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Perioperative management of antiplatelet drugs

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Summary

Antiplatelet drugs, such as aspirin and clopidogrel, are widely used in primary and secondary care and are very commonly encountered in the perioperative setting. In this article we explore the specific uses of antiplatelet drugs, their mechanisms of action and possible consequences of their discontinuation. An algorithm is included to guide decisions on whether to stop drugs in the perioperative period.

INTRODUCTION

Thirty-day mortality of postoperative surgical patients is around 0.7-1.5% in the developed world. In the UK, with approximately 4 million operations per year, this equates to 25,000 to 30,000 postoperative deaths per year, or 70-80 deaths per day. Cardiovascular causes of death are by far the most common at 59%, with respiratory causes accounting for 35% of deaths.[1]

PATHOGENESIS OF ATHEROTHROMBOSIS

Cardiovascular and cerebrovascular events are closely linked to instability of atheromatous plaques within blood vessels and to the thrombogenicity (the ability to form thrombus) of blood. If an unstable plaque ruptures to expose a thrombogenic surface to the passing blood, a platelet clot forms over it leading to an acute thrombotic event. Approximately 66% of sudden cardiac events and 50% of postoperative myocardial infarctions are due to disruption and thrombosis of an unstable plaque.

ANTIPLATELET DRUGS

Antiplatelet drugs are prescribed for cardiovascular events (acute coronary syndromes or myocardial infarction) and cerebrovascular events (transient ischaemic attacks or stroke). These may be for:

- **Primary prevention** in patients with risk factors but no history of an event, or
- **Secondary prevention** for those who have had an event, e.g. a transient ischaemic attack.

In the arterial side of the circulation, clot formation is more dependent on platelet aggregation, in contrast to the venous side where clotting factors and fibrin deposition play a more important role. Aspirin and clopidogrel specifically inhibit platelet function and are the antiplatelet drugs most commonly encountered by anaesthetists in the perioperative period.

Aspirin

Aspirin irreversibly inhibits the enzyme cycloxygenase-1 (COX-1), leading to inhibition of thromboxane-A_2 production. This results in reduced platelet activation and vasodilation. It is an irreversible effect, with the function of each platelet inhibited for its lifespan. Platelets are replaced at the rate of about 10% per day

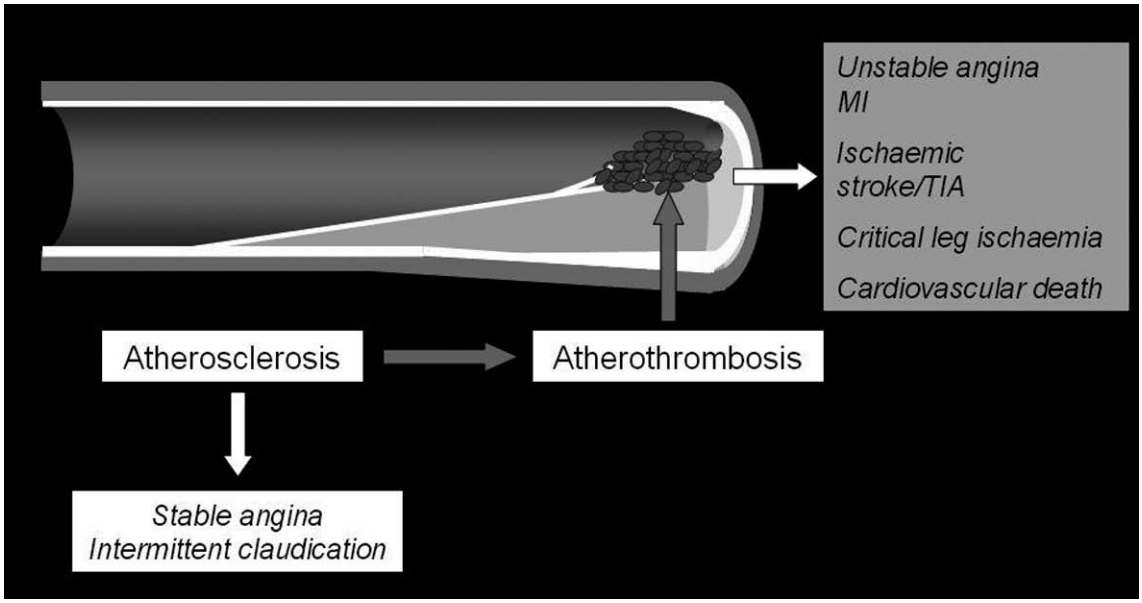

Figure 1. *A summary of atherothrombosis - a generalised and progressive process: MI - myocardial infarction; TIA - transient ischaemic attack*

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and so, after stopping aspirin, it takes about ten days to fully recover platelet function by replacing all affected platelets.

Clopidogrel

Clopidogrel is a prodrug, metabolised by the cytochrome p450 enzyme system to an active metabolite with a half-life of about four hours. It is a non-competitive, irreversible antagonist of the platelet adenosine diphosphate (ADP) receptor (*P2Y12*), inhibiting ADP induced platelet aggregation for 7 days.

Dipyridamole

Dipyridamole inhibits platelet aggregation and causes vasodilation by inhibiting the breakdown of cyclic adenosine monophosphate (cAMP) by phosphodiesterase within platelets. Elevated cAMP levels result in a reduced response to several stimuli, including platelet activating factor and ADP, thus inhibiting aggregation. Dipyridamole also inhibits the uptake of adenosine into platelets, erythrocytes and endothelial cells. The resultant raised surrounding adenosine concentration acts at the platelet A2 receptor also leading to a rise in intracellular cAMP, this time by promoting the action of adenylate cyclase.

INDICATIONS FOR ANTIPLATELET DRUGS

- **Aspirin** is used alone in 'low risk' primary prevention.
- **Clopidogrel** is used where aspirin is not tolerated or with aspirin in high risk cases, especially after coronary stent insertion.
- For secondary prevention of transient ischaemic attacks, **aspirin plus dipyridamole** (usually the modified release form) is recommended for two years, followed by aspirin alone.

Aspirin reduces the incidence of death, myocardial infarction (by 30%) and stroke (by 25%) in a wide range of patients at high risk of occlusive vascular disease.[2] Long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction, or vascular death,[3] although it only causes approximately 50% inhibition of maximum platelet aggregation in response to ADP. The combination of both drugs has a greater anti-platelet effect than either alone because they work by different mechanisms.

Coronary stents

A subgroup of patients taking these drugs for secondary prevention of coronary events have undergone percutaneous coronary intervention (PCI), which consists of balloon dilatation and/or stenting of one or more coronary arteries. These patients are at particularly high risk of a further cardiac event if their antiplatelet therapy is stopped.

Coronary stents are placed across a narrowing in a coronary artery, stenting it open and preventing further occlusion. There are two main types of stent - bare metal (BMS) or drug eluting (DES).

Bare metal stents provide a thrombogenic surface when initially inserted, but as endothelium grows over them (over approximately 3 months) this risk is reduced. However, as the endothelium thickens the risk of re-occlusion gradually increases. Re-stenosis necessitates re-intervention in 15–20% of patients treated with a BMS within one year.

Drug eluting stents are impregnated with antimitotic chemotherapeutic drugs, such as rapamycin and paclitaxel, that inhibit endothelial growth. The stent remains uncovered and the requirement for re-intervention is reduced to about 5% per year. The thrombogenic metal of the stent is however in contact with blood for longer.

For both types of stent it is recommended that aspirin be continued for life. Dual therapy with aspirin and clopidogrel is 'mandatory' until re-endothelialisation, i.e. 6 weeks for a bare metal stent and 12 months for a drug eluting stent. For PCI without stenting both drugs should given for 2 to 4 weeks.

WHEN TO STOP ANTIPLATELET DRUGS

A major side-effect of these drugs is bleeding, which is relevant to both the surgeon and anaesthetist over the perioperative period. When considering whether to continue or stop antiplatelet therapy, first it is important to determine whether the agent is given for primary or secondary prevention, and second whether the patient is at high or low risk of occlusive disease. A balance must be considered between the risks of morbidity and mortality due to bleeding or clotting.

Traditionally there is an overriding concern about the risk of bleeding and so a tendency towards stopping antiplatelet drugs in the peroperative period. If antiplatelet drugs are continued, the average increase in blood loss when continuing aspirin alone is 2.5–20%. Blood loss increases by 30-50% with aspirin and clopidogrel used in combination.[4] The transfusion rate increases by about 30% and so it appears that increased bleeding is a justifiable concern. The risk of an ischaemic event is similar to the risk observed in patients with stable coronary artery disease, i.e. 2-6% for non-fatal myocardial infarction and 1-5% for cardiac mortality.[4]

However, withdrawal of antiplatelet drugs results in a rebound hypercoagulable state, which aggravates the hypercoagulability caused by surgery, greatly increasing the likelihood of a cardiovascular event. Withdrawing aspirin in a patient with coronary artery disease leads to a 2 to 4 fold increase in the rate of death or myocardial infarction. Stopping antiplatelet drugs in patients with coronary stents is the major independent predictor of stent occlusion. The non-fatal myocardial infarction rate increases to 35% and average mortality increases to 20-40%.[4]

Although it is true that increased bleeding is a risk in patients where antiplatelet therapies are continued, it is clear that some patients are exposed to a far greater risk by stopping these drugs. In addition the bleeding risk is partially negated by careful surgery, blood transfusion and platelet therapy if required. The balance of risks must be considered before deciding which drugs to continue for each patient, with a specific comorbidity, undergoing a specific surgical procedure.

GUIDANCE ON STOPPING OR CONTINUING ANTIPLATELET DRUGS

Several groups have suggested guidelines to aid this decision making process. The decision rests on patient factors such as:

- Why are they taking the drug?

- Is it for primary or secondary prevention?
- Are they particularly high risk, i.e. do they have a coronary stent in situ?
- If so which type (drug eluting or bare metal) and how long have they been in situ?

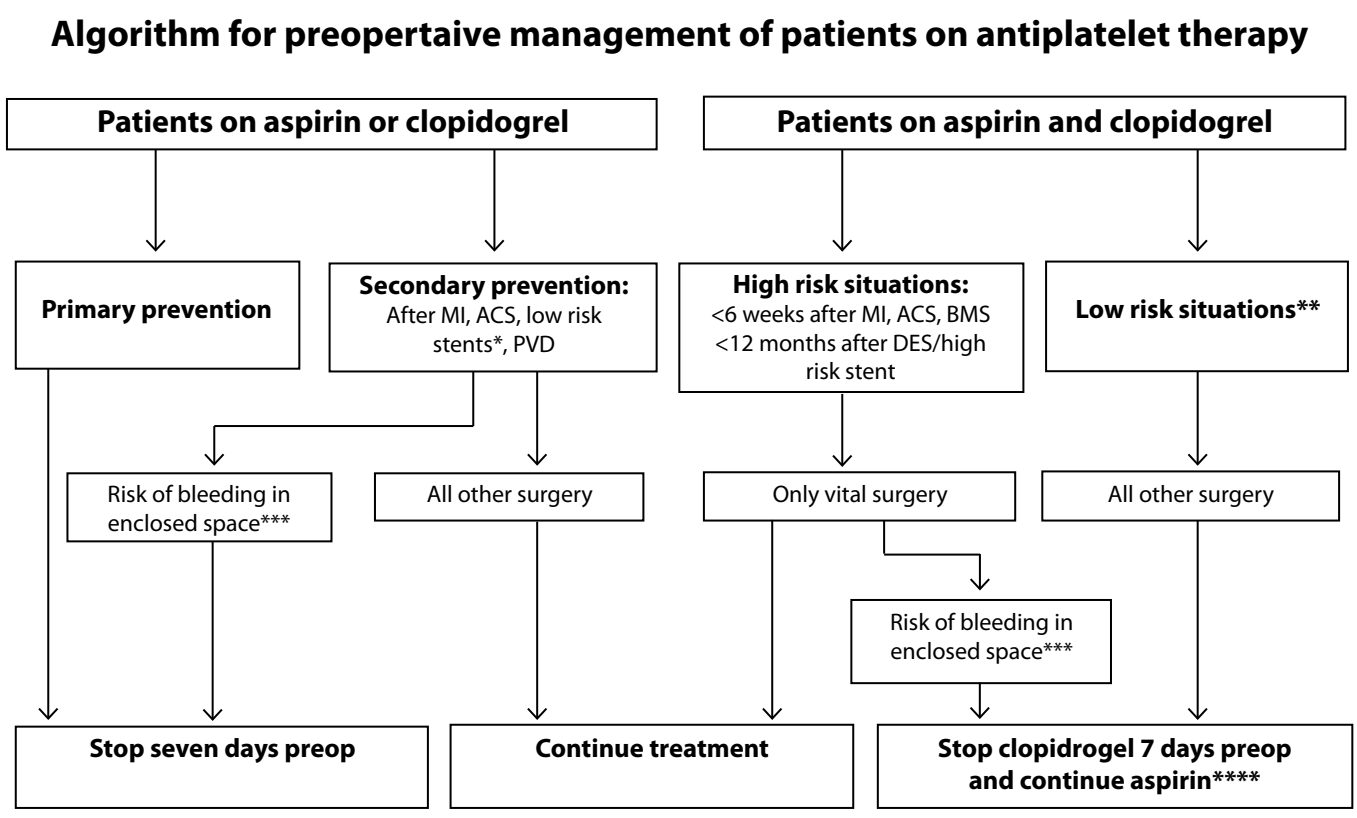
Surgical factors such as the site of surgery and type of surgery should also be considered. In some types of surgery, bleeding in closed spaces (such as intracranial neurosurgery) can have devastating consequences and some types of plastic surgery with large raw areas can have high bleeding potential.

The American Heart Association/American College of Cardiology have recommended that patients have 12 months of dual antiplatelet therapy after ANY drug eluting stent insertion and the postponement of ALL elective operations during this period. They suggest that aspirin should NEVER be stopped. It has also been suggested that 'Apart from low coronary risk situations, patients on antiplatelet drugs should continue their treatment throughout surgery. However operations traditionally associated with excessive blood loss should be postponed unless vital'[4]

Given this complexity of decision making, the following algorithm (Figure 1) has been proposed to help decide which patients should continue their antiplatelet therapies in the perioperative period and which patients should have them witheld.[5]

Patients should have their therapies restarted as soon as is safe postoperatively. Loading doses of the drugs should be given to reduce the thrombosis risk as soon as possible. In the event of not being able to give the drugs (for example because the patient is nil by

Figure 1. *Algorithm for preoperative management of patients on antiplatelet therapy (reproduced from Reference 4 by kind permission of Oxford University Press).*



Abbreviations
MI - myocardial infarction; ACS - acute coronary syndrome; PVD - peripheral vascular disease; PCI - percutaneous coronary intervention; BMS - bare metal stent; DES - drug eluting stent;

* Low risk stents: those receiving aspirin only

** Examples of low risk situations: 3 months after BMS, uncomplicated MI and PCI without stenting

*** Risk of bleeding in closed space: closed space spinal surgery, posterior eye chamber surgery

**** In high risk situations discuss with consultant anaesthetist/cardiologist and consider "bridging" therapy (e.g. simultaneous unfractionated heparin and GP IIb/IIIa antagonist infusions)

Withdrawing aspirin must be evaluated for each case individually; if aspirin or clopidogrel are stopped, early postoperative re-institution is important.

mouth) other anticoagulation methods should be considered. Bear in mind that many of the alternative drugs affect the venous side of the circulation more than the arterial and so are not providing comparable protection from arterial events.

In the event of bleeding, platelet transfusion is the only effective method of reversing the effect of these drugs. DDAVP (desamino D-arginine vasopressin)[6] and aprotinin (an anti-fibrinolytic agent)[7] may increase platelet function to some degree.

CONCLUSIONS

In summary the management of patients taking antiplatelet drugs is complex and our current level of understanding is poor. There is a significant potential to do severe harm to patients if their drugs are stopped inappropriately, or indeed if they bleed following surgery whilst still taking them. The default position in many settings seems to be that the decision to stop or not is undertaken preoperatively by surgeons and their favoured decision is to stop clopidogrel almost always and aspirin very frequently.

It is likely that the full implications of stopping antiplatelet drugs are not fully appreciated and, understandably, a fear of bleeding predominates. We suggest that it would be more appropriate to fear the cardiovascular effects of stopping the drugs. Deferring surgery until the patient is 'safe' to stop clopidogrel, or accepting a risk of increased bleeding and adopting strategies to cope with this, if the patient cannot be deferred is more appropriate. Further research in this area will provide the evidence base for robust guidelines to advise management of each patient taking antiplatelet drugs.

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