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.

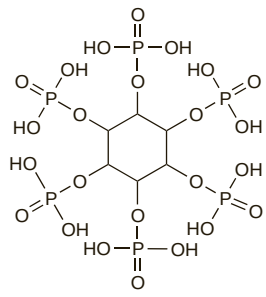
Sodium Fytate *(rINNM)*

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

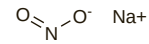
Dusitan sodný; E250; Natrii nitris; Natrio nitritas; Natrium Nitrosum; Natriumnitriitti; Natriumnitrit; Nátrium-nitrit; Nitrito sódico; Sodium, nitrite de; Sodu azotyn; Sodyum Nitrit.

$NaNO_2$ = 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