Abstract—The thienopyridines ticlopidine and clopidogrel are inhibitors of platelet function in vivo. Their mode of action has not been defined, but it appears that they require conversion to as yet unidentified metabolites that are noncompetitive antagonists of the platelet ADP receptor. Inhibition of platelet aggregation with these compounds is delayed until 24 to 48 hours after administration. Maximum inhibition occurs after 3 to 5 days, and recovery is slow after drug withdrawal. Ticlopidine is effective in preventing cardiovascular events in cerebrovascular, cardiovascular, and peripheral vascular disease, with an efficacy that is similar to aspirin. However, its use is associated with significant and sometimes fatal adverse reactions, specifically neutropenia and bone marrow aplasia. Gastrointestinal side effects and skin rashes are common and result in discontinuation of therapy in up to 10% of patients. Clopidogrel is at least as effective as aspirin in preventing cardiovascular events in patients with a history of vascular disease. It appears to be safer than ticlopidine, although its efficacy in acute coronary syndromes or post–coronary-stent insertion has not been reported. Important outstanding issues are whether clopidogrel adds to the benefit of aspirin and whether the combination of these agents is safe. If so, this combination may become the standard for antithrombotic therapy in cardiovascular disease. (Circulation. 1999;100:1667-1672.)

Key Words: antiplatelets • clopidogrel • ticlopidine

Introduction

Ticlopidine and clopidogrel (Figure 1) inhibit platelet aggregation induced by ADP. Ticlopidine is widely used to prevent thrombosis during coronary stent placement and has been found to be at least equivalent to aspirin in the prevention of events in patients with cerebrovascular disease. However, there is major concern regarding the safety of ticlopidine, which is associated with severe and sometimes fatal blood dyscrasias. Clopidogrel has similar pharmacological activity but produces fewer side effects. It is at least as effective as aspirin in preventing serious cardiovascular events in patients with stable vascular disease.1

Adenosine Diphosphate

ADP is a platelet activator that is released from red blood cells, activated platelets, and damaged endothelial cells and that induces platelet adhesion and aggregation.2-5 The platelet response to ADP is mediated by a family of membrane-bound nucleotide receptors called P2 receptors (Figure 2). These are further subdivided into P2X ligand-gated ion-channel receptors and P2Y G-protein–linked receptors.4 Two separate subtypes of these receptors, P2X1 and P2Y1, have been cloned from platelet cDNA libraries. However, only the P2X1 subtype has been demonstrated at the protein level.5,6 P2X1 induces transmembrane calcium flux in response to ADP but does not play a major role in platelet aggregation and is unaffected by the thienopyridines.7 The cloned P2Y1 receptor behaves in a similar manner to the platelet ADP receptor when expressed in other cell types and appears to be important in the platelet response to ADP.8,9

There is good evidence to indicate the presence of a third as yet unidentified ADP receptor. Binding studies indicate the presence of both high- and low-affinity P2Y receptors on platelets, and a proportion (30%) of these are insensitive to the thienopyridines.10 Functional experiments with specific P2Y1 antagonists suggest that some of these receptors are linked to the inhibition of adenylate cyclase (P2TAC), whereas a second population (P2T PLC) is linked to activation of phospholipase C, platelet shape change, and intracellular calcium mobilization.11,12 Inhibition of either receptor subtype prevents aggregation, which suggests that coordinated signaling through both these receptors is required for full platelet activation.13 The thienopyridines (1) inhibit ADP-induced inhibition of adenylate cyclase,14 (2) prevent the ADP-induced inhibition of the cytoskeletal associated protein VASP (vasodilator-stimulated phosphoprotein) phosphorylation,15 and (3) prevent the association of labeled G proteins with the platelet membrane.16 In contrast, they fail to inhibit ADP-induced platelet shape change or calcium flux. These data suggest that thienopyridines inhibit the as yet unidentified platelet P2TAC. On the other hand, inhibition of adenylate cyclase does not alter their platelet inhibitory effect, which implicates other mechanisms of action.17 In summary, although thienopyridines appear to act through the ADP receptor, the precise mechanism for their platelet inhibitory effects has not been identified.
Pharmacokinetics

Ticlopidine and clopidogrel require metabolism by the hepatic cytochrome P450-1A enzyme system to acquire activity. Plasma from treated patients leads to inhibition of untreated platelets, which indicates the presence of an active metabolite that has yet to be identified. Because of the structural similarities of ticlopidine and clopidogrel, it is possible that both compounds produce the same active metabolite; however, this has not been defined. Ticlopidine is rapidly absorbed and metabolized after an oral dose. Its bioavailability is increased by food and decreased by antacids. Clopidogrel is also extensively metabolized, and peak plasma concentrations of the main circulating metabolite, an inactive carboxylic acid derivative, occur at 1 hour. Its bioavailability is unaffected by food.

Pharmacodynamics

Ticlopidine and clopidogrel prolong bleeding time, inhibit platelet aggregation, and delay clot retraction. By inhibiting the effects of ADP released from platelet dense granules and inhibiting granule release, they also inhibit platelet aggregation induced by other agonists, including thromboxane analogues, platelet activating factor, collagen, and low concentrations of thrombin. However, high concentrations of strong platelet agonists can still overcome these inhibitory effects.

Ex vivo, ticlopidine and clopidogrel produce dose- and time-dependent inhibition of platelet aggregation, reaching a maximum of 40% to 60% inhibition of ADP-induced aggregation after 3 to 5 days. Similarly, recovery of platelet function is delayed after discontinuation of these agents, occurring slowly over 3 to 5 days. Bleeding time is significantly prolonged with both agents and reaches a maximum of 1.5- to 2-fold of baseline at 3 to 7 days.

Side Effects

Diarrhea, nausea, and vomiting are common with ticlopidine and occur in 30% to 50% of recipients. Skin rash is also a common problem. Neutropenia is the most serious side effect reported with ticlopidine and occurs in 2.1% of ticlopidine-treated patients. This can be severe (<450 neutrophils per mm$^3$ in 0.9% of patients) and has resulted in a number of fatalities. Most cases develop within the first 3 months of therapy and initially may be clinically silent. Full blood counts should be performed every 2 weeks during the first 3 months of therapy to identify these potential complications. Bone marrow aplasia and thrombotic thrombocytopenic purpura have also been reported. Fortunately, these are usually reversible after drug withdrawal.

Ticlopidine has also been associated with cholestatic jaundice, the mechanism of which is unknown. Elevated levels of liver enzymes rarely occur with ticlopidine, and levels usually return to normal after discontinuation of therapy. Ticlopidine has been reported to increase serum cholesterol by an average of 9%, although without an apparent increase in cardiovascular morbidity.

Clopidogrel has a more favorable side-effect profile than ticlopidine, and fatal complications have not been reported. Once again, gastrointestinal problems are the commonest side effect. In the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events), clinically severe rash was more frequent with clopidogrel than with aspirin (0.26% versus 0.10%, $P<0.05$), whereas clinically severe gastrointestinal hemorrhage was more common in aspirin-treated patients (0.71% versus 0.49%, $P<0.05$). Neutropenia was rare and indeed was less frequent in the clopidogrel-treated than the aspirin-treated group. Overall, bleeding was uncommon, and the frequency of any bleeding event was similar for aspirin and clopidogrel (9.27% versus 9.28%).

Drug Interactions

The combinations of aspirin and ticlopidine or clopidogrel have synergistic antiplatelet effects. Similarly, ticlopidine has been shown to enhance the inhibitory effects of a glycoprotein IIb/IIIa receptor antagonist. Phenytoin toxicity has been reported when combined with ticlopidine, probably owing to inhibition of its metabolism. Increased carbamazepine and theophylline levels have also been reported.

Clinical Trials

Cerebrovascular Disease

Several studies have examined the use of ticlopidine in the secondary prevention of cerebrovascular disease (Table 1).

Figure 1. Structure of ticlopidine and clopidogrel.

Figure 2. Three separate platelet ADP receptors have been proposed: a P2X1 ligand-gated ion-channel receptor; a P2Y$\alpha$C linked to phospholipase C, platelet shape change, and aggregation; and a P2Y$\alpha$C linked to inhibition of adenylate cyclase and platelet aggregation.
The Canadian American Ticlopidine Study (CATS) compared ticlopidine 500 mg/d with placebo in a randomized, double-blind fashion in 1053 patients within 4 months of a thromboembolic stroke. There was a relative reduction in the risk of recurrent stroke, vascular death, and myocardial infarction of 30.2% (95% CI 7.5% to 48.3%), with an annual event rate of 15.3% in the placebo-treated group and 10.8% in the ticlopidine-treated group.\(^2\) The Ticlopidine Aspirin Stroke Study (TASS) compared ticlopidine 500 mg/d with aspirin 1300 mg/d in a randomized, blinded fashion in 3069 patients with a history of a transient ischemic attack, amaurosis fugax, or minor stroke.\(^3\) Follow-up continued for 2 to 6 years. There was a 12% reduction (95% CI 2% to 26%) in the risk of nonfatal stroke or death of any cause compared with aspirin. The benefit of ticlopidine therapy was evident in the first year of therapy and persisted throughout the 6 years of the study.

In the CAPRIE trial, clopidogrel was slightly superior to aspirin in the prevention of vascular death, nonfatal or fatal stroke, and myocardial infarction in treated patients. In the 6431 patients recruited with a history of atherothrombotic stroke within the previous 6 months, the clopidogrel-treated patients had an average annual event rate of 7.15% compared with 7.71% for aspirin (\(P=0.07\)).\(^5\) Aspirin was no better than placebo in the non–Q-wave myocardial infarction, including those enrolled initially with a stroke or peripheral vascular disease, revealed a nonsignificant risk reduction of 7.4% (95% CI 1% to 15%).\(^6\) The ongoing CURE study (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) in patients with unstable angina and non–Q-wave myocardial infarction is designed specifically to examine the effect of the combination of clopidogrel and aspirin in coronary thrombosis.

### Coronary Artery Stenting

A number of randomized trials have examined the combination of aspirin and ticlopidine in patients after coronary artery stenting (Table 2). The STARS study (STent Anticoagulation Restenosis Study) randomized low-risk patients after successful stent implantation,\(^4\) the FANTASTIC (Full Anticoagulation versus Aspirin and Ticlopidine after stent implantation) and ISAR (Intracoronary Stenting and Antithrombotic Regimen) studies evaluated intermediate- or mixed-risk patients, and the MATTIS study (Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting) randomized high-risk patients.\(^5\) The ISAR study demonstrated a significant reduction in major cardiac events with aspirin-ticlopidine therapy compared with aspirin-antiplatelet therapy. Similar trends were seen in the MATTIS trial at 30 days (5.6% versus 11%, \(P=0.07\)) and at 6 weeks in the FANTASTIC trial (5.7% versus 8.3%, \(P=0.37\)). The STARS study compared aspirin and ticlopidine (n=546). The combined primary end point of death, myocardial infarction, angiographically evident thrombosis, or revascularization of the stented segment was 5.2% compared with 7.4% (95% CI 1% to 15%).

### Myocardial Infarction and Unstable Angina

Clopidogrel and ticlopidine are effective in some animal models of arterial thrombosis and prevent reocclusion and facilitate clot lysis after thrombolysis.\(^45\) However, there has only been 1 study that examined ticlopidine in unstable angina.\(^46\) There was a 6.3% (from 13.6% to 7.3%, \(P=0.009\)) reduction in the combined end point of vascular death and nonfatal myocardial infarction with ticlopidine compared with no antiplatelet therapy in the 652 patients enrolled, similar to the benefit seen with aspirin in unstable angina.\(^47\) However, there was no placebo arm, and the study was performed on an open-label basis. In the CAPRIE trial, the patients who were enrolled with myocardial infarction as their incident event did not have a significant reduction in the primary end point of death, myocardial infarction, or vascular death compared with aspirin-treated patients. A post hoc analysis of all patients (n=8446) with a history of myocardial infarction, including those enrolled initially with a stroke or peripheral vascular disease, revealed a nonsignificant risk reduction of 7.4% (95% CI 1% to 15%).\(^6\) The ongoing CURE study (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) in patients with unstable angina and non–Q-wave myocardial infarction is designed specifically to examine the effect of the combination of clopidogrel and aspirin in coronary thrombosis.

### TABLE 1. Prevention of Major Vascular Events by Ticlopidine and Clopidogrel in Patients With a History of Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Follow-Up, y</th>
<th>Comparison</th>
<th>Absolute Risk Reduction, %</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATS</td>
<td>1053</td>
<td>3</td>
<td>Ticlopidine vs placebo</td>
<td>4.5</td>
<td>0.006</td>
</tr>
<tr>
<td>TASS</td>
<td>3069</td>
<td>2–6</td>
<td>Ticlopidine vs aspirin</td>
<td>2</td>
<td>0.048*</td>
</tr>
<tr>
<td>CAPRIE†</td>
<td>6431</td>
<td>1–3</td>
<td>Clopidogrel vs aspirin</td>
<td>0.56</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*For cumulative Kaplan-Meier estimates.†The subgroup of patients recruited with cerebrovascular disease.

In the TASS study, the primary events were the combination of fatal and nonfatal strokes. In the CAPRIE and CATS studies, the primary events included stroke, myocardial infarction, or vascular death.

### TABLE 2. Prevention of Major Cardiac Events After Coronary Artery Stent Insertion: Ticlopidine Compared With Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Population Risk</th>
<th>Absolute Risk Reduction in Cardiac Events, %</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FANTASTIC</td>
<td>485</td>
<td>Mixed</td>
<td>2.6</td>
<td>0.37</td>
</tr>
<tr>
<td>MATTIS</td>
<td>350</td>
<td>High</td>
<td>5.4</td>
<td>0.07</td>
</tr>
<tr>
<td>ISAR</td>
<td>517</td>
<td>Mixed</td>
<td>4.6</td>
<td>0.01</td>
</tr>
<tr>
<td>STARS</td>
<td>1652</td>
<td>Low</td>
<td>1.9</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Cardiac events included death due to cardiac causes, myocardial infarction, repeat PTCA of the stented vessel, or bypass surgery at 30 days in the ISAR, MATTIS, and STARS studies. In the FANTASTIC study, cardiac events (death, myocardial infarction, and stent occlusion) were secondary end points and did not include repeat PTCA or bypass surgery.
the target lesion within 30 days occurred in 3.6% of patients randomized to aspirin monotherapy, 2.7% assigned to aspirin-warfarin therapy, and 0.5% assigned to aspirin-ticlopidine therapy (P<0.001), demonstrating the superiority of combined aspirin-ticlopidine therapy over aspirin-anticoagulant and aspirin monotherapy. In the ISAR, FANTASTIC, and MATTIS trials, hemorrhagic and peripheral vascular complications were less frequent with antiplatelet therapy. In the STARS study, the rate of these complications was equivalent in the aspirin-ticlopidine group and the aspirin-anticoagulant group, although these rates were higher than in the aspirin monotherapy group. The combination of antiplatelet therapies resulted in shorter hospital stays, and the early clinical benefit of antiplatelet therapy persisted for up to 12 months, although no reduction in restenosis was seen.53 The benefit of antiplatelet therapy was also apparent in high-risk patients and was independent of stent design (although the majority of trials used the Palmaz-Schatz stent).54,55

One issue raised by the trials was the timing of drug administration. In the FANTASTIC study, the acute (≤24 hour) occlusion rate was higher for the antiplatelet-treated group (2.4% versus 0.4%, P=0.06). Furthermore, in the ISAR study, the benefit of combined antiplatelet therapy did not appear until 3 days after the procedure.51 Ticlopidine was delayed until after stent insertion in these trials. Ex vivo studies of platelet function indicate that ticlopidine administered after stent placement may not provide maximum periprocedural and early postprocedural protection. Platelet activation peaks at 48 to 72 hours after stent implantation,56 whereas the antiplatelet effects of ticlopidine peak at 3 to 5 days. Ticlopidine administration >24 hours before intervention results in significant inhibition of platelet aggregation at the time of the procedure.57 Furthermore, the duration of ticlopidine therapy before intervention correlates with a reduction in procedure-related non–Q-wave myocardial infarctions.58 Thus, earlier administration of ticlopidine may provide greater benefit.

In a porcine model of stent thrombosis, clopidogrel produced rapid (within 30 minutes) and dose-dependent inhibition of stent thrombosis.59 Its combination with aspirin was synergistic and produced 95% to 98% inhibition of thrombosis. The efficacy of clopidogrel in combination with aspirin is being studied in the CLOpidogrel ASpirin Stent International Cooperative Study (CLASSICS). Whether clopidogrel can replace ticlopidine is as yet unclear. However, the lower rate of serious side effects reported with clopidogrel would make it an attractive alternative in this setting.

Peripheral Vascular Disease

Ticlopidine has been reported to improve pain-free and maximum walking distance in patients with peripheral arterial disease60 and to reduce the need for vascular surgery.61 It has also been shown to reduce reocclusion after thrombendarterectomy and to significantly improve long-term patency of peripheral saphenous vein grafts.62,63 Ticlopidine and clopidogrel also reduce the high cardiac morbidity (60% over 10 years64) in patients with a history of peripheral arterial disease.65,66 In the CAPRIE trial, clopidogrel was slightly superior to aspirin in the prevention of stroke, myocardial infarction, and vascular death in the patients enrolled with peripheral arterial disease, with an average annual event rate in the clopidogrel-treated group of 3.71% versus 4.86% in the aspirin-treated group (P=0.0028). The combination of clopidogrel with aspirin therapy may prove more effective, but this issue has not been addressed in clinical trials.

Conclusions

Ticlopidine and clopidogrel are effective antiplatelet agents and are useful in the prevention of stroke, myocardial infarction, and vascular death in patients with vascular disease. Serious, sometimes fatal blood dyscrasias are seen with ticlopidine use. In contrast, clopidogrel has proved to be safe in long-term trials and to be at least as effective as aspirin. Although clopidogrel would be an attractive alternative to ticlopidine, it remains to be seen whether it can prevent the thrombotic complications of coronary stent placement. Perhaps the most important issue for antithrombotic therapy, however, is whether clopidogrel adds to the benefit seen with aspirin. If so, clopidogrel will have a major effect on the management of cardiovascular disease.

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References


