Role of Ticlopidine for Prevention of Stroke

Gregory W. Albers, MD

Background: Ticlopidine, an antiplatelet agent with a unique mechanism of action, is now available for clinical use in the United States and Canada.

Summary of Comment: Recently two large randomized trials demonstrated that ticlopidine can reduce the risk of subsequent stroke in patients presenting with a transient ischemic attack or stroke. One study found that ticlopidine was more effective than aspirin for stroke prevention; however, it was less well tolerated than aspirin and was associated with severe but reversible neutropenia in almost 1% of patients.

Conclusions: Ticlopidine is effective for both primary and secondary stroke prevention. It has a favorable risk/benefit ratio and is a particularly attractive option for patients who are unable to take aspirin. (Stroke 1992;23:912–916)

Key Words • platelet aggregation • stroke management • ticlopidine

Pharmacological properties

Ticlopidine is a thienopyridine derivative with a structure and mechanism of action that are distinct from other clinically available antiplatelet agents. Unlike aspirin or dipyridamole, ticlopidine does not inhibit cyclooxygenase or phosphodiesterase. Although the precise mechanism of action of ticlopidine remains unclear, its primary effect appears to be inhibition of adenosine diphosphate (ADP)-induced platelet aggregation. There is evidence that ticlopidine inhibits ADP-induced exposure of the fibrinogen binding site, the glycoprotein IIb/IIIa complex, on activated platelets. Platelet aggregation induced by platelet-activating factor, arachidonic acid, collagen, and thrombin is also inhibited by ticlopidine. However, these effects may be indirect, since a variety of platelet agonists may elicit ADP release.

Maximal antiplatelet effects are seen at a dose of 500 mg per day. Three to 5 days are required for maximal inhibition of platelet aggregation. After discontinuation of ticlopidine, the rate of recovery of platelet aggregation mirrors platelet turnover time (approximately 1 week), suggesting that ticlopidine has an irreversible antiplatelet effect.

The half-life of ticlopidine increases during the initial weeks of therapy, suggesting autoinhibition of metabolism. Elimination half-lives of 24–96 hours have been reported; however, twice daily administration is recommended to improve gastrointestinal tolerance. Ticlopidine’s antiplatelet activity is much more prominent in ex vivo studies than in in vitro studies. This suggests that ticlopidine metabolites may be primarily responsible for ticlopidine’s antiplatelet activity. However, these metabolites have not been clearly identified.

In general, oral bioavailability of ticlopidine is high (80–90%), and administration with meals improves both bioavailability and gastrointestinal tolerance. Greater than 98% of the drug is protein bound.

Adverse Effects

In various studies, ticlopidine-treated patients typically discontinue the medication because of adverse effects about twice as frequently as placebo patients. In general, however, most of the adverse effects of ticlopidine are minor and do not cause significant morbidity.

Gastrointestinal complaints are the most common adverse reactions to ticlopidine and occur in about 20% of patients. Diarrhea, nausea, and epigastric discomfort are the most frequent complaints; however, these side effects may diminish if the medication is taken with meals. Gastrointestinal side effects typically are most significant during the first few weeks of therapy and often respond to temporary dose reduction. Despite this, about 6% of patients will permanently discontinue ticlopidine because of gastrointestinal effects, primarily diarrhea.

Dermatologic reactions are the second most common side effects and occur in about 10% of ticlopidine-treated patients. The most common reactions are a maculopapular rash and urticaria. About 3% of ticlopi...
Ticlopidine prolongs bleeding time to a greater extent than other antiplatelet agents and has been associated with minor bleeding complications in about 5% of patients. However, significant hemorrhage occurs in <1% of ticlopidine-treated patients. In a large randomized trial of aspirin-tolerant patients, gastrointestinal bleeding was three times more common in patients treated with 1,300 mg per day of aspirin than in patients treated with 500 mg per day of ticlopidine. Adequate comparisons with lower doses of aspirin have not been reported.

Total cholesterol levels increase by about 8–10% during ticlopidine therapy. However, in general, no significant change in the ratio of high-density lipoprotein to low-density lipoprotein has been documented. It is unclear if the lipoprotein effects are clinically significant.

Potentially the most serious adverse effect of ticlopidine is neutropenia. In the two major stroke prevention trials, neutropenia (absolute neutrophil count <1,200/mm³) occurred in 50 of 2,048 ticlopidine-treated patients (2.4%), in 12 of 1,527 aspirin-treated patients (0.8%), and in six of 536 placebo-treated patients (1.1%). Severe neutropenia (absolute neutrophil count <450/mm³) was seen in 17 patients (0.8%) on ticlopidine. Ticlopidine-induced neutropenia virtually always occurs during the first 3 months of therapy and appears to be uniformly reversible with discontinuation of the drug. In patients who developed severe neutropenia in the two largest studies of ticlopidine, the mean time to nadir of the neutrophil count was 39 days (range, 26–62 days), and mean time to recovery (absolute neutrophil count ≥1,200/mm³) after discontinuation was 13 days (range, 4–21 days) (Reference 9 and unpublished observations, Syntex Laboratories, Inc., Palo Alto, Calif., 1991). Biweekly blood counts are required during the first 12 weeks of therapy. If the absolute neutrophil count drops to <1,000/mm³ the drug should be discontinued.

Drug Combinations

Because aspirin and ticlopidine inhibit platelet aggregation by different mechanisms, combination therapy might be predicted to provide superior antithrombotic protection. Unfortunately, few studies using combination therapy have been performed. In one small normal volunteer study, various doses of ticlopidine were found to potentiate the effects of aspirin (500 mg per day) on collagen-induced platelet aggregation. A small study of patients with cerebrovascular disease found that combination therapy with low doses of ticlopidine (100 mg per day) and aspirin (81 mg per day) has broader ex vivo antiplatelet effects than higher doses of either agent alone. However, an increase in minor bleeding was noted in the combination therapy group. Adequate clinical trials are necessary to determine the role of combination therapy with aspirin and ticlopidine.

Only minimal data are available regarding combined therapy with anticoagulants and ticlopidine. Preliminary data suggest that combining ticlopidine with either low-dose subcutaneous heparin or oral anticoagulation does not lead to significant potentiation of either agent. However, until more safety data are available, combination therapy with ticlopidine and anticoagulants cannot be recommended.

Efficacy of Ticlopidine for the Prevention of Stroke

Over the last few years several trials have suggested that ticlopidine has potential for preventing strokes in patients with a history of cerebral ischemia. Reliable data regarding the safety and efficacy of ticlopidine for stroke prevention are now available from CATS and TASS.

The Canadian-American Ticlopidine Study (CATS) in Thromboembolic Stroke

CATS randomized 1,053 patients who had suffered a recent ischemic stroke to treatment with ticlopidine, 250 mg b.i.d., or a placebo in a randomized, double-blind study. Patients with an atherothrombotic or lacunar infarction within 1 week to 4 months of trial entry were eligible (cardioembolic events were excluded). Participants were required to have residual neurological effects from the stroke at the time of study entry; however, individuals who were likely to remain bedridden or had severe comorbidity were excluded. Clinical assessments were made every 4 months up to a maximum of 3 years. The average follow-up obtained was 24 months. Laboratory assessments were performed every 2 weeks for the first 3 months. The primary outcome event cluster was ischemic stroke, myocardial infarction, or vascular death.

An efficacy analysis that excluded events occurring >28 days after permanent discontinuation of the study drug found that primary outcome events occurred in 10.8% per year of ticlopidine patients versus 15.3% per year in the placebo group (risk reduction, 30.2%; 95% confidence interval [CI], 7.5–48.3%; p = 0.006). All outcomes were analyzed using one-tailed tests of significance. A secondary analysis indicated that ticlopidine also significantly reduced the incidence of stroke or stroke death (risk reduction, 33.5%; p = 0.008). An intention-to-treat analysis of the primary outcome events estimated a 23% reduction attributable to ticlopidine (95% CI, 1.0–40.5%; p = 0.02) (Table 1). There was no difference between the beneficial effects of ticlopidine in men versus women (approximately 40% of the participants were women).

Permanent discontinuation of study medication before the end of the study occurred in 40% of the placebo group and 52% of the ticlopidine group. Adverse effects were the primary cause of discontinuation in 3% of the placebo group patients compared with 12% on ticlopidine (p < 0.001).

CATS was the first large-scale trial to document the effectiveness of ticlopidine for stroke prevention. CATS used a placebo, rather than aspirin, as the comparison drug because there was little direct evidence from clinical trials that aspirin was effective for stroke prevention in patients with moderate or severe completed strokes. Only a single large trial, performed by the Swedish Cooperative Study Group, has focused exclusively on patients with completed stroke. The Swedish trial failed to document a beneficial effect of aspirin over placebo; however, a number of methodological
Table 1. Intention-to-Treat Analysis of Outcome Events in the Canadian-American Ticlopidine Study and the Ticlopidine Aspirin Stroke Study

<table>
<thead>
<tr>
<th>Study and treatment</th>
<th>Fatal or nonfatal stroke (%)</th>
<th>Death or nonfatal stroke (%)</th>
<th>Stroke, MI, or vascular death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TASS (n=3,069)</td>
<td>20 (650 mg b.i.d.)</td>
<td>36 (250 mg b.i.d.)</td>
<td>12 (250 mg b.i.d.)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>13</td>
<td>19</td>
<td>...</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>10*</td>
<td>17*</td>
<td>...</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.7</td>
<td>...</td>
<td>14.8</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>8.5†</td>
<td>...</td>
<td>11.3‡</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; TASS, Ticlopidine-Aspirin Stroke Study; CATS, Canadian-American Ticlopidine Study.

*p<0.05 (Kaplan-Meier, two-sided significance level).
†p=0.06 (Kaplan-Meier, one-sided significance level).
‡p<0.05 (Kaplan-Meier, one-sided significance level).

Concerns about this trial have been raised, including the fact that it did not have the power to detect a risk reduction of 30% (the degree of risk reduction observed in CATS). Evidence of the efficacy of aspirin for the prevention of stroke in patients with transient ischemic attack (TIA) and minor stroke is well established. In addition, subgroup analysis of patients in the European Stroke Prevention Study and the French AICLA Study revealed a substantial reduction in the outcomes of stroke, or stroke and death, in patients with completed stroke treated with aspirin or a combination of aspirin and dipyridamole. Therefore, since the underlying pathophysiology is not qualitatively different between TIA and stroke, aspirin is generally considered to be effective for stroke prevention in patients with either TIA or completed stroke. Therefore, a direct comparison between aspirin and ticlopidine would be more relevant than the use of a placebo control. Such a comparison was provided in TASS.

Ticlopidine-Aspirin Stroke Study (TASS)

In TASS, 3,069 patients with transient cerebral or retinal ischemia or minor stroke were randomized to treatment with ticlopidine, 250 mg b.i.d., or aspirin, 650 mg b.i.d., in a double-blind study design. Qualifying events must have occurred within 3 months of entry into the study. Patients with a history of peptic ulcer disease or gastrointestinal bleeding were excluded from the study. Laboratory assessments were performed every 2 weeks for the first 3 months. Patients were evaluated at 4-month intervals throughout the trial. The average follow-up was 3.3 years; however, during the nearly 6 years of the trial, approximately 50% of the patients discontinued the study medication. As a result, the mean duration of treatment was 2.3 years. Death from any cause and nonfatal stroke were the primary outcome events and were analyzed using the intention-to-treat principle (Table 1).

Ticlopidine produced a significant reduction in the occurrence of the primary outcome events. Although this effect was small in magnitude, it was detectable during the first year of the trial and persisted throughout the study. The 3-year rate of death or nonfatal stroke was 17% in the ticlopidine group compared with 19% in the aspirin group (risk reduction, 12%; 95% CI, -2% to 26%; p=0.048).

A larger risk reduction was obtained for the secondary outcome of fatal or nonfatal stroke, with a 3-year event rate of 10% in the ticlopidine group versus 13% in the aspirin group (risk reduction, 21%; 95% CI, 4-38%; p=0.024). Using an efficacy analysis, this outcome was reduced by 27%. The reduction in fatal or nonfatal stroke attributable to ticlopidine was considerably higher at 1 year than at 3 years. Using an intention-to-treat analysis, the incidence of this outcome was reduced by 46% at 1 year (48% by efficacy analysis).

As in CATS, ticlopidine produced significant benefit in both men and women, but adverse effects accounted for a substantial rate of permanent discontinuation of study drug (20.9% in the ticlopidine group versus 14.5% in the aspirin group; p<0.05). However, there was not a significant difference between the total number of patients who reported any side effect. In addition, there did not appear to be a significant difference in the number of patients with serious adverse effects. Severe neutropenia (absolute neutrophil count <450/mm³) occurred in 0.9% of the ticlopidine group (Table 2). This effect was promptly reversed in all patients after discontinuation of the medication. However, one patient developed an infection and died of renal failure secondary to antibiotic toxicity. The rate of intracranial hemorrhage (intracerebral hemorrhage or hemorrhagic infarction) was low in both the aspirin and ticlopidine groups (0.7% in each group).

Despite the exclusion of patients with a history of peptic ulcer disease or gastrointestinal bleeding from the study, gastritis, gastrointestinal hemorrhage, or peptic ulcer developed in 6% of the aspirin-treated patients, nearly three times the rate in the ticlopidine group (Table 2). This advantage of ticlopidine over aspirin was probably enhanced by the high dose of aspirin chosen for this trial (1,300 mg per day). Although there continues to be controversy regarding the optimal dose of aspirin for stroke prevention, many physicians currently use a dose of ≤325 mg per day.

Noncerebrovascular Uses of Ticlopidine

Before the recent ticlopidine stroke prevention trials, there was considerable clinical experience outside the
United States with ticlopidine in patients without cerebrovascular disease.

Intermittent Claudication

There is evidence from several double-blind, placebo-controlled trials that ticlopidine is of benefit for patients with intermittent claudication due to peripheral vascular disease. A number of studies have documented improvements in walking distance and walking speed as well as systolic ankle/arm blood pressure ratios. In one study, ticlopidine was shown to be superior to the calcium antagonist flunarizine for increasing lower extremity blood flow in patients with peripheral vascular disease.

Cardiovascular Events

A meta-analysis of four studies evaluating ticlopidine in patients with intermittent claudication suggested a significant reduction in cardiovascular events in ticlopidine-treated versus placebo-treated patients (risk reduction, 66%; p < 0.006). In addition, the Swedish Ticlopidine Multicentre Study randomized 687 claudication patients to treatment with ticlopidine or matching placebo and demonstrated a lower mortality from ischemic heart disease in the ticlopidine group. In addition, a recent, large, unblinded, Italian trial documented a 46.3% reduction in risk of vascular death or nonfatal myocardial infarction in unstable angina patients treated with ticlopidine (p = 0.009). However, two double-blind, placebo-controlled studies have documented similar reductions in the incidence of myocardial infarction or cardiac death in unstable angina patients treated with aspirin.

In addition, no significant difference in the rate of fatal or nonfatal myocardial infarction was observed in ticlopidine-treated patients compared with aspirin-treated patients in TASS. Therefore, a randomized trial in patients at high risk for myocardial infarction would be necessary to determine how ticlopidine compares with aspirin for prevention of myocardial infarction.

Bypass Graft Occlusion

Ticlopidine was documented to be beneficial for the prevention of bypass graft occlusion after coronary artery bypass graft surgery in a randomized, placebo-controlled trial. In addition, no significant difference was seen between ticlopidine and the anticoagulant acenocoumarol on patency rates of coronary bypass grafts in a randomized trial.

Diabetic Retinopathy

The French Ticlopidine Microangiopathy of Diabetes (TIMAD) Study Group recently reported very encouraging data from a well-designed, placebo-controlled trial. This group found that ticlopidine significantly reduced the progression of retinopathy in patients with nonproliferative diabetic retinopathy. Insulin-dependent diabetics treated with ticlopidine had a sevenfold reduction of microaneurysm progression (p = 0.03) in addition to a reduced incidence of new vessels (p = 0.056). A previous study using aspirin alone or in combination with diprydamole had failed to document a reduced rate of progression in nonproliferative diabetic retinopathy.

Ticlopidine Versus Aspirin for Stroke Prevention: Risk/Benefit Analysis

TASS findings suggest that if 100 patients with a recent history of TIA or nondisabling stroke are treated with ticlopidine instead of aspirin for a 2-year duration, three fewer strokes would be expected. In addition, if ticlopidine is chosen instead of a 1,300 mg per day dose of aspirin, approximately four major gastrointestinal complications (gastritis, peptic ulcer, and gastrointestinal hemorrhage) would be avoided. If a lower dose of aspirin is preferred (325 mg), then perhaps only one or two fewer gastrointestinal complications might be expected.

In contrast to these significant advantages of ticlopidine, there are several disadvantages. Of 100 patients treated with ticlopidine instead of 1,300 mg per day of aspirin, diarrhea would be expected in about 10 additional patients, and about five more adverse dermatologic reactions would occur. More significantly, one patient could be expected to develop severe neutropenia. Also, ticlopidine patients would be inconvenienced by the requirement for additional blood tests (for hematological monitoring) as well as the requirement for b.i.d. dosing. Finally, ticlopidine is considerably more expensive than aspirin.

Because of these disadvantages, it is improbable that ticlopidine will become the first option for stroke prevention for most patients. Since it is more complex than aspirin to administer, it should be avoided in unreliable patients or those who cannot understand the importance of hematological monitoring. However, ticlopidine is extremely useful for a number of patient subgroups. Clearly, ticlopidine is a very attractive option for patients with risk factors for gastrointestinal hemorrhage or previous aspirin intolerance. One study has already shown that ticlopidine can be tolerated by the majority of aspirin-intolerant patients. In addition, ticlopidine is a viable option for patients who continue to have ischemic events despite aspirin therapy. Subgroup analysis of TASS indicates that ticlopidine was more effective than aspirin in patients who had previously been taking anticoagulant or antiplatelet therapy.

Because of data suggesting that it can increase amputation in patients with peripheral vascular disease, ticlopidine should be considered for stroke-prone patients who also have claudication. In addition, the encouraging results of the TIMAD study suggest that ticlopidine may become the preferred choice for a patient with nonproliferative diabetic retinopathy. It has been argued that ticlopidine should be the "definite drug of choice" for stroke prevention in women because early studies failed to show benefit of other antiplatelet agents in women. However, both the European and French stroke prevention trials have documented similar benefits of aspirin in both sexes, and therefore the optimal choice for stroke prevention in women remains uncertain.

Future options requiring additional exploration include the combination of low-dose ticlopidine with either low-dose aspirin or low-intensity anticoagulation in hopes of improved efficacy for prevention of vascular ischemic events.

References


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G W Albers

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