephrocalcinosis, renal calculi, and, in severe cases, cardiac arrhythmias and coma. Too rapid intravenous injection of calcium salts may also lead to many of the symptoms of hypercalcaemia as well as a chalky taste, hot flushes, and peripheral vasodilatation. Mild asymptomatic hypercalcaemia will usually resolve on stopping administration of calcium and other contributory drugs such as vitamin D (see also Vitamin D-mediated Hypercalcaemia, p.1148). If hypercalcaemia is severe, urgent treatment is required as outlined on p.1148.

Precautions

Solutions of calcium salts, particularly calcium chloride, are irritant, and care should be taken to prevent extravasation during intravenous injection. Calcium salts should be given cautiously to patients with impaired renal function, or diseases associated with elevated vitamin D concentrations such as sarcoidosis. In addition, they should generally be avoided in patients with calcium renal calculi, or a history of renal calculi. Calcium chloride, because of its acidifying nature, is unsuitable for the treatment of hypocalcaemia caused by renal insufficiency or in patients with respiratory acidosis or failure.

Plasma-calcium concentrations should be monitored closely in patients with renal insufficiency and during parenteral administration and if large doses of vitamin D are used concurrently.

Interactions

Hypercalcaemia has occurred when calcium salts are coadministered with thiazide diuretics or vitamin D. Vitamin D increases the gastro-intestinal absorption of calcium and thiazide diuretics decrease its urinary excretion. Plasma-calcium concentrations should be monitored in patients receiving the drugs concurrently.

Bran decreases the gastro-intestinal absorption of calcium, and may therefore decrease the efficacy of calcium supplements.

Calcium enhances the effects of digitalis glycosides on the heart and may precipitate digitalis intoxication; parenteral calcium therapy is best avoided in patients receiving cardiac glycosides. Citrate salts increase the absorption of aluminium from the gastro-intestinal tract (p.1177), therefore patients with renal failure taking aluminium phosphate should avoid taking calcium citrate. Calcium salts reduce the absorption of a number of other drugs such as bisphosphonates, fluoride, some fluoroquinolones, and tetracyclines; administration should be separated by at least 3 hours.

Pharmacokinetics

Calcium is absorbed predominantly from the small intestine by active transport and passive diffusion. About one-third of ingested calcium is absorbed although this can vary depending upon dietary factors and the state of the small intestine; also absorption is increased in calcium deficiency and during periods of high physiological requirement such as during childhood or pregnancy and lactation. 1,25-Dihydroxycholecalciferol (calcitriol), a metabolite of vitamin D, enhances the active phase of absorption.

Excess calcium is predominantly excreted renally. Unabsorbed calcium is eliminated in the faeces, together with that secreted in the bile and pancreatic juice. Minor amounts are lost in the sweat, skin, hair, and nails. Calcium crosses the placenta and is distributed into breast milk.

Human Requirements

Calcium is the most abundant mineral in the body and is an essential body electrolyte. However, defining individual calcium requirements has proved difficult and guidelines vary widely by country and culture. Some authorities have adopted a factorial approach. For example, in the UK the dietary reference value (DRV) represents the apparent calcium requirements of healthy people under the prevailing dietary circumstances. The amount of calcium absorbed varies according to several factors including the requirements of the body, but is normally only about 30 to 40% of the dietary intake.

The richest dietary sources of calcium are milk and milk products. Significant amounts can also be consumed in green leafy vegetables, fortified flour, and hard water.

In the United Kingdom dietary reference values (see p.1332) have been published for calcium.[1] In the USA recommended dietary allowances (RDA) had been set,[2] and have recently been replaced by dietary reference intakes (see p.1332).[3] In the UK the estimated average requirement (EAR) for adults is 525 mg (13.1 mmol) daily and the reference nutrient intake (RNI) for adults is 700 mg (17.5 mmol) daily; these figures are based on a mean absorption of calcium of 30% from mixed diets. In the USA the traditional RDA was 800 mg daily for adults aged over 25 years; this figure was based on an absorption rate of 40%. Under the new dietary reference intakes, adequate intakes (AI) for calcium have been set, which are higher in some age groups than the previous RDAs.[3] For adults aged up to 50 years the AI is 1 g daily, and for those 51 years or older, it is 1.2 g daily.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989.
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1997.

Uses and Administration

Calcium salts are used in the management of **hypocalcaemia** (p.1148) and **calcium deficiency states** resulting from dietary deficiency or ageing (see also Osteoporosis, p.731). Doses may be expressed in terms of mmol or mEq of calcium, mass (mg) of calcium, or mass of calcium salt (for comparative purposes, see Table 1, below).

Table 1. Some calcium salts and their calcium content.

Calcium salt	Calcium content per g		
	mg	mmol	mEq
Calcium acetate (anhydrous)	253	6.3	12.6
Calcium carbonate	400	10.0	20.0
Calcium chloride (dihydrate)	273	6.8	13.6
Calcium citrate (tetrahydrate)	211	5.3	10.5
Calcium glubionate (monohydrate)	66	1.6	3.3
Calcium gluceptate (anhydrous)	82	2.0	4.1
Calcium gluconate (monohydrate)	89	2.2	4.5
Calcium glycerophosphate (anhydrous)	191	4.8	9.5
Calcium lactate (anhydrous)	184	4.6	9.2
Calcium lactate (trihydrate)	147	3.7	7.3
Calcium lactate (pentahydrate)	130	3.2	6.5
Calcium lactate gluconate (dihydrate)	129	3.2	6.4
Calcium lactobionate (dihydrate)	51	1.3	2.5
Calcium laevulinate (dihydrate)	131	3.3	6.5
Calcium hydrogen phosphate (dihydrate)	233	5.8	11.6
Calcium phosphate [$10CaO.3P_2O_5.H_2O$]	399	10.0	19.9
Calcium pidolate (anhydrous)	135	3.4	6.7
Calcium sodium lactate (tetrahydrate)	78	1.9	3.9

In simple deficiency states calcium salts may be given by mouth, usually in doses of 10 to 50 mmol (400 mg to 2 g) of calcium daily adjusted to the individual patient's requirements.

In severe acute hypocalcaemia or hypocalcaemic tetany parenteral administration is necessary, generally by slow intravenous injection or continuous infusion of calcium chloride or calcium gluconate (see also Administration, below). A typical dose is 2.25 mmol of calcium by slow intravenous injection, either repeated as required, or followed by continuous intravenous infusion of about 9 mmol daily. 2.25 mmol of calcium is provided by 10 mL of calcium gluconate 10%. Calcium gluceptate and calcium glycerophosphate with calcium lactate have been given by the intramuscular route; the chloride and gluconate are unsuitable for this route because of their irritancy. The intravenous route is used in children.

Intravenous calcium salts are also used to reverse the toxic cardiac effects of potassium in the emergency treatment of severe **hyperkalaemia** (p.1149), and as an antidote to magnesium in severe **hypermagnesaemia** (p.1148). For these indications, 2.25 to 4.5 mmol of calcium (10 to 20 mL of calcium gluconate 10%) is commonly used.

Individual calcium salts have specific uses. Calcium carbonate or acetate are effective phosphate binders and are given by mouth to reduce phosphate absorption from the gut in patients with **hyperphosphataemia**; this is particularly relevant to patients with chronic renal failure in order to prevent the development of renal osteodystrophy (p.732). The initial dose of calcium carbonate is 2.5 g daily titrated to a maximum of 17 g daily. The initial dose of calcium acetate is 3 or 4 g daily; most patients require 6 to 12 g daily.

Calcium carbonate, administered by mouth, is also widely used for its **antacid** properties (p.1167).

The calcium salts discussed here also have *pharmaceutical uses*. Calcium carbonate is employed as a diluent in capsules and tablets and as a buffer and dissolution aid in dispersible tablets. Other applications include its use as a basis for some dental formulations. Calcium phosphate is also used as a diluent for solid dose forms and sometimes as a disintegrant and anticaking agent. Calcium hydrogen phosphate is another tablet or capsule diluent and is employed for its abrasive properties in toothpastes.

Calcium phosphate (Calcarea Phosphorica; Calc. Phos.) is used in homoeopathic medicine.

Administration. Views have been expressed that calcium chloride rather than calcium gluconate is the calcium salt of choice for parenteral preparations.[1,2] This opinion is based on the fact that the body's retention of calcium chloride is greater and more predictable than its retention of calcium gluconate and that the increase in extracellular ionised calcium concentration is unpredictable for the gluconate.

It should, however, be remembered that calcium chloride is considered to be the most irritant of the calcium salts in general use (see under Adverse Effects, above).

Calcium gluconate has also been administered by the intraperitoneal route[3] for the treatment of chronic hypocalcaemia after parathyroidectomy in a patient undergoing continuous ambulatory peritoneal dialysis, resulting in improved systemic bioavailability compared with oral and intravenous administration.

1. Worthley LIG, Phillips PJ. Intravenous calcium salts. *Lancet* 1980; **ii:** 149.
2. Broner CW, *et al.* A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children. *J Pediatr* 1990; **117:** 986–9.
3. Stamatakis MK, Seth SK. Treatment of chronic hypocalcemia with intraperitoneal calcium. *Am J Health-Syst Pharm* 1995; **52:** 201–3.

Bites and stings. Calcium gluconate 10% solution has been administered intravenously as an alternative to the use of conventional muscle relaxants for neurotoxic spider envenomation (p.1534). Mention has been made of such use of calcium in the management of *Latrodectus mactans* (black widow spider) envenomation.[1] Although the precise mechanism of action of calcium in the alleviation of neuromuscular symptoms is unknown it is believed to be due to the replenishment of

calcium stores in the sarcoplasmic reticulum of muscle depleted by stimulation.

1. Binder LS. Acute arthropod envenomation: incidence, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 163–73.

Bone disease. Calcium is essential for the development and maintenance of normal bone, and calcium salts may be indicated in the treatment of some bone disorders associated with calcium deficiency, such as certain types of osteomalacia and rickets (p.730). Doses of 1 to 3 g of calcium daily are used in osteomalacia.

Oral calcium supplements can also be used as an adjunct in the management of osteoporosis (p.731).

Fluoride toxicity. Inorganic fluoride is corrosive to skin and mucous membranes and acute intoxication disrupts many physiological systems and severe burns and profound hypocalcaemia may ensue. Absorption of the fluoride can be prevented by conversion to an insoluble form such as calcium fluoride and thus irrigation of skin (or gastric lavage as appropriate) with lime water, milk, or a 1% solution of calcium gluconate is recommended. Immediate treatment should also consist of 10 mL of calcium gluconate 10% intravenously repeated after one hour; 30 mL should be given if tetany is present. In the short term affected skin and tissue should be injected with a 10% solution of calcium gluconate at a dose of 0.5 mL per cm^2 and burned skin treated with a calcium gluconate 2.5% gel.[1]

See also under Hydrofluoric Acid, p.1589.

1. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; **5:** 79–85.

Hypertension. Two recent meta-analyses report that calcium supplementation results in a small reduction in systolic, but not diastolic, blood pressure.[1,2] Both studies concluded that the effect was too small to support the use of calcium supplementation for preventing or treating hypertension (p.788), but the authors of the second study considered it possible that calcium supplementation might have beneficial effects on blood pressure in those with an inadequate intake.[2]

1. Allender PS, *et al.* Dietary calcium and blood pressure: a meta-analysis of randomized clinical trials. *Ann Intern Med* 1996; **124:** 825–31.
2. Bucher HC, *et al.* Effects of dietary calcium supplementation on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275:** 1016–22.

PREGNANCY. A meta-analysis of 14 trials involving 2459 women concluded that calcium supplementation during pregnancy reduced systolic and diastolic blood pressure and the incidence of pre-eclampsia and hypertension.[1] However, inclusion criteria for this meta-analysis have been criticised.[2] Moreover, results from a double-blind, placebo-controlled trial in a total of 4589 women indicated that calcium supplementation during normal pregnancy did not prevent pre-eclampsia, pregnancy-associated hypertension without pre-eclampsia, and a number of other related disorders.[3]

For discussions of hypertension in pregnancy and eclampsia and pre-eclampsia, see p.788 and p.338, respectively.

1. Bucher HC, *et al.* Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275:** 1113–17. Correction. *ibid.*; **276:** 1388.
2. Various. Effects of calcium supplementation on pregnancy-induced hypertension. *JAMA* 1996; **276:** 1386–7.
3. Levine RJ, *et al.* Trial of calcium to prevent preeclampsia. *N Engl J Med* 1997; **337:** 69–76.

Preparations

BP 1998: Calcium Chloride Intravenous Infusion; Calcium Gluconate Injection; Calcium Gluconate Tablets; Calcium Lactate Tablets; Effervescent Calcium Gluconate Tablets;
BPC 1973: Calcium with Vitamin D Tablets;
USP 23: Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution; Calcium Acetate Tablets; Calcium Chloride Injection; Calcium Glubionate Syrup; Calcium Gluceptate Injection; Calcium Gluconate Injection; Calcium Gluconate Tablets; Calcium Lactate Tablets; Calcium Levulinate Injection; Calcium with Vitamin D Tablets; Dibasic Calcium Phosphate Tablets; Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Modified Lactated Ringer's and Dextrose Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection.

Proprietary Preparations (details are given in Part 3)
Aust.: Calcilin; ***Austral.:*** Calcium-Sandoz†; Celloids CP 57; DCP 340†; Nephrex; Sandocal; ***Belg.:*** Calcium-Sandoz; ***Canad.:*** Cal Gel; Calais; Calciject†; Calcimax; Calcium-Sandoz; H-F Antidote†; Nu-Cal; Topol†; ***Fr.:*** Calcium Corbiere; Calcium-Sandoz; Ostram; ***Ger.:*** Calcedon†; Calcipot; Calcitrans†; Calcium-Sandoz; Cerasorb; Dobo 600†; Dreisacal†; RMS; Spuman c. Acid. lactic. 5%†; ***Irl.:*** Calcium-Sandoz; ***Ital.:*** Calcioport; Calcium-Sandoz; Rubrocalcium; ***Neth.:*** Calcium-Sandoz; ***Norw.:*** Calcium-Sandoz; Phos-Ex; ***S.Afr.:*** Calcium-Sandoz; Glucal†; ***Spain:*** Calbion; Calcio 20 Emulsion; Calcium-Sandoz; Ibercal; Ostram; Royen; ***Swed.:*** Calcium-Sandoz; Phos-Ex; ***Switz.:*** Calcium-Sandoz; ***UK:*** Calcium-Sandoz; Ostram; Phosex; ***USA:*** Calphron; Citracal; Neo-Calglucon; Phos-Ex†; PhosLo; Posture; Prelief.

Multi-ingredient: numerous preparations are listed in Part 3.

Used as an adjunct in: **Swed.:** Deltison.

Magnesium (1170-k)

Mg = 24.305.

Magnesium is a cation administered as various magnesium-containing salts. Magnesium salts have been reported to be **incompatible** with a wide range of drugs.

Magnesium Acetate (1171-a)

$C_4H_6MgO_4,4H_2O$ = 214.5.
CAS — 142-72-3 (anhydrous magnesium acetate); 16674-78-5 (magnesium acetate tetrahydrate).
Pharmacopoeias. In *Br.*

Odourless or almost odourless colourless crystals or a white crystalline powder. Each g of magnesium acetate (tetrahydrate) represents approximately 4.7 mmol of magnesium and the equivalent of bicarbonate. Magnesium acetate (tetrahydrate) 8.83 g is approximately equivalent to 1 g of magnesium.

Freely **soluble** in water and in alcohol. A 5% solution in water has a pH of 7.5 to 8.5.

Magnesium Ascorbate (12907-x)

$(C_6H_7O_6)_2Mg$ = 374.5.
CAS — 15431-40-0.

Each g of magnesium ascorbate (anhydrous) represents approximately 2.7 mmol of magnesium. Magnesium ascorbate (anhydrous) 15.4 g is approximately equivalent to 1 g of magnesium.

Magnesium Aspartate (600-z)

Magnesium aminosuccinate tetrahydrate.
$C_8H_{12}MgN_2O_8,4H_2O$ = 360.6.
CAS — 7018-07-7.
Pharmacopoeias. In *Ger.* and *It.*

Ger. specifies the racemic salt ((*RS*)-aspartate) whereas *It.* makes no statement regarding the isomer. *Ger.* also includes the dihydrate form of the (*S*)-aspartate.

Each g of magnesium aspartate (tetrahydrate) represents approximately 2.8 mmol of magnesium. Magnesium aspartate (tetrahydrate) 14.8 g is approximately equivalent to 1 g of magnesium.

Magnesium Chloride (1172-t)

Chlorure de Magnésium Cristallisé; Cloreto de Magnésio; Magnesii Chloridum Hexahydricum; Magnesium Chloratum.
$MgCl_2.6H_2O$ = 203.3.
CAS — 7786-30-3 (anhydrous magnesium chloride); 7791-18-6 (magnesium chloride hexahydrate).
Pharmacopoeias. In *Eur.* (see p.viii), which also includes Magnesium Chloride 4.5-Hydrate, *Pol.*, and *US.*

Colourless, odourless, deliquescent or hygroscopic crystals or flakes. Each g of magnesium chloride (hexahydrate) represents approximately 4.9 mmol of magnesium and 9.8 mmol of chloride. Magnesium chloride (hexahydrate) 8.36 g is approximately equivalent to 1 g of magnesium.

Very **soluble** in water; freely soluble in alcohol. A 5% solution in water has a pH of 4.5 to 7.0. **Store** in airtight containers.

Magnesium Gluceptate (12909-f)

Magnesium Glucoheptonate.
$C_{14}H_{26}MgO_{16}$ = 474.7.

Each g of magnesium gluceptate (anhydrous) represents approximately 2.1 mmol of magnesium. Magnesium gluceptate (anhydrous) 19.5 g is approximately equivalent to 1 g of magnesium.

Magnesium Gluconate (1203-w)

Magnesium D-gluconate hydrate.
$C_{12}H_{22}MgO_{14}$ (+xH_2O) = 414.6 (anhydrous).
CAS — 3632-91-5 (anhydrous magnesium gluconate); 59625-89-7 (magnesium gluconate dihydrate).
Pharmacopoeias. In *US* which allows either anhydrous or the dihydrate.

Colourless odourless crystals or a white powder or granules. Each g of magnesium gluconate (anhydrous) represents approximately 2.4 mmol of magnesium. Magnesium gluconate (anhydrous) 17.1 g is approximately equivalent to 1 g of magnesium. Freely **soluble** in water; very slightly soluble in alcohol; practically insoluble in ether. A 5% solution in water has a pH of 6.0 to 7.8.

Magnesium Glycerophosphate (1938-m)

Magnesium Glycerinophosphate.
$C_3H_7MgO_6P$(+xH_2O) = 194.4 (anhydrous).
CAS — 927-20-8 (anhydrous magnesium glycerophosphate).

Each g of magnesium glycerophosphate (anhydrous) represents approximately 5.1 mmol of magnesium. Magnesium glycerophosphate (anhydrous) 8 g is approximately equivalent to 1 g of magnesium.

Magnesium Lactate (12911-c)

Magnesium 2-hydroxypropionate.
$C_6H_{10}MgO_6$ = 202.4.
CAS — 18917-93-6.

Each g of magnesium lactate (anhydrous) represents approximately 4.9 mmol of magnesium. Magnesium lactate (anhydrous) 8.33 g is approximately equivalent to 1 g of magnesium.

Magnesium Phosphate (703-f)

Tribasic Magnesium Phosphate; Trimagnesium Phosphate.
$Mg_3(PO_4)_2,5H_2O$ = 352.9.
CAS — 7757-87-1 (anhydrous magnesium phosphate); 10233-87-1 (magnesium phosphate pentahydrate).
Pharmacopoeias. In *US.*

Ger. includes Dibasic Magnesium Phosphate Trihydrate (Magnesium Hydrogen Phosphate Trihydrate).

A white odourless powder. Practically **insoluble** in water; readily soluble in dilute mineral acids.

Each g of magnesium phosphate (pentahydrate) represents approximately 8.5 mmol of magnesium and 5.7 mmol of phosphate. Magnesium phosphate (pentahydrate) 4.84 g is approximately equivalent to 1 g of magnesium.

Magnesium Pidolate (12912-k)

Magnesium Pidolate *(pINNM).*

Magnesium Pyroglutamate. Magnesium 5-oxopyrrolidine-2-carboxylate.
$(C_5H_6NO_3)_2Mg$ = 280.5.
CAS — 62003-27-4.

Each g of magnesium pidolate (anhydrous) represents approximately 3.6 mmol of magnesium. Magnesium pidolate (anhydrous) 11.5 g is approximately equivalent to 1 g of magnesium.

Magnesium Sulphate (1174-r)

518; Epsom Salts; Magnesii Sulfas; Magnesium Sulfate; Magnesium Sulfuricum Heptahydricum; Sal Amarum; Sel Anglais; Sel de Sedlitz.
$MgSO_4,7H_2O$ = 246.5.
CAS — 7487-88-9 (anhydrous magnesium sulphate); 10034-99-8 (magnesium sulphate heptahydrate).
Pharmacopoeias. In *Chin., Eur.* (see p.viii), *Jpn, Pol.*, and *US.*

US allows the dried form, the monohydrate, or the heptahydrate form.

Dried Magnesium Sulphate (Dried Epsom Salts) is included in *Aust., Br.*, and *Pol.*

Magnesium sulphate (heptahydrate) is a white crystalline powder or brilliant, colourless crystals. It effloresces in warm dry air. Each g of magnesium sulphate (heptahydrate) represents approximately 4.1 mmol of magnesium. Magnesium sulphate (heptahydrate) 10.1 g is approximately equivalent to 1 g of magnesium. **Soluble** 1 in 0.8 of water and 1 in 0.5 of boiling water; freely but slowly soluble 1 in 1 of glycerol; sparingly soluble or practically insoluble in alcohol. A 5% solution in water has a pH of 5.0 to 9.2.

Dried magnesium sulphate is a white odourless or almost odourless powder, prepared by drying magnesium sulphate (heptahydrate) at 100° until it has lost about 25% of its weight; it contains 62 to 70% of $MgSO_4$. Freely **soluble** in water; more rapidly soluble in hot water.

Adverse Effects

Excessive parenteral administration of magnesium salts leads to the development of hypermagnesaemia, important signs of which are loss of deep tendon reflexes and respiratory depression, both due to neuromuscular blockade. Other symptoms of hypermagnesaemia may include nausea, vomiting, flushing of the skin, thirst, hypotension due to peripheral vasodilatation, drowsiness, confusion, muscle weakness, bradycardia, coma, and cardiac arrest.

Hypermagnesaemia is uncommon after oral administration of magnesium salts except in the presence of renal impairment. Ingestion of magnesium salts may cause gastro-intestinal irritation and watery diarrhoea.

Effects on the gastro-intestinal tract. Although oral magnesium salts stimulate peristalsis, paralytic ileus has occurred in a woman receiving an intravenous infusion of magnesium sulphate for premature labour; magnesium

concentrations were within the normal range.[1] See also Pregnancy, under Precautions, below.

1. Hill WC, *et al.* Maternal paralytic ileus as a complication of magnesium sulfate tocolysis. *Am J Perinatol* 1985; **2:** 47–8.

Hypersensitivity. Hypersensitivity reactions characterised by urticaria have been described in 2 women after receiving magnesium sulphate intravenously.[1]

1. Thorp JM, *et al.* Hypersensitivity to magnesium sulfate. *Am J Obstet Gynecol* 1989; **161:** 889–90.

Treatment of Adverse Effects

The management of hypermagnesaemia is reviewed on p.1148.

A patient with supralethal hypermagnesaemia was successfully treated using assisted ventilation, calcium chloride administered intravenously, and forced diuresis with mannitol infusions.[1]

1. Bohman VR, Cotton DB. Supralethal magnesemia with patient survival. *Obstet Gynecol* 1990; **76:** 984–6.

Precautions

Parenteral magnesium salts should generally be avoided in patients with heart block or severe renal impairment. They should be used with caution in less severe degrees of renal impairment and in patients with myasthenia gravis. Patients should be monitored for clinical signs of excess magnesium (see above), particularly when being treated for conditions not associated with hypomagnesaemia such as eclampsia. An intravenous preparation of a calcium salt should be available in case of toxicity. When used for hypomagnesaemia, serum-magnesium concentrations should be monitored.

Magnesium crosses the placenta. When used in pregnant women, fetal heart rate should be monitored and administration within 2 hours of delivery should be avoided.

Oral magnesium salts should be used cautiously in patients with impaired renal function. Administration with food may decrease the incidence of diarrhoea. Chronic diarrhoea due to long-term administration may result in electrolyte imbalance.

Hepatic disorders. Severe hypermagnesaemia and hypercalcaemia developed in 2 patients with hepatic encephalopathy following the administration of magnesium sulphate enemas; both patients died, one during and one after asystole. It was recommended that patients with liver disease who might develop renal impairment, or in whom renal failure is established, should not be prescribed enemas containing magnesium for treatment of hepatic encephalopathy as serious magnesium toxicity can occur, which may contribute to death.[1]

1. Collinson PO, Burroughs AK. Severe hypermagnesaemia due to magnesium sulphate enemas in patients with hepatic coma. *Br Med J* 1986; **293:** 1013–14.

Pregnancy. The meconium-plug syndrome (abdominal distention and failure to pass meconium) has been described in 2 neonates who were hypermagnesaemic after their mothers had received magnesium sulphate for eclampsia.[1] It was believed that the hypermagnesaemia may have depressed the function of intestinal smooth muscle. See also Effects on the Gastro-intestinal Tract, above.

In a study in 12 women with pre-eclampsia there was a decrease in short-term fetal heart rate variability when women were administered intravenous magnesium sulphate; however, although variability is considered a sign of fetal well-being the decrease was considered clinically insignificant.[2]

1. Sokal MM, *et al.* Neonatal hypermagnesemia and the meconium-plug syndrome. *N Engl J Med* 1972; **286:** 823–5.
2. Atkinson MW, *et al.* The relation between magnesium sulfate therapy and fetal heart rate variability. *Obstet Gynecol* 1994; **83:** 967–70.

Interactions

Parenteral administration of magnesium sulphate potentiates the effects of neuromuscular blockers such as tubocurarine, suxamethonium, and vecuronium (p.1307). The neuromuscular blocking effects of parenteral magnesium and aminoglycoside antibacterials may be additive. Similarly, parenteral magnesium sulphate and nifedipine have been reported to have additive effects (p.919).

Oral magnesium salts decrease the absorption of tetracyclines and bisphosphonates, and administration should be separated by a number of hours.

Pharmacokinetics

Approximately one third to one half of magnesium is absorbed from the small intestine following oral administration and even soluble magnesium salts are generally very slowly absorbed. The fraction of magnesium absorbed increases if magnesium intake decreases. In plasma, about 25 to 30% of magnesium is protein bound. Parenterally administered magnesium salts are excreted mainly in the urine, and orally administered magnesium salts are eliminated in the urine (absorbed fraction) and the faeces (unabsorbed fraction). Small amounts are distributed into breast milk. Magnesium crosses the placenta.

Human Requirements

Magnesium is the second most abundant cation in intracellular fluid and is an essential body electrolyte which is a cofactor in numerous enzyme systems.

The body is very efficient in maintaining magnesium concentrations by regulating absorption and renal excretion and symptoms of deficiency are rare. It is therefore difficult to establish a daily requirement.

Foods rich in magnesium include nuts, unmilled grains, and green vegetables.

In the United Kingdom dietary reference values (DRV)[1] and in the United States recommended daily allowances (RDA)[2] have been published for magnesium. In the UK the estimated average requirement (EAR) is 200 mg (or 8.2 mmol) daily for adult females and 250 mg (or 10.3 mmol) daily for adult males; the reference nutrient intake (RNI) is 270 mg (or 10.9 mmol) daily for adult females and 300 mg (or 12.3 mmol) daily for adult males; no increment is recommended during pregnancy but an increment of 50 mg (or 2.1 mmol) daily in the RNI is advised during lactation. In the USA under the new dietary reference intakes an EAR of 330 to 350 mg daily has been set in adult males and 255 to 265 mg daily in adult females; the corresponding RDAs are 400 to 420 mg and 310 to 320 mg daily.[2] An increase in RDA to 350 to 360 mg is recommended during pregnancy but the standard RDA is considered adequate during lactation.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1997.

Uses and Administration

Magnesium salts have a variety of actions and uses. Many are given as a source of magnesium ions in the treatment of **magnesium deficiency and hypomagnesaemia** (p.1149). Doses may be expressed in terms of mmol or mEq of magnesium, mass (mg) of magnesium, or mass of magnesium salt (for comparative purposes, see Table 2, below).

In simple deficiency states magnesium salts may be given by mouth in doses of up to 50 mmol of magnesium daily adjusted according to individual requirements. Salts that are, or have been, employed include magnesium aspartate, magnesium chloride, magnesium gluceptate, magnesium gluconate, magnesium glycerophosphate, magnesium lactate, magnesium laevulinate, magnesium orotate, and magnesium pidolate. In acute or severe hypomagnesaemia, magnesium may be given parenterally most usually as the chloride or sulphate. A suggested regimen is to administer 35 to 75 mmol of magnesium by slow intravenous infusion (in glucose 5%) on the first day followed by 25 mmol daily until the hypomagnesaemia is corrected; up to a total of 160 mmol may be required. Alternatively, magnesium sulphate has been given by intramuscular or slow intravenous injection. Careful monitoring of plasma-magnesium and other electrolyte concentrations is essential. Doses should be reduced in renal impairment. Other salts which are, or have been, used parenterally include magnesium acetate, magnesium ascorbate, magnesium aspartate hydrochloride, magnesium laevulinate, and magnesium pidolate.

Table 2. Some magnesium salts and their magnesium content.

Magnesium salt	Magnesium content per g		
	mg	mmol	mEq
Magnesium acetate (tetrahydrate)	113	4.7	9.3
Magnesium ascorbate (anhydrous)	65	2.7	5.3
Magnesium aspartate (tetrahydrate)	67	2.8	5.5
Magnesium chloride (hexahydrate)	120	4.9	9.8
Magnesium gluceptate (anhydrous)	51	2.1	4.2
Magnesium gluconate (anhydrous)	59	2.4	4.8
Magnesium glycerophosphate (anhydrous)	125	5.1	10.3
Magnesium lactate (anhydrous)	120	4.9	9.9
Magnesium phosphate (pentahydrate)	207	8.5	17.0
Magnesium pidolate (anhydrous)	87	3.6	7.1
Magnesium sulphate (heptahydrate)	99	4.1	8.1

Several magnesium salts such as the carbonate, hydroxide, oxide, and trisilicate are widely used for their **antacid** properties (p.1167). Magnesium salts also act as **osmotic laxatives** (see Constipation, p.1168); the salts generally used for this purpose are magnesium sulphate (an oral dose of 5 to 10 g in 250 mL of water being administered for rapid bowel evacuation) and magnesium hydroxide (p.1198).

Parenterally administered magnesium sulphate has some specific uses. It is used for the emergency treatment of some **arrhythmias** such as torsade de pointes (p.782) and those associated with hypokalaemia (p.1150). The usual dose is 2 g of magnesium sulphate (8 mmol of magnesium) administered intravenously over 10 to 15 minutes.

Parenteral magnesium sulphate is also used for the prevention of recurrent seizures in pregnant women with **eclampsia** (see below). A variety of dosage regimens have been used and debate continues as to which is most appropriate. Typically an intravenous loading dose of 4 g of magnesium sulphate (16 mmol of magnesium) is administered over up to 20 minutes. This is then followed by either an infusion of 1 g (4 mmol magnesium) per hour or deep intramuscular administration of 5 g (20 mmol magnesium) into each buttock then 5 g intramuscularly every 4 hours. Should seizures recur under either regimen, then an additional intravenous dose of 2 to 4 g can be administered. It is essential to monitor for signs of hypermagnesaemia, and to stop magnesium administration should this occur. Doses should be reduced in renal impairment.

The use of magnesium sulphate in **acute myocardial infarction** and **premature labour** is discussed below.

Dried magnesium sulphate has been used in the form of Magnesium Sulphate Paste (BP 1998) as an application to inflammatory skin conditions such as boils and carbuncles, but prolonged or repeated use may damage the surrounding skin.

General references.

1. McLean RM. Magnesium and its therapeutic uses: a review. *Am J Med* 1994; **96:** 63–76.

Anaesthesia. Magnesium sulphate has been used to prevent the undesirable haemodynamic response sometimes associated with intubation (p.1302).

Eclampsia and pre-eclampsia. For many years magnesium sulphate has been the preferred treatment in the USA for seizures associated with eclampsia (p.338) and studies have shown it to be more effective than phenytoin[1-3] or diazepam,[2] as well as causing fewer adverse effects.

A commentary[4] on 2 of these studies thought that magnesium sulphate offered considerable advantages. It produced a rapid effect and did not cause sedation in the mother or the infant. It was also considered to have a wide safety margin with the added security of calcium gluconate being an easily available antidote should overdose occur. Subsequently a meta-

analysis[5] of 9 randomised trials reinforced this favourable view. Thus many in the UK now consider magnesium sulphate to be the preferred drug for the treatment of eclampsia. Magnesium sulphate may also be used for prophylaxis in pre-eclampsia, but some uncertainty remains about the degree of benefit; nonetheless, it appears to be more effective than phenytoin.[5] (For a recent study that raised some concerns about the effects of *early* use of magnesium sulphate on the fetus, see Premature Labour, below).

1. Dommisse J. Phenytoin sodium and magnesium sulphate in the management of eclampsia. *Br J Obstet Gynaecol* 1990; **97:** 104–9.
2. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia: evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; **345:** 1455–63. Correction. *ibid.*; **346:** 258.
3. Lucas MJ, *et al.* A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med* 1995; **333:** 201–5.
4. Saunders N, Hammersley B. Magnesium for eclampsia. *Lancet* 1995; **346:** 788–9.
5. Chien PFW, *et al.* Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomised trials. *Br J Obstet Gynaecol* 1996; **103:** 1085–91.

Hypokalaemia. Potassium and magnesium homoeostasis are linked, and hypokalaemia with increased urine potassium excretion may occur in patients with hypomagnesaemia. In this situation, correction of potassium deficit usually requires concomitant magnesium administration. Administration of magnesium sulphate at doses greater than those required to correct hypomagnesaemia has been associated with greater improvements in potassium balance than doses just sufficient to correct hypomagnesaemia.[1]

1. Hamill-Ruth RJ, McGory R. Magnesium repletion and its effect on potassium homeostasis in critically ill adults: results of a double-blind, randomized, controlled trial. *Crit Care Med* 1996; **24:** 38–45.

Myocardial infarction. Magnesium has an important physiological role in maintaining the ion balance in muscle including the myocardium. Administration of magnesium might have an antiarrhythmic effect and might protect the myocardium against reperfusion injury including myocardial stunning (delayed recovery of myocardial contractility function). Intravenous magnesium salts have been used for cardiac arrhythmias and in an overview of studies in patients with suspected myocardial infarction their administration, generally within 12 hours of the onset of chest pain, had reduced mortality.[1] The beneficial effect on mortality appeared to be confirmed by the LIMIT-2 study[2] in which 8 mmol of magnesium was given by intravenous injection before thrombolysis and followed by a maintenance infusion of 65 mmol over the following 24 hours. Benefit was confirmed at follow-up an average of 2.7 years later;[3] however, there was no evidence of an antiarrhythmic effect. These beneficial effects were not borne out by the larger ISIS-4 study,[4] and although there were slight differences in the magnesium regimen and its timing which might have played a part in these contradictory results, at present the routine use of magnesium in myocardial infarction (p.791) cannot be recommended.

Patients with acute myocardial infarction may have magnesium deficiency and long-term treatment with oral magnesium has been tried, but in one study was associated with an increased risk of adverse cardiac events and could not be recommended for secondary prevention.[5]

1. Teo KK, *et al.* Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *Br Med J* 1991; **303:** 1499–1503.
2. Woods KL, *et al.* Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992; **339:** 1553–8.
3. Woods KL, Fletcher S. Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1994; **343:** 816–19.
4. Fourth International Study of Infarct Survival Collaborative Group. ISIS–4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.
5. Galløe AM, *et al.* Influence of oral magnesium supplementation on cardiac events among survivors of an acute myocardial infarction. *Br Med J* 1993; **307:** 585–7.

Porphyria. Magnesium sulphate is one of the drugs that has been used for seizure prophylaxis in patients with porphyria (p.339) who continue to experience convulsions while in remission.

Premature labour. Magnesium sulphate has been given intravenously to suppress initial uterine contractions in the management of premature labour[1-5] and has been found to possess similar efficacy to beta$_2$ agonists (see Salbutamol, p.760). Other magnesium salts have also sometimes been given by mouth. Retrospective observational studies have also found a lower incidence of cerebral palsy in children with birth weights of less than 1500 g when mothers were treated with magnesium sulphate for pre-eclampsia, eclampsia or premature labour.[6,7] However, increased total paediatric mortality was noted in an interim analysis of a recent trial of antenatal magnesium sulphate in preterm labour,[8] and the trial was subsequently discontinued. Although they considered the safety of magnesium sulphate well established in gestation at term, the authors cautioned against the use of magnesium sulphate in very preterm labour.

1. Martin RW, *et al.* Comparison of oral ritodrine and magnesium gluconate for ambulatory tocolysis. *Am J Obstet Gynecol* 1988; **158:** 1440–3.
2. Weiner CP, *et al.* The therapeutic efficacy and cost-effectiveness of aggressive tocolysis for premature labor associated with premature rupture of the membranes. *Am J Obstet Gynecol* 1988; **159:** 216–22.
3. Wilkins IA, *et al.* Efficacy and side effects of magnesium sulfate and ritodrine as tocolytic agents. *Am J Obstet Gynecol* 1988; **159:** 685–9.
4. Ridgway LE, *et al.* A prospective randomized comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis. *Am J Obstet Gynecol* 1990; **163:** 879–82.
5. Dudley D, *et al.* Long-term tocolysis with intravenous magnesium sulfate. *Obstet Gynecol* 1989; **73:** 373–8.
6. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics* 1995; **95:** 263–9.
7. Schendel DE, *et al.* Prenatal magnesium sulfate exposure and the risk for cerebral palsy or mental retardation among very low-birth-weight children aged 3 to 5 years. *JAMA* 1996; **276:** 1805–10.
8. Mittendorf R, *et al.* Is tocolytic magnesium sulphate associated with increased total paediatric mortality? *Lancet* 1997; **350:** 1517–18.

Pulmonary hypertension of the newborn. Preliminary studies have suggested that intravenous magnesium sulphate may be effective in treating persistent pulmonary hypertension of the newborn, as mentioned on p.796.

Respiratory disorders. Magnesium sulphate, administered intravenously over 20 minutes in doses of 1.2 g to patients with acute exacerbations of chronic obstructive pulmonary disease (p.747) who had received inhaled salbutamol, appeared to have moderate efficacy.[1]

Infusion or inhalation of magnesium has been reported to be of benefit in some patients with asthma (p.745) but results have been conflicting.[2-5]

1. Skorodin MS, *et al.* Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med* 1995; **155:** 496–500.
2. Skobeloff EM, *et al.* Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. *JAMA* 1989; **262:** 1210–13.
3. Green SM, Rothrack SG. Intravenous magnesium for acute asthma: failure to decrease emergency treatment duration or need for hospitalization. *Ann Emerg Med* 1992; **21:** 260–5.
4. Ciarallo L, *et al.* Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. *J Pediatr* 1996; **129:** 809–14.
5. Hill J, Britton J. Dose-response relationship and time-course of the effect of inhaled magnesium sulphate on airflow in normal and asthmatic subjects. *Br J Clin Pharmacol* 1995; **40:** 539–44.

Preparations

BP 1998: Magnesium Sulphate Injection; Magnesium Sulphate Mixture; Magnesium Sulphate Paste *(Morison's Paste)*;
USP 23: Magnesium Gluconate Tablets; Magnesium Sulfate in Dextrose Injection; Magnesium Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Aust.: Cormagnesin; Emgecard; FX Passage; Magnesium Diasporal; Magvital; Mg 5-Longoral; Solumag; Ultra-Mag; ***Austral.:*** Celloids MP 65; Magmin; ***Belg.:*** Magnespasmyl; Ultra-Mg; ***Canad.:*** Mag 2; Maglucate; Magnolex; Magnorol; ***Fr.:*** Efimag; Ionimag; Mag 2; Magnespasmyl; Magnogene; Megamag; Solumag; Spasmag; Top Mag; ***Ger.:*** Basti-Mag; Cormagnesin; FX Passage; Lasar mono†; Magium; Magnaspart; Magnerot A; Magnerot Ampullen†; Magnerot Classic; Magnesiocard; Magnesium Diasporal; Magnesium Tonil; Magnetrans†; Magnorbin; Magtrom; metamagnesol; Mg 5-Granulat; Mg 5-Longoral; Mg 5-Sulfat; Mg-nor; Nourymag; ***Ital.:*** Actimag; Mag 2; Solumag; ***Neth.:*** Andrews Laxeerzout†; ***S.Afr.:*** Magnesit; Slow-Mag; ***Spain:*** Actimag; Mag 2; Magnesioboi; Magneston†; Sulmetin; ***Switz.:*** Mag 2; Mag-Min; Magnesiocard; Magnesium Biomed; Magnesium Diasporal; Magnespasmyl; Magnogene; Magvital; Mg 5-Granoral; Mg 5-Longoral; Mg 5-Oraleff; Mg 5-Sulfat; ***USA:*** Almora; Mag-G; Mag-Tab SR; Magonate; Magtrate; Slow-Mag.

Multi-ingredient: numerous preparations are listed in Part 3.

Phosphate (2898-t)

Phosphate is an anion administered as various potassium or sodium salts. Phosphates are **incompatible** with calcium salts; the mixing of calcium and phosphate salts can lead to the formation of insoluble calcium-phosphate precipitates. Incompatibility has also been reported with magnesium salts.

Dibasic Potassium Phosphate (1184-d)

Dikalii Phosphas; Dipotassium Hydrogen Phosphate; Dipotassium Phosphate; E340; Potassium Phosphate. Dipotassium hydrogen orthophosphate.

$K_2HPO_4 = 174.2$.
CAS — 7758-11-4.

Pharmacopoeias. In *Eur.* (see p.viii) and *US.*

Colourless or white, hygroscopic granular powder. Each g of dibasic potassium phosphate represents approximately 11.5 mmol of potassium and 5.7 mmol of phosphate. Freely or very **soluble** in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 8.5 to 9.6. **Store** in airtight containers.

Monobasic Potassium Phosphate (1183-f)

E340; Kalii Dihydrogenophosphas; Monopotassium Phosphate; Potassium Acid Phosphate; Potassium Biphosphate; Potassium Dihydrogen Phosphate. Potassium dihydrogen orthophosphate.

$KH_2PO_4 = 136.1$.
CAS — 7778-77-0.

Pharmacopoeias. In *Eur.* (see p.viii). Also in *USNF.*

Colourless crystals or a white odourless granular or crystalline powder. Each g of monobasic potassium phosphate represents approximately 7.3 mmol of potassium and of phosphate. Freely **soluble** in water; practically insoluble in alcohol. A 1% solution in water has a pH of about 4.5. **Store** in airtight containers.

Dibasic Sodium Phosphate (1196-b)

Dinatrii Phosphas; Disodium Hydrogen Phosphate; Disodium Phosphate; E339; Natrii Phosphas; Sodium Phosphate. Disodium hydrogen orthophosphate.

$Na_2HPO_4.xH_2O$.
CAS — 7558-79-4 (anhydrous dibasic sodium phosphate); 10028-24-7 (dibasic sodium phosphate dihydrate); 7782-85-6 (dibasic sodium phosphate heptahydrate); 10039-32-4 (dibasic sodium phosphate dodecahydrate).

Pharmacopoeias. In *Eur.* (see p.viii), *Jpn, Pol.*, and *US.* The pharmacopoeias may specify one or more states of hydration; monographs and specifications can be found for the anhydrous form (Na_2HPO_4 =142.0), the dihydrate (Na_2HPO_4, $2H_2O$ =178.0), the heptahydrate ($Na_2HPO_4.7H_2O$ =268.1), and the dodecahydrate ($Na_2HPO_4.12H_2O$ =358.1), although not necessarily all will be found in any one pharmacopoeia.

The Ph. Eur. has monographs for the dihydrate and dodecahydrate forms. It specifies for the dihydrate: a white or almost white powder or colourless crystals; for the dodecahydrate: colourless, transparent, very efflorescent crystals. The USP has a monograph for the anhydrous, dihydrate, heptahydrate, and dodecahydrate forms. It specifies for the dried substance: a white powder that readily absorbs moisture; and for the heptahydrate: a colourless or white, granular or caked salt that effloresces in warm, dry air.

Each g of dibasic sodium phosphate (anhydrous) represents approximately 14.1 mmol of sodium and 7.0 mmol of phosphate. Each g of dibasic sodium phosphate (dihydrate) represents approximately 11.2 mmol of sodium and 5.6 mmol of phosphate. Each g of dibasic sodium phosphate (heptahydrate) represents approximately 7.5 mmol of sodium and 3.7 mmol of phosphate. Each g of dibasic sodium phosphate (dodecahydrate) represents approximately 5.6 mmol of sodium and 2.8 mmol of phosphate.

Ph. Eur. **solubilities** for the dihydrate are soluble in water; practically insoluble in alcohol; and for the dodecahydrate: very soluble in water; practically insoluble in alcohol. USP solubilities are for the dried substance: soluble 1 in 8 of water; insoluble in alcohol; and for the heptahydrate: freely soluble in water; very slightly soluble in alcohol. **Store** in airtight containers.

Monobasic Sodium Phosphate (1195-m)

E339; Natrii Dihydrogenophosphas; Natrium Phosphoricum Monobasicum; Sodium Acid Phosphate; Sodium Biphosphate; Sodium Dihydrogen Phosphate. Sodium dihydrogen orthophosphate.

$NaH_2PO_4.xH_2O$.
CAS — 7558-80-7 (anhydrous monobasic sodium phosphate); 10049-21-5 (monobasic sodium phosphate monohydrate); 13472-35-0 (monobasic sodium phosphate dihydrate); 10028-24-7 (monobasic sodium phosphate dihydrate).

Pharmacopoeias. In *Eur.* (see p.viii) and *Pol.* (with $2H_2O$); in *Chin.* (with $1H_2O$). *Br.* also includes monographs for the anhydrous and monohydrate forms. *US* permits the anhydrous, monohydrate, and dihydrate forms.

The BP specifies for the anhydrous form: white, slightly deliquescent crystals or granules; and for the monohydrate and dihydrate: colourless crystals or a white powder. The USP specifies: odourless colourless crystals or white crystalline powder; slightly deliquescent.

Each g of monobasic sodium phosphate (anhydrous) represents approximately 8.3 mmol of sodium and of phosphate. Each g of monobasic sodium phosphate (monohydrate) represents approximately 7.2 mmol of sodium and of phosphate. Each g of monobasic sodium phosphate (dihydrate) represents approximately 6.4 mmol of sodium and of phosphate.

BP **solubilities** are: very soluble in water; very slightly soluble in alcohol. USP solubilities are: freely soluble in water; practically insoluble in alcohol.

A 5% solution of the monohydrate form in water has a pH of 4.2 to 4.5.

Tribasic Sodium Phosphate (14285-f)

E339; Trisodium Orthophosphate; Trisodium Phosphate.

Na_3PO_4 = 163.9.

CAS — 7601-54-9.

Each g of tribasic sodium phosphate (anhydrous) represents approximately 18.3 mmol of sodium and 6.1 mmol of phosphate.

Adverse Effects and Treatment

Excessive administration of intravenous phosphate causes hyperphosphataemia, particularly in patients with renal failure. Hyperphosphataemia leads in turn to hypocalcaemia, which may be severe, and to ectopic calcification, particularly in patients with initial hypercalcaemia. Tissue calcification may cause hypotension and organ damage and result in acute renal failure. Hyperphosphataemia, hypocalcaemia, and tissue calcification are rare after oral or rectal phosphate administration (but see also below).

Adverse effects that may occur with the use of oral phosphates include nausea, vomiting, diarrhoea, and abdominal pain. When oral phosphates are being used for indications other than their laxative effects, diarrhoea may necessitate a reduction in dosage. When administered rectally for bowel evacuation, sodium phosphates may cause local irritation.

Phosphates are administered as the potassium or sodium salts or both; therefore, additional electrolyte disturbances that may be expected on excessive administration include hyperkalaemia, and hypernatraemia and dehydration.

Treatment of adverse effects involves withdrawal of phosphate, general supportive measures, and correction of serum-electrolyte concentrations, especially calcium. Measures to remove excess phosphate such as oral phosphate binders and haemodialysis may be required (see also p.1149).

Effects on electrolytes. Although less common than after intravenous therapy, hyperphosphataemia, accompanied by hypocalcaemia or other severe electrolyte disturbances and resulting in tetany[1,2] and even death,[2] has been reported on a number of occasions following the use of phosphate enemas. Similar effects have also been reported with the use of oral phosphate laxatives.[3,4] Infants or children,[2,5] and those with renal impairment,[1,4] have often been the subjects of these adverse effects. Soft tissue calcification appears to occur rarely with oral phosphate, but nephrocalcinosis has been reported in children with hypophosphataemic rickets treated with calcitriol and phosphate supplements, and was found to be associated with the phosphate dose.[6]

1. Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema. *Lancet* 1985; **ii:** 1433.
2. Martin RR, *et al.* Fatal poisoning from sodium phosphate enema: case report and experimental study. *JAMA* 1987; **257:** 2190–2.
3. Peixoto Filho AJ, Lassman MN. Severe hyperphosphatemia induced by a phosphate-containing oral laxative. *Ann Pharmacother* 1996; **30:** 141–3.
4. Adverse Drug Reactions Advisory Committee. Electrolyte disturbances with oral phosphate bowel preparations. *Aust Adverse Drug React Bull* 1997; **16:** 2.
5. McCabe M, *et al.* Phosphate enemas in childhood: cause for concern. *Br Med J* 1991; **302:** 1074.
6. Verge CF, *et al.* Effects of therapy in X-linked hypophosphatemic rickets. *N Engl J Med* 1991; **325:** 1843–8.

Local toxicity. Rectal gangrene has been associated with the use of phosphate enemas in elderly patients and was believed to be due to a direct necrotising effect of the phosphate on the rectum.[1]

1. Sweeney JL, *et al.* Rectal gangrene: a complication of phosphate enema. *Med J Aust* 1986; **144:** 374–5.

Precautions

Phosphates should not generally be administered to patients with severely impaired renal function. They should be avoided in patients who may have low serum-calcium concentrations, as these may decrease further, and in patients with infected phosphate renal calculi. Potassium phosphates should be avoided in patients with hyperkalaemia and sodium phosphates should generally be avoided in patients with congestive heart failure, hypertension, and oedema. Serum electrolytes and renal function should be monitored during therapy, particularly if phosphates are administered parenterally.

Oral or rectal sodium phosphate preparations for bowel evacuation should not be used in patients with gastro-intestinal obstruction, inflammatory bowel disease, and conditions where there is likely to be increased colonic absorption. They should be used cautiously in elderly and debilitated patients, and in those with pre-existing electrolyte disturbances.

Interactions

Oral phosphate supplements should not be administered concomitantly with aluminium, calcium, or magnesium salts as these will bind phosphate and reduce its absorption. Vitamin D increases the gastro-intestinal absorption of phosphates and therefore increases the potential for hyperphosphataemia.

Hyperphosphataemia, hypocalcaemia, and hypernatraemia are more likely to occur with phosphate enemas or oral laxatives if these are administered to patients receiving diuretics or other drugs that may affect serum electrolytes. The risk of ectopic calcification may be increased by concurrent use of calcium supplements or calcium-containing antacids.

The risk of hyperkalaemia is increased if potassium phosphates are coadministered with drugs that can increase serum-potassium concentrations.

Pharmacokinetics

Approximately two-thirds of ingested phosphate is absorbed from the gastro-intestinal tract. Excess phosphate is predominantly excreted in the urine, the remainder being excreted in the faeces.

References.

1. Larson JE, *et al.* Laxative phosphate poisoning: pharmacokinetics of serum phosphorus. *Hum Toxicol* 1986; **5:** 45–9.

Human Requirements

Phosphorus requirements are usually regarded to be equal to those of calcium.

Most foods contain adequate amounts of phosphate, particularly meat and dairy products, hence deficiency is virtually unknown except in certain disease states, in patients receiving total parenteral nutrition, or in those who have received phosphate-binding agents for prolonged periods; for further details see under Hypophosphataemia, p.1149.

In the United Kingdom dietary reference values (DRV)[1] and in the United States dietary reference intakes including recommended dietary allowances (RDA)[2] have been published for phosphorus. In the UK the reference nutrient intake (RNI) for adults is approximately 550 mg (17.5 mmol) daily; no additional amount is recommended for pregnancy although an additional amount of about 440 mg (14.3 mmol) daily is advised during lactation. In the USA the RDA is 1250 mg daily for those aged 9 to 18 years and 700 mg daily in adults; no increase in RDA is recommended during pregnancy and lactation.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*, London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1997.

Uses and Administration

Phosphates are used in the management of **hypophosphataemia** caused by phosphate deficiency or hypophosphataemic states (p.1149). Doses of up to 100 mmol of phosphate daily may be given by mouth. The intravenous route is seldom necessary, but a dose of up to 9 mmol of monobasic potassium phosphate may be given over 12 hours and repeated every 12 hours as necessary for severe hypophosphataemia (see also below). Plasma-electrolyte concentrations, especially phosphate and calcium, and renal function should be carefully monitored. Reduced doses may be necessary in patients with impaired renal function. Phosphate supplements are used in total parenteral nutrition regimens; typical daily requirements are 20 to 30 mmol of phosphate.

Phosphates act as mild osmotic **laxatives** (p.1167) when administered by mouth as dilute solutions or by the rectal route. Phosphate enemas or concentrated oral solutions are used for bowel cleansing prior to surgery or endoscopy procedures. Preparations typically combine monobasic and dibasic sodium phosphates but the composition and dosage do vary slightly. Phosphate enemas act within 2 to 5 minutes, whereas the oral solutions act within 30 minutes to 6 hours.

Phosphates have also been employed for **other uses**. They lower the pH of urine and have been given as adjuncts to urinary antimicrobials that depend on an acid urine for their activity. Phosphates have also been employed for the prophylaxis of calcium renal calculi; the phosphates reduce urinary excretion of calcium thus preventing calcium deposition. A suggested dose for both uses is 7.4 mmol of phosphate four times daily by mouth.

Butafosfan (1-butylamino-1-methylethylphosphinic acid) and the sodium salt of toldimfos (4-dimethylamino-*O*-tolylphosphinic acid) are used as phosphorus sources in veterinary medicine.

Hypercalcaemia. Intravenous phosphates have been used to lower plasma-calcium concentrations in hypercalcaemic emergencies (p.1148), but because of their potential to cause serious adverse effects other drugs are now preferred. Oral phosphates may be used to prevent gastro-intestinal absorption of calcium in the treatment of hypercalcaemia.

Hypophosphataemia. Phosphate salts are given in the management of hypophosphataemia when a phosphate deficiency is identified, as discussed in Uses and Administration, above. Intravenous phosphates are associated with serious adverse effects if hypophosphataemia is over-corrected, and the rise in serum-phosphorus concentration cannot be predicted from a given dose. Consequently, it has been recommended that intravenous phosphate be used cautiously in the treatment of severe hypophosphataemia.[1-4] However, some advocate a more aggressive fixed-dose regimen in critically ill patients.[5]

1. Vannatta JB, *et al.* Efficacy of intravenous phosphorus therapy in the severely hypophosphataemic patient. *Arch Intern Med* 1981; **141:** 885–7.
2. Anonymous. Treatment of severe hypophosphatemia. *Lancet* 1981; **ii:** 734.
3. Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; **7:** 123–8.
4. Coyle S, *et al.* Treatment of hypophosphataemia. *Lancet* 1992; **340:** 977.
5. Perreault MM, *et al.* Efficacy and safety of intravenous phosphate replacement in critically ill patients. *Ann Pharmacother* 1997; **31:** 683–8.

Osteomalacia. Vitamin D deficiency, or its abnormal metabolism, is the most usual cause of osteomalacia and rickets (p.730); however, phosphate depletion may also contribute, and phosphate supplementation may be given as appropriate.

RICKETS OF PREMATURITY. Dietary deficiency of phosphorus is unusual, but can occur in small premature infants fed exclusively on human breast milk. The phosphate intake in these infants appears to be inadequate to meet the needs of bone mineralisation, and hypophosphataemic rickets can develop. It has been proposed that this condition, variably called metabolic bone disease of prematurity, or rickets of prematurity, could be prevented by giving phosphorus supplements to very low-birth-weight babies (less than about 1000 g) fed on breast milk alone.[1] A suggested regimen is to add 10 to 15 mg of phosphorus per 100 mL of feed (as buffered sodium phosphate) until the infant reached 2000 g. Concomitant calcium and vitamin D supplementation are also recommended.[1] A placebo-controlled study[2] in infants weighing less than 1250 g at birth confirmed that phosphate supplements (50 mg daily) could prevent the development of the bone defects of rickets of prematurity.

1. Brooke OG, Lucas A. Metabolic bone disease in preterm infants. *Arch Dis Child* 1985; **60:** 682–5.
2. Holland PC, *et al.* Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; **335:** 697–701. Correction. *ibid.*; 1408–9.

Preparations

BP 1998: Phosphates Enema;
Ph. Eur.: Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USP 23: Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Methenamine and Monobasic Sodium Phosphate Tablets; Potassium

Phosphates Injection; Sodium Phosphates Enema; Sodium Phosphates Injection; Sodium Phosphates Oral Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Celloids PP 85; Celloids SP 96; *Neth.:* Fleet Klysma†; *UK:* New Era Calm & Clear; *USA:* K-Phos Original.

Multi-ingredient: *Aust.:* Clysmol; Klysma Salinisch; Prepacol; Reducto; Relaxyl; *Austral.:* Cal-Alkyline; Celloid Compounds Magcal Plus; Celloid Compounds Sodical Plus; Duo Celloids PPIP; Duo Celloids PPMP; Duo Celloids SPCF; Duo Celloids SPCP; Duo Celloids SPIP; Duo Celloids SPMP; Duo Celloids SPPC; Duo Celloids SPPP; Duo Celloids SPPS; Duo Celloids SPS; Duo Celloids SPSS; Fleet Phospho-Soda; Fleet Ready-to-Use; Gingo A; Ginkgo Plus Herbal Plus Formula 10; Lifesystem Herbal Plus Formula 11 Ginkgo; Lifesystem Herbal Plus Formula 2 Valerian; Magcal Plus†; Magnesium Plus; ML 20; Phosphate-Sandoz; Sodical Plus†; Travad; Valerian Plus Herbal Plus Formula 12; *Belg.:* Fleet Enema; Fleet Phospho-Soda; Lavement au Phosphate; Normogastryl; Practo-Clyss; Prepacol; *Canad.:* Citrocarbonate; Enemol; Fleet Enema; Fleet Phospho-Soda; Gent-L-Tip; Normo Gastryl; Phosphate-Sandoz; PMS-Phosphates; *Fr.:* Azym; Bactident; Digedryl; Dologastrine†; Gastrilax; Hepargitol; Leuco-4†; Normacol Lavement; Normogastryl; Ortho-Gastrine†; Oxyboldine; Phosphocholine†; Phosphoneuros; Phosphore-Sandoz; Prefagyl; Prepacol; Soker; Solugastryl†; Triphosmag; Uromil; *Ger.:* Eupronerv†; Fluor-Gel†; Hanooxygen†; Isogutt; Klistier; Klysma Salinisch; Klyxenema salinisch†; Lecicarbon; Liquisorb K†; Practo-Clyss; Prepacol; Reducto-spezial; Sepdelen 7†; Somnium†; Stomasal†; *Irl.:* Fleet; Fletchers Phosphate Enema; Phosphate-Sandoz; *Ital.:* Clisflex; Clisma Bieffe Medital†; Clisma Evacuante; Clisma Fleet; Clisma-Lax; Digestivo Dr. Ragionieri†; Enemac; Fosfo-Soda Fleet; Non Acid; Phospho-Lax; Phospho-Soda Fleet†; Ra-Cliss; *Neth.:* Colex; *S.Afr.:* Fosenema†; Lenolax; Phosphate-Sandoz; Sabax Fosenema; *Spain:* Acetuber; Alcalinos Gelos; Boldosal; Darmen Salt; Enema Casen; Eupeptina; Ibsesal†; Lebersal; Normogastryl; *Switz.:* Clisma Fleet†; Freka-Clyss; Lecicarbon; Normogastryl; Practo-Clyss; Reducto-special; *UK:* Carbalax; Fleet Phospho-Soda; Fleet Ready-to-Use; Fletchers Phosphate Enema; Juno Junipah; Phosphate-Sandoz; *USA:* Fleet Enema; Fleet Phospho-Soda; K-Phos MF; K-Phos Neutral; K-Phos No.2; Neutra-Phos; Neutra-Phos-K; pHos-pHaid†; Summer's Eve Post-Menstrual; Thiacide†; Urimar-T; Uro-Phosphate; Urogesic Blue; Uroqid-Acid.

Potassium (1176-d)

K = 39.0983.

Potassium salts covered in this section are those principally given as a source of potassium ions, but consideration should also be given to the effect of the anion. Phosphate salts of potassium are covered under Phosphate, p.1159, and the bicarbonate and citrate salts under Bicarbonate, p.1153.

Potassium Acetate (1177-n)

E261; Kalii Acetas.
$CH_3.CO_2K$ = 98.14.
CAS — 127-08-2.
Pharmacopoeias. In *Eur.* (see p.viii), *Pol.*, and *US.*

Colourless crystals or a white crystalline powder; odourless or with a faint acetous odour. It is deliquescent in moist air. Each g of potassium acetate (anhydrous) represents approximately 10.2 mmol of potassium. Potassium acetate (anhydrous) 2.51 g is approximately equivalent to 1 g of potassium. **Soluble** 1 in 0.5 of water, 1 in 0.2 of boiling water, and 1 in 3 of alcohol. A 5% solution in water has a pH of 7.5 to 9.0. **Store** in airtight containers.

Potassium Chloride (1179-m)

508; Cloreto de Potássio; Kalii Chloridum; Kalium Chloratum.
KCl = 74.55.
CAS — 7447-40-7.
Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, *Jpn*, *Pol.*, and *US.*

Odourless, colourless, cubical, elongated, or prismatic crystals or white crystalline or granular powder. Each g of potassium chloride represents approximately 13.4 mmol of potassium. Potassium chloride 1.91 g is approximately equivalent to 1 g of potassium. **Soluble** 1 in 2.8 of water, and 1 in 2 of boiling water; practically insoluble in alcohol and in dehydrated alcohol.

Potassium Gluconate (1181-x)

577. Potassium D-gluconate.
$CH_2OH.[CH(OH)]_4.CO_2K$ = 234.2.
CAS — 299-27-4 (anhydrous potassium gluconate); 35398-15-3 (potassium gluconate monohydrate).
Pharmacopoeias. In *Fr.*
US permits anhydrous or the monohydrate.

A white or yellowish-white, odourless, crystalline powder or granules. Each g of potassium gluconate (anhydrous) represents approximately 4.3 mmol of potassium. Each g of potassium gluconate (monohydrate) represents approximately 4 mmol of potassium. Potassium gluconate (anhydrous) 5.99 g and potassium gluconate (monohydrate) 6.45 g are each approximately equivalent to 1 g of potassium.

Soluble 1 in 3 of water and 1 in 2.5 of glycerol; practically insoluble in dehydrated alcohol, in chloroform, and in ether. A solution in water is slightly alkaline. **Store** in airtight containers.

Potassium Sulphate (1185-n)

515; Kalium Sulfuricum; Potassii Sulphas; Tartarus Vitriolatus.
K_2SO_4 = 174.3.
CAS — 7778-80-5.
Pharmacopoeias. In *Aust.*, *Jpn*, and *Swiss.*

Each g of potassium sulphate represents approximately 11.5 mmol of potassium. Potassium sulphate 4.46 g is approximately equivalent to 1 g of potassium.

Potassium Tartrate (1187-m)

E336.
$C_4H_4K_2O_6.\frac{1}{2}H_2O$ = 235.3.
CAS — 921-53-9 (anhydrous potassium tartrate).

Each g of potassium tartrate (hemihydrate) represents approximately 8.5 mmol of potassium. Potassium tartrate (hemihydrate) 6.02 g is approximately equivalent to 1 g of potassium.

Adverse Effects

Excessive administration of potassium may lead to the development of hyperkalaemia, especially in patients with renal impairment. Symptoms include paraesthesia of the extremities, muscle weakness, paralysis, cardiac arrhythmias, heart block, cardiac arrest, and mental confusion. Cardiac toxicity is of particular concern after intravenous administration.

Pain or phlebitis may occur during intravenous administration via the peripheral route, particularly at higher concentrations.

Nausea, vomiting, diarrhoea, and abdominal cramps may occur following oral administration of potassium salts. There have been numerous reports of gastro-intestinal ulceration, sometimes with haemorrhage and perforation or with the late formation of strictures, after the use of enteric-coated tablets of potassium chloride. Ulceration has also occurred after the use of sustained-release tablets.

Treatment of Adverse Effects

The treatment of hyperkalaemia discussed on p.1149 also applies when hyperkalaemia occurs during potassium therapy. However, in mild hyperkalaemia that has developed on long-term treatment, discontinuation of the potassium supplement and other drugs that may increase plasma-potassium concentrations, and avoidance of foods with a high potassium content may be sufficient to correct the hyperkalaemia.

In cases of acute oral overdosage of potassium supplements, the stomach should be emptied by gastric lavage in addition to the measures described on p.1149.

References.
1. Saxena K. Clinical features and management of poisoning due to potassium chloride. *Med Toxicol Adverse Drug Exp* 1989; **4**: 429–43.

Precautions

Potassium salts should be administered with considerable care to patients with cardiac disease or conditions predisposing to hyperkalaemia such as renal or adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns. Excessive use of potassium-containing salt substitutes or potassium supplements may lead to accumulation of potassium especially in patients with renal insufficiency. Regular monitoring of clinical status, serum electrolytes, and the ECG is advisable in patients receiving potassium therapy, particularly those with cardiac or renal impairment.

Liquid or effervescent preparations are preferred to solid dosage forms for oral administration; use of the former, with or after food, may reduce gastric irritation. Solid oral dosage forms of potassium salts should not be administered to patients with gastro-intestinal ulceration or obstruction. They should be given with caution to patients in whom passage through the gastro-intestinal tract may be delayed, as in pregnant patients. Treatment should be discontinued if severe nausea, vomiting, or abdominal distress develops.

Potassium chloride should not be used in patients with hyperchloraemia.

Direct injection of potassium chloride concentrates intended for dilution before use may cause instant death.

Interactions

Potassium supplements should be used with caution, if at all, in patients receiving drugs that increase serum-potassium concentrations. These include potassium-sparing diuretics, ACE inhibitors, and cyclosporin, and drugs that contain potassium such as the potassium salts of penicillin. Similarly, the concomitant use of potassium-containing salt substitutes for flavouring food should be avoided. Antimuscarinics delay gastric emptying and consequently may increase the risk of gastro-intestinal adverse effects in patients receiving solid oral dosage forms of potassium.

Pharmacokinetics

Potassium salts other than the phosphate, sulphate, and tartrate are generally readily absorbed from the gastro-intestinal tract. Potassium is excreted mainly by the kidneys; it is secreted in the distal tubules in exchange for sodium or hydrogen ions. The capacity of the kidneys to conserve potassium is poor and some urinary excretion of potassium continues even when there is severe depletion. Some potassium is excreted in the faeces and small amounts may also be excreted in sweat.

Human Requirements

Potassium is an essential body electrolyte. However, requirements are difficult to determine and have been estimated from the amount accumulated during growth and reported urinary and faecal excretion.

Over 90% of dietary potassium is absorbed from the gastro-intestinal tract. Potassium is particularly abundant in vegetables, potatoes, and fruit.

In the United Kingdom dietary reference values (DRV)[1] have been estimated for potassium. The reference nutrient intake (RNI) for adults is 3.5 g (90 mmol) daily. In the United States, no recommended dietary allowance (RDA) has been established for potassium. However a daily intake of 1.6 to 2 g (40 to 50 mmol) is considered adequate for adults.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.

Uses and Administration

Potassium salts in this section are used for the prevention and treatment of potassium depletion and/or **hypokalaemia** (p.1150) and in the prevention of **diuretic-induced hypokalaemia** (p.885). Doses may be expressed in terms of mmol or mEq of po-

Table 3. Some potassium salts and their potassium content.

Potassium salt	Potassium content per g		
	mg	mmol	mEq
Potassium acetate (anhydrous)	398	10.2	10.2
Potassium bicarbonate	391	10.0	10.0
Potassium chloride	524	13.4	13.4
Potassium citrate (anhydrous)	383	9.8	9.8
Potassium citrate (monohydrate)	361	9.3	9.3
Potassium gluconate (anhydrous)	167	4.3	4.3
Potassium gluconate (monohydrate)	155	4.0	4.0
Potassium sulphate (anhydrous)	224	11.5	11.5
Potassium tartrate (hemihydrate)	166	8.5	8.5

tassium, mass (mg) of potassium, or mass of potassium salt (for comparative purposes see Table 3, above). Treatment should be monitored by plasma-potassium estimations because of the risk of inducing hyperkalaemia, especially where there is renal impairment.

Potassium chloride is probably the most commonly used potassium salt; this is because hypochloraemic alkalosis, which is often associated with hypokalaemia, can be corrected by the chloride ions. If a metabolic acidosis, such as occurs in renal tubular acidosis, accompanies the hypokalaemia an alkalinising salt such as potassium acetate, potassium bicarbonate, or potassium citrate may be preferable (see p.1147). Other salts that are or have been employed in the management of potassium deficiency include potassium ascorbate, potassium aspartate, potassium benzoate, potassium gluceptate, potassium gluconate and potassium tartrate. Typical doses for the prevention of hypokalaemia may be up to 50 mmol daily and similar doses may be adequate in mild potassium deficiency. However, higher doses may be needed in more severe deficiency. Patients with renal impairment should receive correspondingly lower doses. Oral treatment is used for prophylaxis and is also suitable for treating most cases of hypokalaemia. Potassium salts by mouth are more irritating than the corresponding sodium salts; they should be taken with or after meals with plenty of fluid and liquid preparations are preferable.

Intravenous administration of a potassium salt may be required in severe acute hypokalaemia. This is normally carried out by infusing a solution containing 20 mmol of potassium in 500 mL over 2 to 3 hours under ECG control. A recommended maximum dose is 2 to 3 mmol of potassium per kg bodyweight in 24 hours. Higher concentrations have been given when an infusion pump has been employed (see Administration below). Adequate urine flow must be ensured and careful monitoring of plasma-potassium and other electrolyte concentrations is essential. Potassium chloride is the salt most commonly employed and solutions intended for intravenous use that are in a concentrated form (such as 1.5 or 2 mmol per mL) *must* be diluted to the appropriate concentration before administration. There should be careful and thorough mixing when adding concentrated potassium chloride solutions to infusion fluids. Potassium chloride is also available as premixed infusions with sodium chloride and/or glucose containing 10 to 40 mmol of potassium per litre. Potassium acetate is also given intravenously.

Amongst **other uses**, the phosphate, sulphate, and tartrate salts of potassium have been given by mouth as osmotic laxatives (p.1167).

Some potassium salts are used as sodium-free condiments when sodium intake must be restricted.

Potassium chloride is sometimes used as a capsule and tablet diluent.

Administration. The standard concentration and rate of administration of potassium chloride for infusion is discussed in Uses and Administration, above. However, higher concentrations (200 or 300 mmol per litre) and faster infusion rates have been used, via an infusion pump, for cases of severe symptomatic hypokalaemia, especially with fluid overload.[1,2]

There has been controversy regarding the preferred route of administration of these higher concentrations of potassium chloride, as discussed by Kruse and Carlson.[1] The central route avoids the problems of pain and phlebitis when potassium is given peripherally. However, it has been suggested that high concentrations of potassium administered centrally may carry a greater risk of cardiac toxicity if the infusion is carried directly to the heart.

Use of lignocaine has improved tolerability of peripheral administration of potassium chloride.[2]

1. Kruse JA, Carlson RW. Rapid correction of hypokalemia using concentrated intravenous potassium chloride infusions. *Arch Intern Med* 1990; **150:** 613–17.
2. Pucino F, *et al.* Patient tolerance to intravenous potassium chloride with and without lidocaine. *Drug Intell Clin Pharm* 1988; **22:** 676–9.

Diabetic ketoacidosis. As discussed on p.316 potassium replacement is given in diabetic ketoacidosis to prevent the hypokalaemia induced by the administration of insulin.

Hypertension. A meta-analysis[1] has reported that potassium supplementation results in reductions of both systolic and diastolic blood pressure. The size of the effect in hypertensive patients was sufficiently great to suggest a possible role in the treatment of hypertension (p.788); effects in normotensive subjects were less marked but consistent with a role for potassium supplementation in preventing hypertension.

1. Whelton PK, *et al.* Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA* 1997; **277:** 1624–32.

Termination of pregnancy. Solutions of potassium chloride are used to reduce fetal numbers in multifetal pregnancies[1,2] by abolishing the fetal cardiac activity. The solution is injected into the thorax of the fetus without affecting the others which are allowed to continue to term.

1. Wapner RJ, *et al.* Selective reduction of multifetal pregnancies. *Lancet* 1990; **335:** 90–3.
2. Berkowitz RL, *et al.* The current status of multifetal pregnancy reduction. *Am J Obstet Gynecol* 1996; **174:** 1265–72.

Preparations

BP 1973: Strong Potassium Chloride Solution;
BP 1998: Bumetanide and Slow Potassium Tablets; Effervescent Potassium Chloride Tablets; Potassium Chloride and Glucose Intravenous Infusion; Potassium Chloride and Sodium Chloride Intravenous Infusion; Potassium Chloride, Sodium Chloride and Glucose Intravenous Infusion; Slow Potassium Chloride Tablets; Sterile Potassium Chloride Concentrate;
USP 23: Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Modified Lactated Ringer's and Dextrose Injection; Potassium Acetate Injection; Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride for Effervescent Oral Solution; Potassium Chloride Extended-release Capsules; Potassium Chloride Extended-release Tablets; Potassium Chloride for Injection Concentrate; Potassium Chloride for Oral Solution; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Dextrose Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride in Sodium Chloride Injection; Potassium Chloride Oral Solution; Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution; Potassium Gluconate and Potassium Chloride for Oral Solution; Potassium Gluconate and Potassium Chloride Oral Solution; Potassium Gluconate and Potassium Citrate Oral Solution; Potassium Gluconate Elixir; Potassium Gluconate Tablets; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution; Trikates Oral Solution.

Proprietary Preparations (details are given in Part 3)
Aust.: Micro-Kalium; Rekawan; *Austral.:* Celloids PC 73; Celloids PS 29; K-San†; Kay Ciel†; KSR; Slow-K; Span-K; *Belg.:* Chloropotassuril; Kalium Durettes; Ultra-K; *Canad.:* Apo-K; K-10; K-Dur; K-Long†; K-Lor; K-Lyte/Cl; K-Med 900†; Kalium Durules; Kaochlor; Kaon; Micro-K; Roychlor; Slow-K; *Fr.:* Diffu-K; Kaleorid; Microkaleorid†; Nati-K; Potassion†; *Ger.:* Kalinor-retard P; Kalitrans retard; Kalium-Duriles; KCl-retard; Rekawan; *Irl.:* Kay-Cee-L; Leo K†; Slow-K; *Ital.:* K-Flebo; Kadalex; Lento-Kalium; *Neth.:* Kalium Durettes; Slow-K; *Norw.:* Kaleorid; Kalilente†; Kalinorm; *S.Afr.:* Micro-K†; Plenish-K; Slow-K; Swiss-Kal SR; *Spain:* Boi K; Boi K Aspartico; Miopotasio†; Potasion; *Swed.:* K-MIC†; Kaleorid; Kalilente†; Kaliport†; Kalitabs; Kalium Duretter; Kalium Retard; *Switz.:* Kaliglutol; Plus Kalium retard; *UK:* Kay-Cee-L; Leo K†; Nu-K†; Slow-K; *USA:* Cena-K; Gen-K; K + 10; K + 8; K + Care; K-Dur; K-G Elixir; K-Lease; K-Lor; K-Lyte/Cl; K-Norm; K-Tab; Kaochlor; Kaon; Kaon-Cl; Kato†; Kay Ciel; Kaylixir; Klor-Con; Klorvess; Klotrix; Micro-K; Potasalan; Rum-K; Slow-K; Ten-K.

Multi-ingredient: numerous preparations are listed in Part 3.

Sodium (1188-b)

Na = 22.98977.

Sodium chloride is the principal sodium salt used as a source of sodium ions. Sodium salts used chiefly as sources of bicarbonate ions, such as the acetate, bicarbonate, citrate, and lactate, are covered under Bicarbonate, p.1153. Phosphate salts of sodium are covered under Phosphate, p.1159.

Sodium Chloride (1191-f)

Chlorure de Sodium; Cloreto de Sódio; Natrii Chloridum; Salt.

NaCl = 58.44.
CAS — 7647-14-5.

NOTE. An aqueous solution of sodium chloride 0.9% is often known as physiological saline.
SALINE is a code approved by the BP for use on single unit doses of eye drops containing sodium chloride 0.9% where the individual container may be too small to bear all the appropriate labelling information. HECL is a similar code approved for hydroxyethylcellulose and sodium chloride eye drops.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, *Jpn*, *Pol.*, and *US.*

Colourless cubic crystals or white crystalline powder. Each g of sodium chloride represents approximately 17.1 mmol of sodium and of chloride. Sodium chloride 2.54 g is approximately equivalent to 1 g of sodium.
Soluble 1 in 2.8 of water; 1 in 2.7 of boiling water; and 1 in 10 of glycerol; slightly soluble in alcohol; practically insoluble in dehydrated alcohol. A 0.9% solution in water is isosmotic, and thus in most cases isotonic with serum and lachrymal secretions.
Solutions of some sodium salts, including sodium chloride, when stored, may cause separation of solid particles from glass containers and solutions containing such particles must not be used.

Adverse Effects

Adverse effects of sodium salts are attributable to electrolyte imbalances from excess sodium; there may also be effects due to the specific anion.

Retention of excess sodium in the body usually occurs when there is defective renal sodium excretion. This leads to the accumulation of extracellular fluid to maintain normal plasma osmolality, which may result in pulmonary and peripheral oedema and their consequent effects.

Hypernatraemia (a rise in plasma osmolality) is usually associated with inadequate water intake, or excessive water losses (see p.1150). It rarely occurs after therapeutic doses of sodium chloride, but has occurred with the use of hypertonic saline for induction of emesis or for gastric lavage and after errors in the formulation of infant feeds. Hypernatraemia may also occur after inappropriate intravenous administration of hypertonic saline.

The most serious effect of hypernatraemia is dehydration of the brain which causes somnolence and confusion progressing to convulsions, coma, respiratory failure, and death. Other symptoms include thirst, reduced salivation and lachrymation, fever, tachycardia, hypertension, headache, dizziness, restlessness, irritability, and weakness.

Gastro-intestinal effects associated with acute oral ingestion of hypertonic solutions or excessive amounts of sodium chloride include nausea, vomiting, diarrhoea, and abdominal cramps.

Excessive administration of chloride salts may cause a loss of bicarbonate with an acidifying effect.

Intra-amniotic injection of hypertonic solutions of sodium chloride, which has been used for abortion induction, has been associated with serious adverse effects including disseminated intravascular coagulation, renal necrosis, cervical and uterine lesions, haemorrhage, pulmonary embolism, pneumonia, and death.

General references.

1. Moder KG, Hurley DL. Fatal hypernatremia from exogenous salt intake: report of a case and review of the literature. *Mayo Clin Proc* 1990; **65:** 1587–94.

Treatment of Adverse Effects

In patients with mild sodium excess, oral administration of water and restriction of sodium intake is sufficient. However, in the event of recent acute oral overdose of sodium chloride, induction of emesis or gastric lavage should be carried out along with general symptomatic and supportive treatment. Serum-sodium concentrations should be measured, and if severe hypernatraemia is present this should be treated (see p.1150).

Precautions

Sodium salts should be administered with caution to patients with hypertension, heart failure, peripheral or pulmonary oedema, impaired renal function, pre-eclampsia, or other conditions associated with sodium retention.

When sodium supplements are administered by mouth, adequate water intake should be maintained. Sustained-release tablets should not be administered to patients with gastro-intestinal disorders associated with strictures or diverticula because of the risk of obstruction.