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INTERACTIONS OF WARFARIN

Olga Řehulková

Clinical Department of R&D, IVAX-CR a. s., Ostravská 29, 747 70 Opava 9, Czech Republic

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In this article, the author reviews and updates the basis of interactions with warfarin, illustrated with appropriate examples. The interactions with drugs, medicinal herbs and foods are summarised.

INTRODUCTION

Optimum anticoagulant therapy should be aimed at an adequate balance between effective prevention of intravascular thrombosis and the production of unwanted bleeding. Many factors may affect an individual patient's response to oral anticoagulants, including age, diet, environmental contaminants and disease status. Interactions with warfarin are of particular importance not only because unexpected loss of anticoagulant control may have serious consequences, but also because warfarin offer a useful mechanistic model to study the whole topic of interactions. The pharmacodynamics of warfarin can be easily and precisely measured, and with modern analytical techniques, such as high-pressure liquid chromatography (HPLC), liquid chromatography-mass spectroscopy (LC-MS), gas liquid chromatography (GLC) and radioimmunoassay (RIA), the pharmacokinetics of the drug can be monitored[1].

DRUG-DRUG INTERACTIONS

A very large number of drug interactions have been reported with warfarin. Interactions may occur through changes affecting either the pharmacodynamics or pharmacokinetics of warfarin. Drugs may interact by more than one mechanism.

1 Pharmacodynamic drug interactions

Warfarin acts by inhibiting the vitamin K_1-dependent γ-carboxylation of clotting factors II (prothrombin), VII, IX and X at a postribosomal stage in the liver, leading to a build-up of biologically inactive precursor clotting proteins[2, 3, 4]. Pharmacodynamic interactions may be a result of a number of different mechanisms.

1.1 Drugs affecting availability of vitamin K

Broad-spectrum antibiotics suppress production of vitamin K by the bowel flora and should theoretically increase the response to warfarin. While certain antibiotics may potentiate warfarin action, these interactions have usually been shown to be due to other mechanisms[5]. Anticoagulated patients fed a vitamin K-free diet developed further prolongation of prothrombin time, while *neomycin* given to suppress vitamin K synthesis by gut bacteria had a little effect on the degree of anticoagulation, suggesting the relative lack of importance of gut bacterial synthesis of vitamin K. This is especially because bacterial synthesis of vitamin K largely takes place in the large bowel, from which absorption is poor[6].

Chloramphenicol may alter the effects of warfarin by decreasing vitamin K production by bacteria in the gut, but other mechanisms such as inhibiting hepatic metabolism and/or altering the production of prothrombin may be involved[7, 8, 9, 10, 11].

Doxycycline and *other tetracyclines, ampicillin, benzylpenicillin* and *aztreonam* decrease vitamin K synthesis secondary to alterations in intestinal flora and, therefore, may enhance the effect of warfarin[4, 12]. However, the significant potentiation is very rare if dietary intake of vitamin K is adequate[4].

Cephamandole may enhance the hypoprothrombinaemic response to warfarin due to interference with vitamin K synthesis in the gastrointestinal tract[13, 14] and/or with synthesis of vitamin K-dependent clotting factors[4]. Related cephalosporines 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. *Cephazolin*, which has similar chain, may enhance the effect of warfarin to some extent[14].

The interactions caused by interference with the bacterial synthesis of vitamin K in the gastrointestinal tract are generally considered unlikely to be of clinical significance except, perhaps, in patients with an inadequate vitamin K intake[12].

*Mineral oils (*such as *liquid paraffin)* may reduce the absorption of vitamin K and enhance the effect of warfarin, but there is a little evidence that this is clinically important[15]. Mineral oils might also impair the absorption of warfarin and lessen the effect of the anticoagulant[7, 16, 17].

Cholestyramine binds vitamin K in the gut, thus preventing its absorption[18]. It also decreases the absorption and may interrupt the enterohepatic recirculation of warfarin, resulting in a reduced anticoagulant effect[19, 20].

Colestipol does not affect the absorption of warfarin. When colestipol is administered with warfarin, no depressant effects on blood levels are seen[21].

1.2 Drugs affecting receptor sensitivity

Estrogens increase the synthesis of various clotting factors and may thus reduce the effect of anticoagulants[22, 23]. Oral contraceptives increase clotting factor concentrations and inhibit warfarin metabolism. The net effect depends on balance between these factors. Oral contraceptives are generally contraindicated in most patients taking warfarin since they are trombogenic[1, 24].

Steroids with anabolic or androgenic properties, such as *oxymetholone*[25, 26, 27]*, stanozolol*[28, 29] and *danazol*[30, 31, 32]*,* may potentiate the action of warfarin allegedly by reducing clotting factor synthesis. The 17-alpha-alkylated steroids appear to be more likely to induce this reaction than the non-substituted steroids[25, 26, 27, 33]. However, there has been a report of topically applied *testosterone*, which does not have 17-alpha-alkyl substituent, enhancing warfarin[34].

Diuretics may antagonise the action of warfarin by two pharmacodynamic mechanisms[18]: (a) patients in cardiac failure have impaired clotting factor synthesis due to hepatic congestion – correction of this state leads to increased clotting factor synthesis; (b) diuretics also reduce the plasma volume producing an increased concentration of clotting factors which may alter the anticoagulant effect of warfarin[35]. *Chlorthalidone*[36] and *spironolactone*[35] have both been associated with a reduction of warfarin activity probably as a consequence of diuresis concentrating the circulating clotting factors. *Bumetanide, furosemide* and *thiazides* appear to have no effect on warfarin[23].

Certain *cephalosporines*, such as *cefotetan*, *cefamandole*, *cefoperazone*, or *moxalactam* may cause marked hypoprothrombinemia and/or prolonged bleeding time at concurrent use with warfarin[38, 39, 40, 41]. The main mechanism of interaction consists in decreasing synthesis of vitamin K-dependent clotting factors.

Clofibrate may potentiate warfarin action, probably by altering receptor sensitivity[23, 37]. Although clofibrate displaces warfarin from albumin binding sites this does not appear to be a principal mechanism of the interaction[42].

Drugs altering thyroid function may affect anticoagulant control, since rates of synthesis and degradation of clotting factors are dependent on thyroid function[7]. *Thyroid compounds* do enhance the activity of oral anticoagulants by increased metabolism of clotting factors[12]. *Dextrothyroxine* increases the anticoagulant effect of warfarin[43, 44]. *Antithyroid compounds* may diminish the effect of anticoagulant[45], although paradoxically *propylthiouracil* has shown to cause hypoprothrombinaemia[12]. The patients on anticoagulant therapy who are euthyroid due to antithyroid agents may develop marked hypoprothrombinemia if the antithyroid medications are ceased and they become thyrotoxic again[46].

The antiepileptic agent valproic acid decreases hepatic synthesis of procoagulant factors and, therefore, may cause an increase in response to warfarin[47].

The ingestion of large amount of tonic water necessitated a reduction in warfarin dosage. The enhanced effect was attributed to *quinine* content in tonic water[48]. The interaction may be explained by decreasing hepatic synthesis of procoagulant factors with quinine[4].

Cyclophosphamide has been associated with an increase in warfarin activity when given with methotrexate and fluorouracil[49], but with a decrease when given with non-antineoplastic drugs[50]. The mechanism of interaction lead to enhancement of warfarin effect consist in decreasing hepatic synthesis of procoagulant factors[4]. *Azathioprine* or *mercaptopurine* (the metabolite of azathioprine) may reduce the anticoagulant activity of warfarin[51, 52]. Mercaptopurine showed to increase prothrombin synthesis or activation in animal studies[53].

The antiarrhytmics *disopyramide*[54] and *quinidine*[55] may enhance the effect of warfarin probably by alteration of procoagulant factor synthesis. However, this interaction does not seem to be consistent[56, 57].

Glucagon has been shown to increase the hypoprothrombinemic effect of warfarin, resulting in bleeding episodes[59]. The precise mechanism for this interaction is not known, although it may be due to a depression of the production of clotting factors in the liver, or an increase in warfarin sensitivity for its receptor site.

1.3 Drugs affecting haemostasis

Any drug that alters platelet function may potentiate warfarin action even though the prothrombin time remains unchanged[1]. *Aspirin* binds irreversibly to the active site of cyclooxygenase in the prostacyclin synthethase pathway, producing irreversible effects on platelet function which persist for the life of the aspirin-treated platelet[60, 61]. Thus, even small doses of aspirin may affect haemostasis. Aspirin in high doses has a direct hypoprothrombinemic effect[62, 63]. The dual impairment of haemostasis by the effect of aspirin on platelet activity and by the effect of warfarin on fibrin formation causes the increased susceptibility to hemorrhagic episodes[64]. Of other salicylates, *sodium salicylate*, *choline salicylate*, *salsalate* and *magnesium salicylate* have little effect on platelet function and cause less gastrointestinal erosion and bleeding[65, 66].

Similar, but usually lesser effects on platelet function than aspirin may be seen with *most other nonsteroidal anti-inflammatory drugs,* such as *phenylbutazone*[1]. *Indomethacin* showed no interaction with warfarin in early study by Vesell, however, isolated reports are suggestive of a clinically significant interaction between the two drugs[63, 68]. It can also cause gastrointestinal ulceration, hemorrhage, and inhibition of platelet aggregation[19, 69, 70]. Of the other non-steroidal anti-inflammatory drugs, *flurbiprofen*[71]*, meclofenamate sodium*[72]*, mefenamic*

acid[73, 74], *piroxicam*[75], *sulindac*[76, 77], *tiaprofenic acid*[78], *tolmetin sodium*[79] may potentiate the anticoagulant effect. 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 these drugs no enhancement of warfarin activity has been demonstrated. The non-steroidal anti-inflammatory drugs with an apparently minimal effect on warfarin activity include *etodolac*[80], *ibuprofen*[81], *naproxen*[82] and *tenidap*[83].

The effects on haemostasis are also seen rarely with *penicillins*, particularly carbenicillin and relative compounds[84].

Abciximab, alteplase, clopidogrel, lepirudin and *reteplase* have an additive anticoagulant effect at concurrent use with warfarin, thus they may significantly enhance the risk of bleeding.

Dipyridamole concurrently used with warfarin may cause bleeding without any alteration in prothrombin time. This interaction has involved a small number of patients[85] and its mechanism consists in inhibition of platelet function by dipyridamole. However, in general it does not appear to increase the risk of bleeding.

Ubidecarenone has been reported to reduce the effect of warfarin and decrease INR values. It is chemically related to vitamin K_2, and has been proposed to have procoagulational effects[87]. Patients should avoid concomitant use of ubidecarenone and warfarin.

2 *Pharmacokinetic drug interactions*

Pharmacokinetic interactions include effects on warfarin absorption, protein binding and metabolism.

2.1 Drugs affecting warfarin absorption

many drugs might decrease the rate or completeness of absorption of warfarin from the gastrointestinal tract, particularly compounds that raise gastric pH (e.g. *antacids* or *H_2-receptor antagonists*), alter gastrointestinal motility (e.g. *laxatives, anticholinergic*) or interfere with normal mucosal function (e.g. *neomycin*). In addition, drugs that form complexes with anticoagulants *(cholestyramine)* or non-absorbable oils that dissolve coumarins may reduce anticoagulant absorption[18]. *Cholestyramine* has been shown to influence warfarin absorption significantly.

Antacids may or may not interact with warfarin. *Bismuth carbonate* and *magnesium trisilicate* may reduce warfarin absorption[88]. *Aluminium hydroxide* and *magnesium hydroxide* had no effect on warfarin, but the latter increased the plasma concentrations of dicoumarol[89]. *Sucralfate* may diminish the effect of warfarin[90, 91, 92].

A marked increase in the effect of warfarin has been reported in one patient taking *cisapride*[93].

Mesalazine has been associated with a reduction in the response to warfarin leading to development of venous thrombosis. Although the mechanism is not known, possible causes include mesalazine inhibiting or preventing the absorption of warfarin[94].

Limited data suggest that *acarbose* may enhance the anticoagulant effect of warfarin, possibly by increasing warfarin absorption[95].

2.2 Drugs causing protein binding displacement

In practice, protein binding displacement has been shown to produce only transient rise in prothrombin time. The drugs frequently quoted as producing significant interactions with warfarin by binding displacement also interact by other mechanisms which are probably of greater significance (e.g. *phenylbutazone*[96], *oxyphenbutazone*[97], *azapropazone*[97] and *clofibrate*[37, 42]).

Diflunisal administered in the dose of 500 mg twice daily increased the percentage of unbound warfarin by 30%, but at the same time there was 28% fall in total plasma warfarin concentration. Thus, free warfarin concentration was unaltered and the prothrombin time remained the same. When diflunisal was continued, warfarin binding rapidly returned to pre-diflunisal levels, but the total warfarin concentration remained depressed for almost 2 weeks – this delay was presumably due to time taken for a new steady-state to be reached. Hence, there was a reduction in the free warfarin concentration and a loss of anticoagulant effect[98]. *Mefenamic acid*[74], *etodolac*[80], *ibuprofen*[81, 99] *and tenidap*[83] may also displace coumarin anticoagulants from protein binding sites. However, the influence of etodolac, ibuprofen and tenidap on warfarin anticoagulant effect is minimal.

Ethacrynic acid[19], quinolone antibacterial *nalidixic acid*[100, 101, 102] and some *oral antidiabetic agent,* such as *glibenclamide*[103] and *phenformin*[104], may enhance the effect of warfarin due to displacement of warfarin from protein-binding sites. Although an interaction between sulfonylureas and dicumarol has been documented, there are no clinical reports indicating that an interaction between warfarin and *tolbutamide* has occurred[105]. Similarly, no report documenting the interaction between *insulin* and warfarin is published[7].

The concomitant use of *chloral hydrate* and warfarin may result in a temporary increase in the hypoprothrombinemic effect of warfarin due to sudden increase in the free blood levels of warfarin. In addition, a reduction in the elimination half-life of warfarin may be observed. Although the majority of patients are minimally affected, some patients may develop a considerable increase in a hypoprothrombinemic response[106, 107]. The increase was probably the result of displacement of warfarin from plasma protein binding sites by the metabolite tricholoroacetic acid[108].

Emergency contraception with *progestogen (levonorgestrel)* may enhance the anticoagulant effect of warfarin[109]. One of the possible explanation of this interaction is displacement of warfarin from binding site F1S on alpha 1-acid glycoprotein by levonorgestrel[110].

2.3 Drugs causing enzyme induction

Induction of hepatic microsomal mixed-function oxygenase activity is well recognised as a cause of interaction with oral anticoagulants. Enzyme induction increases the rate of metabolism of warfarin, decreases plasma half-life and steady-state concentration, and therefore reduces its anticoagulant effect.

Enzyme induction appears to be a property shared by all *barbiturates*[111], though there are differences in the potency of individual barbiturates. The extensively studied inducing agent is *phenobarbitone*. The administration of phenobarbitone to patients receiving long-term warfarin therapy produced a change in warfarin concentration and a loss of anticoagulant effect within 6 days. The maximum effect was usually seen within 2 weeks[112]. *Amobarbital*[112], *phenobarbital*[107], *secobarbital*[107] has also been reported to diminish pharmacological activity of warfarin. A number of other hypnosedatives and anticonvulsant drugs such as *gluthethimide*[107, 113, 114], *carbamazepine*[115, 116, 117, 118] and *phenytoin*[119] induce metabolism of warfarin. *Benzodiazepines* do not interact significantly with warfarin[1]. Reduced anticoagulant activity has been reported with *haloperidol*[120]. The reduction is suggested to be caused by accelerated metabolism of anticoagulant secondary to stimulation of hepatic microsomal enzyme activity[4]. *Meprobamate*[121, 122] and *methaqualone*[107] appear to have no effect on anticoagulants.

Other inducers include *griseofulvin*[121, 123, 124] and *rifampicin*[125, 126]. *Rifampicin* is one of the most potent inducers of microsomal enzyme activity. It increases the rate of clearance of warfarin, thus reducing its anticoagulant effect. The similar effects have been demonstrated with *nafcillin*[127] and *dicloxacillin sodium*[128].

Phenazone, an inducer of enzyme metabolism, reduces plasma concentrations of warfarin and may necessitate an increase in warfarin dosage[12].

Concurrent use of *aminoglutethimide* and warfarin or other oral anticoagulants results in a reduced hypoprothrombinemic effect[130, 131, 132]. Aminoglutethimide induces hepatic microsomal enzymes resulting in enhanced metabolism of warfarin[133]. Concomitant administration of warfarin and *mitotane* has been associated with a reduction in anticoagulant effect of warfarin, necessitating increased warfarin doses to maintain therapeutical prothrombin time[134]. It is speculated that the mitotane, being related to organochlorine insecticides, may accelerate warfarin metabolism secondary to microsomal enzyme induction.

2.4 Drugs causing inhibition of metabolism

H_2-receptor antagonists and proton pump inhibitors: cimetidine may inhibit warfarin metabolism and potentiate its effect resulting in haemorrhage. However, more precise studies have shown that cimetidine has no effect upon the kinetics of more active S enantiomer and only has a moderate effect upon R enantiomer, reducing its plasma clearance[135, 136, 137, 138]. Not all these studies, however, demonstrated an increase in prothrombin time. The effect of cimetidine on warfarin appears to be dose-dependent[135] and to be a subject of interindividual variation[137, 138]. Studies with *ranitidine* have generally been unable to demonstrate the effect on metabolism of warfarin[138, 139], although in one study warfarin clearance was reduced[135]. There is one case report suggesting that potentiation of warfarin by ranitidine may occasionally occur[140]. No significant alteration in the pharmacokinetics or the anticoagulant activity of warfarin developed during the concomitant administration of *famotidine*[141, 142]. Nizatidine had no effect on the anticoagulant response to warfarin[143]. *Omeprazole* may inhibit the metabolism of R-warfarin[144], but the clinically significant effect on activity of warfarin is unlikely. Similarly, *pantoprazole* appears to have no effect on warfarin[145].

Amiodarone and some of its metabolites inhibit the reduction of R-warfarin to R,S-warfarin alcohol-1 and the oxidation of both R- and S-warfarin to phenolic metabolites. Potentiation of warfarin by amiodarone probably depends upon inhibition of P4502C9, the isoenzyme P450 mainly responsible for the conversion of S-warfarin to its major metabolite (S)-7-hydroxywarfarin[146]. Concurrent use of *propafenone* and warfarin has resulted in an increased warfarin concentration and an increased prothrombin time. The mechanism of interaction consists in decreasing warfarin clearance[147].

Sulfinpyrazone has been reported to produce a biphasic effect on warfarin action. The initial effect was an increase in prothrombin time followed by a loss of anticoagulant effect with continued treatment. It is likely that more than one mechanism exists to explain this phenomenon[148]. Sulfinpyrazone exerts stereoselective effect on warfarin metabolism and inhibits S-isomer metabolic clearance[149]. It also affects platelets[7]. *Allopurinol* may enhance warfarin effect by inhibition of its metabolism[150, 151]. However, a number of case reports have demonstrated an inconsistent effect of allopurinol on warfarin therapy[152, 153, 154].

Phenylbutazone stereoselectively inhibits warfarin metabolism[96]. It was demonstrated that the drug inhibits the metabolism of S-warfarin (more potent enantiomer) while increasing the rate of elimination of R-warfarin. The net effect was an increased anticoagulant response to a single dose of racemic warfarin, but no apparent change in the racemic warfarin half-life[155]. The restricted use of phenylbutazone greatly reduces the chance of this potentially fatal interaction being observed. Related drugs such as *oxyphenbutazone*[97], *azapropazone*[156, 157, 158], and *fenprazone*[159, 97] behave similarly and should also be avoided.

Paracetamol was associated with an increased hypoprothrombinemic effect of warfarin. This interaction is proposed to be due to inhibition of its metabolism and interference with formation of clotting factors. Gingival bleeding and hematuria were observed in case reports when paracetamol is given with warfarin[160, 161, 162, 163, 164]. However, due to lack of a safer alternative, paracetamol is still the analgesic and antipyretic of choice in patients

receiving warfarin therapy, as long as excessive amounts and prolonged administration are avoided[165]. A combination of *paracetamol and codeine* has enhanced warfarin activity[163]. The commonly used analgesic *(propoxyphene plus paracetamol)* may potentiate the effect of warfarin[161, 166, 167, 168].

Topical methyl salicylate may potentiate the anticoagulant effect of warfarin[86, 169], probably by inhibition of warfarin metabolism.

Metronidazole and *co-trimoxazole (combination of sulfamethoxazole* and *trimethoprim*) strereoselectively inhibit the metabolism of S-warfarin[170]. The interaction with co-trimoxazole is generally attributed to the sulfamethoxazole moiety and there are isolated reports suggesting that the activity of warfarin may be enhanced by other *sulphonamides* including *sulphafurazole[171]*, *sulphamethizole[172]* and *suphaphenazole[173]*.

Ketoconazole[174], miconazole[175, 176, 177, 178], *fluconazole[179, 180] and itraconazole[181]* have been reported to increase warfarin effect probably due to inhibiting its metabolism.

Enoxacin decreases the clearance of R-warfarin, but not S-warfarin; no prolongation of prothrombin time occurred[182].

Erythromycin inhibits warfarin metabolism and thus may enhance the effect of warfarin[183]. An enhanced response to warfarin has also been reported with *azithromycin[184, 185]* and *roxithromycin*, including reports of spontaneous bleeding with the latter. *Clarithromycin* may potentiate the effect of warfarin, although other factors may also have been involved in this case[186].

Isoniazid may enhance the effect of warfarin possibly by inhibition of its metabolism[187].

Lipid-soluble β-blockers (e.g. *propranolol*) inhibits warfarin metabolism and may thus potentiate the effect of warfarin. However, although a number of studies have shown pharmacokinetic interactions between some beta-blockers and oral anticoagulants, no effect on anticoagulant activity has been found[188].

Influenza vaccine significantly increased prothrombin time and bleeding in two warfarin-stabilised patients[189]. Present data suggests this interaction does not occur in most patients[190, 191, 192].

Increased anticoagulation and serum warfarin concentration necessitating a reduction in warfarin dosage have been shown with *interferon alfa* and *interferon beta*. It was suggested this interaction may have been due to decreased metabolism of warfarin[193]. An enhanced response to warfarin has also been reported with *saquinavir[194]*. The mechanism involves competitive inhibition of warfarin metabolism and might also occur with other *HIV-protease inhibitors*[12].

Disulfiram may augment the activity of warfarin[195, 196]. Although inhibition of liver enzymes by disulfiram was considered responsible[197], a later study suggested that disulfiram directly affecting the hepatic mechanism responsible for hypoprothrombinemia[198].

Fluorouracil decreases synthesis of cytochrome P450 2C9 enzymes which metabolise warfarin and, therefore, may enhance its anticoagulant effect[199, 200, 201, 202, 203].

Tricyclic antidepressants, such as *amitriptyline* and *nortryptiline*, may increase the half-life of oral anticoagulants[204, 205]. However, considerable interindividual differences may be found[206]. There is a theoretical risk of increased warfarin activity with *MAO inhibitors[12]*, *fluvoxamine[207]* and other *selective serotonin reuptake inhibitors*. Increased warfarin activity has been reported in a few patients taking *fluoxetine[208]*.

Concomitant *gemfibrozil* and warfarin therapy has resulted in an increased hypoprothrombinemic response and bleeding. The mechanism of this interaction involves decreasing warfarin metabolism and displacement of warfarin from protein by gemfibrozil[209]. *Lovastatin[210] and fluvastatin[211]* may enhance the effect of warfarin. *Simvastatin* has been reported to potentiate effect of nicoumalone in one patient[212]. However, it did not change the INR in a patient on long-term warfarin[213]. *Pravastatin* does not appear to cause any change in warfarin activity[214].

Tobacco smoke contains many substances that may affect the metabolism of warfarin. Some of these substances will inhibit the metabolism of warfarin, other substances will induce its metabolism. The effect of smoking tobacco on warfarin metabolism may vary from one patient to the next. The INR or prothrombin time should be monitored carefully if the patient begins or stops smoking while taking warfarin[215].

3 Interactions of uncertain and/or unknown mechanisms

Corticosteroids and *corticotrophin* may increase the risk of localised bleeding within the gastrointestinal tract in patients taking warfarin[1, 4, 216]. These drugs may also diminish the effect of anticoagulants by unknown mechanism[217].

Quinolone antibacterials, such as *ciprofloxacin[218, 219, 220, 221, 222, 223]*, *norfloxacin[224] and ofloxacin[225, 226]* may increase the activity warfarin, although for some of these drugs there are also studies indicating no effect. However, in the 64 cases of ciprofloxacin-warfarin coagulopathy reported to the Food and Drug Administration's Spontaneous Reporting System database between 1987 and 1997, the median age of the patient was 72 years old and the mean number of medications which the patient was receiving was 6.5. It appears that this coagulopathy is most prevalent in elderly patients who require polypharmacy[227].

Proguanil may enhance warfarin effect and increase risk of bleeding[228].

The addition of *etretinate* to patients on warfarin therapy may cause a decrease in anticoagulant effect[229].

Tramadol has been reported to enhance anticoagulant activity of warfarin[129, 230, 231].

Etoposide with *vindesine*[232] or with *carboplatin*[233], *ifosfamide* with *mesna*[234] and *tamoxifen*[235, 236, 237] may all produce an increased anticoagulant effect. The antiandrogen *flutamide* may increase the prothrombin time in patients on long-term warfarin[12]. *Cyclophosphamide* may increase[49] (see section 1.2) and/or decrease in warfarin activity[50]. The mechanism of interaction leads to decreasing warfarin effect is unknown[4].

Concurrent therapy with warfarin and *cyclosporine* was associated with reduced effect of both drugs[238, 239].

Moracizine may enhance the anticoagulant effect of warfarin[240].

Bezafibrate has been reported to enhance the effect of phenprocoumon[241], *and fenofibrate* enhanced the effect of warfarin[242].

Piracetam caused an increase in prothrombin time in a patient stabilised on warfarin[243].

Ascorbic acid at large doses may reduce the warfarin activity[244, 245] and high doses of *vitamin A*[246] and *vitamin E*[247] may enhance the activity.

INTERACTIONS WITH MEDICINAL HERBS

At present, herbal drugs are used in increasing numbers. Plant market experiences an unprecedented growth all over the world. Drugs made on the basis of medicinal herbs are generally perceived as harmless. Nevertheless, there are already known and/or potential possibly threatening interactions between various drugs and medicinal herbs[248].

Of herbs, warfarin may interact with feverfew (Chrysanthemum parthenium), garlic (Allium sativum), ginger (Zingiber officinale), Ginkgo biloba, ginseng, St. John's Wort (Hypericum perforatum), mountain arnica (Arnica montana), camomile (Chamomilla recutita), primrose (Primula veris) and common celery (Apium graveolens).

Feverfew inhibits platelet aggregation in vitro and may alter bleeding time. Feverfew interfers with the initial step of thromboxane synthesis, inhibiting the release of the arachidonic acid substrate from platelet phospholipids[249, 250]. With diminished amounts of arachidonic acid, decreased amounts of the proaggregatory prostaglandin thromboxane A2 will be formed, resulting in decreased platelet aggregation. Theoretically, antiplatelet activity of feverfew could lead to additive anticoagulant effects when combined with warfarin.

Garlic possesses the antiplatelet activity[251, 252], thus may potentiate effect of warfarin and increase the risk of bleeding complications. Concomitant use of garlic and warfarin is not recommended. Garlic therapy should be discontinued at least 10 days prior to elective surgery[253]. Regular ingestion of food products containing small amounts of garlic should not pose a problem.

Ginger has been reported to inhibit the synthesis of thromboxane, but clinical significance of such effect is undetermined[254]. Theoretically, any affect of ginger on platelet aggregation could contribute to adverse effects if combined with an anticoagulant agent such as warfarin.

Ginkgo biloba showed to inhibit the platelet activating factor necessary for arachidonate-dependent aggregability of platelets[248]. Co-administration of ginkgo and warfarin may result in increased risk of bleeding complications. Cases of cause bilateral subdural hematoma have been reported in patients taking ginkgo alone[255, 256]. Therefore, patients should not take gingko with any anticoagulant.

The products containing *ginseng* which is usually obtained from Panax ginseng, Panax pseudoginseng var. notoginseng or Panax quinquefolius may reduces the effect of warfarin[248]. The mechanism of this interaction is not clear, but may be associated with anti-platelet effect of its components[257, 258]. Since ginseng was likely involved in the interaction with warfarin in a human case report, ginseng is best avoided in patients taking anticoagulants with narrow therapeutic ranges.

St. John's Wort may induce cytochrome P450 enzymes, including CYP1A2[259]and CYP2C9[260], augmenting warfarin metabolism. Concomitant use of warfarin with St. John's Wort is not recommended. If patients elect to remain on St. John's Wort, symptoms of decreased warfarin efficacy and prothrombin times should be closely monitored. A stable dose of St. John's Wort is recommended and patients should be advised not to discontinue St. John's Wort without consulting their physician.

Fenugreek (Trigonela phoenum-graecum) contains coumarins which may affect blood coagulation[261]. Concomitant use of fenugreek and warfarin is not recommended due to increased risk of bleeding.

DRUG-FOOD INTERACTIONS

Although serum levels of warfarin tend to be lower when administered with food, the total amount of drug absorbed is unaffected[262]. Avocado pears[263] and ice cream[264] have been reported to cause antagonism of warfarin, perhaps due to interference with absorption. Foods high in vitamin K content or those foods capable of enhancing intestinal sources of vitamin K may antagonise the anticoagulant effect of warfarin[265, 266]. Grapefruit juice may enhance warfarin effect by inhibition of R-warfarin metabolism mediated by CYP1A2 and CYP3A4[267].

Long-term *ethanol* consumption caused the induction of drug-metabolising enzymes[268], but when ethanol was administered acutely to volunteers, warfarin clearance was decreased[112]. However, moderate intake of alcohol does not appear to affect anticoagulant control[58].

In the studies on animals, it was demonstrated that *dietary protein* has an influence on the response to warfarin. Rats fed higher protein diets were more tolerant to warfarin[269, 270]. A possible interpretation of the results

implicates the influence of dietary protein on plasma albumin concentrations. Diets deficient in protein have been shown to depress the total albumin mass. It is known that warfarin is tightly bound to plasma albumin, and if this plasma protein is depressed, the possibility of a higher concentration of free warfarin will exist in plasma. In turn, this free warfarin can move more readily into the liver. If at the same time there is a depression of those enzymes involved in warfarin metabolism caused by dietary protein deficiency, the anticoagulant will be more effective in reducing the synthesis of the proteins of the prothrombin complex. Thus, dietary protein deficiency may augment the depression of the prothrombin complex factors induced by warfarin[269].

CONCLUSION

A very large number of drug interactions have been reported with warfarin. The drugs may interact through pharmacodynamic or pharmacokinetic mechanisms. The former include alteration of bioavailability of vitamin K, affecting receptor sensitivity and affecting haemostasis via platelet function. The interactions of a pharmacodynamic nature occurring with one anticoagulant may well apply to another, while this is not necessarily the case with interactions of a pharmacokinetic nature. The pharmacokinetic interactions may be due to effects on warfarin absorption, protein binding and metabolism. Few drugs have been shown to alter warfarin absorption, the importance of protein binding displacement has been exaggerated, and since warfarin is eliminated in a very little extent unchanged by kidney the most important kinetic interactions are those due to inhibition or induction of its metabolism. Examples of hepatic microsomal enzyme-inducing drugs are barbiturates, griseofulvin, rifampicin, phenazone and aminoglutethimide. Inhibition of metabolism of warfarin has been demonstrated with many drugs, such as H_2-receptor antagonists and proton pump inhibitors, phenylbutazone, metronidazole, co-trimoxazole, amiodarone, sulfinpyrazone and macrolide antibiotics. Some drugs may interact by more than one mechanism. In several cases both increased and decreased anticoagulation have been reported for the same drug, so some interacting drugs do not produce predictable effect. The clinically significant interactions have been reported with drugs containing medicinal herbs, such as feverfew, garlic, ginger, ginkgo, ginseng, St. John's Wort, mountain arnica, camomile, fenugreek, primrose and common celery. *Foods or nutritional containing vitamin K, a*vocado pears, ice cream, grapefruit juice and ethanol may affect the anticoagulant effect of warfarin.

Because of possible serious consequences of interference with anticoagulant therapy, special care is required when any medication is added to or withdrawn from patients on anticoagulant therapy. Patient monitoring should be more frequent in such cases. Caution is also necessary in patients taking foods or nutritionals containing vitamin K during anticoagulant therapy.

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