TN2789I

WARFARIN SODIUM

WARIK®

1mg Tablet
2.5mg Tablet
5mg Tablet
ANTICOAGULANT

FORMULATION
Each tablet contains :
Warfarin sodium (as clathrate), BP.....1mg
Warfarin sodium (as clathrate), BP.....2.5mg
Warfarin sodium (as clathrate), BP.....5mg

DESCRIPTION
1mg – Pink to dark pink coloured, circular, biconvex, uncoated tablets, with mottled surface, break line on one side and plain on other side.
2.5mg – Light orange to orange coloured, circular, biconvex, uncoated tablets with break line on one side and plain on other side.
5mg – Light orange to orange coloured, circular, biconvex, uncoated tablets with break line on one side and plain on other side.

PHARMACOLOGY
Warfarin is a coumarin anticoagulant which acts by inhibiting the synthesis of vitamin K-dependent clotting factors II (prothrombin), VII, IX, and X, and of the anticoagulant protein C and its cofactor protein S. Half-lives of these clotting factors are as follows: Factor II – 60 hours, VII - 4-6 hours, IX – 24 hours, and X – 48-72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively. The resultant *in vivo* effect is a sequential depression of Factor VII, Protein C, Factor IX, Protein S, and Factor X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of *γ*-carboxyglutamic acid residues in the proteins which are essential for biological activity.
Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, thereby reducing the regeneration of vitamin K, epoxide. The degree of depression is dependent upon the dosage administered and, in part, by the patient's VKORC1 genotype. Therapeutic doses of Warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

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 reported to be more potent. The *R*- and *S*-isomers are both metabolized in the liver, the *S*-isomer more rapidly than the *R*-isomer; the stereo-isomers may also be affected differently by other drugs. Metabolites, with negligible or no anticoagulant activity, are excreted in the urine following reabsorption from the bile.

INDICATIONS
Warfarin is used in the prevention and treatment of venous thromboembolism, systemic thromboembolism and ischaemic stroke in some patients with atrial fibrillation, prosthetic heart valves or who have suffered a myocardial infarction. It may also have a role in the prevention of myocardial infarction and in the management of stroke or transient ischaemic attacks. Antiplatelet drugs may be given concomitantly.

CONTRAINDICATIONS
Contraindicated in patients with known hypersensitivity to Warfarin or to any components of this product.
Anticoagulation is contraindicated in any localized or general physical condition or personal circumstances in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation, such as:
Pregnancy: Warfarin is contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with Warfarin during pregnancy.
Embryopathy characterized by nasal hypoplasia with or without stippled epiphyses (chondrodysplasia punctata) has been reported in pregnant women exposed to Warfarin during the first trimester. Central nervous system abnormalities also have been reported in pregnant women, including dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy. Ventral midline dysplasia, characterized by optic atrophy and eye abnormalities have been observed. Mental retardation, blindness, and other central nervous system abnormalities have been reported in association with second and third trimester exposure. Although rare, teratogenic reports following in utero exposure to Warfarin include urinary tract anomalies such as single kidney, asplenia, anencephaly, spina bifida, cranial nerve palsy, hydrocephalus, cardiac defects and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia, corneal leukoma, cleft palate, cleft lip, schizencephaly, and microcephaly.
Spontaneous abortion and stillbirth are known to occur and a higher risk of fetal mortality is associated with the use of Warfarin. Low birth weight and growth retardation have also been reported.
Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.
Hemorrhagic tendencies or blood dyscrasias.
Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces.
Bleeding tendencies associated with active ulceration or overt bleeding of: (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (aneurysms-cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis.
Threatened abortion, eclampsia and preeclampsia.
Inadequate laboratory facilities.
Unsupervised patients with senility, alcoholism, or psychosis or other lack of patient cooperation.
Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding.
Miscellaneous: major regional, lumbar block anesthesia, malignant hypertension and known hypersensitivity to Warfarin or to any other components of this product.

DOSAGE AND ADMINISTRATION
The dosage and administration of Warfarin must be individualized for each patient according to the particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR.

Recommended International Normalized 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; atrial fibrillation; cardioversion; mural thrombus; cardiomyopathy.
	3.5	Recurrence of venous thromboembolism when on Warfarin; antiphospholipid syndrome; 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 acute myocardial infarction.
	2.5 to 3.5	Prophylaxis in patients with mechanical prosthetic heart valves; prevention of recurrent myocardial infarction.

The best available information supports the following recommendations for dosing of WARFARIN.
Venous Thromboembolism (including deep venous thrombosis [DVT] and pulmonary embolism [PE]): For patients with a first episode of DVT or PE secondary to a transient (reversible) risk factor, treatment with Warfarin for 3 months is recommended. For patients with a first episode of idiopathic DVT or PE, Warfarin is recommended for at least 6 to 12 months. For patients with two or more episodes of documented DVT or PE, indefinite treatment with Warfarin is suggested. For patients with a first episode of DVT or PE who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions, treatment for 12 months is recommended and indefinite therapy is suggested. For patients with a first episode of DVT or PE who have documented deficiency of antithrombin, deficiency of Protein C or Protein S, or the Factor V Leiden or prothrombin 20210 gene mutation, homocystinemia, or high factor VIII levels (>90th percentile of normal), treatment for 6 to 12 months is recommended and indefinite therapy is suggested for idiopathic thrombosis. The risk-benefit should be reassessed periodically in patients who receive indefinite anticoagulant treatment. The dose of Warfarin should be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations.

Atrial Fibrillation: Oral anticoagulation therapy with Warfarin is recommended in patients with persistent or paroxysmal AF (PAF) (intermittent AF) at high risk of stroke (i.e., having any of the following features: prior ischemic stroke, transient ischemic attack, or systemic embolism, age >75 years, moderately or severely impaired left ventricular systolic function and/or congestive heart failure, history of hypertension, or diabetes mellitus). In patients with persistent AF or PAF, age 65 to 75 years, in the absence of other risk factors, but who are at intermediate risk of stroke, antithrombotic therapy with either oral Warfarin or aspirin, 325mg/day, is recommended. For patients with AF and prosthetic heart valves, anticoagulation with oral Warfarin should be used; the target INR may be increased and aspirin added depending on valve type and position, and on patient factors.
Post-Myocardial Infarction: In most healthcare settings, moderate- and low-risk patients with a myocardial infarction should be treated with aspirin alone over oral vitamin-K antagonist (VKA) therapy plus aspirin. In healthcare settings in which meticulous INR monitoring is standard and routinely accessible, for both high- and low-risk patients after myocardial infarction (MI), long-term (up to 4 years) high-intensity oral Warfarin (target INR, 3.5; range, 3.0 to 4.0) without concomitant aspirin or moderate-intensity oral Warfarin (target INR, 2.5; range, 2.0 to 3.0) with aspirin is recommended. For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on echocardiography, and those with a history of a thromboembolic event, therapy with combined moderate-intensity (INR, 2.0 to 3.0) oral Warfarin plus low-dose aspirin (≤ 100 mg/day) for 3 months after the MI is suggested.
Mechanical or Bioprosthetic Heart Valves: For all patients with mechanical prosthetic heart valves, Warfarin is recommended. For patients with a St. Jude Medical (St. Paul, MN) bileaflet valve in the aortic position, a target INR of 2.5 (range, 2.0 to 3.0) is recommended. For patients with tilting disk valves and bileaflet mechanical valves in the mitral position, a target INR of 3.0 (range, 2.5 to 3.5) is recommended. For patients with caged ball or caged disk valves, a target INR of 3.0 (range, 2.5 to 3.5) in combination with aspirin, 75 to 100 mg/day is recommended. For patients with bioprosthetic valves, Warfarin therapy with a target INR of 2.5 (range, 2.0 to 3.0) is recommended for valves in the mitral position and is suggested for valves in the aortic position for the first 3 months after valve insertion.
Recurrent Systemic Embolism and Other Indications: Patients with valvular disease associated with atrial fibrillation, patients with mitral stenosis, and patients with recurrent systemic embolism of unknown etiology. A moderate dose regimen (INR 2.0 to 3.0) is recommended for these patients.
An INR greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.
Initial dosage: The dosing of Warfarin must be individualized according to patient's sensitivity to the drug as indicated by PT/INR. Use of a large loading dose may increase the incidence of hemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. It is recommended that Warfarin therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations. The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR response to Warfarin.
Maintenance: Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response. Acquired or inherited Warfarin resistance is rare, but should be suspected if large daily doses of Warfarin are required to maintain a patient's PT/INR within a normal therapeutic range. Lower maintenance doses are recommended for elderly and/or debilitated patients and patients with a potential to exhibit greater than expected PT/INR response to Warfarin.
Duration of Therapy: The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.
Missed dose: The anticoagulant effect of Warfarin persists beyond 24 hours. If the patient forgets to take the prescribed dose of Warfarin at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.
Laboratory Control: The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Intervals between subsequent PT/INR determinations should be based upon the physician's judgment of the patient's reliability and response to Warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of 1 to 4 weeks after a stable dosage has been determined. To ensure adequate control, it is recommended additional PT tests be done when other Warfarin products are interchanged with Warfarin sodium tablets, USP, as well as whenever other medications are initiated, discontinued, or taken irregularly. Safety and efficacy of Warfarin therapy can be improved by increasing the quality of laboratory control. Reports suggest that in usual care monitoring, patients are in therapeutic range only 33%-64% of the time. Time in therapeutic range is significantly greater (56%-93%) in patients managed by anticoagulation clinics, among self-testing and self-monitoring patients, and in patients managed with the help of computer programs. Self-testing patients had fewer bleeding events than patients in usual care.
Treatment with Dentistry and Surgery: The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. PT/INR determination is recommended just prior to any dental or surgical procedures. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of Warfarin to maintain the PT/INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of Warfarin therapy. When discontinuing Warfarin even for a short period of time, the benefits and risks should be strongly considered.
Conversion from Heparin Therapy: Since the anticoagulant effect of Warfarin is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to Warfarin may begin concomitantly with heparin therapy or may be delayed 3 to 6 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and that Warfarin therapy be overlapped with heparin for 4 to 5 days, until Warfarin has produced the desired therapeutic response as determined by PT/INR. When Warfarin has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.
Doses of Warfarin sodium should be given at the same time each day. Theoretically, sudden discontinuation of Warfarin may result in rebound hypercoagulability with risk of thrombosis. Therefore, some clinician's tail off long-term treatment over several weeks but the need for this is unclear.

PRECAUTIONS
Warfarin should not be given to patients who are hemorrhaging. In general, it should not be given to patients at serious risk of hemorrhage, although it has been used with very careful control; patients at risk include those with hemorrhagic blood disorders, peptic ulcer disease, severe wounds (including surgical wounds), cerebrovascular disorders, and bacterial endocarditis.
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, and drug interactions.

DRUG INTERACTIONS

Drugs generally recognized 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 recognized is provided in the referenced section below.

Acetamenaphthone	ethchlorvynol
alcohol (chronic ingestion without liver impairment)	glutethimide
aminoglutethimide	griseofulvin
barbiturates	nafcillin
carbamazepine	phytomenadione
dichloralphenazone	rifampicin

Drugs recognized 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 recognized is provided in the referenced section below.

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

The major interactions are summarized in the tables, above. Readers should be aware that while interactions of a pharmacodynamic nature occurring with one anticoagulant may well apply to another, this is not necessarily the case with interactions of a pharmacokinetic nature.

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. Interference with the coagulation process may be responsible for the increased risk of hemorrhage when aspirin, clofibrate, or thyroid hormones are used with anticoagulants. Many other compounds, such as paraginase, 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 hemorrhage should be considered when they are used together.
Where there is a risk of serious hemorrhage from an interaction, then use of the 2 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 stabilized on an anticoagulant commence treatment with an interacting drug, or when patients stabilized 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. Readers should also be aware that 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.
Alcohol
Alcohol has a variable effect on Warfarin. Heavy regular drinkers may experience 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 hemorrhage. Furthermore, some NSAIDs increase the hypoprothrombinemic effect of Warfarin, possibly by an intrinsic effect on coagulation or by displacement of Warfarin from plasma protein binding site. 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.
High doses of aspirin and some other salicylates enhance the hypoprothrombinemic 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.
Concurrent administration of phenylbutazone and Warfarin has led to serious hemorrhage 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. Related drugs such as oxyphenbutazone, azapropazone, and feprazone behave similarly and should also be avoided.
For the following NSAIDs there are few isolated reports suggesting that they may enhance the hypoprothrombinemic effect of Warfarin or other specified oral anticoagulant: diflunisal (with nicoumalone or Warfarin), flurbiprofen (with nicoumalone), indomethacin, ketoprofen, meclofenamate sodium, mefenamic acid, piroxicam, (with Warfarin or nicoumalone), sulindac, tiaprofenic acid (with nicoumalone), and tolmetin sodium. NSAIDs with an apparently minimal effect on Warfarin activity include etodolac, ibuprofen, and naproxen.
In view of the above considerations, paracetamol is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. Caution should, however, be observed since,

although it has no effect on the gastric mucosa or on platelet function, and isolated reports have demonstrated an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant.
Although a study in healthy volunteers indicated that there was no interaction between Warfarin and celecoxib, a selective inhibitor of cyclo-oxygenase-2, there have been several reports of an increase in the INR with concomitant therapy; bleeding has also been reported in some patients. A small increase in INR has also been reported in a study of Warfarin with rofecoxib.

Antiarrhythmics

Amiodarone has been shown in several studies to increase the activity of Warfarin and nicoumalone, probably through inhibition of metabolism. The potentiating effect of amiodarone has been reported to persist for up to 4 months after its withdrawal. Isolated reports with disopyramide and quinidine have suggested that these drugs can enhance the anticoagulant effect of Warfarin.

Antibacterials

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.
There are several reports of an enhanced Warfarin response with co-trimoxazole; stereospecific inhibition of Warfarin metabolism is probably responsible. 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, sulfamethizole, and sulfaphenazole (with phenindione).
There are several reports of potentiation of the effects of Warfarin by erythromycin or its salts; inhibition of Warfarin metabolism probably occurs. An enhance response to Warfarin has also been reported with azithromycin and with roxithromycin, including reports of spontaneous bleeding with the latter. Clarithromycin may potentiate the effect of nicoumalone and of Warfarin, although other factors may also have been involved in this case.
There have been few reports of increased activity of Warfarin (or other specified oral anticoagulant) by quinolone antibacterials including nalidixic acid (with Warfarin or nicoumalone), ciprofloxacin, norfloxacin, and ofloxacin.
There are isolated reports suggesting an enhanced effect of Warfarin (or other specified oral anticoagulant) with aminosalicylic acid, benzylpenicillin, chloramphenicol (with dicoumarol), doxycycline, isoniazid, and neomycin. Manufacturer's warnings of potentiation of Warfarin by aztreonam, trimethoprim, and tetracyclines.
Rifampicin diminishes the effect of Warfarin by induction of metabolizing enzymes in the liver. There are several reports of a similar effect with nafcillin and dicloxacillin sodium.

Antidepressants

Amitriptyline and nortriptyline prolong the half-life of dicoumarol.
There is a theoretical risk of increased Warfarin activity with MAOIs and with fluvoxamine and other SSRIs.
Increased Warfarin activity has been reported in a few patients taking fluoxetine.
An increase in the dose of Warfarin has been required by patients also taking trazodone.

Antidiabetics

An absence of effect has been documented for phenprocoumon and insulin, glibenclamide, or glibornuride, but there is a report of glibenclamide enhancing the effect of Warfarin.
There has been an isolated report of bleeding in a patient taking phenformin and Warfarin.
An enhanced response to Warfarin has been reported in a patient receiving troglitazone.

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. There are reports of phenytoin enhancing the effects of Warfarin and a report of initial enhancement followed by decreased anticoagulant action.

Antifungals

Griseofulvin has been reported to diminish the activity of Warfarin. There are several reports indicating that miconazole, given either systemically or topically as the oral gel, may enhance the activity of oral anticoagulants. There are isolated reports of the potentiation of Warfarin by itraconazole and ketoconazole. There has been a case report of a reduction in the effect of Warfarin by terbinafine.

Antigout drugs

Benziodarone has been reported to enhance the effects of Warfarin.

Antimalarials

The ingestion of large amounts of tonic water by 2 patients necessitated a reduction in their Warfarin dosage. The enhanced effect was attributed to the quinine content of the tonic water.

Antineoplastics and immunosuppressants

Cyclophosphamide for instance has been associated with an increase in Warfarin's activity when given with methotrexate and fluorouracil but with a decrease when given with nonantineoplastic drugs. Fluorouracil has also been reported to increase the effect of Warfarin when given with levamisole. The manufacturers of capecitabine state that altered coagulation parameters and bleeding have been reported in patients taking capecitabine and Warfarin or phenprocoumon.
Aminoglutethimide has led to decreased activity of Warfarin or nicoumalone, probably due to increased Warfarin metabolism. The manufacturers of the anti-androgen flutamide state that increases in prothrombin time have been reported after initiation of flutamide therapy in patients on long-term Warfarin. Mercaptopurine and mitotane have also decreased Warfarin activity. Severe bleeding occurred in a patient on long-term Warfarin treatment after discontinuing azathioprine.

Antiplatelets

The interaction between anticoagulants and dipyridamole is an oddity in that bleeding can occur without any alteration in prothrombin times; special care is therefore required as the usual method of monitoring the anticoagulant effect is of no value. This interaction has involved a small number of patients taking dipyridamole and Warfarin or phenindione; inhibition of platelet function by dipyridamole has been implicated. However, in general it does not appear to increase the risk of bleeding.

Antiprotozoals

Metronidazole enhances the activity of Warfarin through selective inhibition of the metabolism of its S-isomer.

Antivirals

Reductions in dosage of either Warfarin or nicoumalone were necessary. The interactions may have been due to decreased metabolism of the anticoagulant. A similar need for a reduced Warfarin dose has also been noted in other patients taking interferon alfa-2b or interferon beta.
An enhanced response to Warfarin has been reported in a patient taking saquinavir concomitantly. 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.

Anxiolytic sedatives, hypnotics, and antipsychotics

Barbiturates, by inducing liver metabolism, can reduce the activity of anticoagulants; glutethimide has a similar action. Chloral hydrate may increase the anticoagulant activity of Warfarin. 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.
Triclofos sodium appears to increase the activity of Warfarin in a similar way.
Reduced anticoagulant activity has been reported with dichloralphenazone, ethchlorvynol (with dicoumarol), and haloperidol (with phenindione).

Betablockers

Possible potentiation of the effects of Warfarin by propranolol has been reported, particularly those with high lipid solubility such as propranolol, may inhibit the metabolism of Warfarin.

Corticosteroids and Corticotropin

There are several reports of corticosteroids or corticotropin either enhancing or diminishing the effects of anticoagulants.
Dermatological drugs
A patient's Warfarin dose had to be increased when he started treatment with etretinate.

Disulfiram

Two reports suggesting that disulfiram enhances the activity of Warfarin. Although inhibition of liver enzymes by disulfiram was considered responsible, a later study suggested that disulfiram acts directly on the liver to increase hypoprothrombinemia.

Diuretics

Tienilic acid produces the most serious interaction enhancing the activity of Warfarin and has led to hemorrhage. Etacrynic acid has also been reported to enhance the activity of Warfarin.
Chlortalidone and spironolactone have both been associated with a reduction in Warfarin's activity. It has been suggested that this might be a consequence of the diuresis concentrating the circulating clotting factors.

Gastrointestinal drugs

Bismuth carbonate and magnesium trisilicate for example have been reported to reduce Warfarin's absorption. There have been occasional reports of sucralfate diminishing the effect of Warfarin.
There are several reports indicating that cimetidine can enhance the anticoagulant effect of Warfarin and hemorrhage 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.
There is a case report suggesting that potentiation of Warfarin by ranitidine may occasionally occur.
Pantoprazole appears to have no effect on the pharmacokinetics or pharmacodynamics of Warfarin.
A marked increase in the effect of Warfarin has been reported when cisapride was added in a therapy.
A reduction in the response to Warfarin with development of venous thrombosis has been reported in a patient receiving mesalazine, and in another patient receiving sulfasalazine.

Ginseng

Reduction in the response to Warfarin was reported in a patient after taking a ginseng preparation.

Glucagon

A dose-dependent enhancement of Warfarin's anticoagulant activity has been reported with glucagons.

Hypericum

Hypericum has been reported to reduce the anticoagulant effect of Warfarin.

Leukotriene antagonists

Zafirlukast is reported to decrease the clearance of S-Warfarin. The manufacturers of zafirlukast state that it probably inhibits the cytochrome P450 isoenzyme CYP2C9 which is involved in the metabolism of Warfarin. Patients receiving Warfarin may develop prolongation of the prothrombin time when zafirlukast is added and Warfarin dosage should be adjusted accordingly.

Levamisole

An increased INR has been reported in a patient receiving chronic Warfarin therapy after addition of levamisole and fluorouracil.

Lipid regulating drugs

Clofibrate can enhance the activity of Warfarin, sometimes to the point of hemorrhage. Bezafibrate has been reported to enhance the effect of phenprocoumon and Warfarin, and fenofibrate and gemfibrozil have been reported to enhance the effect of Warfarin.
Hypoprothrombinemia and bleeding has been reported to be the effect of Warfarin when lovastatin is given to patients. An increased response to Warfarin has also been reported in a number of patients receiving fluvastatin concomitantly.
Dextrothyroxine increase the anticoagulant effect of Warfarin sodium.
An opposite effect may occur with colestyramine which has reduced Warfarin's serum concentration and half-life as well as its activity. The mechanisms of this interaction include binding of Warfarin to colestyramine and reduced absorption; the enterohepatic recycling of Warfarin may also be interrupted.

Pesticides

Chlorinated insecticides diminished the activity of Warfarin.

Piracetam

Piracetam caused an increase in prothrombin time in a patient who had been stabilized on Warfarin.

Sex hormones

There have been a number of reports of steroids with anabolic or androgenic properties enhancing the activity of anticoagulants to the point of hemorrhage. Reports have covered oxymetholone enhancing Warfarin and nicoumalone; stanozolol enhancing Warfarin and dicoumarol; danazol enhancing Warfarin.
There has been a report of topically applied testosterone, which does not have a substituent, enhancing Warfarin.
There has also been a report of a single course of levonorgestrel for emergency contraception increasing the effect of Warfarin.

Thyroid and antithyroid drugs

Thyroid compounds do enhance the activity of oral anticoagulants possibly by increased metabolism of clotting factors. Propylthiouracil has been reported to have caused hypoprothrombinemia.

Ubidecarenone

Decreased INR values and reduced effect of Warfarin.

Vaccines

There have been a few reports of increased prothrombin time and bleeding in Warfarin-stabilized patients following influenza vaccination.

Vitamins

There have been reports of acetomenaphthone and phytomenadione reducing anticoagulant activity, or of foods or nutritional preparations containing vitamin K compounds doing the same.
There have also been isolated reports suggesting that vitamin E may enhance the activity of Warfarin.

ADVERSE EFFECTS

The major risk from Warfarin therapy is of hemorrhage from almost any organ of the body with the consequent effects of hematomas as well as anemia. Skin necrosis and purple discoloration of the toes (due to cholesterol embolization) have been occasionally occurred. Hypersensitivity reactions are extremely rare. Other effects not necessarily associated with hemorrhage include alopecia, fever, nausea, vomiting, diarrhea, skin reactions, jaundice, hepatic dysfunction, and pancreatitis.

Effects on Pregnancy

Warfarin is a recognized teratogen. Given in the first trimester of pregnancy it can cause a fetal warfarin syndrome or warfarin embryopathy characterized by bone stippling (chondrodysplasia punctata) and nasal hypoplasia. CNS abnormalities may develop following use in any trimester but appear most likely after use 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 hemorrhage.

Effects on the blood

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. Although cumulative risk of bleeding was related to duration of anticoagulation therapy, risk may be highest early in the course.
Withdrawal of Warfarin therapy may lead to rebound hypercoagulability and it has been suggested that Warfarin should be withdrawn gradually.

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 oral anticoagulants which are vitamin K antagonists, may be at increased risk of osteoporosis and fractures.

Effects on the skin and hair

Necrosis of skin and soft tissue associated with Warfarin anticoagulant therapy has been reviewed. Warfarin-induced necrosis occurs rarely and is characterized by a localized, painful skin lesion, initially erythematous or hemorrhagic 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. Patients with protein C deficiency appear to be at highest risk. Treatment with Warfarin anticoagulants should be discontinued on appearance of skin lesions and vitamin K should be given to reverse their effect.

TREATMENT OF ADVERSE EFFECTS

The methods used to manage bleeding and/or excessive anticoagulation during Warfarin therapy, or following Warfarin overdosage, depend upon the degree of bleeding, the value of the International Normalized Ratio (INR), and the degree of thromboembolic risk. If the INR is greater than 5.0 but there is no bleeding or only minor bleeding,
Warfarin should be temporarily withheld until the INR falls to below 5.0. In some cases where the INR is between 5.0 and 6.0 a reduction in Warfarin dose, rather than withdrawal, may be sufficient. For an INR greater than 8.0 administration of phytomenadione (vitamin K1) should also be considered if there are other factors for bleeding; typical doses of phytomenadione are 0.5 mg intravenously or up to 5 mg orally.
If there is any major bleeding Warfarin should be stopped and phytomenadione 5 mg by slow intravenous injection given together with a concentrate of factors II, VII, IX, and X. The dose of concentrate should be calculated based on 50 units of factor IX per kg body-weight. If no concentrate is available fresh frozen plasma should be infused (about one liter for an adult), but may not be as effective. Higher doses of phytomenadione have been used but it should be remembered that phytomenadione takes several hours to act and large doses may reduce the response to resumed therapy with anticoagulants for a week or more.
If bleeding occurs unexpectedly at therapeutic INR values, the possibility of an underlying cause such as renal or alimentary tract disease should be investigated.

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