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REVIEW ARTICLE

The thienopyridine derivatives (platelet adenosine diphosphate receptor antagonists), pharmacology and clinical developments

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Summary

The thienopyridines, ticlopidine and clopidogrel, are antiplatelet drugs. They are prodrugs and are metabolised in the liver to active metabolites that are non-competitive antagonists of the platelet adenosine diphosphate receptor, $P2Y_{12}$. Inhibition of platelet aggregation by these drugs is delayed until 24–48 h after administration, with maximal inhibition achieved after 3–5 days. Recovery of platelet function after drug withdrawal is slow (7–14 days). Ticlopidine and clopidogrel are effective in preventing atherothrombotic events in cardiovascular, cerebrovascular and peripheral vascular disease. Gastrointestinal side effects and skin rashes are common. However, neutropenia and thrombotic thrombocytopenic purpura are significant and sometimes fatal adverse effects of ticlopidine. Clopidogrel appears to offer several advantages over ticlopidine: a more rapid onset of action and a lower incidence of neutropenia and thrombotic thrombocytopenic purpura. A combination of clopidogrel and aspirin has become standard for antithrombotic therapy in cardiovascular disease. The anaesthetic considerations of patients taking the thienopyridine compounds are discussed.

Keywords *Platelet aggregation inhibitors*; clopidogrel, ticlopidine. *Anaesthesia.*

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Atherothrombosis associated with pre-existing atherosclerotic plaques involves platelet activation, aggregation and thrombus formation. Long-term antiplatelet therapy is effective in the secondary prevention of vascular events in patients with acute coronary or cerebrovascular events who are at a high risk of subsequent thrombotic events [1]. The recent development of drugs with greater selectivity, efficacy and decreased side effects resulted from a better understanding of the mechanisms of atherosclerosis, platelet aggregation, coagulation and thrombolysis.

This review will focus on the pharmacology of the thienopyridine derivatives that selectively inhibit platelet activation and aggregation mediated by adenosine diphosphate (ADP), and provide a commentary on perioperative considerations when managing patients taking members of this class of antiplatelet drugs.

Pathophysiology of atherosclerosis and atherothrombosis

Endothelial injury caused by shear stress, hypertension, diabetes or smoking is an important factor in the initiation and progression of arterial disease [1, 2]. Lipids and monocytes accumulate on the intima of damaged arteries. Adherent platelets and macrophages secrete growth factors that activate the migration and proliferation of smooth muscle cells from the media. These smooth muscle cells release collagen, proteoglycans and elastic fibres that together form the fibrous cap of the atheromatous plaques. These atheromatous plaques, usually located at vessel ostia, branches or regions where blood flow changes in velocity or direction, causing high shear stress, later become calcified. High shear stress occurring in the atherosclerotic small arteries and arterioles induces

platelet activation, aggregation and enhances platelet thrombus formation [1, 2].

The disruption of atherosclerotic plaques triggers platelet adhesion, activation and aggregation, causing cerebrovascular, coronary and peripheral vascular ischaemic syndromes that may progress to infarction [1–3]. Platelet adhesion is mediated by the interaction of platelet glycoprotein Ib/IX with subendothelial von Willebrand's factor under high shear conditions, and by platelet glycoprotein Ia/IIb binding to collagen under low shear conditions. The adherent platelets recruit additional platelets into a growing thrombus. Initially, clotting factors assemble on the activated platelet surface and this process enhances thrombin generation. The resultant increase in thrombin activates more platelets and triggers coagulation. The activated platelets also secrete ADP (from their dense granules), which activates nearby platelets. Thromboxane A_2 released by the platelets activates additional platelets.

The role of ADP in platelet activation

ADP is released from activated platelets, erythrocytes and endothelial cells, and induces platelet adhesion and aggregation. ADP activates platelets by binding to membrane-bound nucleotide receptors (purinoceptors) on the platelet surface called P2 receptors [4]. Human platelets possess two major G protein-coupled ADP receptors, the $P2Y_1$ and $P2Y_{12}$ receptors, and a third ionotropic receptor, $P2X_1$. The human $P2Y_1$ receptor is a Gq protein-coupled receptor that activates phospholipase C to form inositol triphosphate (IP_3) and causes calcium to be released from intracellular stores. The $P2Y_1$ receptor is necessary to trigger a response and initiates the formation of platelet pseudopodia in response to low concentrations of thromboxane A_2 or thrombin, and transient platelet aggregation occurs. However, activation of the $P2Y_1$ receptor is insufficient for a full platelet response. The $P2Y_{12}$, formerly known as P(2T), P2T (AC), P2Y (ADP) or P2Y (cyc), receptor is a Gi protein-coupled receptor that inhibits adenylyl cyclase. This results in a decreased platelet cyclic adenosine monophosphate (AMP) level in response to ADP, activating platelet glycoprotein IIb/IIIa (αIIbβ3 integrin) receptors that bind fibrinogen, leading to stabilisation of platelet aggregation and enhanced platelet secretion. Platelets also possess a third ADP receptor, $P2X_1$, which is a ligand-gated ion channel that mediates rapid transient calcium ion influx. However, the $P2X_1$ receptor does not contribute to platelet aggregation (Fig. 1).

The thienopyridine derivatives, ticlopidine and clopidogrel, inhibit ADP-induced platelet activation [3, 4]. The combination of aspirin and clopidogrel or ticlopidine produces synergistic effects because they block complementary pathways of platelet aggregation without blocking thrombin-mediated platelet aggregation. In contrast, glycoprotein IIb/IIIa antagonists block aggregation induced by all agonists by preventing cross-linkage of fibrinogen mediated platelet aggregation.

Pharmacodynamics of thienopyridines

The thienopyridine derivatives, ticlopidine and clopidogrel, are antiplatelet agents that inhibit the $P2Y_{12}$ receptor and are used as antithrombotic drugs. The chemical structures of clopidogrel and ticlopidine are very similar (Fig. 2). Clopidogrel has an additional carboxymethyl side group. Ticlopidine and clopidogrel are inactive *in vitro*

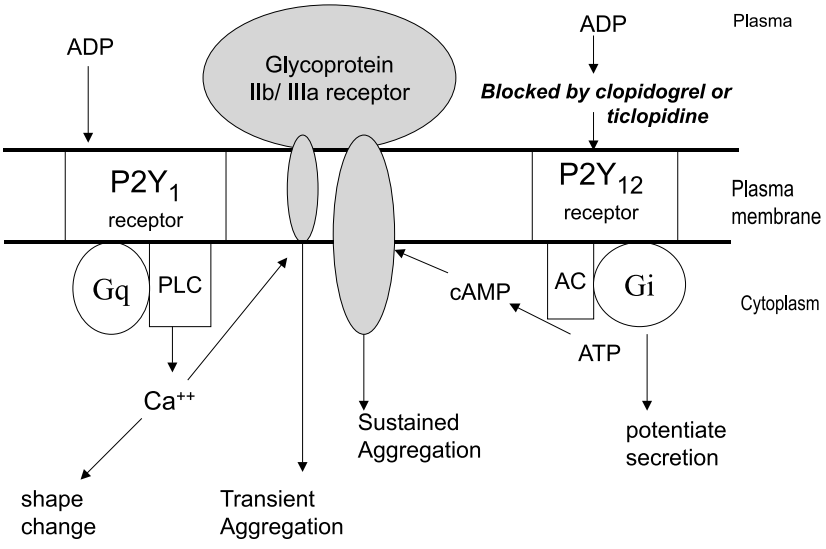

Figure 1 Action of thienopyridines on the adenosine diphosphate receptor, $P2Y_{12}$. ADP, adenosine diphosphate; G, G protein; PLC, phospholipase C; AC, adenylyl cyclase; cAMP, cyclic adenine monophosphate; ATP, adenosine triphosphate.

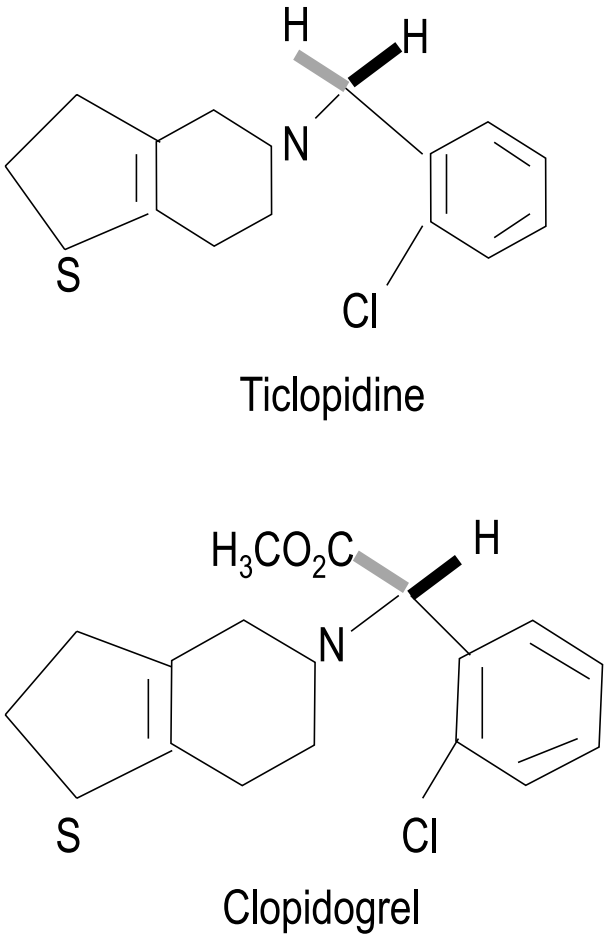

Figure 2 Molecular structures of ticlopidine and clopidogrel.

and are metabolised by hepatic cytochrome P450-1A to produce active metabolites that inhibit platelet aggregation by selective and irreversible binding (via covalent bonds) to the $P2Y_{12}$ receptors. The active metabolite of clopidogrel is a thiol derivative of the parent molecule [4]. Clopidogrel, the *S*-enantiomer of a racemic thienopyridine compound (PCR 4099), is six times more potent than ticlopidine and does not share any common metabolites with ticlopidine [5]. When the thienopyridine compounds bind to the $P2Y_{12}$ receptors, they decrease ADP-induced activation of the GP IIb/IIIa complexes, thrombin receptor agonist peptide (TRAP)-induced fibrinogen binding and P-selectin expression on the platelet membrane surfaces. They do not inhibit ADP-induced platelet shape change or calcium flux. Between 60 and 70% of the ADP receptors are sensitive to the effects of the thienopyridines.

Maximal inhibition of ADP-induced platelet aggregation after a single oral dose of clopidogrel 375–400 mg is 40–50% and is achieved in 2–6 h. This level of inhibition is achieved after 3–7 days of repeated dosing with clopidogrel 75 mg administered once daily [6]. In healthy human volunteer studies, maximal inhibition of platelet aggregation causes a twofold increase in the bleeding time [7]. In animal studies, clopidogrel attenuates thrombin-induced and collagen-induced platelet aggregation transiently [8]. However, clopidogrel ($\geq$ 75 $mg.day^{-1}$) had no effect on collagen-induced platelet aggregation in patients with atherosclerotic disease or in *in vitro* studies using platelet-rich plasma obtained from healthy volunteers [9]. Platelet function recovers completely 7 days after the discontinuation of clopidogrel therapy in healthy volunteers [10].

Pharmacokinetics

About 50% of ingested clopidogrel is absorbed rapidly from the gastrointestinal tract and its bioavailability is unaffected by food or antacids [11]. Clopidogrel undergoes extensive and rapid metabolism by the hepatic cytochrome P450-1A enzymes to produce active and inactive metabolites. The active metabolite has been identified only recently [9]. Unchanged clopidogrel in the plasma may be detected for only $\approx$2 h after ingestion. Clopidogrel is absorbed from the gastrointestinal tract and is rapidly hydrolysed in the liver to the main (85%) inactive metabolite (a carboxylic acid derivative, SR 26334).

The renal clearance of the principal metabolite (SR 26334) is constant over a clopidogrel dose range of 50–150 $mg.day^{-1}$, indicating that clopidogrel has linear pharmacokinetics. The elimination half-life of SR 26334 is $\approx$8 h in young healthy volunteers [11]. Steady-state pharmacokinetics can be achieved with an average of 8 days of oral administration [12, 13]. In patients with renal failure, bleeding times are not prolonged with standard doses of clopidogrel, although the renal clearance of the inactive metabolite SR 26334 is decreased significantly in patients with severe renal failure. The effect on ADP-mediated platelet aggregation by clopidogrel is not affected by liver disease [2]. However, clopidogrel should be used with caution in patients with severe hepatic dysfunction because of increased bleeding risks associated with coagulation disturbances in liver failure. There is no information on the use of clopidogrel in pregnant or lactating women.

Ticlopidine is rapidly and extensively absorbed from the gastrointestinal tract with an oral bioavailability of 80%. Ticlopidine is also metabolised by the hepatic cytochrome P450-1A isoenzyme [14]. The plasma level of the major metabolite peaks $\approx$2 h after oral administration [13]. Unlike clopidogrel, ticlopidine has non-linear pharmacokinetics and its clearance decreases with

repeated dosing. The half-life of ticlopidine is ≈ 12.6 h after a single oral dose but increases to 4–5 days after repeated dosing. Ticlopidine is extensively bound (98%) to plasma proteins and is extensively metabolised in the liver.

Side effects

Clopidogrel has a more favourable side effect profile than ticlopidine. Gastrointestinal problems are the commonest side effects. Clopidogrel is better tolerated than aspirin [15]. Clinically severe rashes are more common with clopidogrel than with aspirin (0.26 vs. 0.10%, $p < 0.05$). Clinically significant gastrointestinal side effects are less frequent with clopidogrel than with aspirin: indigestion/nausea/vomiting (15 vs. 17.6%), diarrhoea (4.46 vs. 3.34%) and gastrointestinal haemorrhage (0.49 vs. 0.71%). Overall, the frequency of bleeding is similar for aspirin and clopidogrel (9.27 vs. 9.28%) [15, 16]. Neutropenia was rare and was less frequent in the clopidogrel group than in the aspirin group. The incidence of thrombotic thrombocytopenic purpura, which is mediated by an immunological mechanism, is between 1:1600 and 1:5000 patients treated with clopidogrel [17].

The adverse effects of ticlopidine are similar to those of clopidogrel, except for neutropenia. The incidence of neutropenia associated with ticlopidine is 1.3–2.1% compared with 0.10 and 0.17% in patients on clopidogrel and aspirin, respectively [8, 16]. Neutropenia in ticlopidine-treated patients can be severe (< 450 neutrophil.mm^{-3}) and has resulted in a number of fatalities. Neutropenia generally occurs within three months of therapy and is usually reversed when the drug is discontinued. Strict haematological monitoring (every two weeks during the first three months of treatment) is therefore recommended for patients on ticlopidine [17]. The lower rate of neutropenia and the more favourable pharmacokinetic profile of clopidogrel make it the ADP-receptor antagonist of choice. The most frequent side effects of ticlopidine are diarrhoea and rashes. These occurred in 20% of patients in the Ticlopidine Aspirin Stroke Study and in ≈ 2% of patients were severe enough to make patients discontinue ticlopidine [18].

Drug interactions

The combination of aspirin and the thienopyridine derivatives causes synergistic antiplatelet effects. Similarly, the thienopyridines enhance the platelet-inhibiting effects of the glycoprotein IIb/IIIa receptor antagonists. A pharmacokinetic interaction (mediated by CYP2C9) causing an intracerebral haemorrhage in an elderly patient with atrial fibrillation was reported with the concomitant use of celecoxib and clopidogrel [19]. Phenytoin toxicity has been reported when combined with ticlopidine, probably caused by inhibition of its metabolism [20]. Increased plasma concentrations of theophylline and carbamazepine have also been reported [21–22].

Clinical trials of ADP antagonists

The clopidogrel vs. aspirin in patients at risk of ischaemic events (CAPRIE) trial, involving 19 185 subjects, was the first randomised, multicentre, double-blind trial to evaluate the efficacy of aspirin (325 mg.day^{-1}) vs. clopidogrel (75 mg.day^{-1}) in patients with recent stroke, recent myocardial infarction or established peripheral arterial disease [15]. There were 939 events in the clopidogrel-treated group and 1021 in the aspirin-treated patient. The annual risk of primary ischaemic events in the clopidogrel group was 5.32% compared with 5.83% in the aspirin group. There was a relative risk reduction of 8.7% with clopidogrel for myocardial infarction, ischaemic stroke or vascular death [15]. In patients with peripheral vascular disease and recent stroke or myocardial infarction, clopidogrel would prevent 24 major ischaemic events per year compared with 19 events prevented by aspirin for every 1000 patients. The trial also showed that in patients with peripheral arterial disease, the average ischaemic event rate per year in the clopidogrel group was 3.71% compared with 4.86% in the aspirin group; a relative risk reduction of 23.8% (confidence interval 8.9–36.2%) in favour of clopidogrel compared with aspirin ($p = 0.0028$). Further analysis of all 19 185 patients in the CAPRIE trial showed a relative risk reduction of 19.2% in favour of clopidogrel for the outcome of myocardial infarction alone compared with aspirin ($p = 0.008$). In a subgroup of patients who had undergone cardiac surgery, there was a 31.2% relative risk reduction of vascular death, myocardial infarction, stroke and rehospitalisation for ischaemia or bleeding [15]. The CAPRIE trial found no significant differences in the frequency of neutropenia between the two groups (clopidogrel = 0.1% vs. aspirin = 0.17%) or in the incidence of thrombocytopaenia. Severe rash and diarrhoea were more common with clopidogrel but upper gastrointestinal discomfort and gastrointestinal bleeding were more common with aspirin. Thrombotic thrombocytopenic purpura has been reported in 11 cases of > 3 000 000 patients treated with clopidogrel worldwide, the majority occurring within two weeks of the start of therapy.

The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) demonstrated the superior efficacy and safety of clopidogrel plus aspirin compared with ticlopidine plus aspirin in patients undergoing

coronary stenting [23]. One thousand and twenty patients were randomised after successful stent placement and were started on a 28-day regimen of: (i) a loading dose of clopidogrel 300 mg and aspirin 325 mg followed by clopidogrel 75 mg.day^{-1} and aspirin 325 mg.day^{-1}; (ii) clopidogrel 75 mg.day^{-1} and aspirin 325 mg.day^{-1}; (iii) ticlopidine 250 mg twice a day and aspirin 325 mg.day^{-1}. The efficacy was similar between the clopidogrel–aspirin and ticlopidine–aspirin groups. Clopidogrel was better tolerated and safer than ticlopidine.

The clopidogrel in unstable angina to prevent recurrent ischaemic events (CURE) study was a randomised, double blind, placebo-controlled trial designed to study the acute and long-term combination of aspirin and clopidogrel vs. aspirin monotherapy in patients with acute coronary syndromes that included unstable angina and myocardial infarction without ST segment elevation [24]. In this study, 12 562 patients who presented within 24 h of the onset of symptoms were randomly allocated to receive clopidogrel (300 mg immediately, followed by 75 mg.day^{-1}) or a placebo, both in addition to aspirin. There was a 20% decrease (9.3% patients in the clopidogrel group vs. 11.4% patients in the placebo group) in the composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or stroke. The rates of bleeding were higher in the clopidogrel and aspirin group (3.7 vs. 2.7%), although the rate of life-threatening bleeding was similar. The percutaneous coronary intervention – clopidogrel in unstable angina to prevent recurrent ischaemic events (PCI-CURE) study showed that, in addition to aspirin, treatment with clopidogrel before percutaneous coronary intervention was beneficial in decreasing the incidence of major cardiovascular events compared with placebo [25]. Overall, there was a 31% reduction in cardiovascular death or myocardial infarction ($p = 0.002$).

The clopidogrel for the reduction of events during observation (CREDO) trial will evaluate the efficacy and safety of clopidogrel, with or without a loading dose, in combination with aspirin given before percutaneous transluminal coronary angioplasty [26].

In summary, efficacy studies indicate that clopidogrel decreases the risk of recurrent ischaemic events when compared with aspirin in high-risk patients with a history of coronary artery bypass surgery, diabetes mellitus and hyperlipidaemia [27]. Clopidogrel is better tolerated than ticlopidine. Gastrointestinal bleeding is significantly less frequent in patients taking clopidogrel compared with those taking aspirin. Clopidogrel is now widely used in combination with aspirin to prevent thrombosis after intravascular stenting procedures. The ongoing management of atherothrombosis with clopidogrel in high-risk patients with recurrent transient ischaemic attack or ischaemic stroke (MATCH) trial will evaluate the safety of clopidogrel plus aspirin vs. clopidogrel alone in patients with cerebrovascular atherosclerosis [28].

The stent anticoagulation restenosis study (STARS), intracoronary stenting and antithrombotic regimen (ISAR) and multicentre aspirin and ticlopidine trial after intracoronary stenting (MATTIS) studies preceded the CLASSICS study and demonstrated the superiority of combined aspirin–ticlopidine therapy over aspirin–anticoagulant and aspirin monotherapy in decreasing the incidence of restenosis in patients in various risk groups who had received successful stent insertion [29–32]. The STARS study, which compared the three antithrombotic regimens (aspirin alone, aspirin and warfarin, aspirin and ticlopidine) demonstrated the superiority of combined aspirin–ticlopidine over the other two regimens in reducing the combined primary end point of death, myocardial infarction, angiographic evident thrombosis or need for revascularisation in patients who had successful coronary stent insertion [29]. The full anticoagulation vs. aspirin and ticlopidine after stent implantation (FANTASTIC) study raised the issue of the timing of drug administration [30]. In this study, the acute (< 24 h) occlusion rate was higher for the antiplatelet-treated group (2.4 vs. 0.4%, $p = 0.06$), and this was related to the delayed administration of ticlopidine (only after stent insertion). Platelet activation peaks 48–72 h after stent implantation, whereas the antiplatelet effects of ticlopidine peak at 3–5 days. Ticlopidine administration > 24 h before coronary stenting provides significant inhibition of platelet aggregation at the time of the procedure.

The Swedish ticlopidine multicentre study (STIMS), which compared the efficacy of ticlopidine (250 mg twice a day) vs. placebo for the prevention of myocardial infarction, stroke and transient ischaemic attacks in 687 patients with intermittent claudication, showed a significant decrease in coronary and cerebrovascular events and total morbidity [33]. Ticlopidine also decreased the need for reconstructive vascular surgery in patients with peripheral vascular disease by ≈ 50% [34].

Ticlopidine is effective in maintaining the patency of vein grafts in patients undergoing femoropopliteal and femorotibial bypass surgery for lower limb occlusive disease. The cumulative patency rate was 82% in patients taking ticlopidine compared with 63% in the placebo group ($p = 0.002$) [35]. However, the use of ticlopidine has been limited by its potential to cause neutropenia. In clinical trials, 2.4% (50/2048) of patients experienced neutropenia. Thrombotic thrombocytopenic purpura was estimated to occur in 1:2000 to 1:4000 patients taking ticlopidine. Close haematological monitoring is recommended during the first three months of therapy [36].

The Antiplatelet Trialists' Collaboration study compared the effects of different antiplatelet regimens on the occurrence of vascular events in high-risk patients, i.e. those with acute, or a history of, myocardial infarction, a history of stroke or peripheral vascular disease. Analysis of 3471 patients in three trials showed a 10% odds reduction in vascular events in favour of ticlopidine over aspirin [37].

Because clopidogrel and ticlopidine act by blocking ADP-dependent activation of platelets, their antiplatelet effects relating to the prevention of occlusive vascular events complement those of aspirin, which inhibits thromboxane-dependent platelet inhibition. Long-term studies of the addition of clopidogrel to aspirin for the prevention of death, myocardial infarction and stroke in high-risk patients and those with 'aspirin failures' are required [38].

Monitoring of platelet function

A quantitative analysis of platelets is important in patients receiving the thienopyridine derivatives because they can cause neutropenia and thrombocytopenia. Ticlopidine-associated thrombocytopenia is thought to occur in 1:1600 to 1:5000 patients treated [39]. Clopidogrel is no more likely than aspirin to cause thrombocytopenia.

The bleeding time, a test of platelet function that measures platelet plug formation *in vivo,* has limited sensitivity and reproducibility. The platelet function analyser (PFA 100, Dade Behring, IL) is designed to measure shear-mediated platelet function in whole blood flowing through a small aperture. It measures the time ('closure time') taken for a platelet plug to occlude a microscopic aperture cut into a membrane coated with collagen and either epinephrine or ADP [40]. The instrument uses two disposable cartridges: a collagen–epinephrine and a collagen–ADP cartridge. The closure time obtained from the collagen–ADP cartridge can be used to assay platelet inhibition after ticlopidine and clopidogrel [41]. The PFA-100 analyser provides a rapid and easy quantitative method for evaluating peri-operative platelet function. The results obtained with the PFA-100 using collagen–ADP cartridges correlate well with optical aggregometry, the gold standard in assessing platelet aggregation [42].

Anaesthetic considerations

The ADP receptor antagonists produce irreversible inhibition of platelet aggregation, and therefore the effect is present for the life of the platelet. Bleeding time returns to normal 10 days after ceasing clopidogrel administration [43]. A platelet count should be performed to exclude neutropenia or thrombocytopenia. Platelet aggregation tests may be useful in patients presenting for elective surgery. Further studies are required to evaluate the value of the point-of-care platelet function monitor (PFA-100) for assessing residual antiplatelet effects in patients receiving the thienopyridines and presenting for urgent or emergency surgery. For elective surgical procedures, these agents should be stopped 7–10 days before surgery, except if the benefit of the antiplatelet effect outweighs the risk of peri-operative bleeding. Clopidogrel treatment in addition to aspirin before percutaneous coronary intervention has been shown to decrease the incidence of coronary occlusive events [44]. Pre-operative clopidogrel treatment may be useful in decreasing the incidence of thrombosis in patients with peripheral arterial disease undergoing vascular interventions, e.g. arterial bypass, endarterectomy or percutaneous transluminal angioplasty [45].

Although experience with the platelet ADP antagonists is increasing, many questions related to the peri-operative risks remain unresolved, and anaesthetists must exercise diligence during the care of patients. The relative risks of bleeding in surgical patients receiving the platelet ADP antagonists either alone or in combination with heparin or aspirin are not known. The safety of regional anaesthetic techniques in patients receiving the thienopyridine derivatives is not defined. In theory, there is an increased risk of the formation of epidural haematomas when epidural or spinal techniques are used in these patients. It would seem prudent to stop the ADP antagonists at least 7–14 days before surgery if an epidural technique is considered to be essential. On the basis of its pharmacological properties, it is recommended that clopidogrel is stopped 7 days before surgery, and ticlopidine 10–14 days before surgery [46].

The haemostatic derangements associated with cardiopulmonary bypass present a significant concern for patients undergoing emergency coronary artery surgery after acute loading with clopidogrel. In the event of acute stent occlusion in a patient who has received a loading dose of clopidogrel, there is a window of opportunity to perform urgent bypass grafting. This arises from the delay in the formation of the active metabolite of clopidogrel. The inhibition of platelet aggregation by clopidogrel commences within 1 h of a 375 mg loading dose and reaches its peak effect at 5 h [47]. In a study of 247 patients undergoing coronary artery bypass graft surgery, the pre-operative use of clopidogrel in combination with aspirin was associated with an increased need for surgical re-exploration (incidence 9.8 vs. 1.6%, $p = 0.01$, odds ratio = 6.9). There were also increases in blood transfusion (3 vs. 1.6 units, $p = 0.0004$) and the use of blood products [47]. Clopidogrel is administered to patients

undergoing off-pump coronary artery bypass (OPCAB) surgery by some cardiac surgeons both before and after surgery to decrease the incidence of graft occlusion [48].

There are no available pharmacological antidotes to the ADP-receptor antagonists. In the case of active, uncontrolled bleeding, platelet transfusion is the only effective treatment. The administration of desmopressin (DDAVP) only improves primary haemostasis temporarily [46]. In animal studies, aprotinin partially reversed the effect of thienopyridines on bleeding time in a dose-dependent manner [49].

Conclusions

The thienopyridine derivatives are modestly more effective than aspirin in preventing serious vascular occlusive events in patients with atherosclerotic disease [50]. They are associated with less serious gastrointestinal complications compared with aspirin, but cause an increase in skin rash and diarrhoea (ticlopidine > clopidogrel). Ticlopidine, but not clopidogrel, is associated with an increased occurrence of neutropenia and thrombotic thrombocytopenic purpura. With the clinical trials of the thienopyridine drugs under way, it is likely that the number of patients receiving these drugs will increase. An understanding of the pharmacology of the thienopyridine derivatives is essential for the anaesthetist so that the peri-operative management surgical patients can be optimised.

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