been reported[5] in renal transplant patients given verapamil and ciclosporin; the authors suggested that if a rapid increase in plasma-ciclosporin concentrations was required, improved formulations of ciclosporin should be used rather than verapamil.

1. Dawidson I, Rooth P. Improvement of cadaver renal transplantation outcomes with verapamil: a review. *Am J Med* 1991; **90** (suppl 5A): 37S–41S.
2. Dawidson I, *et al*. Verapamil improves the outcome after cadaver renal transplantation. *J Am Soc Nephrol* 1991; **2:** 983–90.
3. Chan C, *et al*. A randomized controlled trial of verapamil on cyclosporine nephrotoxicity in heart and lung transplant recipients. *Transplantation* 1997; **63:** 1435–40.
4. Pirsch JD, *et al*. A controlled, double-blind, randomized trial of verapamil and cyclosporine in cadaver renal transplant patients. *Am J Kidney Dis* 1993; **21:** 189–95.
5. Nanni G, *et al*. Increased incidence of infection in verapamil-treated kidney transplant recipients. *Transplant Proc* 2000; **32:** 551–3.

Preparations

BP 2008: Prolonged-release Verapamil Tablets; Verapamil Injection; Verapamil Tablets;
USP 31: Verapamil Hydrochloride Extended-release Tablets; Verapamil Hydrochloride Injection; Verapamil Hydrochloride Oral Solution; Verapamil Hydrochloride Oral Suspension; Verapamil Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Isoptino; Veral; Verapal†; ***Austral.:*** Anpec; Cordilox; Isoptin; Veracaps; Verahexal; ***Austria:*** Isoptin; Verapabene; Verastad; ***Belg.:*** Isoptine; Lodixal; ***Braz.:*** Cordilat; Coronaril; Cronovera†; Dilacard†; Dilacor; Dilacoron; Multicor; Neo Verpamil; Vascord†; Vasoton; Veramil; Veraval; ***Canad.:*** Apo-Verap; Chronovera; Isoptin; Novo-Veramil; Nu-Verap; ***Chile:*** Cardiolen; Isoptina; Presocor; ***Cz.:*** Apo-Verap†; Isoptin; Lekoptin; Verahexal; Verogalid; ***Denm.:*** Geangin; Hexasoptin; Isoptin; Veraloc; ***Fin.:*** Isoptin; Vermin; Verpamil; ***Fr.:*** Isoptine; ***Ger.:*** Azupamil†; durasoptin†; Falicard; Isoptin; Jenapamil†; Vera; Vera-Lich; Verabeta; Veragamma; Verahexal; Veramex; Veranorm; Verasal; Veroptinstada; ***Gr.:*** Brovicarpine†; Elanver†; Isoptin; ***Hong Kong:*** Akilen†; Isoptin; ***Hung.:*** Chinopamil; Isoptin; Verogalid†; ***India:*** Calaptin; Veramil; ***Indon.:*** Cardiover; Isoptin; ***Irl.:*** Isoptin; Veramil; Verap; Verisop; ***Israel:*** Apoacor; Ikacor; Ikapress; Veracor; Verapress; ***Ital.:*** Cardinorm; Isoptin; Kata†; Quasar†; Veraptin; ***Malaysia:*** Akilen; Anpec†; Cintsu†; Isoptin; Verpamil; Viratin†; ***Mex.:*** Cronovera; Dilacoran; Euritmin†; Europave; Serriten; Vepiltax; Veraken; Verdilac; ***Neth.:*** Chronovera†; Geangin; Isoptin; ***Norw.:*** Isoptin; Verakard; ***NZ:*** Civicor†; Isoptin; Verpamil; ***Philipp.:*** Isoptin; Verelan; ***Pol.:*** Isoptin; Lekoptin; Novo-Veramil; Staveran; ***Port.:*** Fibrocard; Isoptin; ***Rus.:*** Finoptin (Финоптин); Isoptin (Изоптин); Lekoptin (Лекоптин); Verogalid (Верогалид); ***S.Afr.:*** Calcicard; Isoptin; Ravamil; Vasomil; Verahexal; ***Singapore:*** Isoptin; Verpamil; ***Spain:*** Manidon; ***Swed.:*** Isoptin; ***Switz.:*** Corpamil†; Flamon; Isoptin; Verapam; ***Thai.:*** Caveril; Civicor†; Isopamil†; Isoptin; Verapin; Vermine; ***Turk.:*** Fibrocard; Isoptin; Ormil; Veroptin; ***UK:*** Cordilox; Half Securon; Securon; Univer; Verapress; Vertab; Zolvera; ***USA:*** Calan; Covera; Isoptin; Verelan; ***Venez.:*** Cronovera; Manidon; Veracor.

Multi-ingredient: ***Arg.:*** Tarka†; ***Austral.:*** Tarka; ***Austria:*** Captocomp; Confit; Tarka; Veracapt; ***Canad.:*** Tarka; ***Cz.:*** Tarka; ***Denm.:*** Tarka; ***Fin.:*** Tarka†; ***Fr.:*** Ocadrik†; Tarka; ***Ger.:*** Cordichin; Isoptin plus; Stenoptin†; Tarka; Udramil†; Veratide; ***Gr.:*** Tarka; Ziaxel; ***Hung.:*** Tarka; ***Indon.:*** Tarka; ***Ital.:*** Tarka; ***Mex.:*** Tarka; ***Neth.:*** Tarka; Ziaxel; ***NZ:*** Ziaxel; ***Philipp.:*** Tarka; ***Pol.:*** Tarka; ***Port.:*** Tarka; Ziaxal; ***Rus.:*** Tarka (Тарка); ***S.Afr.:*** Tarka; ***Spain:*** Tarka; Tricen; ***Swed.:*** Tarka; ***Switz.:*** Tarka; ***Turk.:*** Tarka; ***UK:*** Tarka; ***USA:*** Tarka; ***Venez.:*** Tarka.

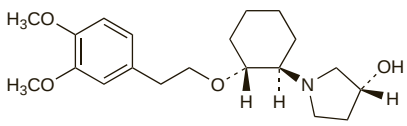
Vernakalant Hydrochloride *(USAN, rINNM)*

Hidrocloruro de vernakalant; RSD-1235; Vernakalant, Chlorhydrate de; Vernakalanti Hydrochloridum. (3*R*)-1-{(1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl}pyrrolidin-3-ol hydrochloride.

Вернаканта Гидрохлорид

$C_{20}H_{31}NO_4$,HCl = 385.9.

CAS — 794466-70-9 (vernakalant); 748810-28-8 (vernakalant hydrochloride).



(vernakalant)

Profile

Vernakalant is an antiarrhythmic under investigation as the hydrochloride for the treatment of atrial arrhythmias.

◊ References.

1. Roy D, *et al*. A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol* 2004; **44:** 2355–61.
2. Fedida D. Vernakalant (RSD1235): a novel, atrial-selective antifibrillatory agent. *Expert Opin Invest Drugs* 2007; **16:** 519–32.
3. Cheng JWM. Vernakalant in the management of atrial fibrillation. *Ann Pharmacother* 2008; **42:** 533–42.

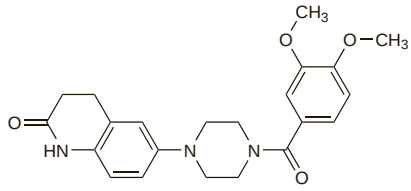
Vesnarinone *(USAN, rINN)*

OPC-8212; Vesnarinona; Vesnarinonum. 1-(1,2,3,4-Tetrahydro-2-oxo-6-quinolyl)-4-veratroylpiperazine.

Веснаринон

$C_{22}H_{25}N_3O_4$ = 395.5.

CAS — 81840-15-5.



Profile

Vesnarinone is a phosphodiesterase inhibitor with positive inotropic activity that has been tried orally in the management of heart failure.

Adverse effects. Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can lead to an increased mortality rate. In a multicentre study of vesnarinone,[1] doses of 120 mg daily resulted in increased mortality whereas 60 mg daily for 6 months was associated with lower morbidity and mortality. Reversible neutropenia occurred in 2.5% of the patients given 60 mg daily. However, in a subsequent larger study,[2] increased mortality was also reported with doses of 30 and 60 mg daily.

1. Feldman AM, *et al*. Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 1993; **329:** 149–55.
2. Cohn JN, *et al*. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med* 1998; **339:** 1810–16.

Warfarin Sodium *(BANM, rINNM)*

Natrii Warfarinum; Sodium Warfarin; Varfariininatrium; Varfarin Sodyum; Varfarino natrio druska; Warfarin sodná sůl; Warfarina sódica; Warfarine sodique; Warfarinnatrium; Warfarin-nátrium; Warfarinum natricum. The sodium salt of 4-hydroxy-3-(3-oxo-1-phenylbutyl)coumarin ; Sodium 2-oxo-3-[(1*RS*)-3-oxo-1-phenylbutyl]-2*H*-1-benzopyran-4-olate.

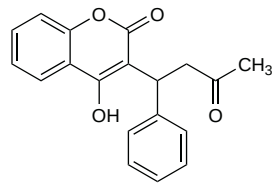
Натрий Варфарин

$C_{19}H_{15}NaO_4$ = 330.3.

CAS — 81-81-2 (warfarin); 2610-86-8 (warfarin potassium); 129-06-6 (warfarin sodium).

ATC — B01AA03.

ATC Vet — QB01AA03.



(warfarin)

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US*.
Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate. *Eur.* has a separate monograph for warfarin sodium clathrate (see below).
Jpn includes Warfarin Potassium.
Ph. Eur. 6.2 (Warfarin Sodium). A white or almost white, hygroscopic, amorphous powder. Very soluble in water and in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.
USP 31 (Warfarin Sodium). A white, odourless, amorphous solid or a crystalline clathrate which is discoloured by light. Very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether. A 1% solution in water has a pH of 7.2 to 8.3. Protect from light.

Adsorption. Studies carried out for periods of 24 hours to 3 months found some adsorption of warfarin sodium by PVC when dissolved in 0.9% sodium chloride solution[1,2] or in 5% glucose solution.[3] In one of these studies,[1] adsorption was decreased by buffering the solution from its initial pH of 6.7 to a pH of 7.4. The second study[2] could demonstrate no adsorption onto polyethylene-lined or glass infusion containers.

1. Kowaluk EA, *et al*. Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Martens HJ, *et al*. Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
3. Moorhatch P, Chiou WL. Interactions between drugs and plastic intravenous fluid bags: part i: sorption studies on 17 drugs. *Am J Hosp Pharm* 1974; **31:** 72–8.

Incompatibility. Solutions of warfarin sodium have been reported to be incompatible with adrenaline hydrochloride, amikacin sulfate, metaraminol tartrate, oxytocin, promazine hydrochloride, and tetracycline hydrochloride. Visual incompatibility has been reported[1] with solutions of warfarin sodium mixed with solutions of aminophylline, bretylium tosilate, ceftazidime, cimetidine hydrochloride, ciprofloxacin lactate, dobutamine hydrochloride, esmolol hydrochloride, gentamicin sulfate, labetalol hydrochloride, metronidazole hydrochloride, or vancomycin hydrochloride. Haze was also reported after 24 hours with sodium chloride 0.9%.

1. Bahal SM, *et al*. Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Warfarin Sodium Clathrate *(BANM)*

Varfariininatriumklatraatti; Varfarino natrio druskos klatratas; Warfarin sodná sůl klatrát; Warfarina sódica, clatrato de; Warfarine sodique clathrate; Warfarinnatriumklatrat; Warfarin-nátrium-klatrát; Warfarinum natricum clathratum. The clathrate of warfarin sodium with isopropyl alcohol in the molecular proportions 2 to 1 respectively.

ATC — B01AA03.

ATC Vet — QB01AA03.

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Eur.* (see p.vii).
Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate.
Ph. Eur. 6.2 (Warfarin Sodium Clathrate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.
Warfarin sodium clathrate contains about 92% of warfarin sodium.

Adverse Effects

The major risk from warfarin therapy is of haemorrhage from almost any organ of the body with the consequent effects of haematomas as well as anaemia. Although good control of warfarin anticoagulation is essential in preventing haemorrhage, bleeding has occurred at therapeutic international normalised ratio (INR) values. In such cases the possibility of an underlying cause such as renal or alimentary tract disease should be investigated. Skin necrosis, and purple discoloration of the toes (due to cholesterol embolisation) have occasionally occurred. Hypersensitivity reactions are extremely rare. Other effects not necessarily associated with haemorrhage include alopecia, fever, nausea, vomiting, diarrhoea, skin reactions, jaundice, hepatic dysfunction, and pancreatitis.

Warfarin is a recognised teratogen. Given in the first trimester of pregnancy it can cause a fetal warfarin syndrome or warfarin embryopathy characterised by bone stippling (chondrodysplasia punctata) and nasal hypoplasia. CNS abnormalities may develop after use in any trimester but appear most likely when used in the second or third trimester. Use of warfarin during pregnancy has been associated with an increased rate of abortion and still-birth, although this may, in part, be the consequence of an underlying maternal condition. Use in the late stages of pregnancy is associated with fetal haemorrhage. Reported incidences of the above complications have varied; one estimate is that if a coumarin anticoagulant is taken during pregnancy, one-sixth of pregnancies will result in an abnormal liveborn infant, and one-sixth will result in abortion or stillbirth.

Effects on the blood. The incidence and risk of haemorrhage during long-term oral anticoagulation has been studied in patients in clinical trials[1,2] and in population-based studies.[1,3-7] The risk of bleeding was generally higher with more intense anticoagulation and in the presence of other risk factors, but the relationship with age was less clear. Some studies have shown higher rates of bleeding in elderly patients, but others have not; the risk of intracranial bleeding, however, does seem to be higher in the elderly.[2,6,7] Although cumulative risk of bleeding was related to

duration of anticoagulation therapy, risk may be highest early in the course.[2]

Withdrawal of warfarin therapy may lead to rebound hypercoagulability and it has been suggested[8] that warfarin should be withdrawn gradually, although there is no clinical evidence to support this.

1. Reynolds MW, *et al.* Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. *Chest* 2004; **126:** 1938–45.
2. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 257S–298S.
3. Gitter MJ, *et al.* Bleeding and thromboembolism during anticoagulant therapy: a population-based study in Rochester, Minnesota. *Mayo Clin Proc* 1995; **70:** 725–33.
4. Fihn SD, *et al.* The risk for and severity of bleeding complications in elderly patients treated with warfarin. *Ann Intern Med* 1996; **124:** 970–9.
5. Palareti G, *et al.* Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996; **348:** 423–8.
6. Palareti G, *et al.* Oral anticoagulation treatment in the elderly: a nested, prospective, case-control study. *Arch Intern Med* 2000; **160:** 470–8.
7. Fang MC, *et al.* Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med* 2004; **141:** 745–52.
8. Palareti G, Legnani C. Warfarin withdrawal: pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet* 1996; **30:** 300–13.

Effects on the bones. Vitamin K is involved in bone metabolism and vitamin K deficiency is associated with an increased risk of osteoporotic fractures. It has been suggested, therefore, that patients on long-term treatment with those oral anticoagulants that are vitamin K antagonists may be at increased risk of osteoporosis and fractures. However, two large observational studies in older women have produced conflicting results. A prospective study[1] of both users and nonusers of warfarin found that warfarin was not associated with decrease in bone density or increase in fracture rates. A retrospective study[2] reported an association between long-term anticoagulant use and increased risk of vertebral and rib fractures, compared with the general population. Overall, however, the risk of any fracture was not significantly increased.

1. Jamal SA, *et al.* Warfarin use and risk for osteoporosis in elderly women. *Ann Intern Med* 1998; **128:** 829–32.
2. Caraballo PJ, *et al.* Long-term use of oral anticoagulants and the risk of fracture. *Arch Intern Med* 1999; **159:** 1750–6.

Effects on the fetus. Fetal complications of coumarin anticoagulants during pregnancy have been reviewed.[1-3]

1. Hall JG, *et al.* Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; **68:** 122–40.
2. Chan WS, *et al.* Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000; **160:** 191–6.
3. Bates SM, *et al.* Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 844S–886S.

Effects on the liver. There have been a few isolated reports of cholestatic liver damage in patients taking warfarin sodium,[1-3] which resolved on withdrawal.

1. Rehnqvist N. Intrahepatic jaundice due to warfarin therapy. *Acta Med Scand* 1978; **204:** 335–6.
2. Jones DB, *et al.* Jaundice following warfarin therapy. *Postgrad Med J* 1980; **56:** 671.
3. Adler E, *et al.* Cholestatic hepatic injury related to warfarin exposure. *Arch Intern Med* 1986; **146:** 1837–9.

Effects on sexual function. There have been reports[1-3] of priapism in patients taking oral anticoagulants such as warfarin.

1. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; **4:** 46–58.
2. Daryanani S, Wilde JT. Priapism in a patient with protein C deficiency. *Clin Lab Haematol* 1997; **19:** 213–14.
3. Zimbelman J, *et al.* Unusual complications of warfarin therapy: skin necrosis and priapism. *J Pediatr* 2000; **137:** 266–8.

Effects on the skin and hair. Skin and soft-tissue necrosis is a rare but well-established adverse effect of coumarin anticoagulants.[1-4] It is characterised by a localised, painful skin lesion, initially erythematous or haemorrhagic in appearance, that becomes bullous and eventually culminates in gangrenous necrosis. Fatalities have occurred. Areas of increased subcutaneous fat such as breast, thigh, and buttocks have most often been involved. The aetiology appears to be thrombotic but the exact pathophysiology is not known. Patients with protein C deficiency appear to be at highest risk. Treatment with coumarin anticoagulants should be stopped if skin lesions appear and vitamin K should be given to reverse their effect. Heparin should be given to provide anticoagulation. Fresh frozen plasma or protein C concentrates may also have a role in reversing the condition. Surgical intervention is usually required if necrosis does develop.

Other skin reactions have also been reported with coumarins. Vasculitis affecting both legs developed in a 74-year-old woman a few weeks after starting treatment with acenocoumarol for deep-vein thrombosis and pulmonary embolism.[5] Acenocoumarol treatment was stopped and the skin lesions steadily improved over 15 days. However, the skin lesions reappeared a few hours after re-exposure to a single dose of acenocoumarol. The patient had also been taking amiodarone which may have contributed to the reaction. Henoch-Schönlein purpura was reported[6] in a 76-year-old woman 2 months after she started treatment with acenocoumarol; it resolved rapidly after the drug was withdrawn.

Increased shedding of telogen hair has been stated to occur in patients given coumarin anticoagulants.[7]

1. Cole MS, *et al.* Coumarin necrosis—a review of the literature. *Surgery* 1988; **103:** 271–7.
2. Comp PC. Coumarin-induced skin necrosis: incidence, mechanisms, management and avoidance. *Drug Safety* 1993; **8:** 128–35.
3. Chan YC, *et al.* Warfarin induced skin necrosis. *Br J Surg* 2000; **87:** 266–72.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Warfarin-induced skin necrosis. *Aust Adverse Drug React Bull* 2005; **24:** 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0512.pdf (accessed 10/03/08)
5. Susano R, *et al.* Hypersensitivity vasculitis related to nicoumalone. *BMJ* 1993; **306:** 973.
6. Borrás-Blasco J, *et al.* Acenocoumarol-induced Henoch-Schönlein purpura. *Ann Pharmacother* 2004; **38:** 261–4.
7. Smith AG. Drug-induced disorders of hair and nails. *Adverse Drug React Bull* 1995 (173); 655–8.

Treatment of Adverse Effects

The methods used to manage bleeding and/or excessive anticoagulation during warfarin therapy, or after warfarin overdosage, depend upon the degree of bleeding, the value of the international normalised ratio (INR), and the degree of thromboembolic risk.

For patients **over-anticoagulated** on warfarin, the *British Society for Haematology* recommends the following:

- in cases where the INR is 0.5 above the target value but less than 6.0, warfarin should be reduced in dose or withdrawn until the INR falls to below 5.0
- if the INR is greater than 6.0 but less than 8.0 and there is no bleeding or only minor bleeding, warfarin should be temporarily withheld until the INR falls to below 5.0
- for an INR greater than 8.0 use of phytomenadione (vitamin K_1) should also be considered if there are other risk factors for bleeding; typical doses of phytomenadione are 0.5 mg intravenously or up to 2.5 mg orally using the intravenous preparation. (The *BNF* allows 5 mg orally for more complete reversal of anticoagulation.)
- if there is any major bleeding warfarin should be stopped and phytomenadione given in a dose of 5 or 10 mg, preferably by slow intravenous injection. A concentrate of factors II, VII, IX, and X should also be given. The dose of concentrate should be calculated based on 50 units of factor IX/kg. If no concentrate is available fresh frozen plasma should be infused (about one litre for an adult), but may not be as effective. Higher doses of phytomenadione have been used (see Over-anticoagulation, p.1997); however phytomenadione takes several hours to act and large doses may reduce the response to resumed therapy with anticoagulants for a week or more.

US guidelines from the *American College of Chest Physicians* are as follows:

- if the INR is above therapeutic range but below 5.0, without significant bleeding, warfarin should be reduced in dose or stopped until the INR falls to therapeutic range
- for an INR of 5.0 or over but less than 9.0, warfarin should be stopped. If the patient is at increased risk of bleeding, phytomenadione 1 to 2.5 mg should be given orally, or up to 5 mg orally for more complete reversal of anticoagulation
- if the INR is 9.0 or above with no significant bleeding, warfarin should be stopped and phytomenadione 2.5 to 5 mg may be given orally
- if there is any major bleeding, warfarin should be stopped and phytomenadione 10 mg given by slow intravenous injection, with fresh plasma, concentrates of factors II, VII, IX, and X, or recombinant factor VIIa.

If bleeding occurs unexpectedly at therapeutic INR values, the possibility of an underlying cause such as renal or alimentary tract disease should be investigated.

See under Effects on the Skin and Hair, above, for the management of skin and soft tissue necrosis.

For **poisoning** in individuals not taking anticoagulant therapy, the *UK National Poisons Information Service* recommends that those who have ingested more than 250 micrograms/kg of warfarin or who have an INR greater than 6.0, should be given phytomenadione 10 to 20 mg orally or intravenously. If there is active bleeding, factor concentrate or fresh frozen plasma should also be given.

Precautions

Warfarin should not be given to patients who are haemorrhaging. In general it should not be given to patients at serious risk of haemorrhage, although it has been used with very careful control; patients at risk include those with haemorrhagic blood disorders, peptic ulcer disease, severe wounds (including surgical wounds), cerebrovascular disorders, and bacterial endocarditis. Consideration should be given to stopping warfarin a few days before an invasive procedure and using an alternative form of antithrombotic therapy. Severe hepatic and renal impairment as well as severe hypertension are considered by some to be contra-indications. Pregnancy is also generally considered to be a contra-indication, especially in the first trimester and during the late stages of pregnancy (see Adverse Effects, above).

Many factors may affect anticoagulant control with warfarin. These include vitamin K status, thyroid status, renal function, bioavailability differences between warfarin preparations, factors affecting absorption of warfarin, genetic variation in warfarin metabolism (see below), and drug interactions. Such factors may be responsible for apparent resistance to warfarin and a few patients have displayed hereditary resistance. Dosage alterations should be guided by regular monitoring of oral anticoagulant therapy and clinical status. Patients should carry anticoagulant treatment booklets.

◊ A discussion of factors affecting the anticoagulant effect of warfarin sodium.[1]

1. Shetty HGM, *et al.* Clinical pharmacokinetic considerations in the control of oral anticoagulant therapy. *Clin Pharmacokinet* 1989; **16:** 238–53.

Breast feeding. Drug concentrations were measured[1] in the plasma and milk of 13 women receiving 2 to 12 mg of warfarin daily. Plasma concentrations varied from 1.6 to 8.5 micromoles/litre but none was detectable in the breast milk or in the plasma of the 7 infants who were breastfed (limit of detection 0.08 micromoles/litre). No anticoagulant effect was found in the 3 breast-fed infants tested. In another report[2] of 2 women (dose of warfarin not specified), no evidence of the drug was found in the milk of one mother, and no anticoagulant effect was found in either infant. The American Academy of Pediatrics considers[3] that warfarin is therefore usually compatible with breast feeding.

1. Orme ML'E, *et al.* May mothers given warfarin breast-feed their infants? *BMJ* 1977; **1:** 1564–5.
2. McKenna R, *et al.* Is warfarin sodium contraindicated in the lactating mother? *J Pediatr* 1983; **103:** 325–7.
3. 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 06/07/04)

Genetic variation. The response to warfarin and dosing requirements vary widely between individuals and between different racial groups.[1] Factors involved include age, indication for anticoagulation, diet, and use of interacting drugs, but much of the variability appears to be related to genetic polymorphism. Two genes appear to be particularly important: the gene for the cytochrome P450 isoenzyme CYP2C9, the major enzyme involved in warfarin metabolism; and the gene for vitamin K epoxide reductase (VKOR), which is involved in the synthesis of clotting factors and is the major target for warfarin and other coumarin anticoagulants.[2] Although polymorphisms in either gene may affect dose requirements, patients with variant alleles for both genes appear to be particularly sensitive to warfarin;[3] initial variability in response may be more strongly associated with VKOR.[4] Identification of affected patients by genetic testing may be used to guide initial warfarin dosage, and a dosage algorithm has been suggested, although it requires validation.[5] Similar effects have also been noted with other coumarins, including acenocoumarol[6] and phenprocoumon.[7]

1. Dang M-TN, *et al.* The influence of ethnicity on warfarin dosage requirement. *Ann Pharmacother* 2005; **39:** 1008–12.
2. Schwarz UI, Stein CM. Genetic determinants of dose and clinical outcomes in patients receiving oral anticoagulants. *Clin Pharmacol Ther* 2006; **80:** 7–12.

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5. Millican EA, *et al.* Genetic-based dosing in orthopedic patients beginning warfarin therapy. *Blood* 2007; **110:** 1511–15.
6. Schalekamp T, *et al.* VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: interaction between both genotypes affects overanticoagulation. *Clin Pharmacol Ther* 2006; **80:** 13–22.
7. Schalekamp T, *et al.* VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. *Clin Pharmacol Ther* 2007; **81:** 185–93.

Macular degeneration. Intra-ocular haemorrhage leading to loss of vision has been reported[1,2] in patients with neovascular (wet) age-related macular degeneration receiving warfarin, and caution has been advised[3] in such patients.

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2. Ung T, *et al.* Long term warfarin associated with bilateral blindness in a patient with atrial fibrillation and macular degeneration. *Heart* 2003; **89:** 985.
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Interactions

Many compounds interact with warfarin and other oral anticoagulants. Details of these interactions are given below for all oral anticoagulants with different groups of drugs; if the anticoagulant is other than warfarin, then its identity is specified. The major interactions are summarised in the tables, below.

Drugs generally recognised as diminishing the effects of oral anticoagulants are included in the following list. Further information on the interactions with these drugs and others where the interaction is not so well recognised is provided in the referenced section below.

acetomenaphthone	ethchlorvynol
alcohol (chronic ingestion without liver impairment)	glutethimide
aminoglutethimide	griseofulvin
barbiturates	nafcillin
bosentan	phytomenadione
carbamazepine	rifampicin
dichloralphenazone	St John's wort

Drugs recognised or generally reported as enhancing oral anticoagulants are included in the following list. Further information on the interactions with these drugs and others where the interaction is not so well recognised is provided in the referenced section below.

alcohol (acute ingestion or chronic ingestion with liver impairment)	ethylestrenol
allopurinol	fluconazole
amiodarone	glucagon
aspirin	itraconazole
cefamandole	ketoconazole
chloramphenicol	metronidazole
cimetidine	miconazole
clofibrate	norethandrolone
cloral hydrate	NSAIDs
co-trimoxazole	oxymetholone
danazol	quinidine
dextropropoxyphene	stanozolol
dextrothyroxine	sulfinpyrazone
dipyridamole	tamoxifen
disulfiram	telithromycin
erythromycin	thyroid agents
etacrynic acid	tramadol
	triclofos sodium

Interactions of a pharmacodynamic nature occurring with one anticoagulant may well apply to another but this may not be the case with pharmacokinetic interactions. Many food and herbal preparations also have the potential to interact with oral anticoagulants; some are discussed below.

An interaction may be due to increased or decreased anticoagulant metabolism; with warfarin some interacting drugs such as cimetidine, co-trimoxazole, or phenylbutazone have a selective effect on its stereoisomers. Altered absorption may sometimes play a part, as with colestyramine. Displacement of oral anticoagulants from plasma protein binding sites has been reported with many drugs, including some analgesics. Not all reports that have recorded an alteration in the pharmacokinetics of the anticoagulant have, however, shown a corresponding change in clinical response.

Interference with the coagulation process may be responsible for the increased risk of haemorrhage when aspirin, clofibrate, or thyroid hormones are used with anticoagulants. Many other compounds, such as asparaginase, some contrast media, epoprostenol, streptokinase, and urokinase also carry this risk; while interactions between these compounds and anticoagulants are not discussed further below, the possibility of an increased risk of haemorrhage should be considered when they are used together.

Where there is a risk of serious haemorrhage from an interaction, then use of both drugs is best avoided. In other instances the anticoagulant activity should be carefully monitored so as to increase or decrease the anticoagulant dose as required. Critical periods are when patients stabilised on an anticoagulant start treatment with an interacting drug, or when patients stabilised on a regimen of an interacting drug and anticoagulant have the interacting drug withdrawn. Depending on the mechanism of the interaction, the clinical response to the interaction may be rapid or may take some days. Interactions involving displacement from plasma protein binding sites are often transient. Some interacting drugs do not produce predictable effects; there have for instance been reports of increased as well as decreased anticoagulant activity with disopyramide, phenytoin, quinidine, and oral contraceptives. Another problem occurs with dipyridamole; it can cause bleeding when given to patients taking anticoagulants but without any changes in the measures used for anticoagulant control.

◊ Reviews.

1. Harder S, Thürmann P. Clinically important drug interactions with anticoagulants: an update. *Clin Pharmacokinet* 1996; **30:** 416–44.
2. Greenblatt DJ, von Moltke LL. Interaction of warfarin with drugs, natural substances, and foods. *J Clin Pharmacol* 2005; **45:** 127–32.

Alcohol. Alcohol has a variable effect on warfarin. Heavy regular drinkers may have a diminished effect, perhaps through enzyme induction, although the effect of warfarin may be increased in the presence of liver impairment; acute ingestion has enhanced the effect of warfarin. A moderate alcohol intake is generally not considered to cause problems.

Analgesics and NSAIDs. All NSAIDs should be used with caution or not at all in patients on warfarin. Many NSAIDs inhibit platelet function to some extent and have an irritant effect on the gastrointestinal tract, so increasing the risk of haemorrhage. Furthermore, some NSAIDs increase the hypoprothrombinaemic effect of warfarin, possibly by an intrinsic effect on coagulation or by displacement of warfarin from plasma protein-binding sites. Many studies have compared the relative displacing action of a range of NSAIDs *in vitro*, but such studies cannot easily be extrapolated to the clinical situation. Changes in plasma concentration of unbound warfarin resulting from displacement from plasma protein-binding sites are usually transient and are most likely to occur in the first few weeks after an NSAID is added to or withdrawn from warfarin therapy; monitoring of anticoagulant therapy is, therefore, most critical during this period.

High doses of *aspirin* and some other *salicylates* enhance the hypoprothrombinaemic effect of warfarin and should generally be avoided in patients on oral anticoagulant therapy. Low-dose aspirin with warfarin may have a role in some patients but the risk of gastrointestinal bleeding is increased. The possibility of an interaction with topical salicylates should also be considered.[1,2]

Use of *phenylbutazone* with warfarin has led to serious haemorrhage and should be avoided. Phenylbutazone affects the metabolism of the *R*- and *S*- isomers of warfarin in complex and different ways with the net effect of enhancing its anticoagulant activity.[3] Related drugs such as *oxyphenbutazone*, *azapropazone*,[4-6] and *feprazone*[7] behave similarly and should also be avoided.

For the following NSAIDs there are a few studies or isolated reports suggesting that they may enhance the hypoprothrombinaemic effect of warfarin or other specified oral anticoagulant: *diflunisal* (with acenocoumarol[8] or warfarin[9]), *flurbiprofen* (with acenocoumarol),[10] *indometacin*,[11,12] *ketoprofen*,[13] *meclofenamate sodium*,[14] *mefenamic acid*,[15] *piroxicam*, (with warfarin[16] or acenocoumarol[17]), *sulindac*,[18,19] *tiaprofenic acid* (with acenocoumarol),[20] and *tolmetin sodium*.[21] In many cases the result of concomitant therapy was an increased prothrombin time which may or may not be clinically significant; in other cases haemorrhage occurred. It should also be noted that for many of the above NSAIDs, perhaps particularly indometacin, there are studies (not cited) in which no enhancement of warfarin activity was found. NSAIDs with an apparently minimal effect on warfarin activity include *etodolac*, *ibuprofen*, and *naproxen*.

Interactions have also been reported with NSAIDs that are selective inhibitors of cyclo-oxygenase-2. As with other NSAIDs, some studies (not cited) have shown a lack of interaction between warfarin and *celecoxib*, but there have been several reports[22-25] of an increase in the INR with concomitant therapy and bleeding has occurred in some patients.[24] Increases in INR have also been reported in studies[25,26] of warfarin with *rofecoxib*; and there have also been reports of bleeding.[27] A small increase in INR was also reported[28] with *etoricoxib* in healthy subjects but was thought unlikely to be of clinical significance in most patients.

In view of the above considerations, *paracetamol* is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. However, caution should be observed since, although it has no effect on the gastric mucosa or on platelet function, some studies (with warfarin, anisindione, dicoumarol, or phenprocoumon)[29,30] and isolated reports[31] have found an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant. An increase in INR has also been reported[32] in a controlled study of the use of paracetamol in patients stabilised on warfarin. Increased monitoring of anticoagulant therapy may be appropriate for those also taking paracetamol regularly.

Opioid analgesics do not generally cause problems. However, there have been reports of enhanced anticoagulant activity in patients given *tramadol* with warfarin[33,34] including 2 deaths from haemorrhagic stroke,[34] and also with phenprocoumon,[35] although a randomised, double-blind, placebo-controlled study[36] in 19 patients failed to find evidence of an interaction between phenprocoumon and tramadol. *Co-proxamol*, a combination of *dextropropoxyphene* and paracetamol, has increased the effect of warfarin.[37-39] *Co-codamol*, a combination of *codeine* and paracetamol, has also enhanced warfarin activity.[40]

Amongst other analgesics, *glafenine* has been reported to possibly enhance the activity of phenprocoumon.[41] *Phenazone*, an inducer of enzyme metabolism, reduces plasma concentrations of warfarin and, in contrast with most other analgesics, may necessitate an increase in warfarin dosage.[42]

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17. Bonnabry P, *et al.* Stereoselective interaction between piroxicam and acenocoumarol. *Br J Clin Pharmacol* 1996; **41:** 525–30.
18. Carter SA. Potential effect of sulindac on response of prothrombin-time to oral anticoagulants. *Lancet* 1979; **ii:** 698–9.
19. Ross JRY, Beeley L. Sulindac, prothrombin time, and anticoagulants. *Lancet* 1979; **ii:** 1075.
20. Whittaker SJ, *et al.* A severe, potentially fatal, interaction between tiaprofenic acid and nicoumalone. *Br J Clin Pract* 1986; **40:** 440.

21. Koren JF, *et al.* Tolmetin-warfarin interaction. *Am J Med* 1987; **82:** 1278–9.
22. Mersfelder TL, Stewart LR. Warfarin and celecoxib interaction. *Ann Pharmacother* 2000; **34:** 325–7.
23. Haase KK, *et al.* Potential interaction between celecoxib and warfarin. *Ann Pharmacother* 2000; **34:** 666–7.
24. Adverse Drug Reactions Advisory Committee (ADRAC). Interaction of celecoxib and warfarin. *Aust Adverse Drug React Bull* 2001; **20:** 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0102.pdf (accessed 19/08/08)
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30. Hylek EM, *et al.* Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* 1998; **279:** 657–62.
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32. Mahé I, *et al.* Paracetamol: a haemorrhagic risk factor in patients on warfarin. *Br J Clin Pharmacol* 2005; **59:** 371–4.
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36. Boeijinga JK, *et al.* Lack of interaction between tramadol and coumarins. *J Clin Pharmacol* 1998; **38:** 966–70.
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42. Whitfield JB, *et al.* Changes in plasma γ-glutamyl transpeptidase activity associated with alterations in drug metabolism in man. *BMJ* 1973; **1:** 316–18.

Antiarrhythmics. *Amiodarone* has been shown in several studies to increase the activity of warfarin[1-5] and acenocoumarol,[6,7] probably through inhibition of metabolism. The potentiating effect of amiodarone has been reported to persist for up to 4 months after its withdrawal.[1] Phenprocoumon has been reported to be either unaffected[8] or potentiated[9] by amiodarone. Isolated reports with *disopyramide*[10] and *quinidine*[11] have suggested that these drugs can enhance the anticoagulant effect of warfarin. In 7 patients on warfarin or dicoumarol treated with disopyramide or quinidine, however, all but one needed a small increase in the weekly anticoagulant dose suggesting that the antiarrhythmic had reduced the anticoagulant effect.[12] Since the effect was observed after conversion of atrial fibrillation to sinus rhythm an involvement of haemodynamic factors was postulated. Several studies (not cited) have failed to show an effect of quinidine on warfarin. There are also reports indicating that *propafenone*[13] and *moracizine*[14] can enhance warfarin.

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2. Almog S, *et al.* Mechanism of warfarin potentiation by amiodarone: dose—and concentration—dependent inhibition of warfarin elimination. *Eur J Clin Pharmacol* 1985; **28:** 257–61.
3. Watt AH, *et al.* Amiodarone reduces plasma warfarin clearance in man. *Br J Clin Pharmacol* 1985; **20:** 707–9.
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5. Kerin NZ, *et al.* The incidence, magnitude, and time course of the amiodarone-warfarin interaction. *Arch Intern Med* 1988; **148:** 1779–81.
6. Arboix M, *et al.* The potentiation of acenocoumarol anticoagulant effect by amiodarone. *Br J Clin Pharmacol* 1984; **18:** 355–60.
7. Richard C, *et al.* Prospective study of the potentiation of acenocoumarol by amiodarone. *Eur J Clin Pharmacol* 1985; **28:** 625–9.
8. Verstraete M, *et al.* Dissimilar effect of two anti-anginal drugs belonging to the benzofuran group on the action of coumarin derivatives. *Arch Int Pharmacodyn Ther* 1968; **176:** 33–41.
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14. Serpa MD, *et al.* Moricizine—warfarin: a possible drug interaction. *Ann Pharmacother* 1992; **26:** 127.

Antibacterials. Several antibacterials have been involved in interactions with warfarin. Only a few reports are of serious effects and it is unlikely that any of the drugs need to be contraindicated with warfarin; careful control should suffice.

Most of the drugs enhance the effects of warfarin. Apart from possible effects on the metabolism or plasma-protein binding of warfarin, some antibacterials may interfere with platelet function or with the bacterial synthesis of vitamin K in the gastrointestinal tract and thus have an anticoagulant effect of their own. This is generally considered unlikely to be of clinical significance except, perhaps, in patients with an inadequate vitamin K intake. Fever itself may increase the catabolism of clotting factors and exaggerate a potential antibacterial-warfarin interaction.

There are several reports of an enhanced warfarin response with *co-trimoxazole*; stereospecific inhibition of warfarin metabolism is probably responsible.[1] The interaction is generally attributed to the *sulfamethoxazole* moiety and there are isolated reports suggesting that the activity of warfarin (or other specified oral anticoagulant) may be enhanced by other sulfonamides including *sulfafurazole*,[2] *sulfamethizole*,[3] and *sulfaphenazole* (with phenindione).[4]

There are several reports of potentiation of the effects of warfarin by *erythromycin* or its salts; inhibition of warfarin metabolism probably occurs. Although no clinically-significant increase in prothrombin time was found in 8 non-infected patients, the potential for an interaction was recognised.[5] An enhanced response to warfarin has also been reported with *azithromycin*,[6,7] with *roxithromycin*,[8] which included reports of spontaneous bleeding, and with *telithromycin*,[9,10] including a case of mild haemoptysis.[9] *Clarithromycin* may potentiate the effect of acenocoumarol[11] and of warfarin,[12] although other factors may also have been involved in this case.

Cefamandole has been reported to enhance the hypoprothrombinaemic response to warfarin.[13,14] Interference with vitamin K synthesis in the gastrointestinal tract and/or liver has been implicated. Related cephalosporins with an *N*-methylthiotetrazole side-chain such as *cefmetazole*, *cefmenoxime*, *cefoperazone*, and *latamoxef* may be expected to behave similarly although there appear to be no reports of an interaction. *Cefazolin*, which has a similar side-chain, may also enhance the effect of warfarin to some extent.[14]

There have been reports of increased activity of warfarin (or other specified oral anticoagulant) by quinolone antibacterials including *nalidixic acid* (with warfarin[15,16] or acenocoumarol[17]), *ciprofloxacin*,[18-20] *gatifloxacin*,[20,21] *levofloxacin*,[20,22] *moxifloxacin*,[20,23] *norfloxacin*,[20,24] and *ofloxacin*,[25,26] although for some of these there are also studies indicating no effect (not cited). *Enoxacin* has been reported to decrease the clearance of *R*-warfarin but not *S*-warfarin; no prolongation of prothrombin time occurred.[27]

There are isolated reports suggesting an enhanced effect of warfarin (or other specified oral anticoagulant) with *aminosalicylic acid*,[28] *benzylpenicillin*,[29] *chloramphenicol* (with dicoumarol),[30] *doxycycline*,[31] *isoniazid*,[32] and *neomycin*.[33] Prothrombin times might be prolonged by broad-spectrum antibacterials such as *ampicillin*, and there has been a report[34] of an increased INR and haematuria in a patient taking warfarin with amoxicillin and clavulanic acid. Manufacturers' warnings of potentiation of warfarin by *aztreonam*, *trimethoprim*, and *tetracyclines* other than doxycycline appear to have only a theoretical basis. *Metronidazole* is discussed under Antiprotozoals, below.

Rifampicin diminishes the effect of warfarin by induction of metabolising enzymes in the liver. There are several reports of a similar effect with *nafcillin*[35-37] and with *dicloxacillin sodium*.[38,39]

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4. Varma DR, *et al.* Prothrombin response to phenindione during hypoalbuminaemia. *Br J Clin Pharmacol* 1975; **2:** 467–8.
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7. Woldtvedt BR, *et al.* Possible increased anticoagulation effect of warfarin induced by azithromycin. *Ann Pharmacother* 1998; **32:** 269–70.
8. Anonymous. Interaction of warfarin with macrolide antibiotics. *Aust Adverse Drug React Bull* 1995; **14:** 11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9508.htm (accessed 19/08/08)
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18. Mott FE, *et al.* Ciprofloxacin and warfarin. *Ann Intern Med* 1989; **111:** 542–3.
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20. Health Canada. Fluoroquinolones and warfarin: suspected interaction. *Can Adverse React News* 2004; **14** (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n3_e.pdf (accessed 23/05/08)
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32. Rosenthal AR, *et al.* Interaction of isoniazid and warfarin. *JAMA* 1977; **238:** 2177.
33. Udall JA. Drug interference with warfarin therapy. *Clin Med* 1970; **77** (Aug.): 20–5.
34. Davydov L, *et al.* Warfarin and amoxicillin/clavulanate drug interaction. *Ann Pharmacother* 2003; **37:** 367–70.
35. Qureshi GD, *et al.* Warfarin resistance with nafcillin therapy. *Ann Intern Med* 1984; **100:** 527–9.
36. Fraser GL, *et al.* Warfarin resistance associated with nafcillin therapy. *Am J Med* 1989; **87:** 237–8.
37. Davis RL, *et al.* Warfarin-nafcillin interaction. *J Pediatr* 1991; **118:** 300–3.
38. Krstenansky PM, *et al.* Effect of dicloxacillin sodium on the hypoprothrombinemic response to warfarin sodium. *Clin Pharm* 1987; **6:** 804–6.
39. Mailloux A, *et al.* Potential interaction between warfarin and dicloxacillin. *Ann Pharmacother* 1996; **30:** 1402–7.

Antidepressants. *Amitriptyline* and *nortriptyline* have been reported to prolong the half-life of dicoumarol in healthy subjects.[1,2] The few reports investigating the effect of tricyclic antidepressants on warfarin have not been able to conclude that a significant interaction exists. *Mianserin* and phenprocoumon have been reported not to interact.[3]

The *BNF* considers that there is a possible risk of increased warfarin activity with *SSRIs*; increased warfarin activity has been reported in a few patients taking *fluoxetine*,[4] in a patient taking *fluvoxamine*,[5] and another taking the SNRI *duloxetine*.[6] There has also been a report of increased anticoagulant activity in a patient taking acenocoumarol and *citalopram*.[7]

An increase in the dose of warfarin has been required by patients also taking *trazodone*.[8,9]

See also St John's Wort, p.1432.

1. Vesell ES, *et al.* Impairment of drug metabolism in man by allopurinol and nortriptyline. *N Engl J Med* 1970; **283:** 1484–8.
2. Pond SM, *et al.* Effects of tricyclic antidepressants on drug metabolism. *Clin Pharmacol Ther* 1975; **18:** 191–9.
3. Kopera H, *et al.* Phenprocoumon requirement, whole blood coagulation time, bleeding time and plasma γ-GT in patients receiving mianserin. *Eur J Clin Pharmacol* 1978; **13:** 351–6.
4. Woolfrey S, *et al.* Fluoxetine-warfarin interaction. *BMJ* 1993; **307:** 241.
5. Limke KK, *et al.* Fluvoxamine interaction with warfarin. *Ann Pharmacother* 2002; **36:** 1890–2.
6. Glueck CJ, *et al.* Interaction of duloxetine and warfarin causing severe elevation of international normalized ratio. *JAMA* 2006; **295:** 1517–18.
7. Borrás-Blasco J, *et al.* Probable interaction between citalopram and acenocoumarol. *Ann Pharmacother* 2002; **36:** 345.
8. Hardy J-L, Sirois A. Reduction of prothrombin and partial thromboplastin times with trazodone. *Can Med Assoc J* 1986; **135:** 1372.
9. Small NL, Giamonna KA. Interaction between warfarin and trazodone. *Ann Pharmacother* 2000; **34:** 734–6.

Antidiabetics. There have been a few early instances of *tolbutamide* enhancing the activity of dicoumarol.[1] However, this effect has not been seen in later studies involving dicoumarol,[1-3] warfarin,[2] and phenprocoumon,[4] although one study did find altered dicoumarol pharmacokinetics.[3] An absence of effect has been documented for phenprocoumon and *insulin*, *glibenclamide*, or *glibornuride*,[4] but there is a report of glibenclamide enhancing the effect of warfarin.[5]

There has been an isolated report of bleeding in a patient taking *phenformin* and warfarin.[6] *Metformin* has been reported to diminish phenprocoumon activity.[7]

An enhanced response to warfarin has been reported in a patient receiving *troglitazone*.[8]

Coumarin anticoagulants may increase the hypoglycaemic effect of *sulfonylureas* (see p.462).

1. Chaplin H, Cassell M. Studies on the possible relationship of tolbutamide to dicumarol in anticoagulant therapy. *Am J Med Sci* 1958; **235:** 706–16.
2. Poucher RL, Vecchio TJ. Absence of tolbutamide effect on anticoagulant therapy. *JAMA* 1966; **197:** 1069–70.
3. Jähnchen E, *et al.* Pharmacokinetic analysis of the interaction between dicoumarol and tolbutamide in man. *Eur J Clin Pharmacol* 1976; **10:** 349–56.
4. Heine P, *et al.* The influence of hypoglycaemic sulphonylureas on elimination and efficacy of phenprocoumon following a single oral dose in diabetic patients. *Eur J Clin Pharmacol* 1976; **10:** 31–6.
5. Jassal SV. *BMJ* 1991; **303:** 789.
6. Hamblin TJ. Interaction between warfarin and phenformin. *Lancet* 1971; **ii:** 1323.
7. Ohnhaus EE, *et al.* The influence of dimethylbiguanide on phenprocoumon elimination and its mode of action: a drug interaction study. *Klin Wochenschr* 1983; **61:** 851–8.
8. Plowman BK, Morreale AP. Possible troglitazone—warfarin interaction. *Am J Health-Syst Pharm* 1998; **55:** 1071.

Antiepileptics. Barbiturates such as *phenobarbital* and *primidone* diminish the activity of warfarin and other coumarins through increased metabolism. *Carbamazepine* is reported to have a similar effect.[1,2] Reports of the effect of *phenytoin* on anticoagulants do not provide a clear picture. There are reports of phenytoin enhancing the effects of warfarin[3,4] and a report of initial enhancement followed by decreased anticoagulant action.[5] Phenytoin has been reported to diminish the effect of dicoumarol.[6] Addition of *felbamate* has been reported[7] to necessitate a reduction in warfarin dosage. In another patient there was a transient increase in response to warfarin when *valproic acid* was started.[8] Valproate also inhibits platelet function and caution is required with warfarin and other anticoagulants.

For the effect of oral anticoagulants on phenytoin, see p.498.

1. Hansen JM, *et al.* Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* 1971; **12:** 539–43.
2. Ross JRY, Beeley L. Interaction between carbamazepine and warfarin. *BMJ* 1980; **280:** 1415–16.
3. Nappi JM. Warfarin and phenytoin interaction. *Ann Intern Med* 1979; **90:** 852.
4. Panegyres PK, Rischbieth RH. Fatal phenytoin warfarin interaction. *Postgrad Med J* 1991; **67:** 98.
5. Levine M, Sheppard I. Biphasic interaction of phenytoin with warfarin. *Clin Pharm* 1984; **3:** 200–3.
6. Hansen JM, *et al.* Effect of diphenylhydantoin on the metabolism of dicoumarol in man. *Acta Med Scand* 1971; **189:** 15–19.
7. Tisdel KA, *et al.* Warfarin—felbamate interaction: first report. *Ann Pharmacother* 1994; **28:** 805.
8. Guthrie SK, *et al.* Hypothesized interaction between valproic acid and warfarin. *J Clin Psychopharmacol* 1995; **15:** 138–9.

Antifungals. *Griseofulvin* has been reported to diminish the activity of warfarin.[1-3] There are several reports indicating that *miconazole*, given either systemically or topically as the oral gel, may enhance the activity of oral anticoagulants (warfarin, ethyl biscoumacetate, acenocoumarol, phenindione, and tioclomarol).[4-11] Absorption of miconazole after intravaginal use may have enhanced the activity of acenocoumarol in 2 patients;[12] it enhanced the activity of warfarin[13] in another. Studies in healthy subjects given a single warfarin dose[14,15] support case reports[16-18] suggesting that *fluconazole* may increase the anticoagulant activity of warfarin. There are isolated reports of the potentiation of warfarin by *itraconazole*[19] and *ketoconazole*,[20] and of unspecified coumarins by topical *bifonazole* or *econazole*.[21] There has been a case report of a reduction in the effect of warfarin by *terbinafine*,[22] although a study[23] in healthy subjects found no clinically significant interaction, and others[24] considered that no interaction usually occurs. A case of potentiation of warfarin by terbinafine has also been reported;[25] the authors speculate that concomitant cimetidine may have contributed to the interaction by increasing plasma-terbinafine concentrations.

1. Cullen SI, Catalano PM. Griseofulvin-warfarin antagonism. *JAMA* 1967; **199:** 582–3.
2. Udall JA. Drug interference with warfarin therapy. *Clin Med* 1970; **77** (Aug.): 20–5.
3. Okino K, Weibert RT. Warfarin-griseofulvin interaction. *Drug Intell Clin Pharm* 1986; **20:** 291–3.
4. Loupi E, *et al.* Interactions médicamenteuses et miconazole: a propos de 10 observations. *Therapie* 1982; **37:** 437–41.
5. Watson PG, *et al.* Drug interaction with coumarin derivative anticoagulants. *BMJ* 1982; **285:** 1045–6.
6. Colquhoun MC, *et al.* Interaction between warfarin and miconazole oral gel. *Lancet* 1987; **i:** 695–6.
7. Bailey GM, *et al.* Miconazole and warfarin interaction. *Pharm J* 1989; **242:** 183.
8. Ariyaratnam S, *et al.* Potentiation of warfarin anticoagulant activity by miconazole oral gel. *BMJ* 1997; **314:** 349.
9. Evans J, *et al.* Treating oral candidiasis: potentially fatal. *Br Dent J* 1997; **182:** 452.
10. Pemberton MN, *et al.* Derangement of warfarin anticoagulation by miconazole oral gel. *Br Dent J* 1998; **184:** 68–9.
11. Ortín M, *et al.* Miconazole oral gel enhances acenocoumarol anticoagulant activity: a report of three cases. *Ann Pharmacother* 1999; **33:** 175–7.
12. Lansdorp D, *et al.* Potentiation of acenocoumarol during vaginal administration of miconazole. *Br J Clin Pharmacol* 1999; **47:** 225–6.
13. Thirion DJG, Farquhar Zanetti LA. Potentiation of warfarin's hypoprothrombinemic effect with miconazole vaginal suppositories. *Pharmacotherapy* 2000; **20:** 98–9.
14. Lazar JD, Wilner KD. Drug interactions with fluconazole. *Rev Infect Dis* 1990; **12** (suppl 3): S327–S333.
15. Black DJ, *et al.* Warfarin–fluconazole II: a metabolically based drug interaction: in vivo studies. *Drug Metab Dispos* 1996; **24:** 422–8.
16. Seaton TL, *et al.* Possible potentiation of warfarin by fluconazole. *DICP Ann Pharmacother* 1990; **24:** 1177–8.
17. Gericke KR. Possible interaction between warfarin and fluconazole. *Pharmacotherapy* 1993; **13:** 508–9.
18. Baciewicz AM, *et al.* Fluconazole—warfarin interaction. *Ann Pharmacother* 1994; **28:** 1111.
19. Yeh J, *et al.* Potentiation of action of warfarin by itraconazole. *BMJ* 1990; **301:** 669.
20. Smith AG. Potentiation of oral anticoagulants by ketoconazole. *BMJ* 1984; **288:** 188–9. Correction. *ibid.*; 608.
21. Alexandra J-F, *et al.* Overanticoagulation with coumarin and cutaneous azole therapy. *Ann Intern Med* 2008; **148:** 633–5.
22. Warwick JA, Corrall RJ. Serious interaction between warfarin and oral terbinafine. *BMJ* 1998; **316:** 440.
23. Guerret M, *et al.* Evaluation of effects of terbinafine on single oral dose pharmacokinetics and anticoagulant actions of warfarin in healthy volunteers. *Pharmacotherapy* 1997; **17:** 767–73.
24. Stockley IH. Terbinafine and warfarin mystery. *Pharm J* 1998; **260:** 408.
25. Gupta AK, Ross GS. Interaction between terbinafine and warfarin. *Dermatology* 1998; **196:** 266–7.

Antigout drugs. The two drugs in this group mostly implicated in interactions with anticoagulants are allopurinol and sulfinpyrazone.

With *allopurinol* there are conflicting reports of patients experiencing no interaction or an enhanced anticoagulant effect with dicoumarol,[1] phenprocoumon,[2] or warfarin.[3,4]

Interactions with *sulfinpyrazone* have usually involved warfarin and, apart from a case of a mixed response,[5] have involved increased anticoagulant activity, sometimes with haemorrhage, so calling for careful control. It is still not clear how sulfinpyrazone exerts its effect, but studies point to a stereoselective effect on warfarin metabolism where the *S*-isomer's metabolic clearance is inhibited;[6] sulfinpyrazone also affects platelets. Sulfinpyrazone has also enhanced the anticoagulant activity of acenocoumarol.[7] A significant interaction with phenprocoumon appears unlikely.[8]

Probenecid has accelerated the elimination of a single dose of phenprocoumon without effect on the prothrombin time.[9]

Benziodarone has been reported to enhance the effects of warfarin, diphenadione, ethyl biscoumacetate, and acenocoumarol, but not of dicoumarol, phenindione, or phenprocoumon.[10] A further study[11] confirmed that benziodarone could increase the half-life of ethyl biscoumacetate, but also found that the effect of phenprocoumon was enhanced. A study[12] of *benzbromarone*, which is structurally related to benziodarone, concluded that it enhanced the effect of warfarin by inhibition of the cytochrome P450 isoenzyme CYP2C9, leading to a stereoselective inhibition of the metabolism of warfarin.

1. Vesell ES, *et al.* Impairment of drug metabolism in man by allopurinol and nortriptyline. *N Engl J Med* 1970; **283:** 1484–8.
2. Jähnchen E, *et al.* Interaction of allopurinol with phenprocoumon in man. *Klin Wochenschr* 1977; **55:** 759–61.
3. Rawlins MD, Smith SE. Influence of allopurinol on drug metabolism in man. *Br J Pharmacol* 1973; **48:** 693–8.
4. Pond SM, *et al.* The effects of allopurinol and clofibrate on the elimination of coumarin anticoagulants in man. *Aust N Z J Med* 1975; **5:** 324–8.
5. Nenci GG, *et al.* Biphasic sulphinpyrazone-warfarin interaction. *BMJ* 1981; **282:** 1361–2.
6. Toon S, *et al.* The warfarin-sulfinpyrazone interaction: stereochemical considerations. *Clin Pharmacol Ther* 1986; **39:** 15–24.
7. Michot F, *et al.* Über die Beeinflussung der gerinnungshemmenden Wirkung von Acenocoumarol durch Sulfinpyrazon. *Schweiz Med Wochenschr* 1981; **111:** 255–60.
8. Heimark LD, *et al.* The effect of sulfinpyrazone on the disposition of pseudoracemic phenprocoumon in humans. *Clin Pharmacol Ther* 1987; **42:** 312–19.
9. Mönig H, *et al.* The effects of frusemide and probenecid on the pharmacokinetics of phenprocoumon. *Eur J Clin Pharmacol* 1990; **39:** 261–5.
10. Pyörälä K, *et al.* Benziodarone (Amplivix) and anticoagulant therapy. *Acta Med Scand* 1963; **173:** 385–9.
11. Verstraete M, *et al.* Dissimilar effect of two anti-anginal drugs belonging to the benzofuran group on the action of coumarin derivatives. *Arch Int Pharmacodyn Ther* 1968; **176:** 33–41.
12. Takahashi H, *et al.* Potentiation of anticoagulant effect of warfarin caused by enantioselective metabolic inhibition by the uricosuric agent benzbromarone. *Clin Pharmacol Ther* 1999; **66:** 569–81.

Antihistamines. There has been a report[1] of a raised INR and severe epistaxis in a patient after the addition of *cetirizine* to long-term acenocoumarol.

1. Berod T, Mathiot I. Probable interaction between cetirizine and acenocoumarol. *Ann Pharmacother* 1997; **31:** 122.

Antimalarials. The ingestion of large amounts of tonic water by 2 patients necessitated a reduction in warfarin dosage. The enhanced effect was attributed to the *quinine* content of the tonic water.[1] A woman stabilised on warfarin developed haematuria and a high prothrombin ratio after taking *proguanil* for malaria prophylaxis.[2]

1. Clark DJ. Clinical curio: warfarin and tonic water. *BMJ* 1983; **286:** 1258.
2. Armstrong G, *et al.* Warfarin potentiated by proguanil. *BMJ* 1991; **303:** 789.

Antimuscarinics. There have been 2 cases reported[1] of *tolterodine* enhancing the effect of warfarin. It was stated that the manufacturers of tolterodine were aware of 6 reports of a possible interaction with warfarin.

1. Colucci VJ, Rivey MP. Tolterodine–warfarin drug interaction. *Ann Pharmacother* 1999; **33:** 1173–6.

Antineoplastics. There have been several reports of interactions between warfarin and antineoplastics. No clear picture emerges from these reports which is not surprising considering that antineoplastics are often given in combination and that they can exert their own haematological effects. *Cyclophosphamide* for instance has been associated with an increase in warfarin's activity when given with *methotrexate* and *fluorouracil*,[1] but with a decrease when given with non-antineoplastic drugs.[2] An increase in the activity of warfarin and mucous membrane bleeding occurred in a patient who had 4 courses of fluorouracil and folic acid at weekly intervals.[3] The patient was also taking indometacin. Warfarin dosage had to be reduced in 5 patients given fluorouracil-based antineoplastic regimens.[4] An increase in the effect of warfarin has been reported when given with fluorouracil and levamisole (see Levamisole, below). *Capecitabine* increases plasma-warfarin concentrations[5] and there have been reports of increased warfarin activity,[5-7] in 1 case resulting in gastrointestinal bleeding;[6] licensed product information for capecitabine states that altered coagulation parameters and bleeding have also occurred with phenprocoumon. There have been 2 cases reported[8] where *trastuzumab* enhanced the effect of warfarin. *Etoposide* with *vindesine*[9] or with *carboplatin*,[10] *ifosfamide* with *mesna*,[11] and *tamoxifen*[12-14] have all produced an increased anticoagulant effect. *Aminoglutethimide* has led to decreased activity of warfarin or acenocoumarol,[15,16] probably due to increased warfarin metabolism. Licensed product information for the anti-androgen *flutamide* states that increases in prothrombin time have been reported after starting flutamide therapy in patients on long-term warfarin. *In vitro* data indicate a similar reaction is likely with *bicalutamide*. *Mercaptopurine*[17] and *mitotane*[18] have also decreased warfarin activity. Licensed product information for *vorinostat* states that prolongation of prothrombin time has been seen when the drug is given with coumarin derivatives; prothrombin time and INR should be monitored in patients given both drugs.

1. Seifter EJ, *et al.* Possible interactions between warfarin and antineoplastic drugs. *Cancer Treat Rep* 1985; **69:** 244–5.
2. Tashima CK. Cyclophosphamide effect on coumarin anticoagulation. *South Med J* 1979; **72:** 633–4.
3. Brown MC. Multisite mucous membrane bleeding due to a possible interaction between warfarin and 5-fluorouracil. *Pharmacotherapy* 1997; **17:** 631–3.
4. Kolesar JM, *et al.* Warfarin–5-FU interaction—a consecutive case series. *Pharmacotherapy* 1999; **19:** 1445–9.
5. Camidge R, *et al.* Significant effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin in patients with cancer. *J Clin Oncol* 2005; **23:** 4719–25.
6. Copur MS, *et al.* An adverse interaction between warfarin and capecitabine: a case report and review of the literature. *Clin Colorectal Cancer* 2001; **1:** 182–4.
7. Janney LM, Waterbury NV. Capecitabine–warfarin interaction. *Ann Pharmacother* 2005; **39:** 1546–51.
8. Nissenblatt MJ, Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment. *JAMA* 1999; **282:** 2299–2300.
9. Ward K, Bitran JD. Warfarin, etoposide, and vindesine interactions. *Cancer Treat Rep* 1984; **68:** 817–18.
10. Le AT, *et al.* Enhancement of warfarin response in a patient receiving etoposide and carboplatin chemotherapy. *Ann Pharmacother* 1997; **31:** 1006–8.
11. Hall G, *et al.* Intravenous infusions of ifosfamide/mesna and perturbation of warfarin anticoagulant control. *Postgrad Med J* 1990; **66:** 860–1.
12. Lodwick R, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1987; **295:** 1141.
13. Tenni P, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1989; **298:** 93.
14. Ritchie LD, Grant SMT. Tamoxifen-warfarin interaction: the Aberdeen hospitals drug file. *BMJ* 1989; **298:** 1253.
15. Lønning PE, *et al.* The influence of a graded dose schedule of aminoglutethimide on the disposition of the optical enantiomers of warfarin in patients with breast cancer. *Cancer Chemother Pharmacol* 1986; **17:** 177–81.
16. Bruning PF, Bonfrèr JGM. Aminoglutethimide and oral anticoagulant therapy. *Lancet* 1983; **ii:** 582.
17. Spiers ASD, Mibashan RS. Increased warfarin requirement during mercaptopurine therapy: a new drug interaction. *Lancet* 1974: **ii:** 221–2.
18. Cuddy PG, *et al.* Influence of mitotane on the hypoprothrombinemic effect of warfarin. *South Med J* 1986; **79:** 387–8.

Antiplatelets. The interaction between anticoagulants and *dipyridamole* is unusual as bleeding can occur without any alteration in prothrombin times; special care is therefore required. This interaction has involved a small number of patients taking dipyridamole and warfarin or phenindione;[1] inhibition of platelet function by dipyridamole has been implicated. However, in general it does not appear to increase the risk of bleeding.[2]

Paradoxically, addition of *ticlopidine* was found to significantly increase acenocoumarol requirements.[3]

See also under Analgesics and NSAIDs (above).

1. Kalowski S, Kincaid-Smith P. Interaction of dipyridamole with anticoagulants in the treatment of glomerulonephritis. *Med J Aust* 1973; **2:** 164–6.
2. Levine MN, *et al.* Hemorrhagic complications of long-term anticoagulant therapy. *Chest* 1989; **95** (suppl): 26S–36S.
3. Salar A, *et al.* Ticlopidine antagonizes acenocoumarol treatment. *Thromb Haemost* 1997; **77:** 223–4.

Antiprotozoals. *Metronidazole* enhances the activity of warfarin[1,2] through selective inhibition of the metabolism of its *S*-isomer.[3]

1. Kazmier FJ. A significant interaction between metronidazole and warfarin. *Mayo Clin Proc* 1976; **51:** 782–4.

2. Dean RP, Talbert RL. Bleeding associated with concurrent warfarin and metronidazole therapy. *Drug Intell Clin Pharm* 1980; **14:** 864–6.
3. O'Reilly RA. The stereoselective interaction of warfarin and metronidazole in man. *N Engl J Med* 1976; **295:** 354–7.

Antithyroid drugs. See Thyroid and Antithyroid Drugs, below.

Antivirals. Reductions in dosage of either warfarin[1] or acenocoumarol[2] were necessary in 2 patients receiving *interferon alfa* for hepatitis C. The interactions may have been due to decreased metabolism of the anticoagulant. A similar need for a reduced warfarin dose had also been noted in other patients taking *interferon alfa-2b* or *interferon beta*.[1] However, in a patient taking interferon alfa-2b with *ribavirin*,[3] the warfarin dose needed to be increased, probably due to the interaction between ribavirin and warfarin.

An enhanced response to warfarin has been reported[4] in a patient taking *saquinavir*. The mechanism may involve competitive inhibition of warfarin metabolism and might also occur with other HIV-protease inhibitors. However, a decreased response to warfarin seemed to be caused by *ritonavir* when it was added to the multidrug therapy of a patient.[5] Ritonavir has also been reported to decrease the response to acenocoumarol.[6]

Up to October 2005 there had been 19 reports[7] received by the Canadian health authorities (Health Canada) of enhanced response to warfarin between 1 and 11 days after starting *oseltamivir*. The increased INR ranged from 3.2 to 10.9; however, there was not enough information to be certain of causality. In 3 other cases there was a decrease in INR on the addition of oseltamivir.

1. Adachi Y, *et al.* Potentiation of warfarin by interferon. *BMJ* 1995; **311:** 292.
2. Serratrice J, *et al.* Interferon-alpha 2b interaction with acenocoumarol. *Am J Hematol* 1998; **57:** 89.
3. Schulman S. Inhibition of warfarin activity by ribavirin. *Ann Pharmacother* 2002; **36:** 72–4.
4. Darlington MR. Hypoprothrombinemia during concomitant therapy with warfarin and saquinavir. *Ann Pharmacother* 1997; **31:** 647.
5. Knoell KR, *et al.* Potential interaction involving warfarin and ritonavir. *Ann Pharmacother* 1998; **32:** 1299–1302.
6. Llibre JM, *et al.* Severe interaction between ritonavir and acenocoumarol. *Ann Pharmacother* 2002; **36:** 621–3.
7. Health Canada. Oseltamivir (Tamiflu) and warfarin: suspected increase in INR. *Can Adverse React News* 2006; **16** (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v16n1-eng.pdf (accessed 19/08/08)

Anxiolytic sedatives, hypnotics, and antipsychotics. *Barbiturates*, by inducing liver metabolism, can reduce the activity of anticoagulants; *glutethimide* has a similar action. The *benzodiazepines* do not generally have any effect although there is the rare report of increased or decreased activity.

Although there is a report suggesting that *cloral hydrate* may decrease the effect of dicoumarol by enzyme induction,[1] other studies and experience indicate an increase in the anticoagulant activity of warfarin.[2-4] However, the increase is only transient and is probably the result of displacement of warfarin from plasma protein binding sites by the metabolite trichloroacetic acid.[2] *Triclofos sodium* appears to increase the activity of warfarin in a similar way.[5]

Reduced anticoagulant activity has been reported with *dichloralphenazone*,[6,7] *ethchlorvynol* (with dicoumarol),[8] and *haloperidol* (with phenindione).[9] Compounds such as *meprobamate* and *methaqualone* appear to have no effect.

1. Cucinell SA, *et al.* The effect of chloral hydrate on bishydroxycoumarin metabolism: a fatal outcome. *JAMA* 1966; **197:** 366–8.
2. Sellers EM, Koch-Weser J. Kinetics and clinical importance of displacement of warfarin from albumin by acidic drugs. *Ann N Y Acad Sci* 1971; **179:** 213–25.
3. Boston Collaborative Drug Surveillance Program. Interaction between chloral hydrate and warfarin. *N Engl J Med* 1972; **286:** 53–5.
4. Udall JA. Warfarin-chloral hydrate interaction: pharmacological activity and clinical significance. *Ann Intern Med* 1974; **81:** 341–4.
5. Sellers EM, *et al.* Enhancement of warfarin-induced hypoprothrombinemia by triclofos. *Clin Pharmacol Ther* 1972; **13:** 911–15.
6. Breckenridge A, Orme M. Clinical implications of enzyme induction. *Ann N Y Acad Sci* 1971; **179:** 421–3.
7. Whitfield JB, *et al.* Changes in plasma α-glutamyl transpeptidase activity associated with alterations in drug metabolism in man. *BMJ* 1973; **1:** 316–18.
8. Johansson S-A. Apparent resistance to oral anticoagulant therapy and influence of hypnotics on some coagulation factors. *Acta Med Scand* 1968; **184:** 297–300.
9. Oakley DP, Lautch H. Haloperidol and anticoagulant treatment. *Lancet* 1963; **ii:** 1231.

Beta blockers. Beta blockers, particularly those with a high lipid solubility such as propranolol, may inhibit the metabolism of warfarin.[1] Although a number of studies have shown pharmacokinetic interactions between some beta blockers and oral anticoagulants, no effect on anticoagulant activity has generally been found. However, possible potentiation of the effect of warfarin by *propranolol*[2] has been reported.

1. Mantero F, *et al.* Effect of atenolol and metoprolol on the anticoagulant activity of acenocoumarin. *Br J Clin Pharmacol* 1984; **17:** 94S–96S.
2. Bax NDS, *et al.* Inhibition of drug metabolism by β-adrenoceptor antagonists. *Drugs* 1983; **25** (suppl 2): 121–6.

Central stimulants. *Methylphenidate* has been reported both to increase the half-life of ethyl biscoumacetate,[1] and to have no effect on its half-life or anticoagulant activity.[2] *Prolintane* had no effect.[2]

1. Garrettson LK, *et al.* Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate: a new action of methylphenidate. *JAMA* 1969; **207:** 2053.
2. Hague DE, *et al.* The effect of methylphenidate and prolintane on the metabolism of ethyl biscoumacetate. *Clin Pharmacol Ther* 1971; **12:** 259–62.

Chamomile. A 70-year-old woman stabilised on warfarin developed multiple internal haemorrhages after she increased her use of chamomile lotion and consumption of chamomile tea to 4 or 5 times per day.[1] The interaction was considered to be due to the coumarin constituent of chamomile.

1. Segal R, Pilote L. Warfarin interaction with Matricaria chamomilla. *Can Med Assoc J* 2006; **174:** 1281–2.

Chinese herbal remedies. There have been a number of reports of increased anticoagulation in patients taking Chinese herbal remedies with warfarin.[1-6] The remedies have ranged from single ingredient herbal preparations to complex multi-ingredient products, sometimes sold under the same brand name but with very different compositions.

1. Yu CM, *et al.* Chinese herbs and warfarin potentiation by 'Danshen'. *J Intern Med* 1997; **241:** 337–9.
2. Izzat MB, *et al.* A taste of Chinese medicine! *Ann Thorac Surg* 1998; **66:** 941–2.
3. Page RL, Lawrence JD. Potentiation of warfarin by dong quai. *Pharmacotherapy* 1999; **19:** 870–6.
4. Chan TYK. Interaction between warfarin and danshen (Salvia miltiorrhiza). *Ann Pharmacother* 2001; **35:** 501–4.
5. Lam AY, *et al.* Possible interaction between warfarin and Lycium barbarum L. *Ann Pharmacother* 2001; **35:** 1199–1201.
6. Wong ALN, Chan TYK. Interaction between warfarin and the herbal product Quilinggao. *Ann Pharmacother* 2003; **37:** 836–8.

Corticosteroids and corticotropin. Corticosteroids are associated with an increase in blood coagulability, but their extensive use with anticoagulants, and very few reports of interaction, suggests that any problems are rare. However, there are some reports of corticosteroids or corticotropin either enhancing[1-3] or diminishing[4] the effects of anticoagulants. A retrospective study[5] in patients on long-term warfarin therapy given short courses of oral corticosteroids found that in most cases (29 of 32) there was an increase in INR, suggesting that careful monitoring is required.

1. Van Cauwenberge H, Jaques LB. Haemorrhagic effect of ACTH with anticoagulants. *Can Med Assoc J* 1958; **79:** 536–40.
2. Costedoat-Chalumeau N, *et al.* Potentiation of vitamin K antagonists by high-dose intravenous methylprednisolone. *Ann Intern Med* 2000; **132:** 631–5.
3. Stading JA, *et al.* Effects of prednisone on the international normalized ratio. *Am J Health-Syst Pharm* 2006; **63:** 2354–6. Correction. *ibid.* 2007; **64:** 130.
4. Chatterjea JB, Salomon L. Antagonistic effect of ACTH and cortisone on the anticoagulant activity of ethyl biscoumacetate. *BMJ* 1954; **2:** 790–2.
5. Hazlewood KA, *et al.* Effect of oral corticosteroids on chronic warfarin therapy. *Ann Pharmacother* 2006; **40:** 2101–6.

Cough suppressants. An increase in the activity of warfarin has been reported in patients taking *noscapine*[1,2] or *oxolamine*.[3] A subsequent study[3] suggested that the dose of warfarin should be reduced by 50% if oxolamine was started.

See also Menthol, below.

1. Scordo MG, *et al.* Warfarin–noscapine interaction: a series of four case reports. *Ann Pharmacother* 2008; **42:** 448–50.
2. Ohlsson S, *et al.* Noscapine may increase the effect of warfarin. *Br J Clin Pharmacol* 2008; **65:** 277–8.
3. Min KA, *et al.* Effect of oxolamine on anticoagulant effect of warfarin. *Am J Health-Syst Pharm* 2006; **63:** 153–6.

Cranberry. Between 1999 and 2003 the UK CSM[1] had received 5 reports suggesting an interaction between warfarin and cranberry juice. In 3 patients the activity of warfarin had been potentiated and one of them had died. In the other patients the INR was either reduced or unstable. By 2004 there had been 7 further reports of suspected interactions and the CSM advised[2] patients to avoid cranberry juice and other cranberry products while taking warfarin. However. despite case reports suggesting an increase in warfarin activity, the potential for a pharmacokinetic effect has been questioned,[3] and pharmacokinetic studies[4,5] have failed to confirm an interaction.

1. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Possible interaction between warfarin and cranberry juice. *Current Problems* 2003; **29:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
2. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Interaction between warfarin and cranberry juice: new advice. *Current Problems* 2004; **30:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
3. Pham DQ, Pham AQ. Interaction potential between cranberry juice and warfarin. *Am J Health-Syst Pharm* 2007; **64:** 490–4.
4. Li Z, *et al.* Cranberry does not affect prothrombin time in male subjects on warfarin. *J Am Diet Assoc* 2006; **106:** 2057–61.
5. Lilja JJ, *et al.* Effects of daily ingestion of cranberry juice on the pharmacokinetics of warfarin, tizanidine, and midazolam—probes of CYP2C9, CYP1A2, and CYP3A4. *Clin Pharmacol Ther* 2007; **81:** 833–9.

Dermatological drugs. A patient's warfarin dose had to be increased when he started treatment with *etretinate*.[1]

1. Ostlere LS, *et al.* Reduced therapeutic effect of warfarin caused by etretinate. *Br J Dermatol* 1991; **124:** 505–10.

Dietary supplements. There have been reports of an increased INR in patients taking warfarin and dietary supplements containing *glucosamine* and *chondroitin*,[1,2] and the UK CHM advises[3] that patients on warfarin should not take glucosamine. A similar effect has been reported[4] with *poliglusam*.

1. Rozenfeld V, *et al.* Possible augmentation of warfarin effect by glucosamine-chondroitin. *Am J Health-Syst Pharm* 2004; **61:** 306–7.
2. Knudsen JF, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: case report and review of the literature and MedWatch database. *Pharmacotherapy* 2008; **28:** 540–8.
3. CHM/MHRA. Glucosamine adverse reactions and interactions. *Current Problems* 2006; **31:** 8. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 31/07/08)
4. Huang S-S, *et al.* Chitosan potentiation of warfarin effect. *Ann Pharmacother* 2007; **41:** 1912–14.

Disulfiram. Two reports suggesting that disulfiram enhances the activity of warfarin[1,2] were confirmed by a study in 8 healthy subjects.[3] Although inhibition of liver enzymes by disulfiram was considered responsible,[3] a later study[4] suggested that disulfiram acts directly on the liver to increase hypoprothrombinaemia. This interaction is complicated by the variable effects of alcohol on warfarin (see above). Special care is therefore called for when these drugs are used together.

1. Rothstein E. Warfarin effect enhanced by disulfiram. *JAMA* 1968; **206:** 1574–5.
2. Rothstein E. Warfarin effect enhanced by disulfiram (Antabuse). *JAMA* 1972; **221:** 1052–3.
3. O'Reilly RA. Interaction of sodium warfarin and disulfiram (Antabuse) in man. *Ann Intern Med* 1973; **78:** 73–6.
4. O'Reilly RA. Dynamic interaction between disulfiram and separated enantiomorphs of racemic warfarin. *Clin Pharmacol Ther* 1981; **29:** 332–6.

Diuretics. *Etacrynic acid* has been reported to enhance the activity of warfarin.[1] *Chlortalidone*[2] and *spironolactone*[3] have both been associated with a reduction in warfarin's activity in healthy subjects and it has been suggested that this might be a consequence of the diuresis concentrating the circulating clotting factors. However, *bumetanide*, *furosemide*, and the *thiazides* appear to have no effect on warfarin.

1. Petrick RJ, *et al.* Interaction between warfarin and ethacrynic acid. *JAMA* 1975; **231:** 843–4.
2. O'Reilly RA, *et al.* Impact of aspirin and chlorthalidone on the pharmacodynamics of oral anticoagulant drugs in man. *Ann N Y Acad Sci* 1971; **179:** 173–86.
3. O'Reilly RA. Spironolactone and warfarin interaction. *Clin Pharmacol Ther* 1980; **27:** 198–201.

Endothelin receptor antagonists. A study in healthy subjects[1] showed that *bosentan* decreased the anticoagulant effect of warfarin; a case report[2] confirmed this.

1. Weber C, *et al.* Effect of the endothelin-receptor antagonist bosentan on the pharmacokinetics and pharmacodynamics of warfarin. *J Clin Pharmacol* 1999; **39:** 847–54.
2. Murphey LM, Hood EH. Bosentan and warfarin interaction. *Ann Pharmacother* 2003; **37:** 1028–31.

Gastrointestinal drugs. Antacids may or may not interact with warfarin. *Bismuth carbonate* and *magnesium trisilicate* for example have been reported to reduce warfarin's absorption,[1] but *aluminium hydroxide* has been observed to have no effect on warfarin or dicoumarol.[2] *Psyllium*[3] and *magnesium hydroxide*[2] have also been reported to have no effect on warfarin, but the latter has increased the plasma concentrations of dicoumarol.[2]

There have been occasional reports of *sucralfate* diminishing the effect of warfarin.[4-6]

Histamine H_2-antagonists have been widely studied. There are several reports indicating that *cimetidine* can enhance the anticoagulant effect of warfarin and haemorrhage has occurred. A number of studies show that cimetidine can increase the plasma concentration and half-life of warfarin and that there is a selective inhibitory effect on the metabolism of its *R*-isomer.[7-10] Not all these studies have, however, found an increase in prothrombin time. The effect of cimetidine on warfarin appears to be dose-dependent[7] and to be subject to interindividual variation;[9,10] careful monitoring is needed. Limited evidence suggests that cimetidine has a similar effect on the metabolism of acenocoumarol[11,12] and phenindione[11] but not of phenprocoumon.[13] Studies with *ranitidine* have generally been unable to show an effect on the metabolism of warfarin,[10,14] although in one study warfarin clearance was reduced.[7] There is a case report suggesting that potentiation of warfarin by ranitidine may occasionally occur.[15]

One study has suggested that *omeprazole* could inhibit the metabolism of *R*-warfarin although a clinically significant effect was unlikely.[16] No evidence of an interaction was found in a retrospective study[17] of patients on acenocoumarol and omeprazole. Similarly, *pantoprazole* appears to have no effect on the pharmacokinetics or pharmacodynamics of warfarin[18] or phenprocoumon.[19]

A marked increase in the effect of warfarin has been reported in a patient when *cisapride* was added.[20]

A study[21] in healthy subjects found that *aprepitant* caused a small decrease in plasma concentration of the more active *S*-isomer of warfarin and there was also a decrease in INR.

A reduction in the response to warfarin with development of venous thrombosis has been reported in a patient receiving *mesalazine*,[22] and in another patient receiving *sulfasalazine*.[23]

1. McElnay JC, *et al.* Interaction of warfarin with antacid constituents. *BMJ* 1978; **2:** 1166.
2. Ambre JJ, Fischer LJ. Effect of coadministration of aluminum and magnesium hydroxides on absorption of anticoagulants in man. *Clin Pharmacol Ther* 1973; **14:** 231–7.
3. Robinson DS, *et al.* Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin Pharmacol Ther* 1971; **12:** 491–5.
4. Mungall D, *et al.* Sucralfate and warfarin. *Ann Intern Med* 1983; **98:** 557.
5. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP Ann Pharmacother* 1991; **25:** 745–6.
6. Parrish RH, *et al.* Sucralfate-warfarin interaction. *Ann Pharmacother* 1992; **26:** 1015–16.
7. Desmond PV, *et al.* Decreased oral warfarin clearance after ranitidine and cimetidine. *Clin Pharmacol Ther* 1984; **35:** 338–41.
8. Choonara IA, *et al.* Stereoselective interaction between the R enantiomer of warfarin and cimetidine. *Br J Clin Pharmacol* 1986; **21:** 271–7.
9. Sax MJ, *et al.* Effect of two cimetidine regimens on prothrombin time and warfarin pharmacokinetics during long-term warfarin therapy. *Clin Pharm* 1987; **6:** 492–5.
10. Toon S, *et al.* Comparative effects of ranitidine and cimetidine on the pharmacokinetics and pharmacodynamics of warfarin in man. *Eur J Clin Pharmacol* 1987; **32:** 165–72.
11. Serlin MJ, *et al.* Cimetidine: interaction with oral anticoagulants in man. *Lancet* 1979; **ii:** 317–19.
12. Gill TS, *et al.* Cimetidine-nicoumalone interaction in man: stereochemical considerations. *Br J Clin Pharmacol* 1989; **27:** 469–74.
13. Harenberg J, *et al.* Cimetidine does not increase the anticoagulant effect of phenprocoumon. *Br J Clin Pharmacol* 1982; **14:** 292–3.
14. Serlin MJ, *et al.* Lack of effect of ranitidine on warfarin action. *Br J Clin Pharmacol* 1981; **12:** 791–4.
15. Baciewicz AM, Morgan PJ. Ranitidine-warfarin interaction. *Ann Intern Med* 1990; **112:** 76–7.
16. Sutfin T, *et al.* Stereoselective interaction of omeprazole with warfarin in healthy men. *Ther Drug Monit* 1989; **11:** 176–84.
17. Vreeburg EM, *et al.* Lack of effect of omeprazole on oral acenocoumarol anticoagulant therapy. *Scand J Gastroenterol* 1997; **32:** 991–4.
18. Duursema L, *et al.* Lack of effect of pantoprazole on the pharmacodynamics and pharmacokinetics of warfarin. *Br J Clin Pharmacol* 1995; **39:** 700–3.
19. Ehrlich A, *et al.* Lack of pharmacodynamic and pharmacokinetic interaction between pantoprazole and phenprocoumon in man. *Eur J Clin Pharmacol* 1996; **51:** 277–81.
20. Darlington MR. Hypoprothrombinemia induced by warfarin sodium and cisapride. *Am J Health-Syst Pharm* 1997; **54:** 320–1.
21. Depré M, *et al.* Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. *Eur J Clin Pharmacol* 2005; **61:** 341–6.
22. Marinella MA. Mesalamine and warfarin therapy resulting in decreased warfarin effect. *Ann Pharmacother* 1998; **32:** 841–2.
23. Teefy AM, *et al.* Warfarin resistance due to sulfasalazine. *Ann Pharmacother* 2000; **34:** 1265–8.

Ginkgo biloba. There is a report[1] of a woman stabilised on warfarin for 5 years who suffered an intracerebral haemorrhage 2 months after starting *Ginkgo biloba*, possibly due to the additive effect of the latter's antiplatelet activity. However, a study[2] in healthy subjects found no evidence that ginkgo affected warfarin pharmacokinetics or coagulation.

1. Matthews MK. Association of Ginkgo biloba with intracerebral hemorrhage. *Neurology* 1998; **50:** 1933–4.
2. Jiang X, *et al.* Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 425–32.

Ginseng. A reduction in the response to warfarin was reported[1] in a patient after taking a ginseng preparation. A study[2] in healthy subjects also found a small reduction in response.

1. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. *Am J Health-Syst Pharm* 1997; **54:** 692–3.
2. Yuan C-S, *et al.* American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. *Ann Intern Med* 2004; **141:** 23–7.

Glucagon. A dose-dependent enhancement of warfarin's anticoagulant activity has been reported with glucagon.[1]

1. Koch-Weser J. Potentiation by glucagon of the hypoprothrombinemic action of warfarin. *Ann Intern Med* 1970; **72:** 331–5.

Glucosamine. See Dietary Supplements, above.

Immunosuppressants. Severe bleeding occurred in a patient on long-term warfarin after stopping *azathioprine*,[1] while another patient[2] required an increased dose of warfarin when it was given with azathioprine.

There have been a few case reports of interaction between warfarin or acenocoumarol and *ciclosporin*, in which the dose of the anticoagulant or ciclosporin or both needed to be altered (see Anticoagulants under Interactions of Ciclosporin, p.1827).

There has been a report[3] of *leflunomide* enhancing the effects of warfarin, causing gross haematuria after the second dose; the patient's INR rose from 3.4 to 11. It was stated that the UK CSM had received 4 reports of increased INR with leflunomide up to the end of 2002.

1. Singleton JD, Conyers L. Warfarin and azathioprine: an important drug interaction. *Am J Med* 1992; **92:** 217.
2. Rotenberg M, *et al.* Effect of azathioprine on the anticoagulant activity of warfarin. *Ann Pharmacother* 2000; **34:** 120–2.
3. Lim V, Pande I. Leflunomide can potentiate the anticoagulant effect of warfarin. *BMJ* 2002; **325:** 1333. Correction. *ibid.* 2003; **326:** 432.

Leukotriene antagonists. *Zafirlukast* is reported to decrease the clearance of *S*-warfarin.[1] Licensed product information for zafirlukast states that it probably inhibits the cytochrome P450 isoenzyme CYP2C9 which is involved in the metabolism of warfarin. Prothrombin time may be significantly prolonged when zafirlukast is added and warfarin dosage should be adjusted accordingly.

A study[2] of *montelukast* and warfarin found no significant interaction between the two drugs.

1. Suttle AB, *et al.* Effect of zafirlukast on the pharmacokinetics of R- and S-warfarin in healthy men. *Clin Pharmacol Ther* 1997; **61:** 186.
2. Van Hecken, *et al.* Effect of montelukast on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *J Clin Pharmacol* 1999; **39:** 495–500.

Levamisole. An increased INR has been reported[1] in a patient taking chronic warfarin therapy after addition of *levamisole* and fluorouracil, possibly due to inhibition of warfarin metabolism. Interactions between warfarin and other fluorouracil-containing regimens have been reported (see Antineoplastics, above) but levamisole might also be involved. In a second patient, a similar reaction was reported[2] after levamisole and fluorouracil and an episode of bleeding subsequently occurred after levamisole alone.

1. Scarfe MA, Israel MK. Possible drug interaction between warfarin and combination of levamisole and fluorouracil. *Ann Pharmacother* 1994; **28:** 464–7.
2. Wehbe TW, Warth JA. A case of bleeding requiring hospitalization that was likely caused by an interaction between warfarin and levamisole. *Clin Pharmacol Ther* 1996; **59:** 360–2.

Lipid regulating drugs. Fibrates have been reported to interact with coumarin anticoagulants. *Clofibrate* can enhance the activity of warfarin, sometimes to the point of haemorrhage. The mechanism of this interaction is not clear, but it does not appear to be a pharmacokinetic effect. Similar enhancement of activity has been reported with clofibrate and dicoumarol or phenindione. *Bezafibrate* has been reported to enhance the effect of phenprocoumon[1] and warfarin,[2] and *fenofibrate*[3] and *gemfibrozil*[4] have been reported to enhance the effect of warfarin, although a study[5] in healthy subjects found that gemfibrozil slightly decreased plasma-warfarin concentrations.

Interactions may also occur between statins and coumarin anticoagulants,[6] although there have been conflicting reports in some cases. Hypoprothrombinaemia and bleeding has been reported in 2 patients on warfarin given *lovastatin*.[7] An increased response to warfarin has also been reported[6,8,9] in a number of patients taking *fluvastatin*. A study[10] with *rosuvastatin* and warfarin reported an increased INR in healthy subjects and in patients on long-term warfarin therapy, although another study[11] found no effect. However, there have been reports of haematoma and raised INR in patients after addition of rosuvastatin to long-term therapy with warfarin[12] or acenocoumarol.[13] An increased response to warfarin has been observed with *simvastatin*,[14] including a fatal cerebral haemorrhage in a patient who was changed from atorvastatin to simvastatin,[15] and potentiation of the effect of acenocoumarol by simvastatin has also been reported.[16] However, the INR in another patient on long-term warfarin remained stable on the addition of simvastatin.[17] Licensed product information for *pravastatin* states that no change in warfarin activity has been seen in patients given both drugs, but there has been a report[18] of bleeding in a patient taking fluindione when pravastatin was added. In a study[19] of 46 patients on warfarin who had been converted from pravastatin to simvastatin, the mean INR increased, but the median weekly warfarin dose did not differ significantly and no episodes of bleeding were reported.

Dextrothyroxine increases the anticoagulant effect of warfarin sodium[20,21] and dicoumarol.[22]

Colestyramine has reduced warfarin's serum concentration[23] and half-life[24] as well as its activity.[23,24] The mechanisms of this interaction include binding of warfarin to colestyramine and reduced absorption;[23] the enterohepatic recycling of warfarin may also be interrupted.[24] Phenprocoumon's activity has also been reduced by colestyramine.[25] However, colestyramine can also reduce vitamin K absorption, and this may result in hypoprothrombinaemia and bleeding.

Use of *omega-3 fatty acids* (as fish oil preparations) in patients taking warfarin and other antithrombotics has been associated with INR elevation[26] and subdural haematoma.[27] However, controlled studies in patients taking fish oil and warfarin[28,29] have failed to show an effect on bleeding episodes or bleeding time.

Benfluorex[30] and *colestipol*[31] have been reported not to interact with phenprocoumon.

1. Zimmermann R, *et al.* The effect of bezafibrate on the fibrinolytic enzyme system and the drug interaction with racemic phenprocoumon. *Atherosclerosis* 1978; **29:** 477–85.
2. Beringer TRO. Warfarin potentiation with bezafibrate. *Postgrad Med J* 1997; **73:** 657–8.
3. Ascah KJ, *et al.* Interaction between fenofibrate and warfarin. *Ann Pharmacother* 1998; **32:** 765–8.
4. Ahmad S. Gemfibrozil interaction with warfarin sodium (Coumadin). *Chest* 1990; **98:** 1041–2.
5. Lilja JJ, *et al.* Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of racemic warfarin in healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 433–9.
6. Andrus MR. Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature. *Pharmacotherapy* 2004; **24:** 285–90.
7. Ahmad S. Lovastatin: warfarin interaction. *Arch Intern Med* 1990; **150:** 2407.
8. Trilli LE, *et al.* Potential interaction between warfarin and fluvastatin. *Ann Pharmacother* 1996; **30:** 1399–1402.
9. Kline SS, Harrell CC. Potential warfarin-fluvastatin interaction. *Ann Pharmacother* 1997; **31:** 790–1.
10. Simonson SG, *et al.* Effect of rosuvastatin on warfarin pharmacodynamics and pharmacokinetics. *J Clin Pharmacol* 2005; **45:** 927–34.
11. Jindal D, *et al.* Pharmacodynamic evaluation of warfarin and rosuvastatin co-administration in healthy subjects. *Eur J Clin Pharmacol* 2005; **61:** 621–5.
12. Barry M. Rosuvastatin–warfarin drug interaction. *Lancet* 2004; **363:** 328.
13. Mondillo S, *et al.* Rosuvastatin–acenocoumarol interaction. *Clin Ther* 2005; **27:** 782–4.
14. Hickmott H, *et al.* The effect of simvastatin co-medication on warfarin anticoagulation response and dose requirements. *Thromb Haemost* 2003; **89:** 949–50.
15. Westergren T, *et al.* Probable warfarin–simvastatin interaction. *Ann Pharmacother* 2007; **41:** 1292–5.
16. Grau E, *et al.* Simvastatin-oral anticoagulant interaction. *Lancet* 1996; **347:** 405–6.
17. Gaw A, Wosornu D. Simvastatin during warfarin therapy in hyperlipoproteinaemia. *Lancet* 1992; **340:** 979–80.
18. Trenque T, *et al.* Pravastatin: interaction with oral anticoagulant? *BMJ* 1996; **312:** 886.
19. Lin JC, *et al.* The effect of converting from pravastatin to simvastatin on the pharmacodynamics of warfarin. *J Clin Pharmacol* 1999; **39:** 86–90.
20. Owens JC, *et al.* Effect of sodium dextrothyroxine in patients receiving anticoagulants. *N Engl J Med* 1962; **266:** 76–9.
21. Solomon HM, Schrogie JJ. Change in receptor site affinity: a proposed explanation for the potentiating effect of D-thyroxine on the anticoagulant response to warfarin. *Clin Pharmacol Ther* 1967; **8:** 797–9.
22. Schrogie JJ, Solomon HM. The anticoagulant response to bishydroxycoumarin: II. The effect of D-thyroxine, clofibrate, and norethandrolone. *Clin Pharmacol Ther* 1967; **8:** 70–7.
23. Robinson DS, *et al.* Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin Pharmacol Ther* 1971; **12:** 491–5.
24. Jähnchen E, *et al.* Enhanced elimination of warfarin during treatment with cholestyramine. *Br J Clin Pharmacol* 1978; **5:** 437–40.
25. Meinertz T, *et al.* Interruption of the enterohepatic circulation of phenprocoumon by cholestyramine. *Clin Pharmacol Ther* 1977; **21:** 731–5.
26. Buckley MS, *et al.* Fish oil interaction with warfarin. *Ann Pharmacother* 2004; **38:** 50–3.
27. McClaskey EM, Michalets EL. Subdural hematoma after a fall in an elderly patient taking high-dose omega-3 fatty acids with warfarin and aspirin: case report and review of the literature. *Pharmacotherapy* 2007; **27:** 152–60.
28. Eritsland J, *et al.* Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coag Fibrinol* 1995; **6:** 17–22.
29. Bender NK, *et al.* Effects of marine fish oils on the anticoagulation status of patients receiving chronic warfarin therapy. *J Thromb Thrombolysis* 1998; **5:** 257–61.
30. De Witte P, Brems HM. Co-administration of benfluorex with oral anticoagulant therapy. *Curr Med Res Opin* 1980; **6:** 478–80.
31. Harvengt C, Desager JP. Effect of colestipol, a new bile acid sequestrant, on the absorption of phenprocoumon in man. *Eur J Clin Pharmacol* 1973; **6:** 19–21.

Menthol. A significant decrease in INR was reported[1] in a patient stabilised on warfarin when he started using a menthol cough preparation.

1. Kassebaum PJ, *et al.* Possible warfarin interaction with menthol cough drops. *Ann Pharmacother* 2005; **39:** 365–7.

Pesticides. Chlorinated insecticides diminished the activity of warfarin in a patient.[1]

1. Jeffery WH, *et al.* Loss of warfarin effect after occupational insecticide exposure. *JAMA* 1976; **236:** 2881–2.

Piracetam. Piracetam caused an increase in prothrombin time in a patient who had been stabilised on warfarin.[1]

1. Pan HYM, Ng RP. The effect of Nootropil in a patient on warfarin. *Eur J Clin Pharmacol* 1983; **24:** 711.

Sex hormones. There have been reports of steroids with anabolic or androgenic properties enhancing the activity of anticoagulants to the point of haemorrhage. Reports have covered *oxymetholone* and warfarin[1-3] or acenocoumarol;[4] *stanozolol* and warfarin[5,6] or dicoumarol;[7] *ethylestrenol* and phenindione;[8] *norethandrolone* and dicoumarol;[9] *methyltestosterone* and phenprocoumon;[10] and *danazol* and warfarin.[11-13] The manufacturer of *oxandrolone* states that an 80 to 85% reduction in warfarin dose was needed when oxandrolone was added to treatment. The mechanism of this interaction is not clear although it is considered that it is not caused by altered pharmacokinetics. Steroids with a 17-α-alkyl substituent appear to be most involved, but there has been a report of topically applied testosterone, which does not have such a substituent, enhancing warfarin.[14]

A retrospective study[15] of women receiving anticoagulant therapy who were started on *HRT* found that *tibolone* enhanced the effect of warfarin and of phenindione, possibly due to its androgenic properties.

Oral contraceptives have also been implicated in interactions. However, while the effects of dicoumarol were diminished by a combined oral contraceptive,[16] those of acenocoumarol were en-

hanced by other preparations.[17] Combined oral contraceptives have increased the clearance of phenprocoumon without altering the anticoagulant effect.[18] There has also been a report[19] of a single course of *levonorgestrel* for emergency contraception increasing the effect of warfarin.

1. Robinson BHB, *et al.* Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; **i:** 1356.
2. Longridge RGM, *et al.* Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; **ii:** 90.
3. Edwards MS, Curtis JR. Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; **ii:** 221.
4. de Oya JC, *et al.* Decreased anticoagulant tolerance with oxymetholone in paroxysmal nocturnal haemoglobinuria. *Lancet* 1971; **ii:** 259.
5. Acomb C, Shaw PW. A significant interaction between warfarin and stanozolol. *Pharm J* 1985; **234:** 73–4.
6. Shaw PW, Smith AM. Possible interaction of warfarin and stanozolol. *Clin Pharm* 1987; **6:** 500–2.
7. Howard W, *et al.* Anabolic steroids and anticoagulants. *BMJ* 1977; **1:** 1659–60.
8. Vere DW, Fearnley GR. Suspected interaction between phenindione and ethyloestrenol. *Lancet* 1968; **ii:** 281.
9. Schrogie JJ, Solomon HM. The anticoagulant response to bishydroxycoumarin: II. The effect of D-thyroxine, clofibrate, and norethandrolone. *Clin Pharmacol Ther* 1967; **8:** 70–7.
10. Husted S, *et al.* Increased sensitivity to phenprocoumon during methyltestosterone therapy. *Eur J Clin Pharmacol* 1976; **10:** 209–16.
11. Goulbourne IA, Macleod DAD. An interaction between danazol and warfarin: case report. *Br J Obstet Gynaecol* 1981; **88:** 950–1.
12. Meeks ML, *et al.* Danazol increases the anticoagulant effect of warfarin. *Ann Pharmacother* 1992; **26:** 641–2.
13. Booth CD. A drug interaction between danazol and warfarin. *Pharm J* 1993; **250:** 439–40.
14. Lorentz SMcQ, Weibert RT. Potentiation of warfarin anticoagulation by topical testosterone ointment. *Clin Pharm* 1985; **4:** 332–4.
15. McLintock LA, *et al.* Interaction between hormone replacement therapy preparations and oral anticoagulant therapy. *Br J Obstet Gynaecol* 2003; **110:** 777–9.
16. Schrogie JJ, *et al.* Effect of oral contraceptives on vitamin K-dependent clotting activity. *Clin Pharmacol Ther* 1967; **8:** 670–5.
17. de Teresa E, *et al.* Interaction between anticoagulants and contraceptives: an unsuspected finding. *BMJ* 1979; **2:** 1260–1.
18. Mönig H, *et al.* Effect of oral contraceptive steroids on the pharmacokinetics of phenprocoumon. *Br J Clin Pharmacol* 1990; **30:** 115–18.
19. Ellison J, *et al.* Apparent interaction between warfarin and levonorgestrel used for emergency contraception. *BMJ* 2000; **321:** 1382.

St John's wort. St John's wort has been reported to reduce the anticoagulant effect of warfarin.[1]

1. Yue Q-Y, *et al.* Safety of St John's wort (Hypericum perforatum). *Lancet* 2000; **355:** 576–7.

Thyroid and antithyroid drugs. Since response to oral anticoagulants is dependent on thyroid status an interaction between oral anticoagulants and thyroid or antithyroid drugs might be expected. Thyroid compounds do enhance the activity of oral anticoagulants possibly by increased metabolism of clotting factors. Dextrothyroxine is discussed under Lipid Regulating Drugs, above. Antithyroid compounds have not, however, been reported to diminish the effect of anticoagulants and paradoxically *propylthiouracil* has been reported to have caused hypoprothrombinaemia (see Effects on the Blood, under Carbimazole, p.2168). However, in a patient given *thiamazole* for Grave's disease, the response to warfarin varied depending on his thyroid status and thiamazole dose.[1]

1. Busenbark LA, Cushnie SA. Effect of Graves' disease and methimazole on warfarin anticoagulation. *Ann Pharmacother* 2006; **40:** 1200–3.

Tobacco. Although tobacco smoking may increase warfarin clearance,[1] an appreciable effect on anticoagulant activity appears unlikely.[1,2] However, there has been a report[3] of an increase in INR in a patient receiving warfarin when he stopped smoking.

1. Bachmann K, *et al.* Smoking and warfarin disposition. *Clin Pharmacol Ther* 1979; **25:** 309–15.
2. Weiner B, *et al.* Warfarin dosage following prosthetic valve replacement: effect of smoking history. *Drug Intell Clin Pharm* 1984; **18:** 904–6.
3. Colucci VJ, Knapp JF. Increase in international normalized ratio associated with smoking cessation. *Ann Pharmacother* 2001; **35:** 385–6.

Ubidecarenone. Decreased INR values and reduced effect of warfarin has been reported[1] in 3 patients given ubidecarenone.

1. Spigset O. Reduced effect of warfarin caused by ubidecarenone. *Lancet* 1994; **344:** 1372–3.

Vaccines. There have been a few reports of increased prothrombin time and bleeding in warfarin-stabilised patients after *influenza vaccination*. Studies investigating this possible interaction have found only a small or inconsistent increase in warfarin activity[1,2] or no effect.[3-5] One study suggested that influenza vaccine decreases rather than increases the prothrombin time.[6] In a group of patients on long-term acenocoumarol therapy, influenza vaccination had no effect on acenocoumarol activity.[7]

1. Kramer P, *et al.* Effect of influenza vaccine on warfarin anticoagulation. *Clin Pharmacol Ther* 1984; **35:** 416–18.
2. Weibert RT, *et al.* Effect of influenza vaccine in patients receiving long-term warfarin therapy. *Clin Pharm* 1986; **5:** 499–503.
3. Lipsky BA, *et al.* Influenza vaccination and warfarin anticoagulation. *Ann Intern Med* 1984; **100:** 835–7.
4. Scott AK, *et al.* Lack of effect of influenza vaccination on warfarin in healthy volunteers. *Br J Clin Pharmacol* 1985; **19:** 144P–145P.
5. Gomolin IH. Lack of effect of influenza vaccine on warfarin anticoagulation in the elderly. *Can Med Assoc J* 1986; **135:** 39–41.
6. Bussey HI, Saklad JJ. Effect of influenza vaccine on chronic warfarin therapy. *Drug Intell Clin Pharm* 1988; **22:** 198–201.
7. Souto JC, *et al.* Lack of effect of influenza vaccine on anticoagulation by acenocoumarol. *Ann Pharmacother* 1993; **27:** 365–8.

Vitamins. Since vitamin K reverses the effects of oral anticoagulants, it is not surprising that there have been reports of *acetomenaphthone* and *phytomenadione* reducing anticoagulant activity, or of foods or nutritional preparations containing vitamin K compounds doing the same.

Occasional reports of *ascorbic acid* reducing the activity of warfarin[1,2] have not been confirmed in subsequent studies.[3,4] There have also been isolated reports suggesting that *vitamin E* may enhance the activity of warfarin[5] or dicoumarol,[6] although no effect was found in a study[7] of patients receiving warfarin and vitamin E.

1. Rosenthal G. Interaction of ascorbic acid and warfarin. *JAMA* 1971; **215:** 1671.
2. Smith EC, *et al.* Interaction of ascorbic acid and warfarin. *JAMA* 1972; **221:** 1166.
3. Hume R, *et al.* Interaction of ascorbic acid and warfarin. *JAMA* 1972; **219:** 1479.
4. Feetam CL, *et al.* Lack of a clinically important interaction between warfarin and ascorbic acid. *Toxicol Appl Pharmacol* 1975; **31:** 544–7.
5. Corrigan JJ, Marcus FI. Coagulopathy associated with vitamin E ingestion. *JAMA* 1974; **230:** 1300–1.
6. Schrogie JJ. Coagulopathy and fat-soluble vitamins. *JAMA* 1975; **232:** 19.
7. Kim JM, White RH. Effect of vitamin E on the anticoagulant response to warfarin. *Am J Cardiol* 1996; **77:** 545–6.

Pharmacokinetics

Warfarin sodium is readily absorbed from the gastrointestinal tract; it can also be absorbed through the skin. It is extensively bound to plasma proteins and its plasma half-life is about 37 hours. It crosses the placenta but does not occur in significant quantities in breast milk. Warfarin is used as a racemic mixture; the *S*-isomer is more potent. The *R*- and *S*-isomers are both metabolised in the liver. The *S*-isomer is metabolised more rapidly than the *R*-isomer, mainly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism; other isoenzymes are also involved in the metabolism of the *R*-isomer. The stereoisomers may be affected differently by other drugs (see Interactions, above). Metabolites, with negligible or no anticoagulant activity, are excreted in the urine following reabsorption from the bile.

◊ References.

1. Mungall DR, *et al.* Population pharmacokinetics of racemic warfarin in adult patients. *J Pharmacokinet Biopharm* 1985; **13:** 213–27.
2. Holford NHG. Clinical pharmacokinetics and pharmacodynamics of warfarin: understanding the dose-effect relationship. *Clin Pharmacokinet* 1986; **11:** 483–504.
3. Takahashi H, Echizen H. Pharmacogenetics of warfarin elimination and its clinical implications. *Clin Pharmacokinet* 2001; **40:** 587–603.

Uses and Administration

Warfarin is a coumarin anticoagulant used in the treatment and prophylaxis of thromboembolic disorders (p.1187). It acts by depressing the hepatic vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX, and X, and of the anticoagulant protein C and its cofactor protein S. For an explanation of the coagulation cascade, see Haemostasis and Fibrinolysis, p.1045. Since warfarin acts indirectly, it has no effect on existing clots. Also as the coagulation factors involved have half-lives ranging from 6 to 60 hours, several hours are required before an effect is observed. A therapeutic effect is usually apparent by 24 hours, but the peak effect may not be achieved until 2 or 3 days after a dose; the overall effect may last for 5 days.

Warfarin is used in the prevention and treatment of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p.1189). If an immediate effect on blood coagulation is required, heparin should be given intravenously or subcutaneously to cover the first 2 to 3 days. Warfarin therapy may be begun with, or shortly after, initial heparin treatment. Warfarin is also used for the prevention of systemic thromboembolism and ischaemic stroke in some patients with atrial fibrillation (p.1160), prosthetic heart valves (see Valvular Heart Disease, p.1187), or who have suffered a myocardial infarction (p.1175). It may also have a role in the prevention of myocardial infarction and in the management of stroke or transient ischaemic attacks (p.1185). Antiplatelet drugs may be given concomitantly.

Some patients may show a hereditary resistance to warfarin. Warfarin is a potent rodenticide although resistance has been reported in *rats*.

Administration and dosage. Warfarin is equally effective either orally or intravenously, but is usually given orally. Dosage must be determined individually as discussed below under Control of Anticoagulant Therapy. When rapid anticoagulation is required, an initial dose of warfarin sodium 10 mg may be given on the first day, although in many cases an initial dose of 5 mg daily is adequate; initial doses of less than 5 mg daily may be used in elderly patients and in those at increased risk of bleeding (see Precautions, above). Subsequent doses depend on the results of coagulation tests, but maintenance doses usually range from 3 to 9 mg daily. If necessary the same dose may be given by slow intravenous injection. Doses of warfarin sodium should be given at the same time each day. Theoretically, stopping warfarin abruptly may result in rebound hypercoagulability with risk of thrombosis. Therefore some clinicians tail off long-term treatment over several weeks but the need for this is unclear and the *British Society for Haematology* suggests that treatment may be stopped abruptly. Anticoagulant treatment booklets should be carried by patients.

Warfarin has also been given as the potassium salt; warfarin-deanol has been tried.

Control of oral anticoagulant therapy. Treatment with oral anticoagulants must be monitored to ensure that the dose is providing the required effect on the vitamin-K-dependent clotting factors; too small a dose provides inadequate anticoagulation, too large a dose puts the patient at risk of haemorrhage. This monitoring is commonly carried out by checking the clotting property of the patient's plasma using a suitable preparation of thromboplastin and a source of calcium. The time taken for the clot to form due to the effect of the thromboplastin preparation on prothrombin is known as the prothrombin time (PT). The prothrombin time ratio (PTR) is the prothrombin time of the patient's plasma divided by that for a standard plasma sample.

So that there is some consistency in prothrombin time ratios measured at different times or at different laboratories, it is now common practice for the manufacturer or control laboratory to calibrate their batches of thromboplastin against the international reference preparation. This calibration produces an international sensitivity index (ISI) appropriate to that thromboplastin. The laboratory measuring the clotting capacity of a sample of plasma is thus able to convert the prothrombin time ratio to an international normalised ratio (INR) using the sensitivity index through the formula

$$INR = PTR^{(ISI)}$$

Thus a prothrombin time ratio of 2.0 obtained with a thromboplastin with a declared international sensitivity index of 1.5 would be converted to an international normalised ratio of 2.8. An international normalised ratio is therefore equivalent to a prothrombin time ratio carried out using the primary international reference preparation of thromboplastin.

This method of standardisation has taken over from methods involving use of a standard reagent such as the British or Manchester comparative thromboplastin. Preparations of thromboplastin derived from *rabbit* brain have superseded or are superseding those from human brain because of the dangers of viral transmission; a recombinant human form is also available.

Recommended target values or ranges of international normalised ratio for patients receiving anticoagulant treatment or cover for various conditions or procedures are given by the *British Society for Haematology* in the UK and the *American College of Chest Physicians*.

These are given in Table 6, below. An INR within 0.5 units of the target value in the UK is generally considered satisfactory. In the USA it is recommended that the INR be maintained at the mid-level of the range. An INR less than 2.0 generally represents inadequate anticoagulation and an INR above 4.5 represents greater risk of haemorrhage.

Measurements should be carried out before treatment and then daily or on alternate days in the early stages of treatment. Once the dose has been established and the patient well stabilised the measurement can be made at greater but regular intervals, for example every 8 weeks; allowances should be made for any events that might influence the activity of the anticoagulant. Self-monitoring may be appropriate in some patients.

◊ General references.

1. Harrington R, Ansell J. Risk-benefit assessment of anticoagulant therapy. *Drug Safety* 1991; **6:** 54–69.
2. Le DT, *et al.* The international normalized ratio (INR) for monitoring warfarin therapy: reliability and relation to other monitoring methods. *Ann Intern Med* 1994; **120:** 552–8.
3. British Society for Haematology: British Committee for Standards in Haematology—Haemostasis and Thrombosis Task Force. Guidelines on oral anticoagulation: third edition. *Br J Haematol* 1998; **101:** 374–87. Also available at: http://www.bcshguidelines.com/pdf/bjh715.pdf (accessed 25/02/05) Updated 2005 guidelines. Update: Baglin T, *et al*, for the British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): third edition—2005 update. *Br J Haematol* 2006; **132:** 277–85. Also available at: http://www.bcshguidelines.com/pdf/oralanticoagulation.pdf (accessed 07/06/06)
4. Hardman SMC, Cowie MR. Anticoagulation in heart disease. *BMJ* 1999; **318:** 238–44.
5. Gage BF, *et al.* Management and dosing of warfarin therapy. *Am J Med* 2000; **109:** 481–8.
6. Hirsh J, *et al.* American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation* 2003; **107:** 1692–1711. Also available at: http://circ.ahajournals.org/cgi/reprint/107/12/1692.pdf (accessed 25/02/05)
7. Fitzmaurice DA, *et al.* British Society of Haematology Taskforce for Haemostasis and Thrombosis. An evidence-based review and guidelines for patient self-testing and management of oral anticoagulation. *Br J Haematol* 2005; **131:** 156–65. Correction. *ibid.* 2006; **132:** 118. Also available at: http://www.bcshguidelines.com/pdf/fitzmaurice_100306.pdf (accessed 27/05/08)
8. Ansell J, *et al.* Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 160S–198S.

Administration and dosage. Algorithms and guidelines have been developed for beginning anticoagulant therapy, based on the method of Fennerty *et al.*[1] Although a loading dose of 10 mg daily for 2 days (depending on the INR) has been widely used, lower doses may be more appropriate, especially in hospitalised patients at greater risk of over-anticoagulation. Studies[2-4] comparing warfarin loading doses of 5 and 10 mg found that for both groups a therapeutic INR in the range of 2.0 to 3.0 was reached in most patients by day 5 of treatment. Although a study of outpatients with venous thromboembolism[5] found that a therapeutic INR was achieved 1.4 days sooner with the larger loading dose, the nomogram used was not designed for inpatients.

In situations where rapid anticoagulation is not necessary, loading doses may not be required and treatment should begin with the estimated maintenance dose. Studies[6,7] have found that the maintenance dose decreases with age and is lower in women than in men, and lower initial doses are therefore recommended in the elderly. Regimens that have been suggested include warfarin in a dose of 4 mg daily for 3 days, then adjusted according to the INR,[8] or, for patients requiring anticoagulation prophylaxis, 2 mg daily for 2 weeks followed by weekly adjustment using an algorithm until the target INR is reached.

1. Fennerty A, *et al.* Flexible induction dose regimen for warfarin and prediction of maintenance dose. *BMJ* 1984; **288:** 1268–70.
2. Harrison L, *et al.* Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997; **126:** 133–6.
3. Crowther MA, *et al.* Warfarin: less may be better. *Ann Intern Med* 1997; **127:** 333.
4. Crowther MA, *et al.* A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med* 1999; **159:** 46–8.
5. Kovacs MJ, *et al.* Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism: a randomized, double-blind, controlled trial. *Ann Intern Med* 2003; **138:** 714–19.
6. Singla DL, Morrill GB. Warfarin maintenance dosages in the very elderly. *Am J Health-Syst Pharm* 2005; **62:** 1062–6.
7. Garcia D, *et al.* Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest* 2005; **127:** 2049–56.
8. Siguret V, *et al.* Initiation of warfarin therapy in elderly medical inpatients: a safe and accurate regimen. *Am J Med* 2005; **118:** 137–42.

Administration in infants and children. Increasing numbers of infants and children are receiving anticoagulants for prophylaxis and treatment of thromboembolism. Doses of warfarin and therapeutic INR ranges have been adapted from adult therapy but cohort studies[1,2] of paediatric patients have found that warfarin requirements may be affected by a number of factors including age, and the use of infant formulas supplemented with vitamin K. Recommendations[3] for the use of oral anticoagulants in children have been published.

1. Tait RC, *et al.* Oral anticoagulation in paediatric patients: dose requirements and complications. *Arch Dis Child* 1996; **74:** 228–31.
2. Streif W, *et al.* Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999; **94:** 3007–14.
3. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S.

Catheters and cannulas. For mention of the use of oral anticoagulants to prevent thrombosis in patients with indwelling infusion devices, see Heparin Sodium, p.1304.

Connective tissue and muscular disorders. Warfarin has been proposed to treat subcutaneous calcium deposition (calcinosis cutis) in patients with dermatomyositis, but its value is disputed, see Polymyositis and Dermatomyositis, p.1510.

Table 6. Recommended International Normalised Ratios (INR).

	INR	Condition or procedure
UK	2.5	Pulmonary embolism; deep-vein thrombosis; recurrence of venous thromboembolism when no longer on warfarin; symptomatic inherited thrombophilia; venous thromboembolism associated with antiphospholipid syndrome; atrial fibrillation; mural thrombus; cardiomyopathy; bioprosthetic heart valves.
	2.5 or 3.0	Cardioversion (higher INR may be appropriate before procedure); some mechanical prosthetic heart valves.
	3.5	Recurrence of venous thromboembolism when on warfarin; some mechanical prosthetic heart valves.
US	2.0 to 3.0	Prophylaxis of venous thromboembolism in high-risk surgical patients; treatment of venous thrombosis and pulmonary embolism; prophylaxis of systemic embolism in patients with atrial fibrillation, valvular heart disease, bioprosthetic heart valves or some mechanical prosthetic heart valves; prevention of recurrent myocardial infarction in patients receiving aspirin.
	2.5 to 3.5	Prophylaxis in patients with some mechanical prosthetic heart valves.
	3.0 to 4.0	Prevention of recurrent myocardial infarction in patients not receiving aspirin; systemic embolism in patients with some mechanical heart valves.

The symbol † denotes a preparation no longer actively marketed

Preparations

BP 2008: Warfarin Tablets;
USP 31: Warfarin Sodium for Injection; Warfarin Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Circuvit; Coumadin; ***Austral.:*** Coumadin; Marevan; ***Belg.:*** Marevan; ***Braz.:*** Coumadin; Marevan; ***Canad.:*** Coumadin; ***Chile:*** Coumadin; ***Cz.:*** Lawarin; ***Denm.:*** Marevan; ***Fin.:*** Marevan; ***Fr.:*** Coumadine; ***Ger.:*** Coumadin; ***Gr.:*** Marevan; Panwarfin; ***Hung.:*** Marfarin; ***India:*** Uniwarfin; Warf; ***Indon.:*** Simarc-2; ***Irl.:*** Warfant; ***Israel:*** Coumadin; ***Ital.:*** Coumadin; ***Malaysia:*** Coumadin; Orfarin; ***Mex.:*** Coumadin; ***Norw.:*** Marevan; ***NZ:*** Coumadin; Marevan; ***Philipp.:*** Coumadin; ***Port.:*** Varfine; ***Rus.:*** Warfarex (Варфарекс); ***S.Afr.:*** Coumadin†; ***Singapore:*** Coumadin; Marevan; Orfarin; ***Spain:*** Aldocumar; Tedicumar; ***Swed.:*** Waran; ***Thai.:*** Befarin; Fargem; Maforan; Orfarin; ***Turk.:*** Coumadin; Orfarin; ***UK:*** Marevan; ***USA:*** Coumadin; Jantoven; ***Venez.:*** Anasmol; Coumadin; Cumar.

Xamoterol Fumarate *(BANM, USAN, rINNM)*

Fumarato de xamoterol; ICI-118587; Ksamoterolfumarat; Ksamoterolifumaraatti; Xamotérol, Fumarate de; Xamoteroli Fumaras. *N*-{2-[2-Hydroxy-3-(4-hydroxyphenoxy)propylamino]-ethyl}morpholine-4-carboxamide fumarate.

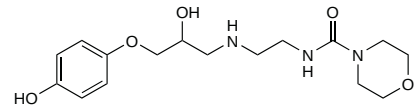
Ксамотерола Фумарат

$(C_{16}H_{25}N_3O_5)_2,C_4H_4O_4$ = 794.8.

CAS — 81801-12-9 (xamoterol); 90730-93-1 (xamoterol fumarate).

ATC — C01CX07.

ATC Vet — QC01CX07.



(xamoterol)

Profile

Xamoterol is a beta-adrenoceptor partial agonist with a selective action on beta$_1$ receptors. As a partial agonist it exerts mainly agonist activity at rest and under conditions of low sympathetic drive which results in improved ventricular function and increased cardiac output; during exercise and during conditions of increased sympathetic drive, such as that occurring in severe heart failure, xamoterol exerts beta-blocking activity. It therefore has the properties of both sympathomimetics (see p.1407) and beta blockers (see p.1225).

Xamoterol has been used in the management of chronic mild heart failure but was associated with deterioration and an excess of deaths in those with more severe disease. It has also been used in orthostatic hypotension secondary to autonomic failure.

◊ References.

1. Anonymous. Xamoterol—more trouble than it's worth? *Drug Ther Bull* 1990; **28:** 53–4.
2. Anonymous. New evidence on xamoterol. *Lancet* 1990; **336:** 24.
3. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990; **336:** 1–6.

Xantinol Nicotinate *(BAN, rINN)*

Ksantinolinikotinaatti; Ksantynolu nikotynian; Nicotinato de xantinol; SK-331A; Xanthinol Niacinate *(USAN)*; Xanthinol Nicotinate; Xanthinol nikotinát; Xantinol, Nicotinate de; Xantinoli Nicotinas; Xantinolnikotinat. 7-{2-Hydroxy-3-[(2-hydroxyethyl)methylamino]propyl}theophylline nicotinate.

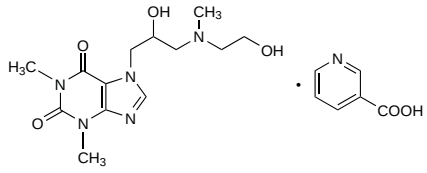
Ксантинола Никотинат

$C_{13}H_{21}N_5O_4,C_6H_5NO_2$ = 434.4.

CAS — 437-74-1.

ATC — C04AD02.

ATC Vet — QC04AD02.



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

Profile

Xantinol nicotinate is a vasodilator with general properties similar to those of nicotinic acid (p.1957), to which it is slowly hydrolysed. Xantinol nicotinate is used in the management of peripheral (p.1178) and cerebral vascular disorders (p.1165) and in hyperlipidaemias (p.1169). Oral doses of up to 3 g daily may be given. It has also been given by intramuscular or slow intravenous injection.