Antiplatelet agents are increasingly being used in the management of all types of atherosclerotic disease, and, accordingly, patients on them are presenting more frequently for anaesthesia. Presentations range from elective patients taking aspirin as monotherapy for primary prevention of cardiovascular morbidity, to those maintained on multiple therapies requiring salvage surgery after a cardiovascular catastrophe. The use of such antiplatelet regimens raises a number of questions for preoperative preparation, surgery, anaesthesia, and postoperative care. This article will look briefly at the pharmacology of the common agents in use, the emerging concept of ‘resistance’, ways in which the effects of antiplatelet drugs can be monitored, and the implications they have for clinical practice.

Individual drugs and combinations

Aspirin

The antiplatelet activity of aspirin is related to its ability to block irreversibly the activity of the enzyme cyclo-oxygenase 1 (COX 1) for the life of the platelet. Platelet turnover is ~10% per day; therefore, after aspirin has been stopped, platelet function will return to normal in 7–10 days as new platelets are formed. COX 1 is responsible for the production of thromboxane A2, a potent vasoconstrictor and stimulator of platelet aggregation derived from arachidonic acid. Aspirin is 50–100 times more effective against COX 1 than COX 2; thus, larger doses are required to achieve anti-inflammatory effects. Aspirin is rapidly absorbed and has a half-life of 15–20 min. In healthy subjects, a single dose of 100 mg leads to a 98% reduction in thromboxane B2 (a breakdown product of thromboxane A2) within 1 h of ingestion, and abnormalities of platelet aggregation can be measured up to 10 days after ingestion. In a meta-analysis of 287 randomized controlled trials of long-term therapy, aspirin has been found to reduce vascular death by 15% and non-fatal vascular events [non-fatal myocardial infarction (MI) or stroke] by ~30% in high-risk patients (those patients with acute or previous vascular disease or some other predisposing condition, e.g. diabetes). The sites of action of aspirin are shown in Figure 1.

Dipyridamole

Dipyridamole is a pyrimidopyrimidine derivative that has both antiplatelet and vasodilating actions. It is usually used in combination with aspirin in the management of cerebrovascular disease. Its effects are mediated by an intracellular increase in cAMP, brought about by phosphodiesterase inhibition, and blockage of the re-uptake of adenosine by platelets, endothelial cells, and erythrocytes. Through its effects on phosphodiesterase, it also has the effect of increasing concentrations of cGMP and potentiates the local effects of nitric oxide. Its excretion is primarily biliary, is subject to enterohepatic circulation, and it has a terminal half-life of ~10 h. Early formulations had variable uptake but a new modified release formulation has been assessed favourably both alone and in combination with aspirin in the European Stroke Prevention Trial (ESPS)-2.

Thienopyridines

The thienopyridines include ticlopidine and clopidogrel. Both act to reduce platelet aggregation by the selective, irreversible inhibition of the P2Y12 ADP receptor on the platelet surface (one of three ADP receptors). They have no direct effects on the metabolism of arachidonic acid. Both are pro-drugs requiring metabolism by the liver for activation and their effects have been evaluated extensively in the management of atherosclerotic disease. Both drugs are capable of causing thrombocytopenia. However, the potential, more severe haematological side effects associated with ticlopidine ( aplastic anaemia and severe neutropenia) have resulted in clopidogrel becoming the drug of choice. Clopidogrel is rapidly absorbed when taken orally and is extensively metabolized. Its metabolism involves formation of an active metabolite, which is responsible for its antiplatelet effects.

Withdrawal of aspirin in patients with coronary artery disease is associated with a 2–4 fold increase in risk of death and myocardial infarction. Aspirin and clopidogrel act synergistically. Over 10% of episodes of acute coronary syndrome in the perioperative period are precipitated by pre-operative cessation of aspirin. There is no ‘antidote’ to aspirin and clopidogrel whilst they remain in the blood. Patients with stents are at high risk of thrombotic events if their therapy is changed, especially in the first 3 months after insertion.

Key points

In general medical practice, secondary prevention with aspirin reduces mortality by up to 30% in high-risk groups.

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Patients with stents are at high risk of thrombotic events if their therapy is changed, especially in the first 3 months after insertion.
Activation is by oxidation of the thiophene ring by components of the cytochrome P450 system. The active metabolite has an elimination half-life of ~8 h and acts by forming a disulphide bridge, with cysteine residues on the ADP receptor, to cause irreversible blockade for the life of the platelet. Maximal inhibition (50–60%) can be achieved with a loading dose of 400 mg after which inhibition can be maintained with an ongoing low-dose regimen. Similar to aspirin, platelet inhibition can be overcome only by platelet transfusion (in the absence of active drug) or by the generation of new platelets.

The sites of action of clopidogrel are shown in Figure 1.

**GP IIb/IIIa receptor antagonists**

GP IIb/IIIa receptor antagonists are used primarily in the management of acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI). They act to block the final common pathway of platelet activation, regardless of the initial stimulus. Abciximab (ReoPro) is a human–murine monoclonal antibody. Platelet aggregation is significantly reduced at 50% receptor occupancy and can be nearly completely abolished by 80% occupation. The bleeding time is severely prolonged only when receptor occupation is >90%. After a loading dose, administration is via continuous infusion for 12 h (both based on body weight) and effects are seen up to 48 h after cessation of the infusion owing to the high affinity of the drug to the receptor.

**Dual therapy**

Aspirin and clopidogrel act synergistically in their antiplatelet actions and can thus produce severe intraoperative haemorrhage or unexpected postoperative haematoma. Dual therapy with aspirin and clopidogrel is currently recommended for the management of patients with non-ST segment elevation (NSTEMI) ACS, those with chronic stable coronary artery disease (CAD) at high risk of developing an MI, and those undergoing PCI with coronary stents. After NSTEMI, ACS patients benefit from dual therapy if taken for 9–12 months; in chronic CAD with high risk, therapy should be indefinite.

Management of patients with coronary stents poses further questions and has been the subject of a recent review article. Compared with balloon angioplasty, bare metal coronary stents (BMS) reduce the risk of re-stenosis. Drug-eluting stents (DES) further improve performance because they delay the epithelialization and neointimal thickening associated with coronary artery dilatation. The delay in epithelialization associated with DES does however carry a longer term risk of thrombosis, and this has been reported up to 15 months after stenting. Current recommendations for dual therapy with stenting are typically 4 weeks with BMS and up to 6 months with DES, depending on the type of stent used. There is increasing evidence for the beneficial role of dual therapy in all patients with stents for a period of 12 months.

**Platelet function analysis**

Platelet function analysis offers the possibility of measuring drug efficacy. Unfortunately, this is not a simple process and, until recently, was limited to specialized centres. However, the increasing use of antiplatelet medications and the concept of resistance have created great interest in the development of convenient monitors. A number of platelet function-testing devices have been developed recently that are simpler to use, test whole blood, and show potential for use as point-of-care instruments.

The first accepted test of platelet function (developed by Duke in 1934) was the bleeding time. An incision is made with a spring-loaded device to produce cuts of a standard depth and width, and a sphygmomanometer cuff is inflated to a pressure of 40 mm Hg. Cessation of bleeding is assessed by regular use of blotting paper, and the time taken for bleeding to stop is recorded. Normal times are between 2 and 10 min. The test is invasive, insensitive, and time consuming but it does test natural haemostasis and does not require expensive equipment.
Platelet aggregometry is now the gold standard and involves the testing of whole-blood or platelet-rich plasma (PRP), with a number of different agonists. Typical agonists include arachidonic acid (AA), thrombin, adenosine diphosphate (ADP), epinephrine, collagen, and ristocetin. In most laboratories, the agonist is added to PRP in a cuvette at 37°C, and the mixture agitated by stirring. Aggregation of platelets results in an increase in light absorption by a photometer and an aggregation curve is plotted. Aggregometry is still a widely used test of platelet function, but it requires trained personnel, transport to a laboratory for processing, and ideally, testing within 2 h of the sample being taken.

A device that overcomes many of these drawbacks is the near-patient platelet function analyser PFA-100. It monitors platelet aggregation on collagen–ADP- and collagen–epinephrine-coated membranes. Citrated whole blood is aspirated through a 147 μm window in the membrane, thus simulating high shear rate conditions. A platelet plug forms within the aperture, and the time taken, the closure time, is the measure of platelet function. The test requires only small volumes of blood, uses disposable cartridges, is easy to perform, and is rapid. Other monitors that have been developed with a similar objective are the cone and plate(let) analyser (which monitors the adhesion of platelets to polystyrene plate under high shear rates), the Ultegra rapid platelet function assay (which uses fibrinogen-coated beads and a platelet activator), and the Plateletworks (which uses ADP or collagen activation).

Thromboelastography (Haemoscope, Skokie, IL, USA) is a test of viscoelastic blood clot formation performed on whole-blood samples and gives information on the clotting cascade, platelet function, platelet–fibrin interaction, and fibrinolysis. Although the thromboelastogram gives a measure of platelet function from the width of its trace, it unfortunately gives erroneous readings in hypofibrinogenaemia and does not give an indication of dysfunction directly because of antiplatelet drugs. Recent modifications to TEG, however, have allowed the effects of aspirin and clopidogrel to be detected. Platelets are activated with AA or ADP in heparinized samples (thrombin is inhibited) containing Activator F. By comparing the unmodified TEG trace with the modified TEG trace the effects of antiplatelet medications can be measured. Early studies seem to show reasonable correlation with aggregometry.8

**Antiplatelet drug resistance**

Although there is little data on dipyridamole or the GP IIb/IIIa receptor antagonists, studies on aspirin and clopidogrel have shown that a proportion of patients on antiplatelet medication still suffer recurrent events. This has led to the concept of ‘resistance’ or ‘non-responders’. Unfortunately, there is little clarity on how to define or detect such a subgroup, partly because of a lack of standardized testing methods. Whether these should incorporate laboratory-based testing, clinical outcomes, or both remains a topic of discussion.

The variability of the prevalence of aspirin resistance (estimates given of between 5 and 60%) is probably partly accounted for by the different patient groups studied and different assays used.9 The roles of dose, duration of therapy, and patient co-morbidity remain uncertain. Mechanisms of aspirin resistance are likely to be multifactorial, including clinical, cellular, and genetic factors. These range from non-compliance, failure to prescribe, failure to absorb, drug interactions (e.g. ibuprofen blocking the active site of aspirin action), genetic factors such as polymorphisms of platelet glycoproteins and the COX 1 gene affecting the binding site of aspirin, and increased platelet aggregation owing to catecholamines, hyperglycaemia, and hypercholesterolaemia. The mechanism of aspirin resistance is summarized in Figure 2.

Up to 25% of patients taking clopidogrel have been described as only partially responsive, with 5–10% being resistant to its effects when tested against standard platelet assays. Again, the inter-patient variability may be owing to a number of factors such as genetic differences in the P2Y12 receptor, inadequate dosing, patient co-morbidities, and variation in the activity of cytochrome p450 enzymes. Unfortunately, for clinical practice, there is no currently accepted method of knowing whether a patient on antiplatelet medication is resistant or not, but PFAs offer the potential for future standardization. The mechanism of clopidogrel resistance is summarized in Figure 3.

**Implications for anaesthesia**

Antiplatelet medication has obvious implications for perioperative management but there are no universally accepted rules to guide clinical practice. The relevant literature is almost completely limited to the use of aspirin, clopidogrel, and their combination. Urgent operations receive scant attention, but this is understandable because the only way to reverse antiplatelet therapy acutely is to administer platelets. This will of course be ineffective if there is still active drug in the blood and is a particular problem in the presence of pro-drug. Experience has taught that surgical technique is critical together with very large platelet transfusions.

For elective patients, studies tend to separate into cardiac and non-cardiac patients: patients with stents form a subgroup. To our knowledge, there are no prospective comparative studies reporting the relative cardiovascular risk of deliberately stopping antiplatelet medication perioperatively; however, there are retrospective data. To do such trials now would be ethically problematical.

**Aspirin**

If low-dose aspirin is stopped, it increases cardiovascular risk by removal of its intended action and by the potential for rebound phenomena. Withdrawal of aspirin in non-surgical patients with CAD is associated with a 2–4 fold increase in risk of death and myocardial infarction.10 Stopping aspirin therapy precedes over 10% of acute coronary syndrome episodes in the perioperative period.11 In non-cardiac surgery where there is accumulating evidence that aspirin increases neither the level of bleeding complications nor mortality, it would appear sensible to continue its use. The definite exceptions to this would be intracranial surgery and the possible exception of prostatectomy and hip surgery. Although
Aspirin is commonly stopped before cardiac surgery, the condition varies from centre to centre and local guidelines should be followed. However, there is significant evidence after coronary artery bypass surgery for the beneficial effects of early re-administration of aspirin after operation when the acute bleeding has stopped; it seems sensible to replicate this if aspirin was stopped for other reasons.

Three large trials failed to show any increased risk of neuraxial haematoma after spinal or epidural block; in addition, the absence of case reports, given the prevalence of NSAID use, would suggest that it is safe to undertake neuraxial regional anaesthesia without stopping low-dose aspirin. This view is supported by the American Society of Regional Anaesthesia and Pain Medicine but not by...
the German and Spanish equivalent organizations. There is a paucity of literature on the effect of aspirin on local infiltration blocks, although some studies have reported a doubling of bleeding complications.

**Clopidogrel**

There are few studies assessing the risk of continued use of thienopyridines perioperatively. The perception of a greater risk of bleeding owing to a more potent effect on platelet function, combined with lack of evidence from large prospective clinical trials, has led to reluctance in recommending their continuation in the perioperative period. Some centres switch patients from clopidogrel to aspirin before operation. Perhaps, the future use of the PFA-100 may provide a more rational approach to such situations.

Current commonly applied recommendation regarding regional anaesthesia is that clopidogrel should be stopped 7 days, and ticlopidine 14 days, before intervention. Again, to reduce the occurrence of adverse cardiovascular events, a patient may be switched to aspirin and the guidelines followed for that.

**Dual therapy**

Combination therapy with aspirin and clopidogrel in cardiac surgery leads to increased blood loss, increased transfusion, and increased re-operation rates. The increased risk of bleeding in non-cardiac patients has been quoted at up to 40%, and consideration should be given to stopping clopidogrel 5–7 days before surgery in suitable patients. However, patients on dual therapy represent a high-risk group for thrombotic events and if at all possible, monotherapy with aspirin should be maintained.

**Stents**

There is an absence of high-level evidence to optimize the perioperative management of patients with stents, particularly soon after their insertion. It does however appear clear that stopping antiplatelet drugs is associated with adverse outcomes. This has led a recent review to suggest the following guidelines.

- All patients should receive low molecular weight heparin prophylaxis, but this alone is not enough.
- During the initial period of up to 3 months after PCI and stenting, only life-saving operations should be performed.
- For operations after this initial period, it is unwise to stop all antiplatelet drugs and it may be best to leave the regimen unchanged.
- In selected operations, a combined aspirin–clopidogrel regimen could be reduced for a short period to aspirin monotherapy combined with low molecular weight heparin.

**Platelet function analysis**

The variability in individual response to a fixed dose of antiplatelet medication is now well established and near-patient platelet function analysis has the potential as a screening tool to identify patients who are either hyper- or hypo-responsive to antiplatelet medication. It also has a role in monitoring clotting during surgery. On their initial promise, they would appear to be the best hope of adding some logic into a field beset by uncertainty.

**Conclusions**

Antiplatelet drugs are increasingly being used to optimize survival and minimize adverse events in patients at risk of cardiovascular complications. Evidence is accumulating that stopping antiplatelet medication puts patients at cardiovascular risk, and anaesthetists need to be aware of this. Although a number of guidelines exist, evidence is insufficient for rigid adherence to these, and in the management of the elective patient, consideration needs to be given on an individual basis to the risks and benefits of cessation of therapy.

**References**