

Chapter 14

Thienopyridines: Ticlopidine and Clopidogrel

- **Mechanism of Action**
- Therapeutic Efficacy
 - Secondary prevention
 - Acute coronary syndromes
 - Percutaneous coronary interventions
- Side Effects
- Dosage
- New Agents

Thienopyridines Clopidogrel

- Clopidogrel is currently the agent of choice in this group.
- Its antiplatelet action is through blockade of ADP platelet receptor.
- It is slightly more effective than aspirin in prevention of cardiovascular events.
- It is recommended in patients undergoing PCI with coronary stenting:
 - In patients with ACS without persistent ST elevation-
 - Possibly in STEMI.
 - To replace aspirin in patients allergic or intolerant to aspirin.
- Its main limitation is cost.
- It is given from 3-12 months.
- In ACS or PCI a loading dose 300-600 mg is given initially followed by a maintenance dose of 75 mg once/day.

MECHANISM OF ACTION

- These agents block the binding of the adenosine diphosphate (ADP) to a specific platelet receptor P_2Y_{12} that activates G_i , thus inhibiting adenylyl cyclase and platelet aggregation.
- There are multiple ADP receptors, all of which are part of the membrane bound nucleotide P_2 receptor family. The thienopyridines can also indirectly inhibit the activity of several other platelet agonists such as arachidonic acid, collagen, thrombin, epinephrine and serotonin.
- Inhibition of fibrinogen binding to GP IIb/IIIa receptors is observed after treatment with these agents secondary to ADP receptor blockade.
- They can inhibit platelet aggregation induced by collagen and thrombin.
- Ticlopidine and clopidogrel are only available in the oral form. They are prodrugs and undergo first pass metabolism through the liver to become biologically active.

THERAPEUTIC EFFICACY

- *Secondary Prevention.*
Prevention of endpoints of vascular death, MI, ischemic stroke.
 - Ticlopidine: reduced the combined endpoint of vascular death, MI and stroke in patients with vascular diseases. When compared with aspirin it produced a 10% relative reduction of the endpoints.
 - Clopidogrel: reduced composite endpoints in patients with stroke, MI and PVD by 8.7% (CAPRIE trial). Patients with PVD derived particular benefit from clopidogrel largely due to reduction in the rate of MI.

- *Acute Coronary Syndromes*
 - ✓ **Non-ST elevation ACS (CURE trial).**
 - Clopidogrel reduces the combined endpoints of vascular death, MI or stroke.
 - Combination of clopidogrel and aspirin produced reduction in the composite endpoint by 20% compared to aspirin plus placebo. Within 24 hours of treatment the benefit becomes evident and persists thereafter.
 - Clopidogrel therapy produced a similar relative risk reduction in low, intermediate and high risk patients. However, the high risk patients derived the greatest absolute benefit.
 - The benefit was largely due to fewer MIs, there was modest reduction in refractory ischemia and need for revascularization.
 - There was significant increase in major bleeding but not in life threatening bleeding or hemorrhagic stroke.
 - *On the basis of the CURE trial, clopidogrel should be administered to patients presenting with an ACS.*
 - ✓ **ST elevation MI**
 - There are few data regarding the efficacy of the ADP antagonists in ST elevation MI (there are two ongoing trials CLARITY-TIMI 28 and COMMIT that address this issue).
 - ADP antagonists may be used as adjunctive antiplatelet therapy.
- *Percutaneous Coronary Interventions (PCI)*
 - ADP antagonists have become standard of care after intracoronary stent deployment to reduce thrombotic complications. This is supported by the trials: -ISAR (comparing aspirin/ticlopidine to anticoagulants). - STARS (comparing aspirin/ticlopidine to aspirin alone). - PCI-CURE (aspirin plus either clopidogrel or placebo for 6 days prior to intervention and for four weeks after intervention).

SIDE EFFECTS

- The use of ticlopidine has been limited by the side effects particularly rare but severe neutropenia in 0.8% of patients. It tends to occur within 3 months of the initiation of treatment and is usually reversible after discontinuation. Thrombotic thrombocytopenic purpura may occur in 0.02% of patients in first month. Regular complete blood count every two weeks for the duration of therapy is recommended.
- Other common side effects of ticlopidine include nausea, vomiting, diarrhea, increased serum cholesterol, and abnormal liver function tests.

- Side effects of clopidogrel are generally mild, and tolerability is similar to that of aspirin. Gastrointestinal hemorrhage occurred in 2.0% of patients treated with clopidogrel compared with 2.7% of those treated with aspirin.
- There is no current recommendation for formal hematologic monitoring as in ticlopidine.
- Combination of clopidogrel plus aspirin is associated with a significant increase in major and minor bleeding, but not life-threatening bleeding events. The bleeding risk appears to be greater in patients with non-ST elevation ACS who require CABG rather than PCI.
- It is recommended that clopidogrel be stopped for at least five and preferably seven days in patients undergoing CABG.

DOSAGE

- Platelet inhibition takes a few days to reach a plateau with either agent: from 3-5 days with ticlopidine, and from 3-7 days with clopidogrel.
- To accelerate platelet inhibition and rapidly achieve a therapeutic effect: a large initial loading dose is given, 500 mg for ticlopidine and 300 to 600 mg for clopidogrel .
- After the initial loading dose a maintenance dose of 250 mg 2x daily of ticlopidine or 75 mg once daily of clopidogrel are administered. Clopidogrel has a faster onset of action than ticlopidine.
- These compounds irreversibly inhibit the platelet P₂Y₁₂ receptor, their inhibitory effect lasts for the rest of the platelet's life span.
- When high (300-600 mg) loading doses of clopidogrel are administered orally, effects on platelet activation, aggregation and adhesion to a collagen surface are observed within 90 minutes of administration.

NEW AGENTS

Prasugrel

- An investigational drug.
- A new powerful thienopyridine P₂Y₁₂ antagonist.
- It has a more potent antiplatelet action than clopidogrel.
- Its safety and efficacy was tested in patients undergoing PCI with intended coronary stenting (JUMBO-TIMI 26 trial, 2004).
- When compared with clopidogrel, there was no difference in bleeding rate, but there was a trend toward lower ischemic event rates with prasugrel.