IN BRIEF

- Antibiotics used in dentistry have the capacity to interact with warfarin producing a clinically significant alteration in anti-coagulation status.
- Evidence can be contradictory as to the effect of certain antibiotics on the action of warfarin.
- A review is presented here outlining important effects that commonly prescribed antibiotics have on the action of warfarin.
- Potential pharmacological mechanisms are described along with suggestions on their management.
- Further research is needed in the form of a systematic review to clarify areas of controversy.

Antibacterial prescribing and warfarin: a review

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Warfarin is the most commonly prescribed oral anticoagulant and is used in the management of thromboembolic disease. The practitioner is regularly faced with the need to prescribe concurrent antimicrobial therapy, either as prophylactic cover or in the therapeutic management of existing infection. Much has been written about the possible influence of antibiotics on the prothrombin time of patients taking warfarin, particularly in the form of isolated case reports, however evidence, in the form of controlled studies, is not always forthcoming. This review attempts to summarise current knowledge and, with reference to basic science, suggest possible management strategies when faced with a prescribing dilemma.

There are two types of oral anticoagulant, the coumarins and indanediones. By far the most commonly used are the coumarin derivatives, of which warfarin is a member, due to their lower incidence of side effects compared with the indanediones.

Warfarin acts by inhibiting the synthesis of active vitamin K dependent proteins involved in blood coagulation, principally factors II (prothrombin), VII, IX, and X (Fig. 1). These factors are synthesised in the liver in precursor form and are activated by carboxylation of specific glutamic acid residues which require vitamin K in its reduced form as a cofactor. Warfarin acts by inhibiting the reductase that converts the epoxide form of vitamin K to its reduced form by competitive antagonism due to the molecular similarity of warfarin and vitamin K. A reduction in the activity and concentration of all four factors is embraced by the portmanteau term 'hypoprothrombinaemia'.

Due to its mechanism of action the anticoagulant effect of warfarin is delayed until the previously synthesised normal factors are metabolised. On administration, therefore, one can expect the prothrombin time, in the form of the International Normalised Ratio (INR), to reach its therapeutic target approximately 48–72 hours later.

INDICATIONS

Warfarin is used in the treatment of a number of conditions and the target INR varies in each situation. An understanding of a patient's medical history, therefore, can give greater initial insight into their degree of anticoagulation than simple knowledge of the dose. Indeed the individual response to warfarin varies between patients and the final therapeutic dose is determined by repeated INR measurements. The main indication for oral anticoagulant therapy is in the prophylaxis of deep vein thrombosis (DVT).[1] Other indications include pulmonary embolism, mechanical prosthetic heart valves, and atrial fibrillation where a risk of embolisation exists.

MECHANISM OF INTERACTION

Several mechanisms are of relevance when considering the interaction of antibiotics with warfarin; however, controversy exists in some cases as to their relative importance. Commonly cited mechanisms are:

- Disturbance of intestinal flora and subsequent reduction in intrinsic vitamin K production
- Decrease in vitamin K absorption due to antibiotic induced malabsorption
- Increase in sensitivity of hepatic receptors to warfarin
- Displacement of warfarin from serum albumin binding site
- Inhibition or potentiation of warfarin metabolism

BROAD-SPECTRUM PENICILLINS

Although penicillins have not been shown in studies to interact with warfarin,[2] isolated cases have been reported associated with broad-spectrum penicillins. There does not appear to be significant evidence to suggest that narrow-spectrum peni-

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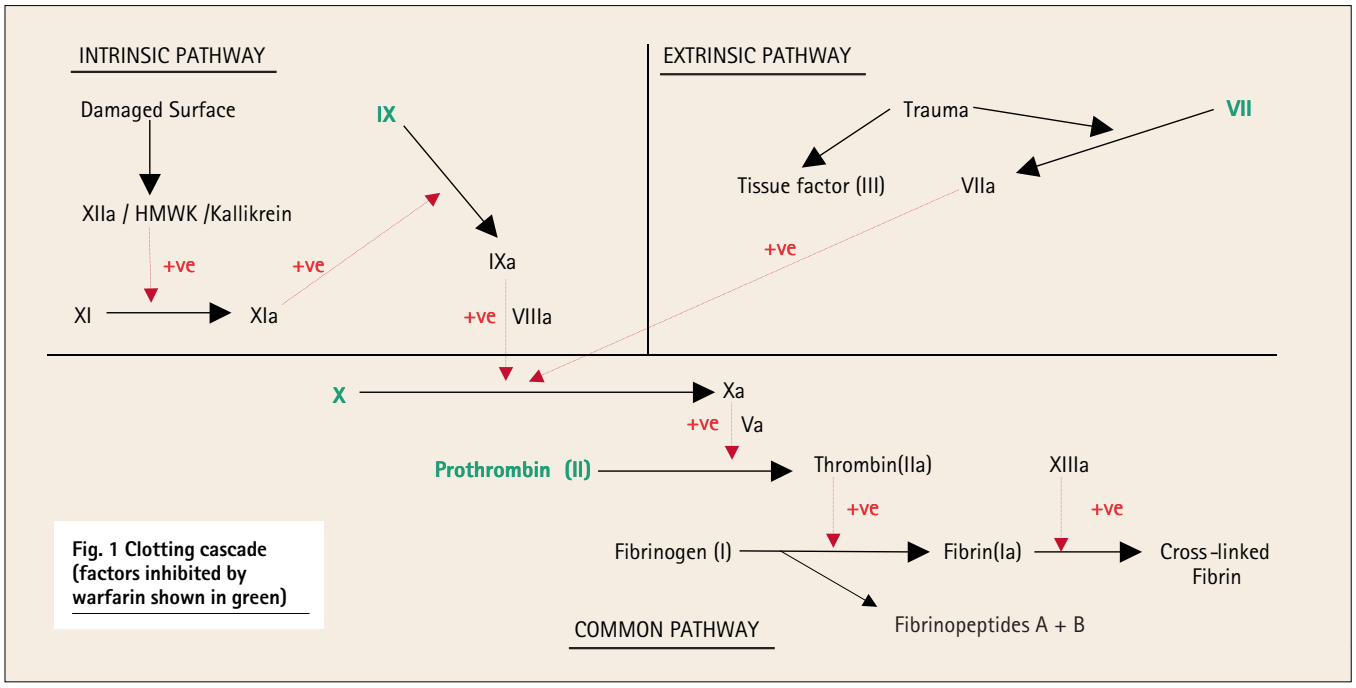

Fig. 1 Clotting cascade (factors inhibited by warfarin shown in green)

cillins commonly used in dentistry interact with warfarin. However, one isolated report did describe hypoprothrombinaemia in one patient on warfarin given 24 million units of benzylpenicillin (penicillin-G) daily, intravenously.[3] Further to this it is a common experience in anticoagulant clinics to find that the INR is altered following a course of oral broad-spectrum antibiotics such as ampicillin.

Clinical evidence

Bearing in mind how frequently penicillins are used in patients taking warfarin documented reports of interactions are relatively rare. Consequently the broad picture suggests that no clinically relevant interaction normally occurs. Despite this one must always consider that atypical effects can occur and exercise caution when prescribing for patients taking warfarin. Buckley suggested the use of orally administered penicillins in patients taking warfarin is safe, provided the patients vitamin K intake is normal.[4] Bandrowsky, describes a case of significant post-extraction haemorrhage in an elderly warfarinised patient which was attributed to amoxycillin.[5] The pre-op INR was 3.51, however, 4 days later he returned with bleeding and the INR was found to be 9.03. Amoxycillin prophylaxis (American Heart Association) had been given followed by a further course of 500 mg tds for 1 week. Wood *et al.* in 1993 reported a fatal increase in INR to 10 in an 85-year-old female patient, previously kept within the therapeutic range, who had received a 7-day course of augmentin (250 mg tds).[6] In the same paper two other cases are described where the post-operative INR increased significantly in patients who received a single prophylactic dose of amoxycillin 3 g. In one of these cases the elevated INR (6.4) was an incidental finding at the patient's anticoagulant clinic and was not associated with post-operative bleeding.

Mechanism

Alteration in the oral flora by broad spectrum antibiotics such as amoxycillin has been suggested to decrease gut floral production and absorption of vitamin K. In the synthesis of certain blood coagulation factors vitamin K is required in its reduced form to act as a cofactor and warfarin, being structurally similar to vitamin K, competes for binding sites in this reduction process. Thus if the available vitamin K decreases then a greater percentage of binding sites will be occupied by warfarin leading to inactive reductants and decreased synthesis of coagulation factors. Most vitamin K is ingested and absorbed from the normal diet[7] and, although it is accepted that continuous intrinsic synthesis in the colon by bacterial activity occurs,[8] there is controversy regarding the importance of this on the coagulation process.[7,9] Other possible mechanisms have been suggested with respect to the penicillins and include changes in antithrombin III activity, blood platelet changes, and alteration in the fibrinogen-fibrin conversion.[10]

Management

It would seem sensible to prescribe single-dose penicillin wherever possible for patients on warfarin, as it may be the case that longer courses would have more of an effect on the gut flora, if indeed this is significant. This is not, of course, foolproof, as the above cases illustrate, and individual clinical judgement is required with particular care in the under or malnourished patient[11] where the role of intrinsically produced vitamin K may be more significant. When considering **antibiotic prophylaxis** for patients taking warfarin it may, therefore, be prudent to consider clindamycin as a first-line. There is, currently, only one case report of clindamycin interacting with warfarin and, in that instance, in addition to the prophylactic dose, it had been used as a 7-day therapeutic dose for local infection.[12] There is no evidence to suggest that single dose clindamycin interacts with warfarin. In the cases described, the increases in INR occurred a few days post-operatively and in one patient was not associated with signs of bleeding. This indicates that initial haemostasis may not be a reliable indicator in predicting problems so the following protocol would be prudent for the **post-operative management** of patients receiving concurrent penicillin and warfarin.

- Consider reviewing patients routinely at 3 days post-op, to check INR, taking appropriate action if it is elevated. Remember the absence of bleeding does not rule out an elevated INR.
- In the undernourished patient or those with malabsorptive disorders consider closer liaison with medical colleagues.
- In multiple extraction cases be aware that problems with eating may compound antibiotic-induced decrease in vitamin K availability.
- If longer courses of penicillin are used then consider routine regular measurement of INR.

It has been shown that low dose (1 mg) oral vitamin K can effectively reduce INR within 24 hours in warfarinised patients who develop asymptomatic increases in INR.[13] Whether there is a case for a prophylactic supplement in selected cases where antibiotics are being used seems to require further assessment.

ERYTHROMYCIN

It is generally accepted that erythromycin has the potential to enhance the anticoagulant effect of warfarin but most patients are unlikely to develop a clinically important reaction.

Clinical evidence

Bartle described the case of a 77-year-old woman on warfarin who developed an increased prothrombin time with haematuria and bruising within a week after being given 2 g of erythromycin stearate.[14] Bachmann carried out a study of 12 normal subjects and showed that the clearance of a single dose of warfarin was reduced by an average of 14% after taking erythromycin 250 mg orally qds for 8 days.[15] Other studies have shown an increase in warfarin activity with erythromycin,[16–23] however, two studies showed only a small increase.[24,25]

Mechanism

Bartle suggested that some of the most clinically significant drug interactions are those that involve an alteration in the metabolism of warfarin. Erythromycin is thought to be involved in this process by stimulating liver enzymes to produce metabolites that bind to cytochrome P450, forming inactive complexes and, thereby, reducing the metabolism of warfarin which enhances its effect.

Management

Concurrent use should be avoided if possible. However, it is worth noting that the effect is unpredictable and by no means occurs in all individuals. Erythromycin is an important antibiotic in the management of dental infections when a patient is allergic to penicillin and its use is justified in patients taking warfarin, however, monitoring of the INR is a sensible precaution. It has been reported that in most cases the effect may not be significant, however, the potential for serious effects in some individuals justifies caution.[26] The elderly would be a group where particular care is indicated as their drug clearance rate may be reduced.

METRONIDAZOLE

The anticoagulant effect of warfarin is markedly increased by metronidazole.

Clinical evidence

Kazmier[27] and Dean[28] reported in separate cases significant bleeding in patients taking metronidazole and warfarin. These clinical findings reinforce the study by O'Reilly[29] who found that a daily dose of 750 mg of metronidazole for 1 week increased the half-life of warfarin by approximately one third in 8 normal subjects.

Mechanism

Warfarin exists as a mixture of two stereoisomers S(-) and R(+) with the S(-) racemate being more potent. It has been suggested that metronidazole inhibits the metabolism (ring oxidation) of the S(-) isomer but not the R(+) so the more potent form is retained. As with erythromycin the inhibition of warfarin metabolism, albeit by a different mechanism, results in a clinically significant drug interaction.

Management

Concurrent use should be avoided. If this is not possible then the warfarin dose should be reduced with close monitoring of the INR and current research suggests the warfarin reduction should be in the order of one third to one half.[30]

TETRACYCLINES

Reports have suggested that tetracycline's can enhance the effect of warfarin although this is by no means the normal outcome.

Clinical evidence

Westfall reported a woman who bled (menorrhagia) while taking warfarin and doxycycline (200 mg daily for 8 days).[31] O'Donnell reported the formation of a right temporal lobe haematoma in a patient taking warfarin one week after starting a course of tetracycline and nystatin. Danos reported a marked increase in INR (2 to 7.66) in a patient taking warfarin and tetracycline (250 mg qds) with changes in INR over the following few months which broadly paralleled the decrease in tetracycline.[32]

Mechanism

The mechanism is not fully understood, however, it has been reported that tetracycline's alone can reduce prothrombin activity.[33] It seems reasonable to assume that occasionally the effect may prove additive or maybe even synergistic with concurrent use.

Management

Concurrent use need not necessarily be avoided as it is an apparently uncommon interaction. However, due to the occasional patient showing increased anticoagulant effects which may be severe, close monitoring of the INR, is indicated.

CLINDAMYCIN

Clindamycin has been reported, in one isolated case report, to enhance the effect of warfarin. The risk of an interaction appears to exist when given therapeutically as an extended course, as opposed to when given as a single dose.

Clinical evidence

Aldous *et al.* described the case of a

Table 1 A summary of the possible effects of antimicrobial therapy in patients taking warfarin

Drug	Interaction	Effect	Management
Broad-spectrum Penicillin's	Possible	INR increased	Monitor INR
Narrow-spectrum penicillins	None documented for oral route Interaction IV with Penicillin-G	–	Appears safe with the possible exception of penicillin-G given IV
Erythromycin	Documented	INR increased	Avoid if possible or monitor INR
Metronidazole	Well documented	INR increased (can be marked)	Avoid
Tetracyclines	Possible	INR increased	Monitor INR
Clindamycin	Rare and not related to single dose.	INR increased	Monitor INR if more than single dose used
Cephalosporins	Possible	INR increased	Avoid or monitor
Aminoglycosides	None parenterally		Appears safe by parenteral route
Glycopeptide antibiotics	Changes documented	Variable (see text)	Caution indicated, especially with teicoplanin
Probenecid	Sparse evidence if any	Possible decrease in INR if at all	Appears safe. Possibly monitor

47-year-old woman on warfarin whose INR rose to 13 after being given clindamycin 300 mg orally for 7 days in addition to a preoperative 600 mg IV prophylactic dose for a dental clearance under general anaesthetic.

Mechanism
The mechanism is unclear, however, it was suggested in the above case that extended administration of clindamycin resulted in decreased production of vitamin K from gut flora, enhancing the effect of warfarin.

Management
A pre-operative single dose for the prevention of endocarditis is not thought to pose a risk. When clindamycin is used therapeutically, or indeed combined with a prophylactic dose, the likelihood of the INR increasing appears to be enhanced. Thus, in this situation, caution is advised and the INR should be closely monitored.

CEPHALOSPORINS
Most cephalosporins do not normally interact with the oral anticoagulants.

Clinical evidence
Angaran reported in 1984 that patients given cephamandole prophylactically before prosthetic valve surgery showed a greater anticoagulant response than those given vancomycin.[34]

Mechanism
Cephalosporins with an N-methylthiotetrazole side chain can act like the oral anticoagulants as vitamin K antagonists to reduce the production of the blood clottiong factors. They can therefore cause bleeding on their own and worsen the risk of bleeding by simple addition if given with conventional anticoagulants. In addition some of them may also inhibit platelet function.[35]

Management
Care should be exercised when considering concurrent use with warfarin most notably involving those cephalosporins with the N-methylthiotetrazole side chain. Patients most at risk may be those with restricted vitamin K intake and those with renal failure.

AMINOGLYCOSIDES
There is no evidence to suggest that parenterally administered aminoglycosides eg gentamycin (used in endocarditis prophylaxis), interact adversely with warfarin.[36] These antibiotics are not absorbed from the normal gut and are generally given parenterally.

Clinical evidence
Neomycin is given orally to sterilise the gut prior to surgery and there is some evidence that the prothrombin time is increased in patients taking warfarin.[37] A thorough literature search did not reveal any evidence of warfarin interactions with parenterally administered aminoglycoside's.

Mechanism
The mechanism related to the neomycin interaction is probably related to a generalised antibiotic-induced malabsorption syndrome.[38]

Management
There is nothing to suggest that an adverse interaction occurs between warfarin and parenterally administered aminoglycosides, which would be the route used in dentistry for endocarditis prophylaxis.

GLYCOPEPTIDE ANTIBIOTICS
Vancomycin possibly causes a small increase in the effects of warfarin. Teicoplanin possibly causes a reduction in the effects of warfarin which may be marked.

Clinical evidence
An isolated case report attributed a marked reduction in the INR of an elderly woman to the concurrent use of teicoplanin and warfarin.[39]

Angaran showed an increase in warfarin activity, attributed to vancomycin, post-operatively in prosthetic cardiac valve patients although in this study the effect was not as great as that with cephalosporins.

Mechanism
Unknown.

Management
Monitoring of patients INR during concurrent use of vancomycin and warfarin is advised. If possible the concurrent use of teicoplanin and warfarin should be avoided, however, if this is not possible careful monitoring for a possible decrease in INR is indicated.

PROBENECID
Probenecid is used to block renal tubular excretion of penicillin to produce higher and more prolonged plasma levels and is not in itself antimicrobial. It is used together with amoxycillin in endocarditis prophylaxis for patients undergoing surgery under general anaesthesia. There is no documentary evidence to suggest that it interacts with warfarin, however, one report did suggest that it decreases the effect of the coumarin anticoagulant phenprocoumon (not listed in BNF).[40]

CONCLUSION AND SUMMARY
Almost all antibiotics have the theoretical potential to interact with warfarin and Table 1 summarises the possible effect of those commonly prescribed in dentistry. This article concentrated on those antibiotics of particular relevance to dentistry and it must be remembered that others, such as co-trimoxazole, can also have a marked effect on the INR in patients taking warfarin. It is apparent that conflict often exists between scientific studies and case reports which illustrates the fact that the response to warfarin therapy can be unpredictable and guidelines on management should take into account the rare and sometimes serious sequelae. Consequently despite the volume of literature covered in the production of this review paper uncertainties clearly still exist in some areas. There is the need, therefore, for further research in the form of a systematic review to clarify current understanding. This would be of enormous help to the many clinicians who prescribe in this important patient group.

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