PROPHYLAXIS. Where the defect in B_{12} handling is irreversible, as in pernicious anaemia, maintenance therapy must continue for life to prevent a recurrence of the deficiency. Therapy must also be given prophylactically after total gastrectomy or total ileal resection, or where gastrointestinal surgery is shown to have impaired absorption of the vitamin. Typically, injection of hydroxocobalamin 1 mg every 3 months is used. In patients whose diet supplies inadequate B_{12}, deficiency may be prevented, in the absence of other causes, by much lower oral doses given as a supplement; up to 150 micrograms of cyanocobalamin daily has been recommended.

Folate-deficiency anaemia. Deficiency of folate may be due to inadequate diet, or malabsorption syndromes (such as coeliac disease or sprue), to increased need (as in pregnancy, one of the most common causes of megaloblastic anaemia, or the increased haematopoiesis of haemolytic syndromes), to increased urinary loss or loss due to haemodialysis, or to an adverse effect of alcohol, antiepileptics, or other drugs.

The clinical features of folate-deficient megaloblastic anaemia are similar to those of disease due to vitamin-B_{12} deficiency except that the accompanying severe neuropathy does not occur, and deficiency may develop much more rapidly. Deficiency may also be associated with neural tube defects (p.1942) if it occurs in pregnancy.

TREATMENT. Once folate deficiency has been established the usual treatment in the UK is folic acid 5 mg by mouth daily. Lower doses of up to 1 mg are suggested in the USA. It is customary to continue therapy for at least 4 months, the time necessary for complete red cell replacement. In patients with malabsorption, therapy may require higher doses, up to 15 mg of folic acid daily. As in B_{12}-deficiency anaemia, the response to therapy is rapid.

PROPHYLAXIS. Long-term maintenance is rarely needed, except in a few patients in whom the underlying cause of folate deficiency cannot be treated (for example in some severe haemolytic syndromes). Doses of 5 mg daily or even weekly have been suggested for prophylaxis in patients undergoing dialysis or with chronic haemolytic states, depending on the diet and rate of haemolysis; a dose of 400 micrograms daily is recommended in the USA.

For primary prophylaxis of megaloblastic anaemia in pregnancy, folic acid is given in the UK in usual doses of 200 to 500 micrograms daily, often with a ferrous salt for prophylaxis of iron deficiency.

Drugs that act as inhibitors of dihydrofolate reductase, such as methotrexate, may produce severe megaloblastic anaemia which cannot be reversed by therapy with folic acid. The adverse effects of such drugs may be largely prevented or reversed by therapy with folinic acid, which can be incorporated into folate metabolism without the need for reduction by the inhibited enzyme. For details of such 'folinic acid rescue', see under Folinic Acid, p.1944.

General references.

1. Wickramasinghe SN. Folate and vitamin B deficiency and supplementation. *Prescribers' J* 1997; **37:** 88–95.
2. Wickramasinghe SN. The wide spectrum and unresolved issues of megaloblastic anemia. *Semin Hematol* 1999; **36:** 3–18.
3. Rasmussen SA, *et al.* Vitamin B deficiency in children and adolescents. *J Pediatr* 2001; **138:** 10–17.
4. Hoffbrand V, Provan D. Macrocytic anaemias. In: Provan D, ed. *ABC of clinical haematology.* 2nd ed. London: BMJ Publishing Group, 2003.
5. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. *Annu Rev Nutr* 2004; **24:** 299–326.

Neural tube defects. There is abnormality in homocysteine metabolism in many women who give birth to children with neural tube defects (p.1942); the enzyme methionine synthase, which converts homocysteine to methionine, requires both folate and vitamin B_{12} as cofactors, and low maternal vitamin B_{12} concentrations may be an independent risk factor for neural tube defects.[1] A case-control study found elevated mid-trimester methylmalonic acid concentrations in women with pregnancies affected by neural tube defects, suggesting that abnormalities of cobalamin metabolism, and subsequent methylation, may be involved in the aetiology of neural tube defects.[2] Decreased vitamin B_{12} concentrations, but no folate deficiency, were found in 3 women with pregnancies affected by neural tube defects.[3] A review[4] of case-control studies found a moderate association between low maternal vitamin B_{12} status and the risk of fetal neural tube defects. If confirmed, this would suggest that additional supplementation with cobalamins may be warranted.[3-5]

1. Mills JL, *et al.* Homocysteine metabolism in pregnancies complicated by neural-tube defects. *Lancet* 1995; **345:** 149–51.
2. Adams MJ, *et al.* Elevated midtrimester serum methylmalonic acid levels as a risk factor for neural tube defects. *Teratology* 1995; **51:** 311–17.
3. Candito M, *et al.* Anomalies du tube neural et vitamine B12: à propos de trois cas. *Ann Biol Clin (Paris)* 2004; **62:** 235–8.
4. Ray JG, Blom HJ. Vitamin B12 insufficiency and the risk of fetal neural tube defects. *Q J Med* 2003; **96:** 289–95.
5. Refsum H. Folate, vitamin B12 and homocysteine in relation to birth defects and pregnancy outcome. *Br J Nutr* 2001; **85** (suppl): S109–S113.

Osteoporosis. An elevated serum homocysteine concentration appears to be a risk factor for osteoporotic fractures in older men and women.[1-3] Treatment with vitamin B_{12} and folate can reduce plasma homocysteine concentrations (see Cardiovascular Disease, under Folic Acid, p.1941). In a placebo-controlled study of patients with hemiplegia following stroke (and at increased risk of hip fracture),[4] those given folate and vitamin B_{12} were found to have a significantly reduced risk of hip fracture despite a lack of effect on bone mineral density. Vitamin B_{12} status has been associated with bone health in a number of studies,[3,5] and it was suggested that the observed effects on fracture might be due to increased concentrations of vitamin B_{12} rather than the lowering of plasma homocysteine.[3,6]

1. van Meurs JBJ, *et al.* Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med* 2004; **350:** 2033–41.
2. McLean RR, *et al.* Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med* 2004; **350:** 2042–9.
3. van Meurs JBJ, Uitterlinden AG. Homocysteine and fracture prevention. *JAMA* 2005; **293:** 1121–2.
4. Sato Y, *et al.* Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA* 2005; **293:** 1082–8. Correction. *ibid.* 2006; **296:** 396.
5. Dhonukshe-Rutten RAM, *et al.* Vitamin B-12 status is associated with bone mineral content and bone mineral density in frail elderly women but not in men. *J Nutr* 2003; **133:** 801–7.
6. Sugiyama T, *et al.* Folate and vitamin B for hip fracture prevention after stroke. *JAMA* 2005; **294:** 792.

Rhinitis. A sublingual formulation of cyanocobalamin (*PreHistin; Cobalis, USA*) has been reported to be under investigation in the management of seasonal allergic rhinitis, but published studies are lacking.

Preparations

BP 2008: Cyanocobalamin Tablets; Hydroxocobalamin Injection;
USP 31: Cyanocobalamin Injection; Hydroxocobalamin Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Benzoral†; Difenac Forte; Lisoneurin B12; Methycobal†; Reedvit†; SL B12; Vitam Doce; ***Austral.:*** Cytamen; Neo-Cytamen; ***Austria:*** Diclo-B; Erycytol; Hepavit; ***Belg.:*** Forta B†; ***Braz.:*** Bedozil; Cianon B12; Cronobe; Enzicoba; Rubranova; Vitadoze†; Zinabol†; ***Canad.:*** Bedoz†; ***Cz.:*** B Ankermann†; Neurobene; ***Denm.:*** Betolvex; Videben; ***Fin.:*** Betolvex; Cohemin; ***Fr.:*** Cobanzyme; Cyanokit; Dodecavit; Epithea; ***Ger.:*** Ambe 12; Aquo-Cytobion†; B 12-L 90†; B12 Depot-Rotexmedica; B12 Rotexmedica; B12 Steigerwald; B Ankermann; B Depot-Hevert; B Vicotrat†; B -ASmedic; Cytobion; Hamo-Vibolex†; Lophakomp-B 12; Lophakomp-B 12 Depot; Novidroxin†; Novirell B Mono; Vicapan N†; ***Gr.:*** Articlox; Idroxocobalamina†; ***Hong Kong:*** Cobamin; Cyanokit; Methycobal; ***Hung.:*** Feroglobin-B12; ***India:*** Mecovit; Methycobal; Myelogen†; ***Indon.:*** Arcored; Berthyco; Cobazim; Ethigobal; Kalmeco; Lapibal; Meconeuro; Megabal; Methycobal; Metifer; Mevrabal; Nerfeco; Neulamin; Nufacobal; Scanmecob; Sohobal; ***Irl.:*** Cytacon; Cytamen; Neo-Cytamen; ***Israel:*** Bedodeka; Bevitex; Nascobal; ***Ital.:*** Cobaforte; Dobetin; Eritrovit B12†; Indusil; Neo-Cytamen; OH B12; ***Jpn:*** Methycobal; ***Malaysia:*** Methycobal; Neuromethyn; ***Mex.:*** Axofor; Biocobal; Biotrefon L; Bissel 12; Compensal; Droxivit†; Duradoce; Exorvit; Fortical; Hidroxovit†; Leo-Doce; Maxibol; Nebal; Neribax†; Neurofor; Rubrina†; Sanovit; Selectofort†; Valamin 12†; ***Neth.:*** Hydrocobamine; ***Norw.:*** Betolvex; ***NZ:*** Neo-B12; Neo-Cytamen; ***Philipp.:*** Drexabion; Heraclene; Hybutin; Jaga; Lixtress; Mecovit; Meganerv; Methycobal; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Rubramin; Supraneuron; Vineuron; ***Port.:*** Algobaz†; Bedoze†; Co-Vibedoze; Cobamet†; Cobaxid; Dozefol; Jaba B ; OH B12; Permadoze; Tridocemine†; ***S.Afr.:*** Cobalatec; Norivite-12†; ***Singapore:*** Hidomin†; Methycobal; Neuromethyn; ***Spain:*** Asimil B12†; Cromatonbic B12; Isopto B 12; Megamilbedoce; Optovite B12; Reticulogen Fortificado†; Zimadoce; ***Swed.:*** Behepan; Betolvex; Betolvidon; ***Switz.:*** Betolvex; Vitarubin; ***Thai.:*** Ampavit; Hitocobamin; Mecobal; Merabin; Methycobal; Neuromet; Redisol†; Sicobal†; ***Turk.:*** Aktibol; Dodex; ***UAE:*** Cynovit; ***UK:*** Cobalin-H; Cytacon; Cytamen; Neo-Cytamen; ***USA:*** CaloMist; Crystamine; Crysti 1000; Cyanokit; Cyomin; Hydro Cobex; Hydro-Crysti-12; LA-12†; Nascobal; Twelve Resin-K; ***Venez.:*** Bedovit Simple; Beplus; Cristadoce; Dobetin; Docebe B12†; Droxofor†; Hidro-Doce; Ibedox; Maxibol.

Multi-ingredient: ***Arg.:*** Acifol-B12; Algio Nervomax; Algio Nervomax Fuerte; Anemidox-Ferrum; Anemidox-Solutab; Betametasona B12; Bioneural B12†; Blastop; Blokium B12; Buta Rut B12; Cobenexol Forte; Cobenexol Fuerte; Corteroid Gesic; CVP B1 B6 B12†; Dastonil; Delta Tomanil B12; Dexabion; Diclogesic Plus B12; Dioxaflex B12; Dolo Nervobion; Dolo Nervobion 10000; Dorixina B1 B6 B12; Doxtran B12; Factofer B12; Ferranin Complex; Ferrocebrina; Flexicamin B12; Flogiatrin B12; Hierro Folico; ITE B12 Forte; Klosidol B1 B6 B12; Nervobion Fuerte; Nervomax TB12; Nucleo CMP†; Oxa B12; Presterin; QX 10; Rodinac B12; Rubiron; Siderblut Folic; Sindrolen†; Tenvic; Tunik B12; Vesalion B12; Virobron B12 NF; Vitalix Complex; Xedenol B12; Yectafer Complex; ***Austral.:*** Medinat PMT-Eze†; ***Austria:*** Ambene; Ambene N; Arca-Be; Beneuran compositum; Diclovit; Neurobion; Neuromerck; Neuromultivit; Pronerv; Rheumesser; ***Belg.:*** Neurobion; Vioneurin†; ***Braz.:*** Aminocid†; Anemofer†; Bicavine; Calcifix B12; Calcinol Complexo; Cianotrat-Dexa; Citoneurin; Cobactin; Cobaglobal; Cobavit; Cobavital; Corabent†; Dexa-Citoneurin; Dexa-Cronobe; Dexa-Neuriberi†; Dexacobal; Dexador; Dexadoze; Dexagil; Dexalgen; Dexaneurin; Dexanevral†; Dozeneurin; Ferroplex; Ferrotrat; Fol Sang; Hematiase B12; Hepatotris†; Iloban; Lisan†; Lisotox; Metiocolin B12; Metiocolin Composto; Nucleo CMP; Tirubin†; Vi-Ferrin; Vitaneuron†; Vitatonus; Xantinon Complex; ***Canad.:*** Acti-B ; Fortiplex†; Penta-3B; Penta-3B + C; ***Chile:*** Betonvit†; Citoneuron; Cronoferril†; Dolotol 12; Ferranem; Ferranim; Foli Doce; Folifer; Nefersil B; Neurobionta; Neurocam; Tol 12; Tol 12 Plus; ***Cz.:*** Aktiferrin Compositum; Dicopac†; Ferro-Folgamma; Milgamma; Milgamma N; Neuromultivit; ***Fin.:*** Neurobion; Neurovitan; ***Ger.:*** Ambene Comp†; B-Komplex forte; B Fol-Vicotrat†; Dolo-Neurobion forte†; Eryfer comp; Eukalisan N; Ferro sanol comp; Ferro-Folgamma; Folgamma; Hepagrisevit Forte-N†; Medivitan N; Medyn; Milgamma N; Neuro-ratiopharm†; Neurobion; NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; Selectafer N†; Telbibur N†; Vitaject†; Vitasprint B †; ***Gr.:*** Neurobion; ***Hong Kong:*** 3B; Neuro B1-6-12†; Neurobion; Neuromin; Neurorubine; Nevramin; Princi-B Fort; Vibion; Vida Neurotab; Vidaclofen-Plus; ***Hung.:*** Atherovit; Ferro-Folgamma; Milgamma; Milgamma N; Neurobion; ***India:*** Alcrin-M; Anemidox; Blosyn; Calcinol; Carboflot†; Conviron-TR; Delphicol; Dexorange; Elferri-Z; Ferrochelate; Fervit†; Genfol; Globac-Z; Hepasules; Hepatoglobine; Jectocos Plus; Macalvit; Omilcal; Ostocalcium B-12; Plastules; Sigmacalvit; Sioneuron; Softeron; Tonoferon; Vitamon; Vitneurin; ***Indon.:*** Abajos; Adfer; Arsinal; Betrion; Bicitron; Biocombin; Biomega; Biomex; Biosanbe; Corobion; Corsaneuron; Daneuron; Dolo Scanneuron; Dolo-Licobion; Dolo-Neurobion; Dolofenac; Farbion; Foraneural; Fundamin-E; Goralgin; Ikaneuron; Ikaneuron Plus; LaktaFit; Lapibion; Licobion; Mecola; Moloco + B12; Neogobion; Nervitone; Nervitone E; Neuralgin RX; Neuro Panstop; Neuro-Beston; Neurobat; Neurobat A; Neurobion; Neurobiovit; Neurodex; Neurohax; Neurophil; Neuropyramin; Neurosanbe; Neurosanbe Plus; Neurotrat; Neurotropic Plus; Neurovit E; Nevradin; Nevramin; Penagon; Ponconeuron; Primabion; Pritagesic; Remasal; Sangobion; Scanneuron; Sohobion; Solaneuron; Stileran; Tocobion; Trimate-E; Tropineuron; ***Israel:*** Tribemin; Tricardia; ***Ital.:*** Adenobeta†; Adenoplex; Adenovit†; Benexol B12; Briogen†; Calcio Dobetin; Co-Carnetina B12; Dobetin con Vitamina B1; Dobetin Totale; Emazian B12†; Emoantitossina†; Emopon; Epargriseovit; Eparmefolin; Fibronevrina; Folepar B12; Fosfo Plus; Fosfoutipi Vitaminico†; Gluta Complex†; Glutamin Fosforo; Hepa-Factor; Hepatos B12; Memovisus†; Memovit B12; Mionevrasi; Neo-Eparbiol†; Neuraben; Porfirin 12; Tonogen; Tricortin; Trinevrina B6; Vitasprint Complex†; Vitasprint†; ***Jpn:*** Neurovitan†; ***Malaysia:*** 3B; Alinamin B12†; Ferrovit; Flavettes Neuroforte; Fundamin-E; Neuro B†; Neurobion; Neurorubine; Neurovit†; Nevramin; Princi-B Fort; Re-B; Sangobion; Vitabion; ***Mex.:*** Ariflam Forte; B1-12-15; Bedoce-Cal; Bedocil†; Benexol B12; Betrox; Ciprolisina; Cobotiaxina; Dexabion; Diclovith-B; Dodemina Tri; Dolo-Neurobion; Dolo-Pangavit; Dolo-Tiaminal; Doxemina; Duciclon; Forvin; Gonakor; Innobion; Intrafer F-800; Iodarsolo B12†; Macrox-5; Milbeta; Neuralin; Neurobion; Neuroflax; Nuro-B; Odexan; Orafer Comp; Pangavit B; Pangavit Hypak; Pangavit Pediatrico; Revitaliv-C; Selectadoce; Suma-B; Tiabexol; Tiamidexal; Tiaminal B ; Tiaminal B Trivalente; Tribedoce; Tribedoce Compuesto; Tribedoxyl†; Trineurovita; Trineurovita Compuesto; Uni-Dox; ***Neth.:*** Neurobion; ***Philipp.:*** Beniforte; Dolo-Neurobion; Essenfer; Glutaphos; Godex; Harvifer; Hinuron-E; Meganerv F-A; Neuroforte-E; Nevramin; Nuron-E; Osteo-4; Sangobion; TriHEMIC; Vitanerv; ***Pol.:*** Additiva Ferrum; Milgamma N; Vegevit B ; ***Port.:*** Linamin Plus†; Neobefol; Neurobion; ***Rus.:*** Ambene (Амбене); Ferro-Folgamma (Феррo-Фольгамма); Milgamma (Мильгамма); Neuromultivit (Нейромультивит); ***S.Afr.:*** Foliglobin; Neurobion; Prohep; Sentinel Ulcer Mixture; ***Singapore:*** Aktiferrin-F; Alinamin B12†; Daneuron; Iron Melts; Neogobion; Neurobion; Neurodex; Neuroforte; Neurorubine; Neurovit; Neuroxel; Nevramin; Princi-B Fort; Sangobion; Wanse; ***Spain:*** Antineurina; Benexol B1 B6 B12; Bester Complex; Calcio 20 Complex; Covitasa B12; Dalamon†; Duplicalcio B12; Enoton; Foli Doce; Hepa Factor; Hidroxil B12 B6 B1; Inzitan; Malandil; Mederebro; Menalgil B6; Nervobion; Neuromade; Neurostop Complex; Refulgin; Rubrocortin†; Taurobetina†; Tonico Juventus; Trofalgon; Viadetres†; Vitafardi C B12; ***Swed.:*** Neurobion; ***Switz.:*** Benexol B12; Neurorubin; Trilagavit; Vitasprint Complex; ***Thai.:*** 3B; Alinamin B12†; Beromin; Cydoxmine-B†; Cyriamine; Douzabox; Genavit; Hemolax; Neubee; Neurobex; Neurobion; Nevramin; Nuro-B; Nuvit; Ostone-B12; Princi-B; Re-B Forte; Trabit†; Tribesian; Tricortin†; Trinsicon†; Trivit-B; Vita-B; Vitabion; Vitamedin†; Vitron; ***Turk.:*** Blood Builder; Epargriseovit; Neurogriseovit; Tribeksol; ***UAE:*** 3V; ***UK:*** Dicopac; Hematinic; ***USA:*** Anemagen†; Bevitamel; Cerefolin; Chromagen; Chromagen FA; Chromagen Forte; Contrin; Fe-Tinic Forte; FeoGen; Ferotrinsic; Ferralet Plus†; Ferrex Forte; Ferrex Forte Plus†; Ferrogels Forte; Fetrin; FOLTX; Fumatinic; Hem Fe; Hemocyte-F; Icar-C Plus; Livitrinsic-f; Metanx; Niferex Forte; Poly-Iron Forte; PremesisRx; Pronemia Hematinic; Tolfinic; TriHEMIC; Trinsicon; ***Venez.:*** Autrin†; Bedoyecta; Beferron; Befosfin; Briomet; Cianofer; Cobalfer; Deca-Lentermina Complex; Dobetin Compuesto; Fefol; Fercobre B-12†; Fercor†; Ferroce con B12; Folifer B-12; Hepafol; Hepafol con B-12; Intafer; Lentermina Complex; Mega-Neubion; Miovit; Neubion; Neuribe; Rubrinal; Rubrinex; Tres-Be.

Vitamin C Substances

Vitamina C.

Several substances have vitamin C activity, notably ascorbic acid and its calcium and sodium salts. Natural products with a high vitamin C content include black currant (p.2267), lemon (p.2332), sweet orange (p.2357), and rose fruit (p.2381).

Ascorbic Acid *(BAN, rINN)*

Acide ascorbique; Ácido ascórbico; Acidum ascorbicum; L-Ascorbic Acid; Askorbiinihappo; Askorbik Asit; Askorbinsyra; Askorbo rūgštis; Aszkorbinsav; Cevitamic Acid; E300; Kwas askorbowy; Kyselina askorbová; Vitamin C. The enolic form of 3-oxo-L-gulofuranolactone; 2,3-Didehydro-L-*threo*-hexono-1,4-lactone.

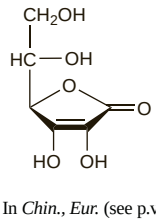
Аскорбиновая кислота

$C_6H_8O_6$ = 176.1.

CAS — 50-81-7.

ATC — A11GA01; G01AD03; S01XA15.

ATC Vet — QA11GA01; QG01AD03; QS01XA15.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Ascorbic Acid). A white or almost white crystalline powder or colourless crystals becoming discoloured on exposure to air and moisture. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 2.1 to 2.6. Store in nonmetallic containers. Protect from light.

USP 31 (Ascorbic Acid). White or slightly yellow crystals or powder. On exposure to light, it gradually darkens. In the dry state, is reasonably stable in air, but in solution rapidly oxidises. Soluble 1 in 3 of water and 1 in 40 of alcohol; insoluble in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Calcium Ascorbate *(BANM, rINNM)*

Ascorbate de Calcium; Ascorbato cálcico; Askorban vápenatý dihydrát; Calcii ascorbas; Calcii Ascorbas Dihydricus; Calcium, ascorbate de; E302; Kalcio askorbatas; Kalciumaskorbat; Kalciumaszkorbát; Kalsiumaskorbaatti.

Кальций Аскорбат

$(C_6H_7O_6)_2Ca,2H_2O$ = 426.3.

CAS — 5743-27-1.

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

Ph. Eur. 6.2 (Calcium Ascorbate). A white or slightly yellowish crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water has a pH between 6.8 and 7.4. Store in nonmetallic containers. Protect from light.

USP 31 (Calcium Ascorbate). A white to slightly yellow, practically odourless, powder. Freely soluble in water (about 1 in 2); slightly soluble in alcohol; insoluble in ether. pH of a 10% solution in water is between 6.8 and 7.4. Store in airtight containers. Protect from light.

Sodium Ascorbate *(BANM, rINN)*

Ascorbate de sodium; Ascorbate sodique; Ascorbato de sodio; Askorban sodný; E301; Monosodium L-Ascorbate; Natrii ascorbas; Natrio askorbatas; Natriumaskorbaatti; Natriumaskorbat; Nátrium-aszkorbát. 3-Oxo-L-gulofuranolactone sodium enolate.

Натрия Аскорбат

$C_6H_7NaO_6$ = 198.1.

CAS — 134-03-2.

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

Ph. Eur. 6.2 (Sodium Ascorbate). A white or yellowish crystalline powder or crystals. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 7.0 to 8.0. Store in nonmetallic containers. Protect from light.

USP 31 (Sodium Ascorbate). White or very faintly yellow, odourless or practically odourless, crystals or crystalline powder. On exposure to light it gradually darkens. Soluble 1 in 1.3 of water; very slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 7.0 and 8.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Ascorbic acid is usually well tolerated. Large doses are reported to cause diarrhoea and other gastrointestinal disturbances. It has also been stated that large doses may result in hyperoxaluria and the formation of renal calcium oxalate calculi and ascorbic acid should therefore be given with care to patients with hyperoxaluria (see Effects on the Kidneys, below). Tolerance may be induced with prolonged use of large doses, resulting in symptoms of deficiency when intake is reduced to normal. Prolonged or excessive use of chewable vitamin C preparations may cause erosion of tooth enamel.

Large doses of ascorbic acid have resulted in haemolysis in patients with G6PD deficiency (see Effects on the Blood, below).

Breast feeding. Vitamin C is excreted into breast milk and thus supplied to breast-feeding infants. Lactating women in developing countries have significantly lower concentrations of ascorbic acid in their breast milk compared with lactating women in developed countries,[1] and seasonal variation in consumption of foods rich in vitamin C leads to variable amounts of ascorbic acid in breast milk.[2] Supplementation with high-dose ascorbic acid (1 g daily for 10 days) led to significant increases in breast-milk concentrations in both European and African women;[1] however, the overall effect was modest in European women compared with a threefold increase observed in African women. Lower doses of 100 mg daily for 10 days approximately doubled the ascorbic acid breast milk content in the latter, as did supplementation with orange juice 3 or 5 times a week; a significant day-to-day effect was also noted, indicating that the ascorbic acid content of breast milk is regulated. In a small study[2] involving four different doses of ascorbic acid supplements, women in West Africa showed that increased intake caused an increase in the ascorbate concentration of breast milk, but concentrations approached a plateau at higher intakes; it was concluded that about 100 to 120 mg of vitamin C daily was needed to achieve acceptable plasma and breast-milk ascorbate concentrations in this population.

1. Daneel-Otterbech S, *et al.* Ascorbic acid supplementation and regular consumption of fresh orange juice increase the ascorbic acid content of human milk: studies in European and African lactating women. *Am J Clin Nutr* 2005; **81:** 1088–93.
2. Bates CJ, *et al.* The effect of vitamin C supplementation on lactating women in Keneba, a West African rural community. *Int J Vitam Nutr Res* 1983; **53:** 68–76.

Effects on the blood. There are reports of haemolysis in patients with G6PD deficiency after large doses of ascorbic acid either intravenously[1,2] or in soft drinks.[3] There has also been a report[4] of a patient with paroxysmal nocturnal haemoglobinuria suffering haemolysis after taking large amounts of ascorbic acid in a soft drink. There is concern that the large quantities of vitamin C in feeds for premature neonates may have a pro-oxidant effect, and lead to haemolysis. However, a double-blind study found no increase in erythrocyte destruction or hyperbilirubinaemia in premature neonates receiving vitamin C.[5]

1. Campbell GD, *et al.* Ascorbic acid-induced hemolysis in G-6-PD deficiency. *Ann Intern Med* 1975; **82:** 810.
2. Rees DC, *et al.* Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency. *BMJ* 1993; **306:** 841–2.
3. Mehta JB, *et al.* Ascorbic-acid-induced haemolysis in G-6-PD deficiency. *Lancet* 1990; **336:** 944.
4. Iwamoto N, *et al.* Haemolysis induced by ascorbic acid in paroxysmal nocturnal haemoglobinuria. *Lancet* 1994; **343:** 357.
5. Doyle J, *et al.* Does vitamin C cause hemolysis in premature newborn infants? Results of a multicenter double-blind, randomized, controlled trial. *J Pediatr* 1997; **130:** 103–9.

Effects on the kidneys. Although renal impairment associated with excessive oxalate excretion has been reported with large doses of ascorbic acid[1-3] it has been considered that healthy persons can ingest large amounts of ascorbic acid with relatively small increases in oxalate excretion[4-6] and without an increased risk of oxalate stone formation. A study of vitamin C supplementation with 1 or 2 g given daily for 3 days in calcium stone-forming patients, and 1 g given daily for 3 days in healthy subjects, found that urinary oxalate excretion and the risk of calcium oxalate crystallisation increased significantly in all groups.[7] A prospective cohort study found that increased vitamin C intake (over 1 g daily) was positively associated with the risk of stone formation; an increased risk was observed even at lower intakes of about 90 to 250 mg daily. The risk was raised for both dietary and supplemental vitamin C intake. However, the relation between vitamin C intake and stone formation had emerged only after the inclusion of dietary potassium in the analysis, with potassium intake positively associated with dietary vitamin C intake, but inversely associated with stone formation. This led the authors to conclude that, while limiting dietary vitamin C intake in men with calcium oxalate nephrolithiasis was unwarranted (because of the high potassium content of vitamin C-rich foods), supplemental vitamin C should be avoided.[8]

1. Reznik VM, *et al.* Does high-dose ascorbic acid accelerate renal failure? *N Engl J Med* 1980; **302:** 1418–19.
2. Swartz RD, *et al.* Hyperoxaluria and renal insufficiency due to ascorbic acid administration during total parenteral nutrition. *Ann Intern Med* 1984; **100:** 530–1.
3. Balcke P, *et al.* Ascorbic acid aggravates secondary hyperoxalemia in patients on chronic hemodialysis. *Ann Intern Med* 1984; **101:** 344–5.
4. Tsao CS. Ascorbic acid administration and urinary oxalate. *Ann Intern Med* 1984; **101:** 405–6.
5. Wandzilak TR, *et al.* Effect of high dose vitamin C on urinary oxalate levels. *J Urol (Baltimore)* 1994; **151:** 834–7.
6. Curhan GC, *et al.* Intake of vitamins B6 and C and the risk of kidney stones in women. *J Am Soc Nephrol* 1999; **10:** 840–5.
7. Baxmann AC, *et al.* Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. *Kidney Int* 2003; **63:** 1066–71.
8. Taylor EN, *et al.* Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol* 2004; **15:** 3225–32.

Effects on mortality. There is some suggestion that serum ascorbic acid concentrations are inversely related to all-cause mortality;[1-4] serum levels were also inversely related to cancer mortality in men but not in women.[1-3] However, a meta-analysis of 3 studies found vitamin C supplementation to have no benefit on mortality in elderly people.[5] A systematic review of antioxidant supplementation in adults also found no significant effect on mortality from studies in which vitamin C was used either singly or with other antoxidants;[6] small beneficial effects or large harmful effects could not be excluded, and since vitamin C can also act as a pro-oxidant, further studies should monitor closely for any harm.

1. Loria CM, *et al.* Vitamin C status and mortality in US adults. *Am J Clin Nutr* 2000; **72:** 139–45.
2. Simon JA, *et al.* Relation of serum ascorbic acid to mortality among US adults. *J Am Coll Nutr* 2001; **20:** 255–63.
3. Khaw K-T, *et al.* Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. *Lancet* 2001; **357:** 657–63.
4. Fletcher AE, *et al.* Antioxidant vitamins and mortality in older persons: findings from the nutrition add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community. *Am J Clin Nutr* 2003; **78:** 999–1010.
5. Ness A, *et al.* Role of antioxidant vitamins in prevention of cardiovascular diseases. *BMJ* 1999; **319:** 577.
6. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Effects on the teeth. A report of dental enamel erosion attributed to the daily ingestion of chewable ascorbic acid tablets over a period of 3 years.[1] The tablets lowered the pH of the saliva to a level at which calcium was lost from the tooth enamel.

1. Giunta JL. Dental erosion resulting from chewable vitamin C tablets. *J Am Dent Assoc* 1983; **107:** 253–6.

Interference with laboratory tests. Ascorbic acid, a strong reducing agent, interferes with laboratory tests involving oxidation and reduction reactions. Falsely-elevated or false-negative test results may be obtained from plasma, faeces, or urine samples depending on such factors as the dose of ascorbic acid and specific method used.

Interactions

For the effect of ascorbic acid on various drugs see under desferrioxamine (p.1440), hormonal contraceptives (p.2068), HRT (p.2076), fluphenazine (under Chlorpromazine, p.975), and warfarin (p.1432). Ascorbic acid may increase the absorption of iron in iron-deficiency states. Omeprazole may affect the bioavailability of dietary vitamin C (see Malabsorption, under Omeprazole, p.1754).

Pharmacokinetics

Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Plasma concentrations of ascorbic acid rise as the dose ingested is increased until a plateau is reached with doses of about 90 to 150 mg daily. Body stores of ascorbic acid in health are about 1.5 g although more may be stored at intakes above 200 mg daily. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. In deficiency states the concentration in leucocytes declines later and at a slower rate, and has been considered to be a better criterion for the evaluation of deficiency than the concentration in plasma.

Ascorbic acid is reversibly oxidised to dehydroascorbic acid; some is metabolised to ascorbate-2-sulfate, which is inactive, and oxalic acid which are excreted in the urine. Ascorbic acid in excess of the body's needs is also rapidly eliminated unchanged in the urine; this generally occurs with intakes exceeding 100 mg daily. Ascorbic acid crosses the placenta and is distributed into breast milk. It is removed by haemodialysis.

Human Requirements

A daily dietary intake of about 30 to 100 mg of vitamin C has been recommended for adults. There is, however, wide variation in individual requirements. Humans are unable to form their own ascorbic acid and so a dietary source is necessary. Most dietary ascorbic acid is obtained from fruit and vegetable sources; only small amounts are present in milk and animal tissues. Relatively rich sources include rose hips (rose fruit), black currant, citrus fruits, leafy vegetables, tomatoes, potatoes, and green and red peppers.

Ascorbic acid is readily destroyed during cooking processes. Considerable losses may also occur during storage.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p.1925) have been published for vitamin C and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women. In the UK the reference nutrient intake (RNI) is 40 mg daily for adult males and females and the estimated average requirement (EAR) is 30 mg daily. In general the amount recommended in the USA for all ages and groups is higher than that set in the UK; the RDA is 90 mg daily for men and 75 mg daily for women.[2] The RDA is increased in smokers by 35 mg daily. The tolerable upper intake level is 2 g daily.[2] The EAR is 75 mg daily for men and 60 mg daily for women.

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 vitamin C, vitamin E, selenium, and carotenoids*. Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)

Uses and Administration

Vitamin C, a water-soluble vitamin, is essential for the synthesis of collagen and intercellular material. Vitamin C deficiency develops when the dietary intake is inadequate. It is rare in adults, but may occur in infants, alcoholics, or the elderly. Deficiency leads to the devel-