12. Phelps DL, *et al*. D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).
13. Reynolds JD, *et al*. Lack of efficacy of light reduction in preventing retinopathy of prematurity. *N Engl J Med* 1998; **338:** 1572–6.
14. Phelps DL, Watts JL. Early light reduction for preventing retinopathy of prematurity in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).

Tardive dyskinesia. Reviews[1,2] on the use of vitamin E in the management of antipsychotic-induced tardive dyskinesia (see under Extrapyramidal Disorders, p.971) concluded that evidence of benefit has generally come from small studies with methodological problems. One review[1] concluded that whereas vitamin E may protect against deterioration of tardive dyskinesia there was no evidence that it produced symptomatic improvement. It was suggested[2] that vitamin E therapy may be most beneficial in those patients with tardive dyskinesia of less than 5-years duration. Some recommend vitamin E as a treatment option in patients with newly diagnosed disease.[3] Further large-scale studies are required to establish its place in treatment.

1. Soares KVS, McGrath JJ. Vitamin E for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 09/01/06).
2. Boomershine KH, *et al*. Vitamin E in the treatment of tardive dyskinesia. *Ann Pharmacother* 1999; **33:** 1195–1202.
3. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Ann Pharmacother* 2005; **39:** 2065–72.

Preparations

BP 2008: Alpha Tocopheryl Succinate Tablets;
USNF 26: Tocopherols Excipient;
USP 31: Vitamin E Capsules; Vitamin E Preparation.

Proprietary Preparations (details are given in Part 3)
Arg.: Antioxidante Natural; E-devit Protectora; Ephynal; Etec; Evion; Risordan†; Senexon E†; Tonovital E; ***Austral.:*** Bioglan Micelle E; Bioglan Natural E; Bioglan Water Soluble E; Chew-E; Dal-E; Macro E†; Mega E†; Vita E†; ***Austria:*** Avigilen; Ephynal; Etocomed; Evitol; Tocovenos; ***Belg.:*** Docviteee; Ephynal; Optovit E; ***Braz.:*** E Plus; E Radicaps; E-Mil†; E-Tabs; Eferol†; Emama; Ephynal; Fonto-Vit E; Fort E; Teutovit-E; Vieta; Vita-E; Vitizin E; Zirvit E; ***Canad.:*** Aquasol E; Kyolic Formula 106; Novo E; Nutrol E; One A Day Cholesterol Health†; Organex†; ***Chile:*** Crevet-E; Egogyn; Etec; ***Cz.:*** Biogelat Vitamin E†; Erevit; Evit†; Sant-E-Gal†; ***Fin.:*** Bio-E-Vitamin; Equiday; Esol†; Ido-E; Tokovitan; Vita-E†; ***Fr.:*** Dermorelle; Ephynal†; Toco; Tocolion; Tocopa; ***Ger.:*** Antioxidans E; Biopto-E; Biosan E; Detulin; E-Mulsin†; E-Tonil; E-Vicotrat; Elex E; Embial†; Ephynal†; Eplonat; Eusovit; Evion; Flexal Vitamin E; Malton E; Mowivit; Optovit; Puncto E; Sanavitan S; Spondyvit; Tocorell; Tocovital; Togasan; Uno-Vit; Vibolex E; Vita-E; Vitagutt Vitamin E†; Vitazell E; ***Gr.:*** E-Vicotrat; Ephynal†; Eviol; ***Hong Kong:*** Clinic†; Keri Vit E; Myra 300-E; Natopherol; Topher-E; ***India:*** Ecap; EEE; Evion; Evitam; Greenpearl†; ***Indon.:*** Bio-E; Dalfarol; Edoti; Evion; Evipon; Lanturol; Natopherol; Natur-E; Naturol; Prima-E; Proxidan; Santa-E; Tocopherine; Vinpo-E; Vitaferol; ***Irl.:*** Ephynal†; ***Israel:*** Ephynal†; Evitex; Evitol; ***Ital.:*** E-Vitum; Ephynal; Evasen Crema; Evion; Natovit; Rigentex; Sursum; ***Malaysia:*** Citrex Vitamin E; E Vita†; Fairy ADE; Juvela†; Natopherol; Toco-E; ***Mex.:*** Bacferol†; E-Fertoc; Egrin; EPH; Eugerminol†; Ixopolet; Revitare E; Vit-E-Far; Vitalle†; ***Norw.:*** Bio-E-Vitamin; Ido-E; Nycoplus E; ***NZ:*** Micelle E; ***Philipp.:*** Enat; Enervon-E; Evion; Myra; Zyme E; ***Pol.:*** Dermovit E; Tokovit E; Vitole E; ***Port.:*** Ephynal; Ve; ***Rus.:*** Evitol (Эвитол); ***S.Afr.:*** Ephynal; Vitaforce E; ***Singapore:*** Myra 300-E; Natopherol; Naturee; ***Spain:*** Auxina E; Ephynal; ***Swed.:*** E-vidon; E-vimin; Ido-E; ***Switz.:*** ecobiosan; Ephynal; Evit; Lipo E†; Optovit; ***Thai.:*** Bio-E; E-Drops; ***Turk.:*** Eforol; Ephynal; Evicap; Evigen; Evon; Grandpherol; Natural E; Natural Wealth; ***UK:*** Ephynal; Prairie Gold; Vita-E; ***USA:*** Aqua-E; Aquasol E; Aquavit-E; E-Gems; Nutr-E-Sol; Vita-Plus E; Vitec; ***Venez.:*** Best; Ecogyn†; Egogyn; Ephynal†; Epol; Missecap; Nat-E; Vit-E-Nat; Vit-E-Var; Vitae; Viteral.

Multi-ingredient: ***Arg.:*** A-Vitel E; Abanta; Acilac; Atomoderma A-E; Brunavera; Cardiax; Cellskinlab C + E; Centella Asiatica Diates; Centella Asiatica Vital; Centellase de Centella Queen; Crema De Ordene; Culuflex H; Dermanova; E-devit; Epitheliale A-Derma; Estri-Atlas; Eurocolor Bronceador; Factor Vit AE; Lipofundin MCT/LCT-E; Liposomas; Nectar G; Oxidermos; Redudiet; SCV 300; Sigmafem; Snella; Snella Vag; Sojasterol†; Solenil Post Solar; Vansame; VNS 45; ***Austral.:*** Althaea Complex; Antioxidant Forte Tablets; Antioxidant Tablets; Arthriforte; Beta A-C; Bioglan Bioage Peripheral; Bioglan Micelle A plus E; Bioglan Primrose-E; Curash Baby Wipes; Curash Babycare; ER Cream†; Eye Health Herbal Plus Formula 4; Ginkgo Complex†; Hair and Skin Formula†; Lifechange Circulation Aid†; Lifesystem Herbal Plus Formula 5 Eye Relief†; Lifesystem Herbal Plus Formula 8 Echinacea†; Macro Natural Vitamin E Cream; ML 20†; Sambucus Complex†; Serenoa Complex†; ***Austria:*** A-E-Mulsin; Arcavit A/E; Coldistop; Droxaryl; Gerogelat; Mamellin; Pasuma-Dragees; Regenerin†; Rovigon; Ulcurilen; Vasovitol; ***Belg.:*** Rovigon; ***Braz.:*** Adeforte; Licovit; ***Canad.:*** Bionagre plus E; Lubriderm Advanced Moisture†; PML Crono†; ***Chile:*** Dermaglos; Dermaglos Plus†; Rovigon; ***Cz.:*** A-E-Mulsin†; Coldastop; Dr Theiss Beinwell Salbe†; Fluocaril Bi-Fluore Vitamin E†; Lipovitan†; Vitazulen†; ***Fin.:*** Aesol; Cellavie†; ***Fr.:*** Alpha 5 DS†; Bakol; BiaZinc†; Bio-Selenium; Cicatryl; Cirkan a la Prednacinolone; Difrarel E; Ophtadil†; Phytolongbronze; Phytosolaire; Reti-Nat; Rovigon†; Seborheane; Tonimer; Topialyse; Topialyse Fluide; Topialyse Plus; ***Ger.:*** A + E Thilo†; A-E-Mulsin†; anabol-loges; Coldastop; Dynef†; Hewekzem novo N; Lipidavit; Lipovitan†; Magnesium Tonil mit Vitamin E; Magnesium-Plus-Hevert; Mapurit; NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; NeyPulpin N (Revitorgan-Dilutionen N Nr 10)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; Protecor; Remederm; Rovigon G†; RubieMag + E†; Salus Herz-Schutz-Kapseln†; Saluscor Herz-Schutz; Tears Again; Ulcurilen N†; Unguentacid; Ureata S†; Vaso-E-Bion; ***Gr.:*** Avegon; Eviol-A; ***Hong Kong:*** Aderma Epitheliale†; Apaisac; Basikol; Difrarel E; Doctor's Choice Omega 3; DS Emulsion; E-Prime†; Eye Q; Pilelife; Pregnacare; Sanjukei Panax Ginseng; Welsan Lipocream; ***Hung.:*** Alksebor; Coldastop; Difrarel E; Magnevital; ***India:*** Cadvion; Elovera; Elovera-SPF; Rovigon†; Sclerobion; Seaking Plus†; Sofderm; Vitexid; ***Indon.:*** Fundamin-E; Garlic-Plus; Hepamax; Jointfit; Juvelon-C; Lanakeloid-E; Lapibion; Legreskin; Lesifit; Lycoq; Nervitone E; Remasal; RG-Q; Tocobion; Trimate-E; Velostin; Voldilex; ***Ital.:*** Angstrom Viso; Apogeo; Babysteril; Capill; Colesterase; Coqun; Derman-Oil; Dermana Crema; Dermana Pasta; Ecamannan; Efagel; Emortrofine; Ener-E†; Eurogel; Forticrin; Granoleina†; Ictom 3†; Midium; Migel; Mirtilene; Pasta Dicofarm; Provitamin A-E; Retinovit; Rovigon; Royal E; Rutisan CE†; Skarflex; Tannidin Plus; Tocalfa; Ultravisin; Vasopt; Vit Eparin; ***Malaysia:*** Balance Elastin E†; Boots Antenatal Massage Cream†; Elovera; Natopherol Dermal-Day†; Prim E; Salonpas; Tocovid; ***Mex.:*** Aveendix; Cardioprotect; Cetopic; Emolin Neo; Hipoglos Cremoso; Nutrem; Panaline†; Periodentyl; ***Neth.:*** Dagravit A-E Forte†; ***NZ:*** Chap Stick; ***Philipp.:*** Elovera; Hinuron-E; Neuroforte-E; Nuron-E; Pynocare 40 Actisome; Remederm; Rovigon; ***Pol.:*** Capivit A + E; Dehalid†; Lecytyna E; MBE; Tokovit A + E; ***Port.:*** Alkagin; Antiestrias; Creme Laser Hidrante; Esclerobion; Nutraisdin; Rilastil Dermo Solar; Rovigon; Synchrorose; Synchrovit; Zolium†; ***Singapore:*** Desitin Creamy†; E-Prime; Erase; ***Spain:*** Auxina A + E; Vitaber A E; Wobenzimal†; ***Switz.:*** Alphastria; Coldistop; Leniderm†; Oravil; Rovigon; Visaline; ***Thai.:*** Men Hormone; Siduol; ***UK:*** Octacosanol; Se-Power; ***USA:*** Aloe Grande; Diaper Guard; Lactinol-E; Lazercreme; Lobana Derm-Aide; Lobana Peri-Garde; Phicon; Tucks; Wound Cleanser; Ze Caps†; ***Venez.:*** Ademina; Kalsis.

Vitamin K Substances

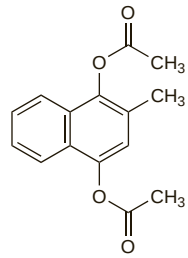
Vitamina K.

The term vitamin K is used for a range of naphthoquinone compounds that includes: acetomenaphthone, menadiol, menadione, menatetrenone, and phytomenadione.

Acetomenaphthone *(BAN)*

Acetomenadione; Acetomenaftona; Acetomenaph.; Menadiol Diacetate; Vitamin K_4 Diacetate. 2-Methyl-1,4-naphthylene diacetate.

$C_{15}H_{14}O_4$ = 258.3.
CAS — 573-20-6.

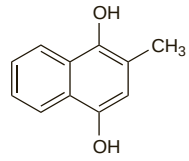


Pharmacopoeias. In *Chin.*

Menadiol Sodium Phosphate *(BANM)*

Menadiol, fosfato sódico de; Menadiol Sodium Diphosphate; Menadiolum Solubile; Vitamin K_4 Sodium Phosphate. 2-Methylnaphthalene-1,4-diyl bis(disodium phosphate) hexahydrate.

$C_{11}H_8Na_4O_8P_2,6H_2O$ = 530.2.
CAS — 481-85-6 (menadiol); 131-13-5 (anhydrous menadiol sodium phosphate); 6700-42-1 (menadiol sodium phosphate hexahydrate); 84-98-0 (menadiol diphosphate).



(menadiol)

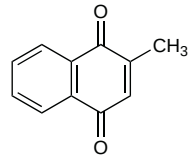
NOTE. Menadiol Potassium Sulfate (Potassium Menaphthosulfate) is *BAN* and Menadiol Sodium Sulfate is *rINN*.

Pharmacopoeias. In *Br.* and *US.*
BP 2008 (Menadiol Sodium Phosphate). A white to pink, hygroscopic, crystalline powder with a characteristic odour. Very soluble in water; practically insoluble in alcohol.
USP 31 (Menadiol Sodium Diphosphate). A white to pink, hygroscopic, powder having a characteristic odour. Very soluble in water; insoluble in alcohol. Its solutions in water are neutral or slightly alkaline to litmus having a pH of about 8. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Menadione *(BAN)*

Menadion; Menadiona; Menadionas; Ménadione; Menadioni; Menadionum; Menaph.; Menaphthene; Menaphthone; Methylnaphthochinonum; Vitamin K_3. 2-Methyl-1,4-naphthoquinone.

$C_{11}H_8O_2$ = 172.2.
CAS — 58-27-5.
ATC — B02BA02.
ATC Vet — QB02BA02.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Menadione). A pale yellow crystalline powder. It is unstable in light. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in toluene. Protect from light.
USP 31 (Menadione). A bright yellow, practically odourless, crystalline powder. It is affected by sunlight. Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 50 of vegetable oils, and 1 in 10 of benzene; sparingly soluble in chloroform. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Handling. Menadione powder is irritating to the respiratory tract and to the skin. The alcoholic solution has vesicant properties.

Menadione Sodium Bisulfite *(rINN)*

Bisulfito sódico de menadiona; Kavitanum; Menadiol Sodyum Bisülfit; Ménadione, Bisulfite Sodique de; Menadione Sodium Bisulphite *(BANM)*; Menadioni Natrii Bisulfis; Menadioninatriumbisulfiitti; Menadionnatriumbisulfit; Menadionu wodorosiarczyn sodowy; Menaph. Sod. Bisulphite; Menaphthone Sodium Bisulphite; Methylnaphthochinonumnatrium Bisulfurosum; Vikasolum; Vitamin K_3 Sodium Bisulphite. Sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxonaphthalene-2-sulphonate trihydrate.

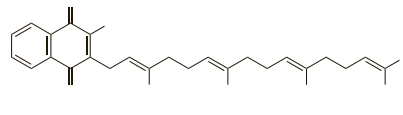
Менадиона Натрия Бисульфит
$C_{11}H_8O_2NaHSO_3,3H_2O$ = 330.3.
CAS — 130-37-0 (anhydrous menadione sodium bisulfite); 6147-37-1 (menadione sodium bisulfite trihydrate).

Pharmacopoeias. In *Chin.* and *Pol.*

Menatetrenone *(rINN)*

E-3100; Ea-0167; Menaquinone-4; Menaquinone 4; Menaquinone K4; Menatetren; Menatetrenona; Ménatétrénone; Menatetrenonum; MK-4; Vitamin $K_{2(20)}$; Vitamin MK 4. 2-Methyl-3-(3,7,11,15-tetramethyl-2,6,10,14-hexadeca-tetraenyl)-1,4-naphthoquinone.

Менатетренон
$C_{31}H_{40}O_2$ = 444.6.
CAS — 863-61-6.

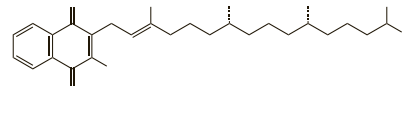


Pharmacopoeias. In *Jpn.*

Phytomenadione *(BAN, rINN)*

Fitomenadion; Fitomenadiona; Fitomenadionas; Fytomenadion; Fytomenadioni; Methylphytylnaphthochinonum; Phylloquinone; Phytomenad.; Phytoménadione; Phytomenadionum; Phytonadione; Vitamin K_1. 2-Methyl-3-[3,7,11,15-tetramethylhexadec-2-enyl] naphthalene-1,4-dione.

Фитоменадион
$C_{31}H_{46}O_2$ = 450.7.
CAS — 84-80-0.
ATC — B02BA01.
ATC Vet — QB02BA01.



Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*
Ph. Eur. 6.2 (Phytomenadione). A mixture of the *trans* (*E*) and *cis* (*Z*) isomers. It contains not less than 75% of *trans*-phytomenadione, and also allows not more than 4% of *trans*-epoxyphytomenadione.
A clear, intense yellow, viscous, oily liquid, which decomposes on exposure to actinic light. Practically insoluble in water; sparingly soluble in alcohol; miscible with fatty oils. Protect from light.
USP 31 (Phytonadione). A mixture of the *E* and *Z* isomers. It contains not more than 21% of the *Z* isomer. A clear, yellow to

amber, very viscous, odourless or practically odourless, liquid. It is stable in air, but decomposes on exposure to sunlight. Insoluble in water; slightly soluble in alcohol; soluble in dehydrated alcohol, in chloroform, in ether, in vegetable oils, and in benzene. Store in airtight containers. Protect from light.

Stability. A polyoxyl castor oil formulation of phytomenadione was stable for at least 30 days at room temperature when repackaged in amber glass dropper bottles.[1] When refrigerated at 4° to 8°, it was stable in both plastic and amber glass bottles.

1. Wong VK, Ho PC. Stability of Konakion repacked in dropper bottles for oral administration. *Aust J Hosp Pharm* 1996; **26:** 641–4.

Adverse Effects and Precautions

Intravenous doses of *phytomenadione* have caused severe reactions resembling hypersensitivity or anaphylaxis. Symptoms have included facial flushing, sweating, chest constriction and chest pain, dyspnoea, cyanosis, and cardiovascular collapse; fatalities have been reported. Anaphylactic reactions have generally been associated with an overly rapid rate of infusion but have also been reported even when the solution was diluted and infused slowly. They are generally thought to be due to polyoxyl castor oil which is present as a surfactant in some parenteral formulations; reports of such reactions with formulations that do not contain polyoxyl castor oil are rare (but see Hypersensitivity, below).

Pain, swelling, and phlebitis may occur at the injection site when phytomenadione is given. Localised skin reactions including atrophy or necrosis have been reported after intramuscular or subcutaneous injection of phytomenadione.

Phytomenadione formulations solubilised with lecithin and a bile salt should be given with caution to patients with severely impaired liver function and to premature neonates weighing less than 2.5 kg, since the bile salt may displace bilirubin.

Giving *menadione* and *menadiol sodium phosphate* to neonates, especially premature infants, or to the mother during late pregnancy has been associated with the development in the infant of haemolytic anaemia, hyperbilirubinaemia, and kernicterus, and such use is not recommended. Phytomenadione has a lower risk of haemolysis. Menadione and menadiol sodium phosphate have also been reported to cause haemolysis in patients with G6PD deficiency or vitamin E deficiency.

Breast feeding. Vitamin K is variably distributed into breast milk; a study found phytomenadione concentrations in the first 10 mL of expressed milk ("fore milk") to be lower than those in the last 10 mL ("hind milk"). These changes may be related to the lipid concentration, which is higher in hind milk. Lipid composition also changes over the course of lactation, with pronounced changes in the first week, and the authors proposed that a mechanism exists whereby vitamin K concentration in milk is higher in the first few days of life so as to meet the neonate's nutritional requirements at a time when vitamin K status is precarious.[1] The American Academy of Pediatrics considers[2] that, as no adverse effects have been seen in breast-fed infants whose mothers were receiving phytomenadione, its use is therefore usually compatible with breast feeding.

1. von Kries R, *et al.* Vitamin K content of maternal milk: influence of the stage of lactation, lipid composition, and vitamin K supplements given to the mother. *Pediatr Res* 1987; **22:** 513–17.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Carcinogenicity. A case-control study from the UK[1] suggested an increased risk of cancer in children who had received vitamin K at birth for the prevention of vitamin K deficiency bleeding (see below). A further study[2] by the same authors indicated that this risk was associated with intramuscular, but not oral, dosage, and was strongest for childhood leukaemia. In response to these data, the British Paediatric Association recommended that the oral route should be preferred for prophylaxis,[3] whereas the American Academy of Pediatrics continued to advocate the intramuscular route,[4] and still does so, concluding there is no association between this route and childhood leukaemia or other cancers.[5]

Subsequent studies from the USA,[6] Sweden,[7] Denmark,[7,8] Germany,[9] and England[10] did not confirm an increased risk of childhood cancer, including leukaemias, after the use of intramuscular vitamin K. More recently, 4 further studies were published.[11-14] Two of these, a case-control study in Scotland[11] and an ecological study in Britain,[12] showed no increased risk of any cancers with the use of intramuscular vitamin K. A third case-control study in England and Wales[13] found a borderline association between intramuscular vitamin K and cancers, particularly leukaemia. In the fourth study, a case-control study in northern England,[14] there was an increased risk (odds ratio 1.79) of acute lymphoblastic leukaemia developing 1 to 6 years after birth in children who had received intramuscular vitamin K. In 1998 a review[15] by an expert working group of the UK CSM concluded that there was no increased risk of solid tumours with vitamin K, and that, although an increased risk of leukaemia could not be excluded, observed results were compatible with chance. Moreover, they could not identify a plausible mechanism for a carcinogenic effect of vitamin K. Since then, a pooled analysis of case-control studies in Great Britain and Germany[16] found no convincing evidence that vitamin K given intramuscularly was associated with childhood leukaemia. A national case-control study in the UK[17] concluded there was no evidence that vitamin K, irrespective of the route, influenced the risk of children developing leukaemia or any other cancer. If there is any increased risk, it is likely to manifest only in a very small subpopulation who are at high risk for some as-yet-unidentified biological reason.[18] The UK Department of Health[19] advocates either oral or intramuscular prophylaxis, and recommends that the parents should be involved in the decision on which route is used.

1. Golding J, *et al.* Factors associated with childhood cancer in a national cohort study. *Br J Cancer* 1990; **62:** 304–8.
2. Golding J, *et al.* Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992; **305:** 341–6.
3. British Paediatric Association. *Vitamin K prophylaxis in infancy.* London, 1992: British Paediatric Association.
4. American Academy of Pediatrics Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993; **91:** 1001–3.
5. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. *Pediatrics* 2003; **112:** 191–2.
6. Klebanoff MA, *et al.* The risk of childhood cancer after neonatal exposure to vitamin K. *N Engl J Med* 1993; **329:** 905–8.
7. Ekelund H, *et al.* Administration of vitamin K to newborn infants and childhood cancer. *BMJ* 1993; **307:** 89–91.
8. Olsen JH, *et al.* Vitamin K regimens and incidence of childhood cancer in Denmark. *BMJ* 1994; **308:** 895–6.
9. von Kries R, *et al.* Vitamin K and childhood cancer: a population based case-control study in Lower Saxony, Germany. *BMJ* 1996; **313:** 199–203.
10. Ansell P, *et al.* Childhood leukaemia and intramuscular vitamin K: findings from a case-control study. *BMJ* 1996; **313:** 204–5.
11. McKinney PA, *et al.* Case-control study of childhood leukaemia and cancer in Scotland: findings for neonatal intramuscular vitamin K. *BMJ* 1998; **316:** 173–7.
12. Passmore SJ, *et al.* Ecological studies of relation between hospital policies on neonatal vitamin K administration and subsequent occurrence of childhood cancer. *BMJ* 1998; **316:** 184–9.
13. Passmore SJ, *et al.* Case-control studies of relation between childhood cancer and neonatal vitamin K administration. *BMJ* 1998; **316:** 178–184.
14. Parker L, *et al.* Neonatal vitamin K administration and childhood cancer in the north of England: retrospective case-control study. *BMJ* 1998; **316:** 189–93.
15. Committee on Safety of Medicines/Medicines Control Agency. Safety of intramuscular vitamin K (Konakion). *Current Problems* 1998; **24:** 3–4. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023232&RevisionSelectionMethod=LatestReleased (accessed 21/07/08)
16. Roman E, *et al.* Vitamin K and childhood cancer: analysis of individual patient data from six case-control studies. *Br J Cancer* 2002; **86:** 63–9.
17. Fear NT, *et al.* Vitamin K and childhood cancer: a report from the United Kingdom Childhood Cancer Study. *Br J Cancer* 2003; **89:** 1228–31.
18. Ross JA, Davies SM. Vitamin K prophylaxis and childhood cancer. *Med Pediatr Oncol* 2000; **34:** 434–7.
19. Department of Health. *Vitamin K for newborn babies.* London, 1998: Department of Health. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Professionalletters/Chiefmedicalofficerletters/DH_4004993?IdcService=GET_FILE&dID=7634&Rendition=Web (accessed 21/07/08)

Effects on the blood. Cerebral arterial thrombosis developed in 2 patients with malabsorption syndromes due to coeliac disease during treatment with vitamin K for severe deficiency of vitamin-K-dependent coagulation factors. An increased tendency to thrombotic events had previously been reported to be present in patients with intestinal inflammatory disorders. It was suggested that if bleeding did occur in such patients treatment should be with plasma infusions or small doses of vitamin K but that vitamin K deficiency should not be specifically treated since a gluten-free diet or corticosteroids given for the gastrointestinal disorder will result in a gradual correction.[1]

1. Florholmen J, *et al.* Cerebral thrombosis in two patients with malabsorption syndrome treated with vitamin K. *BMJ* 1980; **281:** 541.

Hypersensitivity. Hypersensitivity reactions have been reported after subcutaneous,[1-3] intramuscular,[4] intravenous,[5-7] and oral[7] use of vitamin K, although the incidence is low.[6,7]

Subcutaneous doses are considered to pose less risk of **anaphylaxis** than the intravenous route;[5] fatalities have been reported with intravenous use,[7] even after low doses, given slowly, and by dilute infusion.[5,7] There has also been a fatality associated with oral use.[7] While anaphylactoid reactions have been attributed to the polyoxyl castor oil vehicle,[6,7] a direct immune mechanism has also been proposed.[7]

Vitamin K itself appears to be the antigen causing adverse **cutaneous reactions**.[3] Two types of cutaneous reactions have been described: pruritic, erythematous, eczematous plaques usually occurring up to 2 weeks after a dose, and sclerodermoid morphea-like plaques, with or without eczema, which may be delayed.[1,3,4] In addition, there have been rare reports of diffuse maculopapular eruption, but the relationship of this reaction to vitamin K use has been questioned.[3] Despite reports that the eczematous reactions resolve faster than the sclerodermatous reactions,[1] persistent eczema[4] or pruritus has occurred.[3]

Treatment has been largely symptomatic; topical and systemic corticosteroids and antihistamines have been used.[1,3,4] For patients who have previously reacted to phytomenadione injections, the use of menadione either by injection or by mouth has been suggested;[3] cross-reactivity was not anticipated to be a problem. However, cross-reactions on patch testing have been reported.[4] It has been suggested that reactions to vitamin K in patients might signify underlying hepatic disease,[1] although others believe the condition is seen more frequently in patients with liver disease since they are often those requiring vitamin K.[3]

1. Gettler SL, Fung MA. Indurated plaques on the arms of a 52-year-old man. *Arch Dermatol* 2001; **137:** 957–62.
2. Bui L, *et al.* Skin reaction to subcutaneous phytonadione injections. *Am J Health-Syst Pharm* 2004; **61:** 407.
3. Wilkins K, *et al.* Cutaneous reactions associated with vitamin K . *J Cutan Med Surg* 2000; **4:** 163–7.
4. Sommer S, *et al.* Type IV hypersensitivity to vitamin K. *Contact Dermatitis* 2002; **46:** 94–6.
5. Wjasow C, McNamara R. Anaphylaxis after low dose intravenous vitamin K. *J Emerg Med* 2003; **24:** 169–72.
6. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K): a 5-year retrospective review. *Ann Allergy Asthma Immunol* 2002; **89:** 400–406.
7. Fiore LD, *et al.* Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis* 2001; **11:** 175–83.

Overdosage. UK licensed product information states that, while there is no known clinical syndrome attributable to hypervitaminosis of phytomenadione, adverse effects have been reported after overdose in neonates and infants. These include jaundice, hyperbilirubinaemia, increases in liver enzyme values, abdominal pain, constipation, soft stools, malaise, agitation, and skin eruptions. Most adverse events were not considered to be serious, and resolved without any treatment.

Interactions

Vitamin K decreases the effects of oral anticoagulants (see p.1432), and is used to counteract excessive effects of these drugs, see Uses and Administration, below. Vitamin K may reduce the response to resumed therapy with anticoagulants for a week or more.

Pharmacokinetics

The fat-soluble vitamin K compounds phytomenadione and menadione require the presence of bile for their absorption from the gastrointestinal tract; the water-soluble derivatives can be absorbed in the absence of bile. Vitamin K accumulates mainly in the liver but is stored in the body only for short periods of time. Vitamin K does not appear to cross the placenta readily and it is variably distributed into breast milk. Phytomenadione is rapidly metabolised to more polar metabolites and is excreted in bile and urine as glucuronide and sulfate conjugates.

Absorption. Absorption of phytomenadione from the colloidal (micellar) preparation was more irregular and unpredictable after intramuscular than intravenous dosage in healthy adults;[1] when used as an antidote to anticoagulant, this formulation should be given intravenously. In neonates, plasma phytomenadione concentrations were within or above the adult fasting plasma range 24 days after receiving a single dose of the colloidal preparation either orally (3 mg) or intramuscularly (1.5 mg).[2]

1. Soedirman JR, *et al.* Pharmacokinetics and tolerance of intravenous and intramuscular phylloquinone (vitamin K) mixed micelles formulation. *Br J Clin Pharmacol* 1996; **41:** 517–23.
2. Schubiger G, *et al.* Vitamin K concentration in breast-fed neonates after oral or intramuscular administration of a single dose of a new mixed-micellar preparation of phylloquinone. *J Pediatr Gastroenterol Nutr* 1993; **16:** 435–9.

Human Requirements

The minimum daily requirements of vitamin K are not clearly defined but an intake of about 1 microgram/kg daily appears to be adequate. Vitamin K requirements in normal adults can be met from the average diet and from the synthesis of menaquinones (also known as vitamin K_2) by bacterial action in the intestine. Vitamin K occurs naturally as phytomenadione (vitamin K_1), which is present in many foods, especially leafy green vegetables such as cabbage and spinach, and is also present in avocado, meat, cow's milk, egg-yolk, and some cereals.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p.1925) has been set for vitamin K

although an intake of 1 microgram/kg daily was considered to be both safe and adequate for adults; a higher intake of 10 micrograms daily (about 2 micrograms/kg daily) was believed to be justified in infants because of the absence of hepatic menaquinones in early life and reliance on dietary vitamin K alone. It was stated that all babies should receive prophylactic vitamin K at birth[1] and for further details concerning neonatal use, see Vitamin K Deficiency Bleeding, below.

In the USA, adequate intake levels have been determined to be 120 micrograms daily for adult men and 90 micrograms daily for adult women.[2]

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 A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)

Uses and Administration

Vitamin K is an essential cofactor in the hepatic synthesis of prothrombin (factor II) and other blood clotting factors (factors VII, IX, and X, and proteins C and S) and in the function of proteins such as osteocalcin important for bone development.

Vitamin K deficiency may develop in neonates, but is uncommon in adults, although it may occur in patients with malabsorption syndromes, obstructive jaundice or hepatic disease. Deficiency leads to the development of hypoprothrombinaemia, in which the clotting time of the blood is prolonged and spontaneous bleeding can occur. Coumarin anticoagulants interfere with vitamin K metabolism, and their effects can be antagonised by giving vitamin K.

Vitamin K compounds are used in the treatment and prevention of haemorrhage associated with vitamin K deficiency. The dose of vitamin K should be carefully controlled by prothrombin-time estimations.

Phytomenadione is a naturally occurring vitamin K substance. It is the only vitamin K compound used to reverse hypoprothrombinaemia and haemorrhage caused by anticoagulant therapy. It is not effective as a heparin antidote. For **over-anticoagulation**, the dose depends on the international normalised ratio (INR) and the degree of haemorrhage. Typical doses of phytomenadione are 0.5 to 5 mg by slow intravenous injection or up to 5 mg orally (see also Over-anticoagulation, below). Depending on the solubilising agents used, some formulations of phytomenadione are more suitable for intravenous use than others, and dosage details vary. Phytomenadione has also been used in hypoprothrombinaemia due to certain cephalosporins (see Cefamandole, Adverse Effects, p.221).

In the treatment of **vitamin K deficiency bleeding** in neonates, phytomenadione may be given in a dose of 1 mg intravenously, subcutaneously, or intramuscularly; further doses may be given if necessary. As a prophylactic measure, a single dose of 0.5 to 1 mg may be given intramuscularly to the newborn infant, or 2 mg orally followed by a second dose of 2 mg after 4 to 7 days; for further details see below.

Menadiol sodium phosphate is a water-soluble derivative of menadione, a synthetic lipid-soluble vitamin K analogue. It may be used for the prevention of vitamin K deficiency in patients with malabsorption syndromes in whom oral phytomenadione may be inefficiently absorbed. It is given in usual doses equivalent to 10 to 40 mg of menadiol phosphate daily by mouth.

Menadiol dibutyrate has also been used; menatetrenone is used in the management of osteoporosis. Acetomenaphthone has been used in preparations promoted for the relief of chilblains.

◊ General reviews.

1. Shearer MJ. Vitamin K. *Lancet* 1995; **345:** 229–34.
2. Vermeer C, Schurgers LJ. A comprehensive review of vitamin K and vitamin K antagonists. *Hematol Oncol Clin North Am* 2000; **14:** 339–53.
3. Vermeer C, *et al.* Beyond deficiency: potential benefits of increased intakes of vitamin K for bone and vascular health. *Eur J Nutr* 2004; **43:** 325–35.

Action. References to the action of vitamin K and the role of vitamin K-dependent coagulation proteins and carboxyglutamate-containing proteins such as osteocalcin.

1. Friedman PA. Vitamin K-dependent proteins. *N Engl J Med* 1984; **310:** 1458–60.
2. Rick ME. Protein C and protein S: vitamin K-dependent inhibitors of blood coagulation. *JAMA* 1990; **263:** 701–3.
3. Nelsestuen GL, *et al.* Vitamin K-dependent proteins. *Vitam Horm* 2000; **58:** 355–89.
4. Saxena SP, *et al.* Novel vitamin K-dependent pathways regulating cell survival. *Apoptosis* 2001; **6:** 57–68.

Malignant neoplasms. In a small study in women with viral cirrhosis of the liver to establish the effects of vitamin K on bone loss, those given menatetrenone were found to have a lower incidence of hepatocellular carcinoma; larger controlled studies were advocated, with prevention of carcinoma by menatetrenone as a primary end-point.[1] Another study[2] reported reduced recurrence of hepatocellular carcinoma in patients given menatetrenone.

1. Habu D, *et al.* Role of vitamin K in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. *JAMA* 2004; **292:** 358–61.
2. Mizuta T, Ozaki I. Hepatocellular carcinoma and vitamin K. *Vitam Horm* 2008; **78:** 435–42.

Neonatal intraventricular haemorrhage. Vitamin K crosses the placenta slowly and to a limited extent, but sufficiently to warrant studies to assess whether giving phytomenadione to the mother can reduce the incidence or severity of intraventricular haemorrhage (p.1050) in the preterm neonate. Studies have shown conflicting results. A systematic review concluded that vitamin K given to the mother before birth did not significantly prevent periventricular haemorrhage, and could not be recommended for routine clinical use.[1]

1. Crowther CA, Henderson-Smart DJ. Vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).

Osteoporosis. The effects of vitamin K on bone, and its role in osteoporosis (p.1084) have been reviewed.[1-3] It is widely prescribed for the management of osteoporosis in Japan.[3] A reduced risk of vertebral[4] and nonvertebral[5] fracture has been reported from 2 studies in postmenopausal women given menatetrenone 45 mg daily by mouth. Vitamin K_2 (menaquinones such as menatetrenone) appears to have more marked effects on bone than vitamin K_1 (phytomenadione).[3] A systematic review[6] to assess whether vitamin K supplementation can reduce bone loss and prevent fractures identified 13 studies with data on bone loss; 7 reported fracture data. Most studies were conducted in Japan among postmenopausal women. Vitamin K supplements increased bone mineral density (BMD) in all but 1 study. Meta-analyses of the 7 studies with fracture data showed a reduced fracture incidence with menatetrenone supplementation, especially at the hip. The authors advised caution in interpretation of the data, since the studies were not designed to show fracture effects, and quality of many of the trials was poor. In addition, dietary differences in Japan might confound findings. While patients at risk of fracture should be encouraged to consume a diet high in vitamin K, routine supplementation is not justified until these results can be confirmed in a large randomised study with fracture as a primary outcome.

1. Iwamoto J, *et al.* Effects of vitamin K2 on osteoporosis. *Curr Pharm Des* 2004; **10:** 2557–76.
2. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *Am J Health-Syst Pharm* 2005; **62:** 1574–81.
3. Plaza SM, Lamson DW. Vitamin K2 in bone metabolism and osteoporosis. *Altern Med Rev* 2005; **10:** 24–35.
4. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. *Am J Med* 2004; **117:** 549–55.
5. Sato Y, *et al.* Menatetrenone and vitamin D2 with calcium supplements prevent nonvertebral fracture in elderly women with Alzheimer's disease. *Bone* 2005; **36:** 61–8.
6. Cockayne S, *et al.* Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166:** 1256–61.

Over-anticoagulation. Doses of vitamin K for over-anticoagulation with warfarin have traditionally been large, and this continues to be reflected in licensed product information for these products, where recommended oral or parenteral doses range from 2.5 to 25 mg initially, with a maximum dose of 40 to 50 mg. However, large doses of vitamin K may result in overcorrection, and increase the delay before resumed anticoagulant therapy becomes effective. In addition, the time to onset of action is a minimum of 1 to 2 hours, irrespective of dose. There is increasing evidence that lower doses of vitamin K are effective in over-anticoagulation,[1-3] and this is reflected in current guidelines (see Treatment of Adverse Effects of Warfarin, p.1426). The use of vitamin K lowers the elevated INR faster than witholding warfarin alone. However, for patients on phenprocoumon, vitamin K had insufficient effect, and no benefit for those on acenocoumarol; stopping therapy is more effective.[3] The route by which vitamin K is given may also be significant. A meta-analysis[4] of studies of vitamin K for the treatment of over-anticoagulation found that oral or intravenous vitamin K therapy was more effective for warfarin than simply stopping the anticoagulant; however, subcutaneous therapy was not effective. A review[5] noted that over-anticoagulated patients present with a wide range of INR values, and may respond differently to fixed dosing regimens of vitamin K, leaving them outside their target INR 24 hours after treatment and at risk for either haemorrhage or thromboembolism. Patient factors that affect response to vitamin K include age, body-weight, co-morbidity or health status, warfarin daily dose, and genetic polymorphism. The authors called for a more individualised approach to the reversal of over-anticoagulation.

A study has shown that dietary vitamin K intake is an important factor in anticoagulation instability; even brief periods of increased or decreased intake had significant effects on anticoagulation.[6] A high intake of green, leafy vegetables or selected oil-based foods can readily provide a dietary intake of 0.5 mg of vitamin K. Instead of restricting dietary vitamin K, maintenance of a stable intake may result in improved maintenance of therapeutic anticoagulation.[7]

Concern has also been expressed about possible effects on patients taking warfarin if vitamin K is included in their parenteral nutrition.[8]

1. Weibert RT, *et al.* Correction of excessive anticoagulation with low-dose oral vitamin K . *Ann Intern Med* 1997; **125:** 959–62.
2. Fetrow CW, *et al.* Antagonism of warfarin-induced hypoprothrombinemia with use of low-dose subcutaneous vitamin K . *J Clin Pharmacol* 1997; **37:** 751–7.
3. Hanslik T, Prinseau J. The use of vitamin K in patients on anticoagulant therapy: a practical guide. *Am J Cardiovasc Drugs* 2004; **4:** 43–55.
4. DeZee KJ, *et al.* Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med* 2006; **166:** 391–7.
5. Sconce EA, Kamali F. Appraisal of current vitamin K dosing algorithms for the reversal of over-anticoagulation with warfarin: the need for a more tailored dosing regimen. *Eur J Haematol* 2006; **77:** 457–62.
6. Franco V, *et al.* Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. *Am J Med* 2004; **116:** 651–6.
7. Bovill EG, *et al.* Vitamin K and oral anticoagulation: thought for food. *Am J Med* 2004; **116:** 711–13.
8. Bern M. Observations on possible effects of daily vitamin K replacement, especially upon warfarin therapy. *J Parenter Enteral Nutr* 2004; **28:** 388–98.

Vitamin K deficiency bleeding. Vitamin K deficiency bleeding (VKDB; haemorrhagic disease of the newborn; HDN), of which 3 types have been recognised, is associated with a clotting defect due to vitamin K deficiency.[1,2]

- In early VKDB bleeding occurs at the time of delivery or during the first 24 hours of life and is typically seen in infants whose mothers have taken drugs that affect vitamin K metabolism such as warfarin, some antiepileptics, rifampicin, or isoniazid.
- Classic VKDB, the most common type, usually occurs at 2 to 5 days of age and breast feeding is an important factor as human breast milk has a much lower content of vitamin K than either cow's milk or infant formulas.
- Late VKDB presents frequently as intracranial haemorrhage in infants over one month of age. The vitamin-K deficiency in these cases can be either idiopathic (usually in breast-fed infants who did not receive vitamin K at birth) and/or can be a secondary manifestation of other disorders such as chronic diarrhoea, cystic fibrosis or other malabsorption syndromes, biliary atresia, or α_1-antitrypsin deficiency.

Treatment of VKDB involves use of parenteral phytomenadione, usually 1 mg initially with further doses depending on response. More immediate treatment, in the form of blood transfusion or blood clotting factors, may be needed to compensate for severe blood loss and delayed response to vitamin K. VKDB, particularly the late type, carries a high risk of morbidity or death; therefore, the emphasis has been on prevention. It has long been known that giving vitamin K to the neonate soon after birth can reduce the incidence of VKDB. Menadiol sodium phosphate was formerly used, but reports in the 1950s of jaundice and kernicterus in infants given this vitamin K analogue caused concern, and led to the preferential use of phytomenadione either intramuscularly or orally. Giving phytomenadione, usually as a single intramuscular injection, has been standard practice for neonates considered at high risk of VKDB, such as those who had a complicated delivery, those born prematurely, and those whose mothers were receiving antiepileptic therapy. Since it is not possible to selectively identify all neonates that are at risk for VKDB, the routine use of phytomenadione in all neonates has been advocated. However, such practice has been controversial, particularly as regards the route.[2-4] Some have considered that oral dosage is less invasive and more acceptable to parents.[4] However, there has also been concern about the adequacy of absorption of oral phytomenadione, and the lack of a suitable oral formulation. In addition, there was some evidence[2,5-7] to suggest that a single intramuscular dose was more effective than a single oral dose in preventing late VKDB, and that repeated oral doses might be required, which may be less convenient and carry the risk of poor compliance. More recently, a possible increased risk of childhood cancer in neonates treated with intramuscular, but not oral, phytomenadione has been reported (see Carcinogenicity, above). Although the association remains controversial, it led to recommendations for the preferential use of oral vitamin K in neonates at low-risk of VKDB in some countries, including the UK[8] and Germany,[9] whereas other countries, including the USA,[10,11] still preferred the intramuscular route for all neonates.

There is still no agreement on the most effective oral dose and frequency, and study of this has been complicated by the lack of a suitable oral preparation of phytomenadione.[12,13] Options currently available for oral use include the polyoxyl castor oil and polysorbate-80 containing preparations (unlicensed for oral use) and the colloidal, micelle formulation (licensed for oral use in some countries). These preparations are packaged in glass ampoules, therefore are unsuitable for parents to give at home.

The 1992 recommendations of the British Paediatric Society[8] for oral use of the polyoxyl castor oil formulation suggested a single dose of 500 micrograms on the day of birth. For breast-fed babies, additional doses of 500 micrograms at 7 to 10 days and at 4 to 6 weeks, or 200 micrograms at weekly intervals for 26 weeks, or 50 micrograms daily for 26 weeks, were recommended. Current UK doses[14] for the colloidal preparation in healthy term neonates are 2 mg soon after birth, then 2 mg at 4 to 7 days. Exclusively breast-fed infants should be given a third oral dose of 2 mg one month after birth. Further monthly doses of 2 mg have been recommended while the infant remains exclusively breast-fed. A report[15] of the failure of prophylaxis in 3 breast-fed babies (2 of whom had unidentified cholestatic liver disease) who received 2 doses of this formulation, as recommended in Switzerland, emphasises the importance of the third, and possibly, other, follow-up doses. Plasma vitamin K concentrations in breast-fed infants receiving 3 oral doses of this formulation were at least equal to concentrations in those receiving a single intramuscular dose.[16] A study in Germany, however, found the mixed micellar oral formulation to be no more efficacious than older vitamin K preparations,[17] and a pharmacokinetic study found its absorption to be unreliable in infants with conjugated hyperbilirubinaemia;[18] the authors suggest that even 3 oral doses may not provide sufficient protection against VKDB in infants with latent cholestasis. The most recent advice from the UK Department of Health[14] advocates that all newborn infants should receive vitamin K prophylaxis, both oral and intramuscular routes should be available, and that parents should be involved in the decision on which route is used.

Other oral regimens have been investigated or are in use. In the Netherlands a regimen of 1 mg orally or intramuscularly at birth, followed by 25 micrograms daily or 1 mg weekly by mouth from 1 week to 3 months of age has been found satisfactory.[19,20] In Germany[9,20] and Australia[20] the suggested oral regimen for the polyoxyl castor oil formulation was 1 mg at birth, at 3 to 10 days and at weeks 3 to 6, although some failures have been reported in babies receiving this regimen,[9] and the Australian data confirm it is less effective than a single intramuscular dose.[20] One hospital in the USA has satisfactorily used, for many years, a single 2-mg dose given via nasogastric tube to neonates after birth,[21] although the American Academy of Pediatrics still advocates use of the intramuscular route.[11] In Denmark, a 2-mg dose at birth followed by a weekly dose of 1 mg during the first 3 months of life has effectively prevented any late VKDB in healthy breast-fed babies.[22] In France, for formula-fed neonates at no risk of haemorrhage, 2 mg is given orally at birth, followed by a second dose between day 2 and 7; infants who are breast-fed are given weekly oral doses of 2 mg until cessation of exclusive breast feeding. For neonates at high risk of haemorrhage, however, the first dose is given intramuscularly, or even by slow intravenous injection, according to the clinical state of the infant.[2]

Although phytomenadione crosses the placenta slowly and to a limited extent, it is nevertheless recommended that pregnant women receiving drugs that are vitamin K antagonists (particularly antiepileptics) should receive phytomenadione 10 to 20 mg daily from 36 weeks gestation.[2,23] This is in addition to the requirement that their neonates, who are at high risk of VKDB, receive intramuscular phytomenadione soon after birth. Maternal phytomenadione has been investigated as a means of improving vitamin K status in breast-fed neonates. In 1 study,[24] 5 mg daily for 12 weeks was effective for this purpose.

1. Hathaway WE. Haemostatic disorders in the newborn. In: Bloom AL, Thomas DP, eds. *Haemostasis and thrombosis*. 2nd ed. Edinburgh: Churchill Livingstone, 1987: 554–69.
2. Autret-Leca E, Jonville-Béra A-P. Vitamin K in neonates: how to administer, when and to whom. *Paediatr Drugs* 2001; **3:** 1–8.
3. Tripp JH, McNinch AW. Haemorrhagic disease and vitamin K. *Arch Dis Child* 1987; **62:** 436–7.
4. Brown SG, *et al.* Should intramuscular vitamin K prophylaxis for haemorrhagic disease of the newborn be continued? A decision analysis. *N Z Med J* 1989; **102:** 3–5.
5. Clarkson PM, James AG. Parenteral vitamin K : the effective prophylaxis against haemorrhagic disease for all newborn infants. *N Z Med J* 1990; **103:** 95–6.
6. McNinch AW, Tripp JH. Haemorrhagic disease of the newborn in the British Isles: two year prospective study. *BMJ* 1991; **303:** 1105–9.
7. Von Kries R. Neonatal vitamin K. *BMJ* 1991; **303:** 1083–4.
8. British Paediatric Association. *Vitamin K prophylaxis in infancy*. London, 1992: British Paediatric Association.
9. von Kries R, *et al.* Repeated oral vitamin K prophylaxis in West Germany: acceptance and efficacy. *BMJ* 1995; **310:** 1097–8.
10. American Academy of Pediatrics Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993; **91:** 1001–3.
11. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. *Pediatrics* 2003; **112:** 191–2.
12. Barton JS, *et al.* Neonatal vitamin K prophylaxis in the British Isles: current practice and trends. *BMJ* 1995; **310:** 632–3.
13. Rennie JM, Kelsall AWR. Vitamin K prophylaxis in the newborn—again. *Arch Dis Child* 1994; **70:** 248–51.
14. Department of Health. *Vitamin K for newborn babies*. London, 1998: Department of Health. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Professionalletters/Chiefmedicalofficerletters/DH_4004993?IdcService=GET_FILE&dID=7634&Rendition=Web (accessed 21/07/08)
15. Baenziger O, *et al.* Oral vitamin K prophylaxis for newborn infants: safe enough? *Lancet* 1996; **348:** 1456.
16. Greer FR, *et al.* A new mixed micellar preparation for oral vitamin K prophylaxis: randomised controlled comparison with an intramuscular formulation in breast fed infants. *Arch Dis Child* 1998; **79:** 300–5.
17. von Kries R, *et al.* Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F109–F112.
18. Pereira SP, *et al.* Intestinal absorption of mixed micellar phylloquinone (vitamin K) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F113–F118.
19. Cornelissen M, Hirasing R. Vitamin K for neonates. *BMJ* 1994; **309:** 1441–2.
20. Cornelissen M, *et al.* Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. *Eur J Pediatr* 1997; **156:** 126–30.
21. Clark FI, James EJP. Twenty-seven years of experience with oral vitamin K therapy in neonates. *J Pediatr* 1995; **127:** 301–4.
22. Nørgaard Hansen K, Ebbesen F. Neonatal vitamin K prophylaxis in Denmark: three years' experience with oral administration during the first three months of life compared with one oral administration at birth. *Acta Paediatr Scand* 1996; **85:** 1137–9.
23. Delgado-Escueta AV, Janz D. Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. *Neurology* 1992; **42** (suppl 5): 149–60.
24. Greer FR, *et al.* Improving the vitamin K status of breastfeeding infants with maternal vitamin K supplements. *Pediatrics* 1997; **99:** 88–92.

Preparations

BP 2008: Menadiol Phosphate Injection; Menadiol Phosphate Tablets; Phytomenadione Injection; Phytomenadione Tablets;
USP 31: Menadiol Sodium Diphosphate Injection; Menadiol Sodium Diphosphate Tablets; Menadione Injection; Phytonadione Injectable Emulsion; Phytonadione Tablets.

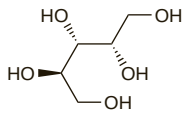
Proprietary Preparations (details are given in Part 3)
Arg.: K1; Konakion; Mestil-Ka; Rupek; ***Austral.:*** K Thrombin†; Konakion; ***Austria:*** Kavitol; Konakion; ***Belg.:*** Konakion; Vitamon K; ***Braz.:*** Kanakion; Kavit; Vikatron; Vita K; ***Chile:*** Auriderm K2; Fitoquinona†; Konakion; ***Cz.:*** Kanavit; ***Denm.:*** Konakion; Menadion; ***Fin.:*** Konakion; ***Ger.:*** Kanavit; Konakion; ***Gr.:*** Konakion; ***Hong Kong:*** Auriderm K2; Konakion; ***Hung.:*** Konakion; ***India:*** Kenadion; ***Indon.:*** Neo-K; ***Irl.:*** Konakion; ***Israel:*** Konakion; ***Ital.:*** Konakion; Vitak; ***Jpn:*** Glakay; Kaytwo; ***Malaysia:*** Konakion; ***Mex.:*** K-50; Konakion; Royken; ***Neth.:*** Konakion; ***Norw.:*** Konakion; ***NZ:*** K-Thrombin; Konakion; ***Philipp.:*** Clotigen; Cycomin; Hema-K; Hemadone; Hemo-K; Konakion; ***Pol.:*** Vitacon; ***Port.:*** Kanakion; ***S.Afr.:*** Konakion; ***Spain:*** Kaergona Hidrosoluble; Konakion; ***Swed.:*** Konakion; ***Switz.:*** Konakion; ***Thai.:*** Glakay; Konakion; KP†; ***Turk.:*** Konakion MM; Libavit K; ***UK:*** Konakion; ***USA:*** Aquamephyton†; Mephyton.

Multi-ingredient: ***Arg.:*** Antidiar†; Estreptocarbocaftiazol; Kacerutin; ***Austral.:*** Chilblain Formula†; ***Chile:*** Hepabil; Katin; Microret K; ***India:*** Cadisper C; CKP; Gynae-CVP; K5 Hair Tincture†; Kalpastic; Siochrome; Styptocid; Styptocip†; ***Indon.:*** Hi-Bone; ***Irl.:*** Bio-Calcium + D + K; ***Mex.:*** Hemosin-K; Microka; Microret K; ***Rus.:*** Vectrum Calcium (Вектрум Кальций); ***Spain:*** Caprofides Hemostatico; Cromoxin K†; ***Thai.:*** Bio-Calcium + D3 + K; Siduol; ***Venez.:*** Dremo-K†.

Xylitol *(BAN)*

E967; Ksilitolis; Ksylitol; Ksylitoli; Xilit; Xilitol; Xylit; *meso*-Xylitol; Xylitolum.

$C_5H_{12}O_5$ = 152.1.
CAS — 87-99-0 (xylitol); 16277-71-7 (D-xylitol).



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.* Also in *USNF*.

Ph. Eur. 6.2 (Xylitol). A white or almost white crystalline powder or crystals. M.p. 92° to 96°. Very soluble in water; sparingly soluble in alcohol.

USNF 26 (Xylitol). White crystals or crystalline powder. Crystalline xylitol has a melting range between 92° and 96°. It has a sweet taste and produces a cooling sensation in the mouth. Soluble 1 in about 0.65 of water; sparingly soluble in alcohol.

Adverse Effects

Large amounts of xylitol taken orally may cause diarrhoea and flatulence. Hyperoxaluria, which can occur with intravenous infusion, is unlikely after oral use. Hyperuricaemia, changes in liver-function tests, and acidosis (including lactic acidosis) have occurred after intravenous infusion.

Hypersensitivity. A report of oral erosions caused by contact hypersensitivity to xylitol-containing chewing gum.[1]

1. Hanakawa Y, *et al.* Xylitol as a causative agent of oral erosive eczema. *Br J Dermatol* 2005; **152:** 821–2.

Uses and Administration

Xylitol is a polyhydric alcohol (polyol) related to the pentose sugar, xylose (p.2416). It is used as a bulk sweetener in foods and as a sweetener or excipient in pharmaceuticals. Xylitol is also used as a sweetening agent in sugar-free preparations as it is non-cariogenic and is less likely to cause dental caries than sucrose. It is under investigation for the prevention of dental caries and acute otitis media. It was formerly considered as a substitute for glucose in intravenous nutrition but such use has generally been abandoned due to adverse effects.

Dental caries. Chewing-gum containing xylitol appears to have a useful role in the prevention of dental caries (p.180).[1-5]

1. Edgar WM. Sugar substitutes, chewing gum and dental caries—a review. *Br Dent J* 1998; **184:** 29–32.
2. Gales MA, Nguyen T-M. Sorbitol compared with xylitol in prevention of dental caries. *Ann Pharmacother* 2000; **34:** 98–100.
3. Maguire A, Rugg-Gunn AJ. Xylitol and caries prevention—is it a magic bullet? *Br Dent J* 2003; **194:** 429–36.
4. van Loveren C. Sugar alcohols: what is the evidence for caries-preventive and caries-therapeutic effects? *Caries Res* 2004; **38:** 286–93.
5. Burt BA. The use of sorbitol- and xylitol-sweetened chewing gum in caries control. *J Am Dent Assoc* 2006; **137:** 190–6. Correction. *ibid.*; 447.

Otitis media. It has been suggested that xylitol chewing gum[1,2] and xylitol syrup[2,3] may have a preventative effect against acute otitis media (p.182). However, a randomised study[4] found xylitol to be ineffective when given only during an acute respiratory-tract infection.

1. Uhari M, *et al.* Xylitol chewing gum in prevention of acute otitis media: double blind randomised trial. *BMJ* 1996; **313:** 1180–4.
2. Uhari M, *et al.* A novel use of xylitol sugar in preventing acute otitis media. *Pediatrics* 1998; **102:** 879–84.
3. Uhari M, *et al.* Xylitol in preventing acute otitis media. *Vaccine* 2001; **19:** S144–S147.
4. Tapiainen T, *et al.* Xylitol administered only during respiratory infections failed to prevent acute otitis media. Abstract: *Pediatrics* 2002; **109:** 302. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/2/e19 (accessed 08/11/05)

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Trident; ***Ger.:*** Xylit; ***Philipp.:*** Xylogel.

Multi-ingredient: ***Arg.:*** Emoform Total; Fluorogel 2001 Chiquitos; Fluorogel 2001 para Dientes Sensibles; Hyper Sensitive; Periobacter; Periodent; Solucion Oral; ***Chile:*** Oralgene; ***Fr.:*** Exova†; ***Ger.:*** Cardioplegin N†; Kalium-Magnesium-Asparaginat†; Saseem; ***Mex.:*** Dentsiblen; Fluoxytil; Periodentyl; Perioxidin; ***Philipp.:*** Xylorinse; ***UK:*** Biotene Oralbalance; BioXtra†; Saliva Natura; Saliva Orthana; ***USA:*** Optimoist.

Dried Yeast

Brewers' Yeast; Cerevisiae Fermentum Siccatum; Faex Siccata; Fermento de Cerveja; Levadura desecada; Levedura Sêca; Levure de Bière; Saccharomyces Siccum; Trockenhefe.

Сушёные Дрожжи

Pharmacopoeias. In *Jpn.*

Profile

Dried yeast consists of unicellular fungi belonging to the family Saccharomycetaceae, dried by a process that avoids decomposition of the vitamins present. The chief species are *Saccharomyces cerevisiae*, *S. carlsbergensis*, and *S. monacensis*. Dried yeast contains thiamine, nicotinic acid, riboflavin, pyridoxine, pantothenic acid, biotin, folic acid, cyanocobalamin, aminobenzoic acid, inositol, and chromium.

Dried yeast is a rich source of vitamins of the B group. It has been used for the prevention and treatment of vitamin B deficiency in doses of 1 to 8 g daily by mouth. Yeast is an ingredient of some preparations for treating haemorrhoids, and some preparations intended to restore normal gastrointestinal flora. Yeast is widely used in brewing.

Antibiotic-associated colitis. Although other organisms, including *Candida* spp., have been implicated in antibiotic-associated diarrhoea, colonisation of the colon with *Clostridium difficile*, a toxin-producing Gram-positive anaerobe, is the most common identifiable cause of antibiotic-associated colitis (p.171) and pseudomembranous colitis. There are reports of benefit with dried yeast in patients with *C. difficile*-associated diarrhoea;[1,2] commercially available brewers' yeast tablets were used, at a dose of 3 tablets three times daily (strength unspecified), in 3 patients refractory to standard treatment,[1] or as adjunctive therapy in 11 patients, using the same dose.[2]

1. Schellenberg D, *et al.* Treatment of Clostridium difficile diarrhoea with brewer's yeast. *Lancet* 1994; **343:** 171–2.
2. Barthram J, *et al.* Further research warranted. *Pharm J* 1997; **259:** 371.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Bioflorin†; Florax†; Ginofloraxt; Levedo; Lomvit†; ***Fr.:*** Microlev†; ***Ger.:*** AgioStop; Furunkulosin†; Hamadin N; Imoflora; Levurinetten N†; Omniflora Akut; Perocur; Santax S; Yomogi; ***India:*** Laviest; ***Ital.:*** Nutrivit†; Zimocel; ***Mex.:*** Levifusa; ***Port.:*** Lio-Levedura†; ***Thai.:*** Brewers Yeast; ***UK:*** Bio-Strath.

Multi-ingredient: ***Arg.:*** Bifena; Karbonetas; ***Austral.:*** ML 20†; Plantiodine Plus†; Preparation H†; ***Austria:*** Levurinetten; Sperti Praparation H; ***Braz.:*** Composto Emagrecedor†; Emagrevit†; Manolio†; ***Canad.:*** Preparation H; ***Chile:*** Sperti Preparation H; ***Cz.:*** Preparation H; ***Fr.:*** Actisoufre; Calciforte; Calciforte Vitamin D ; Carbolevure; D'Contract; Levure Or; Phytophanere; Preparation H; Solacy; Spasmag; ***Ger.:*** Pantovigar N; Sperti Praparation H†; ***Gr.:*** Preparation H; ***India:*** Elfern†; Livogen†; Medithane; Plastules; Softeron-Z; ***Irl.:*** Preparation H; ***Israel:*** Preparation H; ***Ital.:*** Bifilact; Eurogel; Florelax; Lactisporin; Lactivis; Lactolife; Levudin†; Lievitosohn;