Antiplatelet Agents

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Aspirin

Aspirin is the oldest and still the most widely used antiplatelet agent. Aspirin exerts its antithrombotic effect by irreversibly inhibiting platelet cyclooxygenase (COX) through acetylation of serine at position 529 leading to steric hindrance of the enzyme. This prevents the formation of the platelet agonist thromboxane A_2 leading to inhibition of platelet function.

In most patients, platelet cyclooxygenase can be inhibited by aspirin doses as small as 30 mg per day. In clinical trials, aspirin doses ranging from 1200 to 30 mg daily have been shown to be effective for prevention of thrombosis. Gastrointestinal side effects are diminished by the lower doses. Currently, the recommended dosage of aspirin is 81–325 mg/day with less side effects seen with doses less than 100 mg. Aspirin is rapidly metabolized by the liver, and when the drug is taken in low doses, most platelet inhibition occurs in the portal vein. Since the platelet inhibition lasts the life of the platelet, the biological half-life of aspirin of 5–7 days is considerably longer than the plasma half-life of 20 minutes. The only drug interactions are with COX-1 inhibitor such as ibuprofen and naproxen which block aspirin from acetylating COX-1. This interaction is not seen with more COX-2 selective drugs such as celecoxib and diclofenac. This negative interaction can be lessened with taking aspirin before other COX-1 inhibitors or if chronic use is required using more COX-2 selective agents.

Aspirin is the initial therapy for any arterial ischemic disorder. Clinical trials have shown aspirin to be effective in ischemic heart disease, angioplasty, coronary artery bypass surgery, and cerebrovascular disease.

Aspirin is effective in secondary prevention of myocardial infarctions. In a meta-analysis by the Antiplatelet Trialists' Collaboration, aspirin use after myocardial infarction reduces the risk of non-fatal strokes by 42%, non-fatal MI by 31%, and vascular death by 13%. Aspirin use in acute myocardial infarction reduces strokes by 45%, re-infarction by 49%, and vascular death by 22%.

Recent clinical trials looking at aspirin for primary prevention of vascular events have found little to no benefit and a consistent risk of bleeding. While older trials suggested a use of aspirin in primary prevention, in the current era of good blood pressure control and statin use, aspirin is no longer recommended for primary prevention except for patients who have evidence of vascular disease – angina, claudication, etc.

Aspirin effect is achieved very rapidly with oral ingestion of more than 160 mg; this dose or higher should be used when a rapid antiplatelet

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effect is desired such as in acute myocardial infarction. Since platelet cyclooxygenase is permanently inhibited, the antiplatelet effect of aspirin will last until the majority of circulating platelets have been replaced; this may take up to 5 days. Coated aspirin – especially enteric coated – may not be as well-absorbed especially in obese patients. Consideration should be given to either using higher (>81 mg) doses or chewable aspirin.

The major side effect of aspirin is bleeding. Minor bleeding complications are increased by 5%. Randomized trials suggest that the incidence of severe or fatal bleeding with aspirin use is increased by 0.5%/year of use with chronic use.

There has been interest in identifying patients who in testing appear to be "aspirin-resistant." Several difficulties with this concept are that the incidence of aspirin resistance varies with the techniques used to study this and true biochemical resistance appears to be rare. Far more common is the "resistance" of the patient to taking aspirin.

Uncertainty now exists for management of a bleeding emergency in the patient taking aspirin. In a study of patients with non-traumatic intracranial hemorrhage on aspirin, the transfusion of platelets significantly worsened outcomes. Also, studies have suggested transfused platelets do not reverse the impaired platelet function in patients taking aspirin. It has been reported that DDAVP will reverse aspirin inhibition and may be effective for emergency surgery or for patients with minor bleeding.

Platelet P2Y12 Receptor Antagonists

Clopidogrel

Clopidogrel is the most widely use thienopyridine and is dosed at 75 mg once per day. Clopidogrel takes 4–7 days to achieve full platelet inhibition, so for acute situations, a loading dose of 300–600 mg is used. The antiplatelet effect can last for 7 days after cessation of therapy. In early trials, single-agent clopidogrel was found to be slightly better than aspirin in prevention of myocardial infarctions and strokes than aspirin, so it can substitute for aspirin in patients who are aspirin-intolerant or aspirin failures.

Most studies have looked at clopidogrel in combination with aspirin. For patients with acute coronary syndromes, this combination leads to improved outcomes and should be continued for a year. Patients with stents also benefit from combined therapy – bare metal for 4 weeks and drug eluting up to a year as described in Chap. 20. Combined therapy for acute coronary syndromes after 1 year, chronic ischemic heart disease, or primary prevention appears not to be effective. For patients with strokes, combined therapy has been shown to be harmful. The only exception is immediately after a stroke or TIA, combined therapy does reduce the risk of new events.

Two factors in theory may decrease effectiveness of clopidogrel. One is that many proton pump inhibitors (especially omeprazole) in theory block conversion of clopidogrel to the active metabolite, but this appears to be clinically irrelevant as most clinical data from large trials do not support lowered effectiveness. Second is that up to 30% of people carry a CYP2C19 loss-of-function polymorphism that also decreased the conversion of drug to the active form. While this appears to translate into these patients having less platelet inhibitor by clopidogrel, again overall clinical significance of this appears not to be relevant.

The amount of platelet inhibition by clopidogrel is more variable than that seen with aspirin. While the notion of using platelet testing such as the VerifyNow P2Y12 to identify low-responding patients and then altering therapy is appealing, clinical trials to date have shown no benefit to this approach.

Although it first appeared that, like ticlopidine, clopidogrel was also associated with the development of TTP, the incidence now appears to be much lower than that seen with ticlopidine at 0.0001%.

Management of patients on clopidogrel who are bleeding is uncertain for the same reasons as discussed for aspirin and use of DDAVP may be helpful.

Prasugrel

Prasugrel is a thienopyridine that binds and blocks the ADP receptor. Unlike clopidogrel it requires one, not two, step for activation resulting in quicker platelet inhibition within 30 minutes of ingestion. It is dosed as a 60 mg loading dose and then 10 mg daily in combination with aspirin. The Triton-TIMI 38 trial showed that prasugrel is more effective than clopidogrel in therapy of acute coronary syndromes undergoing PCI but is associated with an increased risk of bleeding – including fatal bleeding, especially in patients over the age of 75, with history of stroke, or who weigh less than 60 kg. In a trial of patients with acute coronary syndrome not undergoing an intervention, the outcomes with prasugrel and clopidogrel were similar.

Prasugrel has also been reported to rarely cause TTP – perhaps an incidence similar to clopidogrel.

Ticagrelor

Ticagrelor is a non-thienopyridine that reversibly binds and blocks the ADP receptor. A loading dose of 180 mg of ticagrelor is used, and the maintenance dose is 90 mg twice a day. The PLATO trial showed that this drug combined with aspirin is more effective in acute coronary syndrome than aspirin plus clopidogrel and even reduced mortality. A peculiarity of this trial was that this benefit was only seen if the aspirin dose was less than 100 mg. The major non-bleeding side effect of ticagrelor is dyspnea which can be seen in 10% or more of patients. Despite its reversibility, the platelet inhibition caused by ticagrelor does persist for up to 5 days. Since ticagrelor is metabolized by CYP3A4 inducers or inhibitors, it should not be used with these types of drugs. It is also contraindicated in patients with a history of intracranial hemorrhage as the rate of recurrence of bleeding is high. Its use is recommended for patients who have a new event on clopidogrel, and some guidelines recommend its use combined with aspirin after stenting especially if the patient is not at risk for bleeding or felt to be at high risk of stent thrombosis.

Cangrelor

Cangrelor is similar to ticagrelor being a non-thienopyridine P2Y12 inhibitor. It has a very short half-life of 5–7 minutes and is given intravenously. In clinical trials its effectiveness was the same, slightly better than clopidogrel with similar rates of bleeding. It is also being studied to "bridge" patients who have recent coronary stents but need to come off longer-acting antiplatelet agents for surgery.

Other Platelet Antagonists

Dipyridamole

Dipyridamole blocks degradation of cAMP, resulting in modest platelet inhibition. Due to lack of consistent effect in clinical trials, single-agent dipyridamole had fallen out of favor as an antiplatelet agent. Trials using a novel-sustained release form of dipyridamole and aspirin showed greater benefit in secondary stroke prevention than aspirin alone. But this combination was no more effective than clopidogrel but had increased intracranial hemorrhage. Another issue is this pill had no benefit in cardiovascular disease. One common issue is severe headaches with starting this pill. Some patients benefit by starting with combination pills at night (along with an 81 mg aspirin in the morning) and then starting the twice daily dosing in 1 week. It should also be remembered that the effective trials utilized a special form of dipyridamole and that using the generic short-acting dipyridamole in combination with aspirin has been clearly demonstrated *not* to be effective.

Vorapaxar

This antiplatelet agent functions by inhibiting protease activated receptor 1 which is the main platelet thrombin receptor. Vorapaxar is dosed at 2.5 mg twice a day. In patients who had a myocardial infarction in the prior 2 weeks to 12 months, use of vorapaxar was shown to reduce

ischemic events plus cardiovascular death but with increased bleeding. Most of the patients in this trial were also on aspirin and clopidogrel. In patients with acute coronary syndrome, the use of vorapaxar given first as a loading dose of 40 mg and then a maintenance dose leads to excess bleeding with no benefit.

Given vorapaxar half-life of 200 hours, it is unlikely that platelet transfusions will reverse the platelet inhibition caused by this drug.

Glycoprotein IIb/IIIa Inhibitors

Abciximab

Glycoprotein IIb/IIIa is a key platelet receptor that binds fibrinogen and von Willebrand protein to form the platelet aggregate. Activation of GP IIB/IIIa represents the "final common pathway" of platelet activation. No matter how the platelet is activated, the GP IIb/IIIa receptor must be activated for platelet aggregation to occur.

Abciximab is a novel antibody that blocks the GP IIb/IIIa and leads to profound suppression of platelet function. The antibody is a chimeric human-mouse antibody. Furthermore, its Fc portion is cleaved off, so it can only bind and inhibit platelet functions but will not lead to splenic uptake and thrombocytopenia. Abciximab is administered in the dose of 0.25 mg/kg bolus and then 0.125 ug/kg/min (maximum 10 mg/min) infusions for 12 hours. Abciximab needs to bind to more than 80% of the GP IIb/IIIa sites to impair platelet function. Soon after the infusion is ended, the antibody undergoes rapid redistribution, and the antiplatelet effects wear off rapidly.

Tirofiban

Tirofiban is the first of a large number of non-antibody GP IIb/IIIa inhibitors to be FDA-approved. Tirofiban is an intravenous synthetic non-peptide platelet antagonist. The dosing is weight-based with bolus of 0.4 ug/kg/min for 30 minutes and then an infusion of 0/1 ug/kg/min until resolution of the syndrome or for 12–24 hours after angiography. Patients with low creatinine clearances (<30 mL/min) should receive half the dose.

Eptifibatide

Eptifibatide is the second non-antibody anti-GP IIb/IIIa agent available. For acute coronary syndromes, the dose is 180 ug/kg bolus followed by 2 ug/kg/min for up to 72 hours. For patients undergoing PCI, the dose is a bolus of 180 ug/kg followed by a second bolus of 180 ug/kg 10 minutes later. A continuous infusion of 2 ug/kg/min should be started after the first bolus.

Current Role of GP IIb/IIIa Inhibitors

In the pre-thienopyridine era, GP IIb/IIIa inhibitors were associated with improved outcomes in patient undergoing PCI and for those with acute coronary syndromes. Now benefit seems limited to with acute coronary syndromes who are troponin-positive or PCI patients at high risk of thrombotic complications.

GP IIb/IIIa Complications

The major side effect of these new agents is bleeding and thrombocytopenia. Bleeding is treated by giving platelet transfusions. This leads to redistribution of inhibitors and return of platelet function. In the EPIC trial, no excess bleeding was seen in patients who had to undergo an emergency bypass, but other investigators have reported severe bleeding in these patients. It may be judicious to give a platelet transfusion before bypass or early in the operation in patients who have received GP IIa/IIIa inhibitors and need an emergency bypass if excessive bleeding is noted.

Severe thrombocytopenia has been reported in 0.5–2.0% of patients receiving IIb/IIIa inhibitors. The mechanism of thrombocytopenia is unknown but is speculated to be related to conformational changes in GP IIb/IIIa induced by binding of the inhibitors.

If a patient who has received an IIb/IIIa inhibitor presents with severe thrombocytopenia, one

should examine the blood smear to ensure that the low platelet count is not due to clumping of the platelets in the blood sample. If the patient has received heparin in the last 3 months, one should also consider heparin-induced thrombocytopenia in the differential.

Experience with abciximab has shown that infusion of immune globulin or the use of steroids is not helpful. The inhibitors should be promptly stopped. Platelet transfusions result in a prompt rise in platelet count if severe thrombocytopenia is present.

Aspirin

- Dose: 81–325 mg/day. Dose over 162 mg should be used for acute ischemia

Indications:

- Primary prevention of myocardial infarction
- Secondary prevention of myocardial infarction
- Secondary prevention of stroke after TIA or stroke
- Acute therapy of myocardial infarction
- Acute therapy of unstable angina
- Prevention of saphenous vein bypass thrombosis

Toxicities:
- GI upset
- Bleeding
- Drug Interactions: COX-1 inhibitors – ibuprofen, naproxen
- Reversal: Platelet transfusion (???), desmopressin

Thienopyridines

Clopidogrel

- Dose: 75 mg po once per day

Indications:

- Secondary prevention of ischemic disease in patients intolerant of aspirin or aspirin failures
- Prevention of coronary stent thrombosis in combination with aspirin
- Toxicities: Gastrointestinal upset (10%)
- Reversal: Desmopressin, platelet transfusions – two plateletpheresis units (???)

Prasugrel

- Dose 60 mg loading, 10mg daily (consider 5 mg in patients <60 kg)

Indications

- Secondary prevention of ischemic disease in patients intolerant of aspirin or aspirin failures
- Prevention of coronary stent thrombosis in combination with aspirin
- Reversal: Desmopressin, platelet transfusions – two plateletpheresis units (???)

Reversible P2Y12 Inhibitors

Ticagrelor

- Dose: 180 mg load, 90 mg BID after

Indications:

- Secondary prevention of ischemic disease in patients intolerant of aspirin or aspirin failures
- Prevention of coronary stent thrombosis in combination with aspirin
- Reversal: Desmopressin, platelet transfusions (???)

Cangrelor

- Dose: 30 ug/kg bolus then 4 ug/kg/min infusion
- Indications: PCI, bridging
- Reversal: Stopping infusions

Other Antiplatelet Agents

Sustained Release Dipyridamole/Aspirin

- Dose: 1 pill BID
- Indication: Secondary prevention of stroke
- Reversal: Desmopressin, platelet transfusion (???)

Vorapaxar (Thrombin Receptor inhibitor)

- Dose 2.5 mg bid
- Indication: Recent myocardial infarction
- Reversal:?

Glycoprotein IIb/IIIa Inhibitors

Abciximab

- Dose: 0.25 mg/kg plus 0.125 ug/kg/min (maximum 10 mg/min) for 12 hours after PCI, along with
- Heparin: 70 units/kg (maximum 7000 units) bolus with additional bolus to achieve an ACT of 200 s

Tirofiban

- Dose: 0.4 ug/kg/min for 30 minutes then an infusion of 0.1 ug/kg/min until resolution of the pain syndrome or for 12–24 hours after PCI

Eptifibatide

- Dose:Unstable angina:180 ug/kg bolus followed by 2 ug/kg/min for up to 72 hours
- PCI: 180 ug/kg bolus and then 2 ug/kg/min for 18–24 hours. Second 180 ug/kg bolus 10 minutes after the first

Toxicities common to all:

- Bleeding
- Thrombocytopenia

Suggested Reading (See Also Chap. 20)

Berger JS. Oral antiplatelet therapy for secondary prevention of acute coronary syndrome. Am J Cardiovasc Drugs. 2018;18(6):457–72.

Danielak D, Karaźniewicz-Łada M, Główka F. Ticagrelor in modern cardiology – an up-to-date review of most important aspects of ticagrelor pharmacotherapy. Expert Opin Pharmacother. 2018;19(2):103–12.

Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e89S–119S. https://doi.org/10.1378/chest.11-2293.

Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. Lancet. 2015;386(9990):281–91. https://doi.org/10.1016/S0140-6736(15)60243-4.

Ridker PM. Should aspirin be used for primary prevention in the post-statin era? N Engl J Med. 2018;379(16):1572–4.

Shah R, Rashid A, Hwang I, Fan TM, Khouzam RN, Reed GL. Meta-analysis of the relative efficacy and safety of oral P2Y12 inhibitors in patients with acute coronary syndrome. Am J Cardiol. 2017;119(11):1723–8.

Wiviott SD, Steg PG. Clinical evidence for oral antiplatelet therapy in acute coronary syndromes. Lancet. 2015;386(9990):292–302. https://doi.org/10.1016/S0140-6736(15)60213-6.