Interactions between complementary medicines and warfarin

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SYNOPSIS

Many complementary medicines have confirmed or potential interactions with warfarin. These interactions can increase or decrease the anticoagulant effect of warfarin and have the potential to cause serious adverse events. A number of herbs and foods alter the metabolism of warfarin by acting on cytochrome P450 enzymes. Other potentially interacting complementary medicines include those with possible effects on platelets and those containing natural coumarins. Warning both consumers and prescribers of warfarin about the potential for interactions with complementary medicines may reduce the risk of these interactions. Such warnings are appropriate for a drug that has a narrow therapeutic window and requires regular monitoring. In view of these interactions, prescribers should check the international normalised ratio within a week of a patient commencing or ceasing a complementary medicine.

Index words: anticoagulation, herbal medicines.

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Introduction

Interactions with warfarin can lead to either an increased or decreased anticoagulant effect. Those that increase the anticoagulant effect significantly increase the risk of serious haemorrhage. Interactions that decrease the anticoagulant effect significantly increase the risk of thromboembolic complications of the condition for which warfarin was prescribed.

Drug and dietary interactions with warfarin

Coumarins (mainly warfarin) are currently known to interact with approximately 250 different drugs. Interactions can increase or decrease the international normalised ratio (INR).

Haemostasis involves interaction between the vessel wall, platelets and coagulation factors. In addition to drug interactions that may alter the INR, medications may alter platelet activity and modify haemostasis resulting in prolonged bleeding time without affecting the INR. Antiplatelet agents will prolong bleeding time and may increase the risk of serious haemorrhage when taken with warfarin. As these drugs have a different action the INR may be unchanged despite the increased risk of bleeding.

Dietary factors may affect the action of warfarin and the resultant INR. Deficiency of vitamin K will increase the INR, while a diet high in vitamin K will decrease it. Dietary substances that inhibit or induce the cytochrome P450 pathway may alter warfarin's metabolism and increase or decrease its half-life.

While the anticoagulant effect of warfarin generally begins within 24 hours of taking the drug, the peak effect may take up to four days. As the effective half-life of warfarin is about 40 hours, and the anticoagulant effect is delayed, it takes several days after any dosing change before plasma concentrations and anticoagulant effects reach a steady state.

Interactions between warfarin and complementary medicines

A wide range of complementary medicines, both nutritional supplements and herbal preparations, have confirmed or potential interactions with warfarin.

Nutritional supplements that have documented interactions with warfarin include vitamin K, vitamin C and coenzyme Q_{10} which have been associated with a decrease in INR. Vitamin E has been associated with increases in INR, but there is conflicting evidence in the literature.[1]

A small number of herbal preparations have documented interactions with warfarin. The strength of the evidence to support these associations varies widely. Herbs with a documented increase in the anticoagulant effect include garlic[2] (*Allium sativum*), dong quai[3] (*Angelica sinensis*), danshen[4] (*Salvia miltiorrhiza*) and devil's claw[5] (*Harpagophytum procumbens*). Herbs with a documented decrease in the anticoagulant effect include Korean ginseng[6] (*Panax ginseng*) and green tea (*Camellia sinensis*).[7] The mechanism of these interactions is not always known and the majority of this literature is based on single cases.

In some cases the mechanism is understood. One medicinal plant and two foods have been shown to increase the metabolism of warfarin through their action on the cytochrome P450 pathways leading to the lowering of the INR. Substances known to induce P450 include St John's wort[8] (*Hypericum perforatum*), broccoli[9] and Brussels sprouts[10]. These interactions occurred with a standard dose of St John's wort extract (900 mg daily) and diets rich in broccoli and Brussels sprouts. Grapefruit juice, a known inhibitor of cytochrome P450, does not appear to alter warfarin metabolism.[11]

Potential interactions

A significant number of the substances cited in the literature as posing a risk should be defined as potential, rather than established, risks as the data on which the assessment has been made are an extrapolation from known chemical constituents within the substance or from *in vitro* studies. While these substances may indeed pose a risk, it remains theoretical until evidence exists from human cases or studies. Plants with potential risk include those with possible actions on platelets and those containing natural coumarins.

A wide range of herbal preparations have demonstrated **antiplatelet** activity *in vitro* and may potentially increase bleeding time.[12] These include a number of the most popular herbs on the Australian market: feverfew (*Tanecetum parthenium*), garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), ginger (*Zingiber officinale*), Korean ginseng (*Panax ginseng*), and liquorice (*Glycyrrhiza glabra*). Attributing *in vivo* activity based on laboratory investigation is inappropriate and in a number of cases clinical trials have failed to show similar effects in humans. For example, the role of garlic and ginger[13] as antiplatelet agents remains controversial. They may not possess antiplatelet activity, but if they do it may depend on specific formulations that concentrate an appropriate profile of active constituents.

Many herbs contain coumarins that may **potentiate the activity of warfarin**.[14] These include alfalfa (*Medicago sativa*), angelica (*Angelica archangelica*), aniseed (*Pimpinella anisum*), arnica (*Arnica montana*), asafoetida (*Ferula spp.*), celery (*Apium graveolens*), German chamomile (*Matricaria recutita*), Roman chamomile (*Anthemis nobilis*), fenugreek (*Trigonella foenum-graecum*), horse chestnut (*Aesculus hippocastanum*), prickly ash (*Zanthoxylum americana*, *Z. clava-herculis*), quassia (*Picrasma excelsa*), and red clover (*Trifolium pratense*).[12]

Concurrent use of complementary medicines and pharmaceutical drugs

United States data suggest that 18% of adults use prescription drugs concurrently with herbal or vitamin supplements[15]; 15 million people may be at risk of drug-supplement interactions. The review of Traditional Chinese Medicine (TCM) undertaken by the Victorian, New South Wales and Queensland Departments of Health in 1995 estimated from a sample of 274 patients that 39% took pharmaceutical drugs with their Chinese herbal medicine.[16] If this can be generalised to all users of complementary medicines and we apply this to the 1993 estimate of one in two Australians using at least one complementary medicine per year, then 19.5% of the Australian population use prescription drugs concurrently with complementary medicines. This suggests that 3.7 million Australians may be at risk of drug-supplement interactions.

Despite these figures, confirmed interactions are uncommon and reported adverse events are relatively sparse. Adverse reactions to complementary medicines probably remain under-reported[17], so the totals of adverse events and interactions are probably higher. However, it is unlikely that an epidemic of adverse events with complementary medicines remains undetected in Australia.

Strategic management of potential interactions

Two approaches are possible to limit the potential public health risk of drug interactions between complementary medicines and warfarin. The first is to place a warning label on all complementary medicines with any known interaction with warfarin where the causality has been demonstrated beyond a reasonable doubt. The second is to place a warning about the concurrent use of complementary medicines in the product information of warfarin and to educate warfarin prescribers to ask about complementary medicines use by their patients.

While these two approaches are not mutually exclusive, it can be argued that their risk management is substantially different. Labelling any medication with a warning statement can only be undertaken when there is clear evidence for such a warning. The number of complementary medicines with a potential to interact with warfarin is large, however, the number with clear evidence of such an interaction is small. Labelling the few medications where the evidence is clear will not reduce the risk of potential interactions with a large number of complementary medicines.

Given that the number of recognised drug interactions with warfarin has increased over time, it is appropriate to conclude that the number of interacting complementary medicines will also increase over time. We can safely assume that there are a number of currently unidentified interactions that will be found in the future.

Warning both consumers and prescribers of warfarin about the potential for interactions with all complementary medicines may reduce the risk of interactions, not only with preparations that have definitive and potential interactions, but also with those where the interaction is currently unidentified. Such a warning is in keeping with a drug that has a narrow therapeutic range and requires regular monitoring.

Warfarin prescribers need to be aware of complementary medicines usage and monitor the INR more frequently if this usage changes. As a precaution, patients on warfarin should have INR measurements about two and seven days after starting or changing any herbal treatment.[18] Prescribers need to alert patients to the clinical symptoms associated with minor and major bleeding and be prepared to cease both warfarin and the complementary medicine. In patients at special risk, such as the elderly and the debilitated, concurrent use of complementary medicines and warfarin should be undertaken with considerable caution. If the complementary medicine is necessary, it should be continued with the same care given to pharmaceutical drugs with a high risk of interaction.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 75)

1. Complementary medicines may increase the risk of bleeding in patients taking warfarin without affecting the international normalised ratio (INR).
2. Vitamin K supplements may decrease the effect of warfarin.

CD review

John Murtagh. The General Practice Series – Single User CD-ROM.

Price $195. 10% discount for *Australian Prescriber* readers.*

Ieva Ozolins, General Practitioner, Kangaroo Island Medical Clinic, Kingscote, SA

'The General Practice Series' is an interactive CD-ROM encompassing three books written by one of Australia's most eminent general practitioners and educators. It is presented as the 'on-screen' alternative to the print versions of Murtagh's 'General Practice', 'Practice Tips' and 'Patient Education'. After confirming with my practice manager that my office computer fulfilled the system requirements of the CD-ROM, I managed to install the software and subsequently use the program without expert assistance.

I found the program useful in providing patient education sheets in the office, as it allowed me to call up and print out single page information sheets and to discuss the information with the patient on the spot. The software also provided an easily accessible reference for the diagnosis and management of common and unusual patient presentations. The on-screen format of 'General Practice' mirrors that of the original 1994 textbook currently sitting on the bookshelves in my practice, with some additional chapters and content in many of the chapters. The font used in the text is appropriate for reading on screen, however I found that it is still easier to read longer entries from the print version, rather than scrolling through each page on the computer. The drop-down menu system is easy to operate, and the 'Help' icon will get you going if you are not confident when first opening the program. Generally I used the drop-down menu looking for specific conditions, although the package allows for searching through the individual texts by providing a contents page for each book, accessed from the home page.

As in the original print versions, information is presented in a clear, methodical manner. Professor Murtagh's approach is simple to follow whether looking at a symptom or symptom complex, or for a specific condition. Pointing to a reference number in the body of the text easily accessed key references. Unfortunately the text has not been updated to reflect some of the more recent changes faced in general practice, for example, in the childhood immunisation schedule and the availability of new forms of delivery of hormonal contraception and hormone replacement therapy. With this caution, 'The General Practice Series' software package should prove invaluable to medical students, registrars and many experienced general practitioners, just as the printed texts have in the past.

Minimum system requirements
Microsoft Windows 95, 98 or NT 4 operating system
PC with 486 MHz processor
16 MB RAM for Windows 95 or 98, or 32 MB for NT
Mouse or other pointing device
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SVGA colour monitor, 256 colours with 800 x 600 resolution (higher recommended)
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