tinued if tetany occurs and should only be restarted cautiously after plasma ionised and total calcium concentrations indicate a need for further treatment and tetany has stopped. Calcium supplements may be given intravenously for hypocalcaemia but should be used with extreme caution in patients with tetany, particularly in digitalised patients since the effect of the digitalis may be reversed.

◊ References.

1. Morgan BW, *et al.* Adverse effects in 5 patients receiving EDTA at an outpatient chelation clinic. *Vet Hum Toxicol* 2002; **44:** 274–6.
2. Prabha A, *et al.* Chelation therapy for coronary heart disease. *Am Heart J* 2002; **144:** E10.

Inappropriate administration. There have been fatalities in both children and adults when they were given sodium edetate instead of *sodium calcium edetate* (p.1462), which is a chelator used for the treatment of lead poisoning.[1,2] The FDA had received reports of 11 deaths associated with the use of sodium edetate over the period 1971 to 2007;[3] in 5 cases, sodium edetate was given instead of sodium calcium edetate, and in 2 cases, sodium edetate was given instead of *etomidate* (p.1783). In some cases, confusion had arisen due to the use of the term EDTA in prescribing the drug. The FDA has subsequently recommended that the full product name be used, and that prescribers should consider including the indication for use on the prescription.[2]

1. CDC. Deaths associated with hypocalcemia from chelation therapy—Texas, Pennsylvania, and Oregon, 2003-2005. *MMWR* 2006; **55:** 204–7. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5508a3.htm (accessed 25/01/08)
2. FDA Public Health Advisory. Edetate disodium (marketed as Endrate and generic products) (issued 16th January 2008). Available at: http://www.fda.gov/cder/drug/advisory/edetate_disodium.htm (accessed 25/01/08)
3. FDA. Questions and answers on edetate disodium (marketed as Endrate and generic products) (issued 16th January 2008). Available at: http://www.fda.gov/cder/drug/infopage/edetate_disodium/QA.htm (accessed 25/01/08)

Precautions

Sodium edetate is contra-indicated in patients with renal impairment and should be used with caution in patients with hypokalaemia, tuberculosis, impaired cardiac function, diabetes mellitus, or a history of seizures. Plasma-electrolyte concentrations, particularly ionised calcium, and renal function should be monitored regularly; daily urinalysis is also recommended. Sodium edetate is irritant to the tissues and must be diluted before infusion; the recommended rate should not be exceeded.

Uses and Administration

Sodium edetate is a chelator with a high affinity for calcium, with which it forms a stable, soluble complex that is readily excreted by the kidneys. It has been given intravenously, as the disodium and trisodium salts, in the emergency treatment of hypercalcaemia (p.1668); it has also been used to control digitalis-induced cardiac arrhythmias, although less toxic agents are generally preferred (p.1260). It is also used topically to treat calcium deposits in the eye.

Sodium edetate also chelates other polyvalent metals but, unlike sodium calcium edetate, which is saturated with calcium, it is not used for the treatment of heavy metal poisoning since hypocalcaemia rapidly develops.

In the treatment of hypercalcaemia, injections containing varying amounts of disodium and trisodium edetate are used. In the UK, the trisodium salt is generally used. A dose of up to 70 mg/kg daily has been suggested for adults; children may be given up to 60 mg/kg daily. It should be given by slow intravenous infusion over 2 to 3 hours and each gram of trisodium edetate should be diluted with 100 mL of glucose 5% or sodium chloride 0.9%. In the USA, disodium edetate is given in an adult dose of 50 mg/kg in 24 hours by slow intravenous infusion; the maximum daily dose is 3 g. Children may be given 40 to 70 mg/kg in 24 hours. The injection should be diluted with 500 mL of sodium chloride 0.9% or glucose 5% for adults or to a concentration not greater than 3% for children, and infused over 3 hours or more, preferably 4 to 6 hours. The dosage may be repeated for a further 4 days followed by a two-day interval before subsequent courses of treatment. If necessary, up to fifteen doses may be given in total.

Sodium edetate is used in the treatment of calcium deposits from calcium oxide or calcium hydroxide burns of the eye and in the treatment of calcified corneal opacities, either by topical application after removing the appropriate area of corneal epithelium or by iontophoresis. Irrigation has also been suggested for zinc chloride injury to the eye, but treatment may be ineffective unless started within 2 minutes. In the UK, a 0.4% solution of the trisodium salt is used for topical application to the eye; in the USA, a 0.35 to 1.85% solution of the disodium salt has been suggested.

Sodium edetates are also used in cleaners for contact lenses and as antoxidant synergists in cosmetic and pharmaceutical preparations.

Atherosclerosis. Calcium is thought to be necessary for several steps in atherogenesis and removal of calcium from atherosclerotic plaques using a chelator such as disodium edetate has been tried in patients with atherosclerosis (p.1159). However, reports of beneficial clinical responses are largely anecdotal or from small, short-term, or uncontrolled clinical studies; a meta-analysis[1] of controlled trials concluded that there was insufficient evidence of benefit or harm, and a further randomised trial[2] in patients with coronary heart disease found no benefit with sodium edetate treatment. In addition, adverse effects are common with chelation therapy, and fatalities have been reported;[3] literature reviews[4,5] considering both uncontrolled and controlled studies have concluded that in view of the potential toxicity of such treatment it should be considered obsolete.

1. Villarruz MV, *et al.* Chelation therapy for atherosclerotic cardiovascular disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 04/10/05).
2. Knudtson ML, *et al.* Chelation therapy for ischemic heart disease: a randomized controlled trial. *JAMA* 2002; **287:** 481–6.
3. Magee R. Chelation treatment of atherosclerosis. *Med J Aust* 1985; **142:** 514–15.
4. Ernst E. Chelation therapy for peripheral arterial occlusive disease: a systematic review. *Circulation* 1997; **96:** 1031–3.
5. Ernst E. Chelation therapy for coronary heart disease: an overview of all clinical investigations. *Am Heart J* 2000; **140:** 139–41.

Preparations

BP 2008: Trisodium Edetate Intravenous Infusion;
USP 31: Edetate Disodium Injection.

Proprietary Preparations (details are given in Part 3)
Fr.: Chelatran; ***Irl.:*** Limclair; ***UK:*** Limclair†; ***USA:*** Endrate; ***Venez.:*** Edetil.

Multi-ingredient: ***Mex.:*** Adapettes; ***NZ:*** Conditioning Solution†; ***UK:*** Uriflex G; Uriflex R.

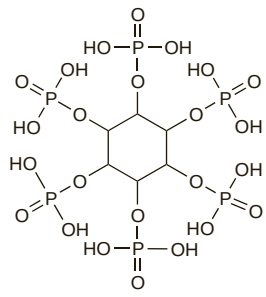
Sodium Fytate *(rINNM)*

Fitato sódico; Fytate de Sodium; Natrii Fytas; Phytate Sodium *(USAN)*; Sodium Phytate; SQ-9343. The nonasodium salt of *myo*-inositol hexakis(dihydrogen phosphate); Sodium cyclohexanehexyl(hexaphosphate).

Натрий Фэитат

$C_6H_9Na_9O_{24}P_6$ = 857.9.

CAS — 83-86-3 (fytic acid); 7205-52-9 (sodium fytate).



(fytic acid)

Profile

Sodium fytate reacts with calcium in the gastrointestinal tract to form non-absorbable calcium fytate which is excreted in the faeces. Sodium fytate has been used in a similar manner to sodium cellulose phosphate (p.1463) to reduce the absorption of calcium from the gut in the treatment of hypercalciuria. It also binds other metals; fytic acid has been used as an antoxidant, and as an adjunct in topical preparations for hyperpigmentation disorders.

Sodium fytate labelled with technetium-99m (p.2055) has been used intravenously for imaging of the liver.

Preparations

Proprietary Preparations (details are given in Part 3)
Hung.: Fyton.

Multi-ingredient: ***Ital.:*** Lightening; Phytic Acid.

Sodium Nitrite

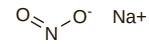
Dusitan sodný; E250; Natrii nitris; Natrio nitritas; Natrium Nitrosum; Natriumnitriitti; Natriumnitrit; Nátrium-nitrit; Nitrito sódico; Sodium, nitrite de; Sodu azotyn; Sodyum Nitrit.

$NaNO_2$ = 69.00.

CAS — 7632-00-0.

ATC — V03AB08.

ATC Vet — QV03AB08.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Sodium Nitrite). Hygroscopic, colourless crystals or mass, or yellowish rods. Freely soluble in water; soluble in alcohol. Store in airtight containers.
USP 31 (Sodium Nitrite). A white to slightly yellow granular powder, or white or practically white, opaque fused masses or sticks. It is deliquescent in air. Soluble 1 in 1.5 of water; sparingly soluble in alcohol. Its solutions are alkaline to litmus. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects

Sodium nitrite may cause nausea and vomiting, abdominal pain, dizziness, headache, flushing, cyanosis, tachypnoea, and dyspnoea; vasodilatation resulting in syncope, hypotension, and tachycardia may occur. Overdosage may result in cardiovascular collapse, coma, convulsions, and death. Ionised nitrites readily oxidise haemoglobin to methaemoglobin, causing methaemoglobinaemia.

Sodium nitrite is a precursor for the formation of nitrosamines, many of which are carcinogenic in *animals*, but a relationship with human cancer has not been established.

Methaemoglobinaemia. Severe methaemoglobinaemia has been reported after the consumption of nitrite-contaminated meat,[1,2] as well as following inadvertent ingestion of sodium nitrite.[3,4]

1. Walley T, Flanagan M. Nitrite-induced methaemoglobinaemia. *Postgrad Med J* 1987; **63:** 643–44.
2. Kennedy N, *et al.* Faulty sausage production causing methaemoglobinaemia. *Arch Dis Child* 1997; **76:** 367–8.
3. Finan A, *et al.* Methaemoglobinaemia associated with sodium nitrite in three siblings. *BMJ* 1998; **317:** 1138–9.
4. Anonymous. Methemoglobinemia following unintentional ingestion of sodium nitrite—New York, 2002. *MMWR* 2002; **51:** 639–42.

Treatment of Adverse Effects

When toxicity results from the ingestion of nitrites, treatment is supportive and symptomatic; oxygen and methylthioninium chloride may be required for methaemoglobinaemia although methylthioninium chloride should not be given if cyanide poisoning is suspected since cyanide may be displaced. Exchange transfusion may be considered when methaemoglobinaemia is severe.

Uses and Administration

Sodium nitrite is used with sodium thiosulfate in the treatment of cyanide poisoning (p.2045). Sodium nitrite produces methaemoglobinaemia and it is thought that cyanide ions combine with the methaemoglobin to produce cyanmethaemoglobin, thus protecting cytochrome oxidase from the cyanide ions; however, other mechanisms may have a significant role. As the cyanmethaemoglobin slowly dissociates, the cyanide is converted to relatively non-toxic thiocyanate and is

excreted in the urine. Sodium thiosulfate provides an additional source of sulfur for this reaction and this accelerates the process.

The usual dosage regimen in adults is 300 mg of *sodium nitrite* (10 mL of a 3% solution) given intravenously over 5 to 20 minutes followed by 12.5 g of *sodium thiosulfate* (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over a period of about 10 minutes. A suggested dosage regimen in children is about 4 to 10 mg/kg of *sodium nitrite*, given as a 3% solution (0.13 to 0.33 mL/kg), to a maximum of 300 mg (10 mL), followed by about 400 mg/kg of *sodium thiosulfate*, as a 25 or 50% solution (1.65 mL/kg of a 25% solution) to a maximum of 12.5 g (50 mL of a 25% solution). The methaemoglobin concentration should not be allowed to exceed 30 to 40%. If symptoms of cyanide toxicity recur, the injections of nitrite and thiosulfate may be repeated after 30 minutes at half the initial doses.

Sodium nitrite has also been suggested in the treatment of hydrogen sulfide poisoning (see p.1690).

Sodium nitrite has been used as a rust inhibitor, for example in instrument disinfectants. It is also used as a preservative in foods such as cured meats but should not be used in food for infants under the age of 3 months due to the risk of methaemoglobinaemia. Potassium nitrite is also used as a food preservative.

Preparations

USP 31: Sodium Nitrite Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: O A R†.

Multi-ingredient: ***Ital.:*** Citrosil Alcolico Azzuro; ***S.Afr.:*** Tripac-Cyano; ***USA:*** Cyanide Antidote Package.

Sodium Polystyrene Sulfonate

Natrii polystyrenesulfonas; Natrii Polystyrensulfonas; Natrio polistirensulfonatas; Natriumpolystyreenisulfonaatti; Natriumpolystyrensulfonat; Natrium-polystyrensulfonát; Poliestirenosulfonato sódico; Polystyrène sulfonate sodique; Sodium Polystyrene Sulphonate.

CAS — 9003-59-2; 9080-79-9; 25704-18-1.

ATC — V03AE01.

ATC Vet — QV03AE01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Sodium Polystyrene Sulphonate). An almost white to light brown powder. It contains 9.4 to 11.0% of sodium, calculated with reference to the dried substance. Each g exchanges 2.8 mmol to 3.4 mmol of potassium, calculated with reference to the dried substance. Practically insoluble in water, in alcohol, and in dichloromethane. Store in airtight containers.
USP 31 (Sodium Polystyrene Sulfonate). A golden brown, fine, odourless powder containing not more than 10% of water. The sodium content is not less than 9.4% and not more than 11.5%, calculated on the anhydrous basis. Each g exchanges not less than 110 mg and not more than 135 mg of potassium, calculated on the anhydrous basis. Insoluble in water.

Adverse Effects

Anorexia, nausea, vomiting, constipation, and occasionally diarrhoea may develop during treatment with sodium polystyrene sulfonate. Constipation may be severe; large doses in elderly patients and in children may result in faecal impaction and gastrointestinal concretions have occurred after oral use in neonates. If necessary a mild laxative may be used to prevent or treat constipation (but see Precautions, below, for laxatives that should be avoided).

Serious potassium deficiency can occur with sodium polystyrene sulfonate and signs of severe hypokalaemia may include irritability, confusion, ECG abnormalities, cardiac arrhythmias, and severe muscle weakness. Like other cation-exchange resins, sodium polystyrene sulfonate is not totally selective and its use may result in other electrolyte disturbances such as hypocalcaemia. Significant sodium retention may also occur, especially in patients with renal impairment, and may lead to heart failure.

Effects on the gastrointestinal tract. Colonic necrosis, including some fatalities, has been reported[1-3] after use of enemas containing sodium polystyrene sulfonate in sorbitol. Studies in *animals*[1] suggested that the use of sorbitol was a contributory factor, although failure to irrigate the colon adequately, as recommended by the manufacturer, was also suggested[4,5] as a possible cause. Both colonic[6] and upper gastrointestinal necrosis[7] have also been reported after oral or nasogastric sodium polystyrene sulfonate with sorbitol, and there has also been a report[8] of colonic necrosis with oral sodium polystyrene sulfonate alone.

1. Lillemoe KD, *et al.* Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. *Surgery* 1987; **101:** 267–72.
2. Wootton FT, *et al.* Colonic necrosis with Kayexalate-sorbitol enemas after renal transplantation. *Ann Intern Med* 1989; **111:** 947–9.
3. Rogers FB, Li SC. Acute colonic necrosis associated with sodium polystyrene sulfonate (Kayexalate) enemas in a critically ill patient: case report and review of the literature. *J Trauma* 2001; **51:** 395–7.
4. Burnett RJ. Sodium polystyrene-sorbitol enemas. *Ann Intern Med* 1990; **112:** 311–12.
5. Shepard KV. Cleansing enemas after sodium polystyrene sulfonate enemas. *Ann Intern Med* 1990; **112:** 711.
6. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. *Am J Surg Pathol* 1997; **21:** 60–9.
7. Abraham SC, *et al.* Upper gastrointestinal tract injury in patients receiving kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. *Am J Surg Pathol* 2001; **25:** 637–44.
8. Cheng ES, *et al.* Colonic necrosis and perforation following oral sodium polystyrene sulfonate (Resonium A /Kayexelate) in a burn patient. *Burns* 2002; **28:** 189–90.

Effects on the lungs. Particles of sodium polystyrene sulfonate were found at autopsy in the lungs of 3 patients who had taken the resin orally and were associated with acute bronchitis and bronchopneumonia in 2 and with early bronchitis in the third.[1] It was suggested that, where possible, it may be preferable to give sodium polystyrene sulfonate rectally, but if it has to be given orally the patient should be positioned carefully to avoid aspiration.

1. Haupt HM, Hutchins GM. Sodium polystyrene sulfonate pneumonitis. *Arch Intern Med* 1982; **142:** 379–81.

Precautions

Sodium polystyrene sulfonate should not be given orally to neonates, and is contra-indicated by any route in neonates with reduced gut motility or in any patient with obstructive bowel disease. Care is also needed with rectal use in neonates and children in order to avoid impaction of the resin. Treatment should be discontinued if clinically significant constipation develops. Although sorbitol has been recommended for the prophylaxis and treatment of constipation, there have been reports of colonic necrosis in patients receiving this combination (see Effects on the Gastrointestinal Tract, above) and licensed product information advises against the use of sorbitol with polystyrene sulfonates. Magnesium-containing laxatives are also contra-indicated (see Interactions, below).

Patients receiving sodium polystyrene sulfonate should be monitored for electrolyte disturbances, especially hypokalaemia. Since serum concentrations may not always reflect intracellular potassium deficiency, symptoms of hypokalaemia should also be watched for and the decision to stop treatment assessed individually.

Use of sodium polystyrene sulfonate can result in sodium overloading and it should be used cautiously in patients with renal failure or conditions requiring a restricted sodium intake, such as heart failure and severe hypertension; calcium polystyrene sulfonate (p.1438) may be preferred in these patients.

The possible effects of sodium polystyrene sulfonate on serum electrolytes should be considered when interpreting diagnostic measurements.

After use of sodium polystyrene sulfonate retention enemas, the colon should be irrigated to ensure removal of the resin.

Interactions

Sodium polystyrene sulfonate is not totally selective for potassium and may also bind other cations. When given orally with cation-donating antacids and laxatives such as magnesium hydroxide, aluminium hydroxide, or calcium carbonate, competition for binding sites may reduce the potassium-lowering effect of the resin. In addition, particularly in patients with renal impairment, metabolic alkalosis may develop due to binding of the cation by the resin; this prevents neutralisation of bicarbonate ions in the small intestine. Seizures have been reported due to metabolic alkalosis in a patient given magnesium hydroxide with sodium polystyrene sulfonate and use of magnesium-containing laxatives should therefore be avoided.

Ion-exchange resins may also bind other drugs, reducing their absorption. Drugs that have been affected include levothyroxine (see p.2173) and lithium salts.

Hypokalaemia may exacerbate the adverse effects of digoxin and sodium polystyrene sulfonate should be used with caution in patients receiving cardiac glycosides.

Uses and Administration

Sodium polystyrene sulfonate, the sodium salt of sulfonated styrene copolymer with divinylbenzene, is a cation-exchange resin that exchanges sodium ions for potassium ions and other cations in the gastrointestinal tract when given orally or rectally. The exchanged resin is then excreted in the faeces. Each gram of resin exchanges about 3 mmol of potassium *in vitro*, and about 1 mmol *in vivo*.

Sodium polystyrene sulfonate is used to enhance potassium excretion in the treatment of hyperkalaemia, including that associated with anuria or severe oliguria (caution is required due to the sodium content). An effect may not be evident for several hours or longer, and in severe hyperkalaemia, where a rapid effect is required, other measures must also be considered (see p.1669).

Serum-electrolyte concentrations should be monitored throughout treatment and doses given according to response.

The usual oral dose is 15 g up to four times daily as a suspension in water or syrup or as a sweetened paste. It should not be given in fruit juices that have a high potassium content. A suggested oral dose for children is 1 g/kg daily in divided doses for acute hyperkalaemia, reduced to a maintenance dose of 500 mg/kg daily; the oral route is not recommended for neonates.

When oral use is difficult, sodium polystyrene sulfonate may be given rectally as an enema. The usual daily dose is 30 g given as a suspension in 100 mL of 2% methylcellulose '450' and 100 mL of water and retained, if possible, for at least 9 hours; higher doses, shorter retention times, and alternative vehicles have also been used. After retention of the enema the colon should be irrigated to remove the resin. Initial therapy may involve both oral and rectal routes. Children and neonates may be given rectal doses similar to the oral doses suggested for children; particular care is needed with rectal use in children as excessive dosage or inadequate dilution could result in impaction of resin.

Other polystyrene sulfonate resins include calcium polystyrene sulfonate (p.1438), which is used similarly to the sodium resin and potassium polystyrene sulfonate (p.1460), which has been used in the treatment of hypercalciuria. Aluminium polystyrene sulfonate, ammonium polystyrene sulfonate, and magnesium polystyrene sulfonate have all occasionally been used.

Preparations

USP 31: Sodium Polystyrene Sulfonate Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Resonium A; ***Austria:*** Resonium A; ***Belg.:*** Kayexalate; ***Canad.:*** K-Exit; Kayexalate; ***Denm.:*** Resonium; ***Fin.:*** Resonium; ***Fr.:*** Kayexalate; ***Ger.:*** Elutit-Natrium; Resonium A; ***Gr.:*** Kayexalate; ***Hong Kong:*** Resonium A; ***Hung.:*** Resonium A; ***Irl.:*** Resonium A†; ***Israel:*** Kayexalate; ***Ital.:*** Kayexalate; ***Malaysia:*** Resonium A†; ***Neth.:*** Resonium A; ***NZ:*** Resonium A; ***Pol.:*** Resonium A; ***Port.:*** Resonium; ***S.Afr.:*** Kexelate; ***Singapore:*** Resinsodio; ***Spain:*** Resinsodio; ***Swed.:*** Resonium; ***Switz.:*** Resonium A; ***Thai.:*** Kayexalate; Resinsodio; Resonium A; ***UK:*** Resonium A; ***USA:*** Kayexalate; Kionex; SPS; ***Venez.:*** Kayexalate.

Multi-ingredient: ***Ger.:*** Ujostabil†.