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Dual antiplatelet therapy

Management in general practice

Background

Prasugrel and ticagrelor are two new antiplatelet agents being used in the management of acute coronary syndromes. The number of patients in the community managed on these medications is growing, and thus, it is essential that general practitioners have a good understanding of these agents and their evidence-based applications.

Objective

The pharmacokinetic and pharmacodynamic properties of common and new antiplatelet agents will be reviewed, along with the evidence supporting their use. Safety and side effect profiles will be discussed, and some common general practice case scenarios presented.

Discussion

Aspirin is still the mainstay of therapy in patients with acute coronary syndromes. The addition of clopidogrel, prasugrel or ticagrelor can reduce morbidity and mortality in selected patients. Patient factors including bleeding risk, renal function and time since coronary stent insertion must be reviewed before these agents are initiated and before making any changes to the medication regimen.

Keywords

platelet aggregation inhibitors; acute coronary syndrome; perioperative care

coronary syndrome, which was treated conservatively. She complains of frequent nosebleeds and heavy periods. A gastroscopy shows mild erosive gastritis. How would you review her antiplatelet therapy to balance her risk of bleeding and the risk of a recurrent coronary event?

An acute coronary syndrome (ACS) is defined as an acute cardiac event due to complete or partial obstruction of a coronary artery. It encompasses ST segment elevation acute coronary syndrome (STEACS), non-ST segment elevation acute coronary syndrome (NSTEMACS) and unstable angina pectoris. Diagnosis is made based on clinical findings, electrocardiogram changes and positive biomarkers, such as troponin.

Case study 1

Mr Smith, 65 years of age, presents to your practice for the resection of a skin lesion on his forearm. He was recently started on prasugrel and aspirin after being treated for an ST segment elevation acute coronary syndrome with primary percutaneous coronary intervention and single coronary stent placement at a nearby tertiary hospital. Is it safe to stop the antiplatelet agents to prevent excess bleeding and, if so, for how long?

Case study 2

Ms Jones, 49 years of age, presents with symptomatic anaemia after being on dual anti-platelet therapy (aspirin and ticagrelor) for 18 months for a non-ST segment elevation acute

Platelet inhibition constitutes an important element in the management of ACS: aspirin and clopidogrel have long been the agents of choice in this setting.¹ Dual antiplatelet therapy has been recommended in the latest Australian guidelines for ACS management as necessary for the prevention of stent thrombosis.²

Pharmacokinetics of current antiplatelet agents

The pharmacokinetics of current antiplatelet agents are listed in *Table 1*.

Aspirin irreversibly inhibits cyclooxygenase 1 (COX-1) and hence the production of thromboxane A₂ (TXA₂, a promoter of platelet aggregation). It works almost immediately and inhibition of platelet function occurs at very low doses (75 mg). Platelet function is not restored until new platelets are made, which takes about 7–10 days.³

Table 1. Pharmacokinetics of current antiplatelet agents^{3–6}

| | Aspirin | Clopidogrel | Prasugrel | Ticagrelor |
|-----------------------|--------------------------|-------------------------|-------------------------|----------------------------|
| Mode of action | Inhibits COX-1 synthesis | ADP receptor antagonist | ADP receptor antagonist | ADP receptor antagonist |
| Prodrug | No | Yes | Yes | No |
| Metabolism | Hepatic CYP 2C9 | Hepatic CYP 2C19 | Hepatic CYP 3A4 and 2B6 | Hepatic CYP 3A4 |
| Elimination | Urine | Urine/faecal | Urine | Urine/faecal |
| Half-life | 3 hours | 30 minutes | 7 hours | 6–12 hours |
| Dose | 100 mg orally daily | 75 mg orally daily | 10 mg orally daily | 90 mg orally twice per day |

Clopidogrel is a prodrug that is converted into its active metabolite by the cytochrome P450 (CYP450) system. The active metabolite binds and inhibits the P2Y₁₂ subset of the adenosine diphosphate (ADP) receptors on the platelet irreversibly, and so prevents platelet aggregation and thrombus formation.⁴ It takes several days to reach therapeutic levels, and often a loading dose (600 mg) is given to hasten this process.

Prasugrel is a new antiplatelet agent that has been approved for use in Australia. It is also an irreversible antagonist of the P2Y₁₂ subset of the ADP receptors but has a faster onset of action: within 30 minutes if a loading dose is given.⁵

Ticagrelor binds reversibly to the P2Y₁₂ subset of the ADP receptors. It works faster than clopidogrel and has a longer half-life.⁶ Both ticagrelor and prasugrel bind more potently to the ADP receptor than clopidogrel and so confer stronger platelet inhibition.^{7,8}

Genetics

Some patients have reduced response to clopidogrel due to genetic variations in CYP450 genes, with certain alleles converting less clopidogrel into its active metabolite.^{9,10}

For example, patients with a common variation of the CYP 2C19 allele have significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition and a higher rate of adverse cardiovascular events, including stent thrombosis, subsequent myocardial infarction, stroke and death.^{9,11} It is estimated that 30% of Caucasian populations may be resistant to clopidogrel, and this rate is higher in some Asian communities.¹²

Common functional CYP genetic variants do not affect active drug metabolite levels, inhibition

of platelet aggregation, or clinical cardiovascular event rates in people treated with prasugrel or ticagrelor.¹³ A recent review recommended patients with known clopidogrel resistance be treated instead with either of these agents.¹⁴

Drug interactions

Other medications can diminish the effect of clopidogrel through inhibition of CYP450 enzymes required for its metabolic activation. Both atorvastatin and omeprazole are competitive inhibitors of particular CYP isoenzymes. Hence, patients taking clopidogrel at the same time will have lower levels of its active metabolite.^{15,16} One study showed that patients taking both a proton pump inhibitor and clopidogrel had a 40% relative increase (compared to those treated with clopidogrel alone) in the risk of subsequent myocardial infarction in a 3-month period after an ACS.¹⁷

There are no known drug–drug interactions with prasugrel and ticagrelor that inhibit or promote its antiplatelet effect to a clinically significant degree.

Clinical trials

The PLATO (PLAtelet Inhibition and Patient Outcomes) and TRITON TIMI-38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis In Myocardial Infarction) trials demonstrated both ticagrelor and prasugrel were superior to clopidogrel in preventing myocardial infarction, but did increase rates of bleeding in some select groups of higher risk patients.^{18,19}

The PLATO study was a multicentre, double blind, randomised trial that compared ticagrelor with clopidogrel in patients admitted

to hospital with an ACS. It found ticagrelor reduced the rate of myocardial infarction (1.1% ARR, $p=0.005$) and total mortality (1.4% ARR, $p<0.001$), but not stroke (0.2% ARR, $p=0.22$). However, the predefined primary endpoint, a composite of death from vascular causes, myocardial infarction or stroke, was significantly less in those using ticagrelor (1.9% ARR, $p<0.001$). Ticagrelor was associated with a higher rate of major bleeding not related to coronary artery bypass grafting (0.7% ARI, $p=0.03$).

The TRITON TIMI-38 trial was also a double blind, randomised trial that compared prasugrel to clopidogrel in patients with ACS. The predefined primary endpoints were cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. At 30 days, 6.5% of individuals randomised to prasugrel had met the primary endpoint compared with 9.5% randomised to clopidogrel ($p=0.0017$). This effect continued to 15 months, and there was significantly increased bleeding with prasugrel.

Although both trials demonstrate superiority of these new agents, there is no long-term data regarding their efficacy and safety. These trials were both funded by the companies that market these agents, but they had no editorial rights over their publication. National and international peak bodies have assessed both studies to be scientifically sound and have included these agents in guidelines for the management of ACS.

Guidelines

Available evidence indicates aspirin should be given indefinitely after any ischaemic event or after elective stent placement.²⁰ Current

Australian guidelines suggest in patients with STEACS undergoing PCI, the use of prasugrel or ticagrelor should be considered as an alternative to clopidogrel for subgroups at high risk of recurrent ischaemic events (eg. those with diabetes, stent thrombosis, recurrent events on clopidogrel, or high burden of disease on angiography). It is recommended that antiplatelet therapy is continued for a period of 12 months, regardless of the definitive management strategy adopted (conservative, invasive or surgical).

Side effects and risks

The use of these newer agents should, however, be carefully considered in patients at increased risk of bleeding. Prasugrel is indicated only for those patients that are clopidogrel naïve, and is contraindicated in patients aged >75 years, those with history of stroke or transient ischaemic attack or in those with a body weight <60 kg.² In patients with NSTEMI and low bleeding risk, prasugrel or ticagrelor are used in preference to clopidogrel. Clopidogrel remains first line in patients at high risk of bleeding.²¹

Ticagrelor has been associated with the side effects of bradycardia and dyspnoea. On most occasions these have not translated into clinically significant events, nevertheless, ticagrelor should not be given to patients with a history of cardiac conduction defects.¹⁸

Elective interventions

The recommended duration of therapy for the prevention of a stent thrombosis after elective

stent placement is variable, depending on the type of stent used, the number of stents placed, vessels treated and the size of the vessels. Common practice is for clopidogrel, prasugrel or ticagrelor to be continued for 3 months after bare metal stent (BMS) or 6–12 months after drug eluting stent (DES) placement.²¹

Dual antiplatelet therapy can be continued for longer periods for those at higher risk of stent thrombosis or coronary ischaemia at the discretion of the treating cardiologist.

Cessation of therapy

Indications for the cessation of the new antiplatelet agents are primarily based on clinical judgement and encompass situations such as acute clinically significant bleeding or anaemia, adverse drug reaction, or intolerance and surgery. Where possible, the treating cardiologist should be consulted, especially in the first 3 months after elective stent placement or in the 12 months after ACS before cessation of antiplatelet therapy.

Perioperative period

Peak body Australian guidelines recommend that elective non-cardiac surgery should be deferred for at least 6 weeks and ideally 3 months following PCI with BMS and 12 months following PCI with DES, due to the high risk of death, myocardial infarction and in-stent thrombosis associated with the cessation of dual antiplatelet therapy.²²

Aspirin should be continued in most patients up to the time of surgery, and clopidogrel,

prasugrel or ticagrelor be continued in many patients with prior coronary artery stenting undergoing non-cardiac surgery. In patients undergoing cardiac surgery, aspirin can be continued, but the second antiplatelet agent should be stopped. For patients undergoing spinal, intracranial, extraocular, transurethral prostatectomy or major plastic reconstructive procedures, patients at low risk of stent thrombosis should have their antiplatelet therapy routinely ceased perioperatively.²² It is important to consult the treating cardiologist before stopping dual antiplatelet therapy in those at very high risk of stent thrombosis.

Platelet inhibition by ticagrelor is reversible, and studies have shown up to 57% inhibition persists after 24 hours,²¹ hence cessation 5 days prior seems reasonable and safe. It is recommended to cease clopidogrel or prasugrel 5 days before surgery and recommence as soon as it is safe to do so.²³ Recommended perioperative management is outlined in *Table 2*.

Case study 1 continued

This man is at high risk of stent thrombosis or recurrent myocardial infarction if the dual-antiplatelet therapy were to be ceased after recent STEACS and stent placement. The optimal strategy for this patient would be to postpone if suitable, the resection of the skin lesion until 12 months after the STEACS. After 12 months you could stop the prasugrel but continue the aspirin and perform surgery. However,

Table 2. Recommended perioperative management in American guidelines^{21–26}

| Procedure | Timing | Aspirin | Clopidogrel | Prasugrel | Ticagrelor |
|---|--|--------------------------|--------------------|------------------------|--------------------|
| Non-cardiac | Delay 3 months post-BMS and 12 months post-DES | Continue through surgery | Cease 5 days prior | Cease 5–10 days prior* | Cease 5 days prior |
| Coronary artery bypass graft | N/A | Continue through surgery | Cease 5 days prior | Cease 5–10 days prior | Cease 5 days prior |
| Spinal, intracranial, extraocular, transurethral resection of the prostate (TURP) and plastic | Delay 3 months post-BMS and 12 months post-DES | Cease 7–10 days prior | Cease 5 days prior | Cease 5–10 days prior | Cease 5 days prior |

*Variation exists in the recommended time to cease between current Australian and American Cardiac Society Guidelines^{21,22} (5 days) and Prasugrel product information²⁵ (7–10 days).

if the skin lesion needs resection urgently, this needs to be done without ceasing dual antiplatelet therapy. Other strategies to minimise bleeding with this minor operation should be put in place.

Case study 2 continued

This woman was managed conservatively after NSTEMI. The recommended duration of dual antiplatelet therapy in this situation is only 12 months. You can confidently stop the ticagrelor but continue aspirin therapy with enteric-coated variety. You may also consider a proton pump inhibitor for erosive gastritis, iron supplements (if iron deficient) and, perhaps, tranexamic acid (for menorrhagia).

Key points

- Several new antiplatelet agents are present on the market, each with a unique pharmacokinetic profile.
- Choice of agent should be based on the patient's bleeding risk and previous cardiac and interventional history.
- The cessation of these agents should occur after a specified window post-cardiac intervention and the need for any other surgical intervention would ideally be timed around this window.

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