

Warfarin, antiplatelet drugs and their interactions

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SYNOPSIS

Patients who are being treated with warfarin may sometimes be prescribed or buy antiplatelet drugs, such as aspirin. As warfarin and antiplatelet drugs increase the risk of bleeding, their combination can put patients at risk of a major haemorrhage. This risk may be further increased by the patient's age and other illnesses. A thorough history is therefore important in assessing the risk of haemorrhage. Patients need to be informed of the risk and should be encouraged to have their international normalised ratio checked regularly.

Index words: anticoagulants, aspirin, non-steroidal anti-inflammatory drugs, thienopyridines, dipyridamole, IIb/IIIa antagonists.

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Introduction

Decisions about anticoagulation require an assessment of the benefits of therapy versus the hazards, namely bleeding, for each patient. Clinical trials provide strong evidence for the benefit of anticoagulants in treating thromboembolic disease. Translating this evidence from selected patient groups to the general community requires closer scrutiny of the risks of bleeding. These considerations are even more important given the widespread community usage of medications, such as antiplatelet drugs, which interact with warfarin. We need to consider the:

- mechanism of antithrombotic action (and haemorrhage) of these drugs
- potential risks of combining warfarin with antiplatelet drugs
- assessment of a patient's haemorrhagic risk
- strategies to minimise the risk of haemorrhage.

Platelets and the mechanism of thrombosis

The earliest events in thrombus formation include platelet adhesion, platelet activation, subsequent platelet aggregation and granule release. These events are inseparable from the initiation of the coagulation cascade principally by tissue factor, thrombin generation and cross-linked fibrin formation. The interactions between platelet and coagulation events during thrombus formation are numerous. Activated platelets provide the physical surface for efficient thrombin formation.

In turn, the thrombin generated by activation of the coagulation cascade is a potent platelet agonist. The importance of platelets in thrombus formation is evident by the therapeutic efficacy of antiplatelet drugs in thromboembolic disease, especially arterial vascular disease.

The biochemistry of platelet adhesion, activation and aggregation is complex. Many of these events are co-ordinated by surface receptors. Platelets adhere to immobilised Von Willebrand Factor and also collagen at functional glycoprotein Ib/IX/V and collagen receptors. Adhesion results in initial platelet activation by internal signalling pathways often involving reduced intra-platelet cyclic adenosine monophosphate. Important platelet agonists *in vivo*, including thrombin, adenosine diphosphate, thromboxane A₂ and collagen, all act via specific platelet surface receptors. The final common pathway of platelet aggregation is activation of the glycoprotein IIb/IIIa receptor. An aggregate consists of platelets linked together by fibrinogen and Von Willebrand Factor bound to multiple glycoprotein IIb/IIIa receptors. Despite our limited understanding of these pathways a broad range of antiplatelet drugs has been developed (Table 1).

Antiplatelet drugs

The activation, aggregation and adhesion of platelets may all be altered by a variety of drugs. There needs to be a balance between their beneficial effects and the risk of haemorrhage.

Haemorrhagic effects of antiplatelet drugs

By a variety of mechanisms antiplatelet drugs are associated with an increased risk of haemorrhage.

Aspirin

The beneficial effect of aspirin therapy in ischaemic stroke may be associated with an excess of two symptomatic intracranial haemorrhages for every 1000 patients treated. Aspirin's antiplatelet action is probably not dose dependent beyond 75–100 mg daily so there is no additional antiplatelet effect at higher doses. However, aspirin's effect on the gastric mucosa is dose dependent. The incidence of major gastrointestinal haemorrhage is 1.5% at 300 mg/day and 2.3% at 1200 mg/day. As aspirin irreversibly blocks platelet cyclo-oxygenase its effect lasts for 5–7 days after the drug is stopped. The antithrombotic effect can be reversed by platelet transfusion in an emergency.^{1,2}

Table 1

Actions of antiplatelet medications

| Antiplatelet drug | Mechanism of action | Antiplatelet effects | Additional haemorrhagic effects |
|---|--|--|--|
| Aspirin | Irreversible blockade of platelet cyclo-oxygenase preventing the formation of thromboxane A ₂ | Partial inhibition of platelet activation. Does not prevent platelet adhesion. | Non-specific cyclo-oxygenase blockade leads to gastric mucosal damage and increases the risk of gastrointestinal haemorrhage |
| Non-steroidal anti-inflammatory drugs | Reversible blockade of platelet cyclo-oxygenase affecting platelet thromboxane A ₂ activity | Partial inhibition of platelet activation. Does not prevent platelet adhesion. | Gastric mucosal damage and increased risk of gastrointestinal haemorrhage |
| COX-2 inhibitors | Specific inhibitors of cyclo-oxygenase-2 | No direct antiplatelet effects | Cause less gastrointestinal tract mucosal damage than conventional NSAIDs. May prolong the INR. |
| Dipyridamole | Inhibition of adenosine uptake by the platelets. Weak inhibition of platelet cAMP* phosphodiesterase. | Weak inhibition of platelet aggregation | Often prescribed in combination with aspirin |
| Thienopyridines (ticlopidine and clopidogrel) | Block adenosine diphosphate mediated activation of the glycoprotein IIb/IIIa complex | Inhibition of platelet aggregation | Rarely thrombocytopenia and thrombotic thrombocytopenic purpura have been reported |
| IIb/IIIa receptor inhibitors (abciximab, eptifiban and tirofiban) | Direct antagonism of the platelet receptor for fibrinogen and Von Willebrand Factor. Several classes of drug available which include an antibody, synthetic peptide or synthetic non-peptide forms which require intravenous delivery. | Potent inhibition of platelet adhesion, activation and aggregation | 0.3–1.0% incidence of thrombocytopenia reported. Pseudothrombocytopenia can occur with abciximab but is not an indication for cessation. |

* cAMP cyclic adenosine monophosphate

Non-steroidal anti-inflammatory drugs (NSAIDs)

This heterogeneous group of drugs is associated with a significant prevalence (10–20%) of dyspepsia. The incidence of NSAID-induced gastrointestinal haemorrhage is variably quoted as 1–4% and depends on the individual drug and probably its dose. For every 1000 patients with rheumatoid arthritis who take NSAIDs for one year, 13 will suffer a serious gastrointestinal complication including bleeding. NSAID-induced upper gastrointestinal tract bleeding has a significant mortality rate of 5–10%. These drugs are widely available so large numbers of patients are exposed. The lifetime risk of major gastrointestinal haemorrhage is substantial and increases with the concomitant use of warfarin.

In contrast to aspirin most NSAIDs have short-lived antiplatelet effects. However, a platelet transfusion may still be required in an emergency such as a major haemorrhage.³

Trials have shown that cyclo-oxygenase-2 (COX-2) inhibitors do not directly affect platelet function.⁴ Recently meloxicam, an NSAID with preferential inhibition of COX-2, has also been released. Major antiplatelet effects have not been demonstrated with its use.⁵

Dipyridamole

Significant haemorrhage is rarely attributable to dipyridamole, a relatively weak and short-lived inhibitor of platelet function. Even in combination with aspirin there is no evidence of dipyridamole increasing the risk of bleeding. The dose-related adverse effects of dyspepsia, gastro-oesophageal reflux and headache are common reasons for stopping therapy.¹

Thienopyridines

In recent studies, treatment with a thienopyridine (ticlopidine, clopidogrel) was more effective than aspirin for the prevention of vascular disease without an increase in bleeding complications. In the CAPRIE study, there was a 1.38% incidence of major haemorrhage in the clopidogrel group which did not statistically differ from that of aspirin (1.55%).⁶ However in the CURE study⁷, the combination of aspirin and clopidogrel increased the rate of major bleeding (3.7%) compared to aspirin alone (2.7%). These bleeds were mostly gastrointestinal haemorrhages requiring blood transfusion or bleeding at sites of arterial puncture. There was no significant increase in fatal or intracerebral haemorrhage.⁷

The antiplatelet effect of thienopyridines is irreversible and persists for the 7–10 day lifespan of the circulating platelet. There is no antidote, and reversibility with platelet transfusion has not been well studied.^{8,9}

Platelet glycoprotein IIb/IIIa receptor antagonists

In early studies, patients receiving abciximab had higher bleeding rates than placebo. In later studies, where the dose of concurrent heparin was reduced, bleeding rates were not increased. However, abciximab and tirofiban have been reported to cause pulmonary haemorrhage. Eptifibatid in combination with heparin and aspirin is associated with increased bleeding and the need for transfusion. Platelet transfusions are required if bleeding occurs particularly if the patient has drug-induced thrombocytopenia, which is sometimes profound.^{9,10}

These intravenous drugs are most commonly used as an adjunct to percutaneous invasive coronary interventions as a means of reducing ischaemic complications. They are often given as an intravenous bolus (with or without a short-term infusion) in combination with various regimens of unfractionated heparin and aspirin. There is some evidence of benefit in the primary medical therapy of acute coronary syndromes.

Oral glycoprotein IIb/IIIa receptor antagonists have been associated with a significant increase in mortality and higher rates of bleeding compared to placebo or standard antiplatelet treatment.¹⁰

Warfarin

Warfarin inhibits the vitamin K-dependent synthesis of clotting factors II, VII, IX and X in the liver. The antithrombotic effect, and mechanism of haemorrhage, relates to low levels of these coagulation factors and a reduction in their activity in thrombus formation.

The effect of warfarin is influenced by many factors. These include the dose, patient compliance, diet and vitamin K status, various lifestyle factors such as alcohol intake, concomitant medications which affect the metabolism of warfarin, and comorbid illness especially liver and cardiac disease. The effect of warfarin on the coagulation system is assessed by a simple *in vitro* clotting assay, the international normalised ratio (INR). The dose of warfarin is adjusted according to the target INRs set for particular indications.

In practice, warfarin is a difficult drug to manage, because of its narrow therapeutic index and the need to individualise dosing. Major haemorrhage is unfortunately common. It occurs in 1–5% of patients per year and has a case fatality rate of 25–30%. Antiplatelet drugs which inhibit platelet function impose additional risks for haemorrhage by affecting primary haemostasis and further inhibition of thrombus formation. Some antiplatelet drugs may also alter warfarin metabolism and lead to an unstable INR.^{11,12,1}

Drug interactions: warfarin and antiplatelet drugs

While generally the combination is avoided, antiplatelet drugs and warfarin are sometimes deliberately used in patients with embolic phenomena from prosthetic and diseased heart valves or those with refractory arterial ischaemia.

The combination of antiplatelet drugs and oral anticoagulants increases the risk of both major and minor bleeding in several ways:

- additive effects on platelet function
- interference with warfarin metabolism with a subsequent increase in the INR
- unique adverse effect profiles which increase the risk of bleeding (for example gastrointestinal tract erosions with aspirin and NSAIDs).

Warfarin and aspirin

In clinical studies of patients with prosthetic valves, the frequency of bleeding when oral anticoagulation is combined

with antiplatelet therapy varies depending on the intensity of treatment and the type of antiplatelet therapy. In patients who receive high-intensity warfarin (target INR of 3.0–4.5), the addition of aspirin 100 mg daily results in higher rates of major (12.9% versus 10.3%) and total (38.7% versus 26.1%) bleeding.¹

There is a general impression that bleeding rates are also increased with the combination of aspirin and warfarin even when the target INR is 2–3.⁹

Warfarin and dipyridamole

The addition of dipyridamole to warfarin therapy in patients with prosthetic valves does not appear to increase the risk of haemorrhage. In patients who used a combination of aspirin, dipyridamole and warfarin, the risk of bleeding depended significantly on the target INR. Patients anticoagulated to an INR of 3.0–4.5 experienced a 21% incidence of bleeding compared with 4% in the group anticoagulated to an INR of 2.0–2.9. Most of the bleeding seen with this combination was gastrointestinal in origin.¹

Warfarin and NSAIDs

NSAID-associated gastropathy increases the risk of haemorrhage in patients taking warfarin, so combined use should be generally discouraged. Some NSAIDs also alter warfarin metabolism. COX-2 inhibitors are an option should NSAID therapy be necessary. They have a lower incidence of gastrointestinal adverse effects, but all COX-2 inhibitors may alter warfarin metabolism resulting in instability of the INR. Celecoxib and rofecoxib have both now been reported as interacting with warfarin.^{13,14}

Warfarin and thienopyridines

Caution should be exercised if this particular combination is to be used because there are no safety data to support it. Oral anticoagulation has been an exclusion criterion in the trials involving thienopyridines.

Warfarin and glycoprotein IIb/IIIa receptor antagonists

There are no safety data from clinical trials as patients on warfarin have been excluded from studies of glycoprotein IIb/IIIa receptor antagonists. Patients on oral anticoagulants should have their therapy ceased or fully reversed before having coronary interventions with glycoprotein IIb/IIIa receptor antagonists. These intravenous therapies are often given in coronary care units, and their direct effect and short half-lives mean that the risk of haemorrhage occurs early, within a few hours of therapy. This class of drug therefore tends not to be as important when considering anticoagulant and antiplatelet interactions in the community.¹⁰

Suggested strategies to minimise the risk of bleeding

Recognise the risk

To minimise the risks of taking anticoagulant and antiplatelet drugs it is crucial to recognise the patient's risk of bleeding. Various scoring systems to stratify the risk of bleeding in

patients on warfarin have been proposed.¹⁵ Risk factors for haemorrhage include:

- older age group
- high target INR
- cerebrovascular disease
- history of gastrointestinal bleeding or ulceration
- liver disease
- renal disease
- other comorbid disease such as heart failure, anaemia, hypertension, malignant disease and diabetes
- personal or family history of bleeding disorders.

In one study, patients classified as high risk had a 48% risk for major bleeding during 12 months of warfarin therapy. The relevance of these scoring systems to everyday practice requires prospective validation. These scoring systems highlight the importance of a simple history in identifying patients with an increased risk of bleeding, and in practice common sense should be applied.¹⁵

Optimise warfarin therapy

A key element for reducing bleeding in patients taking warfarin, especially if they are also taking an antiplatelet drug, is to optimise therapy.¹⁶

Appropriate target INR

Recent Australian Consensus Guidelines for warfarin therapy summarise the appropriate target INR and INR ranges for different clinical scenarios.¹¹

Appropriate duration of therapy

When patients are prescribed warfarin the duration of therapy should be determined in advance. Periodic re-evaluation of the patient's harm:benefit ratio for warfarin should also occur. In venous thromboembolic disease in particular, there are conflicting recommendations regarding the optimum duration of warfarin treatment. In general, 4–6 months of warfarin is adequate after pulmonary embolism. For a deep vein thrombosis due to a transient event like surgery or immobilisation, 8–12 weeks of therapy is probably sufficient. In contrast, unprovoked deep vein thrombosis, recurrent venous thromboembolism or venous thromboembolism occurring in association with an underlying hypercoagulable state all warrant a longer duration of warfarin treatment. The optimum duration needs to be tailored to the individual and specialist advice may be warranted.¹¹

Minimise patient risk factors for bleeding

Patient compliance with drug therapy and monitoring should be encouraged. Additional lifestyle factors should also be addressed, including the consistency of dietary intake of vitamin K, minimising alcohol use, avoidance of binge drinking, and reducing activities with considerable risk of injury.¹⁶

Managing the INR

Conscientious management of the INR is the key to minimising bleeding. In order to ensure the INR is as stable as possible, a blood test every 1–2 weeks may be required.

Once the target INR is set, a narrow range of tolerance is preferred. Dose adjustments need to be made on every occasion the INR is outside this range. The frequency of testing needs to be increased when dose adjustments are made. These regular checks also provide the practitioner with an opportunity to seek other relevant information regarding the patient's general health, any changes to their medications (including complementary medicines), and the presence of any symptoms of bleeding.

Antiplatelet drugs and warfarin

If antiplatelet drugs are to be concurrently used, it is prudent to keep the patient's INR at the lower end of the desired target range. These patients, by virtue of their higher risk of haemorrhage, also require frequent testing every 1–2 weeks, to enhance the control of the INR.

Using the lowest aspirin dosage possible may reduce the additive risks of haemorrhage without necessarily increasing the thromboembolic risks. Concomitant use of NSAIDs should be discouraged.

Anticipate the possibility of bleeding

Instability of the INR can be predicted. A change in a patient's health or medications should prompt their doctor to monitor the INR more frequently. Patients should be educated regarding warfarin therapy and INR management, and be vigilant for symptoms and signs of blood loss. They should be encouraged to ask for increased monitoring of their INR if their health or medications change.

Conclusion

There are risks in adding antiplatelet medications to warfarin therapy. Patient-specific risks of haemorrhage are often harder to assess than the perceived benefit of the proposed therapy. Patient selection is important to minimise the risk of bleeding. Rigorous management of the INR is required for patients taking warfarin with antiplatelet drugs.

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FURTHER READING

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 99)

1. The INR is not affected by COX-2 inhibitors.
2. Non-steroidal anti-inflammatory drugs have a more prolonged antiplatelet effect than aspirin.

Managing constipation in children

Constipation, defined as difficulty, delay or pain on defecation, is common in children and is often difficult to manage. Here, we review the assessment and treatment of affected children and the support that they, and their families, may need.

Background

Breastfed babies have a mean of about three bowel movements daily, while formula-fed babies have about two. With age, the frequency falls to about one movement daily in children over three years.¹ In one study, 96% of children aged 1–4 years had somewhere between one bowel movement every other day to three movements daily.² So as long as the child is pain free, parents can usually be reassured that some infrequency in defecation is likely to be normal.

Various factors may cause or increase the likelihood of constipation. Delay in passing meconium more than 48 hours after birth, or constipation in early infancy, suggests the possibility of Hirschsprung's disease, especially if there is also excessive vomiting, abdominal distension or failure to gain weight. Constipation may result from inadequate food or fluid intake, while children who drink a lot of milk may have hard stools that are difficult to pass. Chronic constipation might be associated with an intolerance to cow's milk³, although this is more commonly associated with diarrhoea. Some medicines can induce constipation (e.g. opiate analgesics, anticholinergic drugs). Children may withhold defecation and this may make them liable to constipation. Risk factors for withholding include: 'fear' of previous treatments for constipation or coercive potty training, sometimes coinciding with the developmental stage between two and three years of age when children typically refuse to obey their parents; lack of privacy (especially in school lavatories); domestic stress; sexual abuse; or pain on defecation due to anal fissures or a perianal skin infection.

When the rectum is chronically obstructed with faeces (or incompletely emptied), it may enlarge to form a megarectum. Children with a megarectum may not sense the faecal matter in the rectum, and have diminished urgency to defecate^{4,5}, which may lead to faecal soiling. It is important to distinguish

this involuntary soiling from encopresis, in which the child voluntarily passes normal stools in unacceptable places.

Assessment

It is important to take a detailed history of the illness from the parent and, where possible, the child, including noting of relevant dietary, family and social factors. Clinical examination should appraise the child's general health and check for poor growth and neurological problems. Palpation of the abdomen may reveal distension or faecal loading in the colon. Rectal examination can be distressing for the child and is usually unnecessary. In most instances, inspection of the perineum is sufficient to check for the presence of anal fissures, infection, skin disease, anal ectopia or anal abuse.

There is no need for a routine abdominal X-ray to diagnose constipation⁶, but it may help confirm overflow incontinence in a child with faecal impaction who initially presents with diarrhoea. A potentially more helpful hospital investigation involves the child swallowing radio-opaque gut transit markers over three days and then taking an abdominal X-ray on day five.⁷ This test may confirm: fast intestinal transit in children with episodes of faecal incontinence; rectal retention in children with megarectum; or pancolonial delay (colonic inertia) in older children.

Treatment

The general principles in managing childhood constipation are to: clear any faecal impaction; establish a regular and effective pattern of defecation; and to prevent recurrence.^{1,8} Where possible, underlying causes should be resolved, for example, stopping constipating medicines, treating painful anal conditions and addressing possible psychosocial causes. There is a lack of evidence from randomised controlled trials to guide management choices.

Dietary intervention

Constipation can often be relieved by increasing dietary fluid and fibre. However, children may be reluctant to eat high-fibre foods such as fruit, vegetables and cereals, especially if the rest of the family eat a different diet. If the child's appetite is poor,