

Antiplatelet Drugs

KEITH KELLY, MB, BS, FANZCA
Prince of Wales Hospital, Sydney

Dr Kelly is a Visiting Anaesthetist at Prince of Wales, Sydney Childrens Hospital and The Eastern Heart Clinic, Sydney. He has an interest in anaesthesia for cardiothoracic procedures.

INTRODUCTION

In the evolutionary sense, clotting is good for you. A complex system has developed, involving the coagulation cascade, platelets and fibrinolysis, all interacting and controlled by local and systemic factors. This benefits the organism by making sure that minor, and sometimes not so minor, injuries do not result in uncontrolled haemorrhage.

Humans have come a long way since this mechanism developed. With increased affluence has come a change in diet and lifestyle, and modern medicine has ensured that we live longer. With these changes, there has been an increase in atherosclerosis and the accompanying diseases: cardiac, cerebrovascular and peripheral vascular. Platelet aggregation and embolisation is central to these and may result in myocardial infarction, TIA or CVA.

Antiplatelet agents act to decrease this aggregation. Platelets have multiple receptors and enzyme systems which may be manipulated by drugs, which are being produced to inhibit the process at a number of sites of action including thromboxane synthesis, the ADP receptor and by acting directly on the GP IIb/IIIa receptor. This receptor is central to aggregation allowing cross linking of fibrinogen, thus binding platelets together into aggregates. Drug actions at the multiple sites are complementary, and patients may be treated with several medications.

Atherosclerosis — Pathology

Endothelial injury is the precursor of atherosclerosis. It is increased by shear stress, diabetes, cigarette smoking and hypertension. A series of events follows the injury, resulting in the formation of atheromatous plaques usually located at vessel ostia, branches or other locations where there is a change in blood velocity. These plaques may rupture or fissure, exposing subendothelial structures. When exposed to this abnormal material, platelets may adhere and this is followed by aggregation and the coagulation cascade to form a haemostatic plug. This plug may occlude the vessel or embolise, either of which may produce symptoms. Major clinical manifestations include:

- Cerebral arterial: transient ischaemic attacks, ischaemic strokes
- Coronary arterial: myocardial ischaemia and infarction
- Peripheral arterial: intermittent claudication, rest pain, gangrene, necrosis.

In particular, intracoronary stents act as foreign bodies promoting platelet activity. Re-epithelialisation may be delayed for some time, leaving the vessel at risk of thrombosis.

Many compounds are effective in decreasing platelet activity. These include:

- Complementary medications: garlic, ginkgo, ginseng
- NSAIDs
- Aspirin
- ADP receptor antagonists: ticlodipine, clopidogrel
- GP IIb/IIIa receptor antagonists: abciximab (“Reopro”), tirofiban (“Aggrastat”)

The main focus of this paper will be the GP IIb/IIIa and ADP receptor antagonists. Several review articles have recently appeared on this topic.^{1,2,3,4}

GP IIb/IIIa RECEPTOR ANTAGONISTS

These include the intravenous agents abciximab, tirofiban and eptifibatide (not currently available in Australia). There are also several oral agents: orofiban, xemilofiban and ibrafiban.

Pharmacology

Abciximab

Abciximab is the Fab fragment of a monoclonal antibody. It is administered intravenously and has a long duration of action (greater than 12 hours) which may lead to increased bleeding problems. It causes bradycardia and, being a foreign protein, is also associated with hypersensitivity reactions. Its use may be decreasing due to these unwanted effects.

Tirofiban

Tirofiban is a non-peptide, tyrosine based drug, which is administered intravenously and excreted by the kidneys. It has more favourable pharmacokinetics than abciximab, with rapid onset and offset of action. It results in approximately 90% inhibition of platelet function within 30 minutes of infusion and has a short half life of two hours. Following cessation of an intravenous infusion, 50% of platelet function is observed at 1.5 hours and 100% by eight hours. Haemostasis can be expected within four hours.

Oral agents

Several oral GP IIb/IIIa receptor antagonists have been involved in unfavourable trials, including: EXCITE (xemilofiban), SYMPHONY I & II (sibrafiban), BRAVO (iotrofiban) and OPUS-TIMI 16 (orofiban). A review of 33,326 patients showed a 36% increase in death, which is statistically significant with a *P* value of 0.00001. With these death rates, the drugs probably will not be released in Australia.

The present use of these drugs is by short term intravenous infusion in percutaneous coronary intervention (PCI, stents) for treatment of unstable angina.

From the physician’s perspective

Assuming a class effect, the benefits and adverse effects of GP IIb/IIIa inhibitors can be summarised as:

Unstable Angina/Non-ST-segment elevation myocardial infarction

- significant decrease in MI or death (NNT=77) (Level 1a evidence)
- significant increase in severe bleeding (NNH=1000) (Level 1a)

Percutaneous Coronary Intervention (PCI)

- significant decrease MI or death (NNT=29) (Level 1a)
- significant decrease in revascularization procedures (NNT=29) (Level 1a)

- significant increase in severe bleeding (NNT=100) (Level 1a)
- abciximab: significant decrease in MI or revascularisation or death compared with tirofiban (NNT=64) (Level 1b)

(NNT=number needed to treat, NNH=number needed to harm)

A Cochrane Review⁵ concludes: “Intravenous GP IIb/IIIa blockers reduce the risk of death at 30 days and markedly that of death or MI at 30 days and 6 months in patients submitted to percutaneous coronary revascularization, at a price of a moderate increased risk of severe bleeding. In contrast, in patients with unstable angina/non-ST-segment elevation myocardial infarction, these agents do not reduce mortality, only slightly reduce the risk of death or MI, and slightly increase the risk for severe bleeding.”

From the anaesthetist’s perspective

These drugs have been most studied in the context of cardiac surgery, but data is not extensive and there is little data relating to use in non-cardiac surgery.

In a cohort study (n=88, 23% on tirofiban), Bizzarri⁶ studied urgent CABG on aspirin, heparin±tirofiban. The tirofiban group showed a significant decrease in blood loss (200 mls), transfusion rate (NNT=3), transfusion volume (3U) and length of stay LOS (7.5 days) (Level 2b). These results were postulated to be due to “platelet anaesthesia”. The EPIC study⁷ involved urgent CABG within 48 hours of abciximab (2.8% of 2099 PCI patients). There was a trend ($P=0.11$) to increased death (NNH=5) (Level IIb). The EPILOG/EPiSTENT trial⁸ involved urgent CABG within 48 hours of aspirin, heparin±abciximab (1.6% of 5191 PCI patients). In abciximab patients, it showed a trend ($P=0.059$) to increased platelet transfusion (NNH=5) (Level IIb), a trend ($P=0.21$) to increased surgical re-exploration (NNH=11), a significantly decreased need for urgent CABG (NNT=112) and a trend to decreased MI or death (NNT=8).

ADP RECEPTOR ANTAGONISTS

The ADP receptor antagonists clopidogrel and ticlodipine are chemically thienopyridines.

Ticlodipine

Ticlodipine has more adverse effects than clopidogrel and thus its use is decreasing. Compared with clopidogrel, it is longer acting, causes increased neutropaenia and increased thrombotic thrombocytopenia.

Clopidogrel

The use of clopidogrel is increasing. In the near future, it may be prescribed for up to 3 million people in the USA alone. Its cost is approximately \$AU1,000 per patient year. Absorbed orally, the parent drug is inactive and metabolized to an active metabolite. A loading dose, usually 300 mg, results in action within two hours and has a peak action at about eight hours. It is a non-competitive antagonist, meaning it acts for the life of the platelet.

From the physician’s perspective

Clopidogrel usage has been studied in the spectrum of atheromatous disease —

cardiac, cerebral and peripheral, but especially in relation to PCI, unstable angina and non-ST-segment elevation MI. Multiple trials involving thousands of patients followed for months to years have shown risk reduction in ischaemic events, and there are a number of ongoing trials looking at atrial fibrillation, cerebrovascular events and peripheral arterial disease, as well as continuing trials in myocardial ischaemia and percutaneous coronary intervention.

The CURE study⁹, with a subset of patients who underwent Percutaneous Coronary Intervention, the PCI-CURE study, has been one of the major studies. Summarising the results which demonstrate why clopidogrel use will increase:

- CURE: 20% relative risk reduction of first co-primary endpoint (cardiovascular death, MI or stroke) at 12 months ($P < 0.001$, $n = 12562$).
- PCI-CURE: 30% relative risk reduction for composite of cardiovascular death, MI or urgent revascularization ($P = 0.03$, $n = 2658$ at 30 days).

The CURE study was conducted in 482 sites in 28 countries, including 742 patients from 25 sites in Australia. The major complication of clopidogrel treatment was bleeding, especially gastrointestinal. Major bleeding, requiring significant medical or surgical intervention was about 35% more likely than with standard therapy, and minor bleeding about twice as likely.

Patients with acute coronary syndromes are increasingly being treated by their physicians with clopidogrel. Endothelial hyperplasia may cause stent stenosis, so drug eluting stents are increasingly popular. However, these delay re-endothelialisation and so persist for longer periods as an intravascular foreign body. Consequently, the treatment duration is longer. A "typical protocol" (Clopidogrel Stent Protocol, Eastern Heart Clinic, Randwick, Sydney) is aspirin 150 mg daily and clopidogrel 300 mg 2 days prior to stent, then 75 mg per day.

The duration of therapy is:

- Normal stent: 1-3 months
- Drug eluting stent: 3-12 months
- Brachytherapy: Lifetime

From the anaesthetist's perspective

The "bottom line" is that patients have significantly fewer ischaemic events if on clopidogrel, but have increased bleeding. As anaesthetists, we are being presented with more clopidogrel taking patients for both emergency and elective surgery.

Clopidogrel and cardiac surgery

The CURE study found no significant excess in "major bleeds" after bypass surgery in the clopidogrel-treated patients. Discontinuation of study medication for more than five days prior to surgery ($n = 910$) resulted in no difference in major bleeding between the two treatment arms (4.4% clopidogrel+standard therapy vs 5.3% standard therapy alone, NS). Discontinuation of study medication for less than five days prior to surgery ($n = 912$) resulted in a trend for increased major bleeding (NS), which was within the same range as in the overall CURE population (9.6% clopidogrel+ standard therapy vs 6.3% standard therapy alone, $P = 0.06$).

Yende¹⁰ studied CABG patients on clopidogrel, with 94% also on aspirin and 65% receiving aprotinin with a cohort study ($n = 247$, 21% on clopidogrel). This study found a significantly increased need for transfusion (NNH=5, Level IIb), significantly increased usage of: RBC (1.4U), cryoprecipitate (1.2U), platelets (2.6U) and signifi-

Table 1
Transfusion requirements in Cardiac Surgery, POWH

% patients transfused with	No antiplatelet agents (n=1055)	Aspirin <4 days (n=1098)	Clopidogrel <4 days (n=31)	Tirofiban <24 hours (n=40)
Packed Cells	54	49	67	52
FFP	23	15	32	10
Platelets	20	16	51	20

cantly increased surgical re-exploration (NNH=12). At my own institution (Prince of Wales Hospital, Sydney) similar results are apparent. (See Table 1.)

Clopidogrel and non-cardiac surgery

Unfortunately, while non-cardiac surgery is where the majority of anaesthetists will encounter patients taking clopidogrel, this is also the area where there is least data. The present situation might best be summarized by the following caution:

“Anecdotal reports of uncontrollable haemorrhage during surgery associated with very recent administration (of clopidogrel) are occurring and caution should be exercised even if the drug has been stopped within 7-10 days of surgery.” (Victorian Consultative Council on Anaesthetic Mortality and Morbidity, 2002. www.health.vic.gov.au/vccamm/warnings.htm)

There are no good controlled trials, but much Level 4 “advice” to discontinue clopidogrel for 7-10 days prior to surgery:

- “On the basis of its pharmacological properties, it is recommended that clopidogrel is stopped 7 days before surgery.”²
- “It is recommended that clopidogrel is discontinued 7 days and ticlopidine 10-14 days before elective surgery.”⁴
- “If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 5 days prior to surgery.” (Plavix product information.)

Clopidogrel and Regional Anaesthesia

Cervical epidural haematoma has been described following a cervical epidural in a patient taking NSAID, aspirin and clopidogrel. There has also been a death following lumbar sympathectomy in a patient who had discontinued clopidogrel three days prior. Autopsy showed a 2-3 litre haematoma in the psoas muscle. The American Society for Regional Anesthesia consensus statements on regional anesthesia and anticoagulation³ suggested:

- The recommended time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel. For the platelet GP IIb/IIIa inhibitors, the duration ranges from eight hours for eptifibatide and tirofiban to 48 hours following abciximab administration.
- Conservatively, the consensus statements on Neuraxial Anaesthesia and Anti-coagulation may be applied to plexus and peripheral techniques.

What to do when the patient is taking clopidogrel

In all these cases the benefits and timing of surgery, as opposed to the risks

associated with clopidogrel and the potential risks of stopping the medication, need to be considered. Where surgery is elective and the reasons for anticoagulation are valid, alternate anticoagulants may be required perioperatively if clopidogrel is stopped.

It would be reasonable to proceed where bleeding was not likely to be problem and could be easily controlled, or where the surgery cannot wait.

For the first 24-48 hours, platelet transfusion may be less effective, due to the presence of drug and/or metabolites. After 48 hours, platelet transfusion is likely to be more effective. After four to five days, there will be considerable improvement in coagulation; cardiac surgery should be uneventful, but regional anaesthesia will still be a problem. After seven to ten days, the patient's coagulation should be back to normal.

Table 2
Take home messages

Tirofiban

OK for surgery after 4h

OK for regional anaesthesia after 8 hours

Clopidogrel

Use will increase

Action irreversible and lasts for life of platelet

In non cardiac surgery, while there are no good studies there are anecdotal reports of severe haemorrhage

Decision to stop is on case by case basis

After cessation

Cardiac surgery should be OK after 4 days

Regional anaesthesia should be OK after 7 days

Summary

A reasonable approach for anaesthetists to take in relation to these drugs is summarized as "Take Home Messages" in Table 2. It is likely that direct thrombin inhibitors will soon be in clinical use.

Acknowledgements

The author wishes to thank Ms M. Madigan, Cardiovascular Research Nurse at Prince of Wales Hospitals, as well as anaesthetists from that hospital and cardiologists from the Eastern Heart Clinic for their help in preparation of this paper, which was developed from a NSW continuing education lecture.

REFERENCES

1. Hankey GJ, Eikelboom JW, Antiplatelet drugs. *Med J Aust* 2003. 178(11):568-574.
2. Kam PC, Nethery CM, The thienopyridine derivatives (platelet adenosine diphosphate receptor antagonists), pharmacology and clinical developments. *Anaesthesia* 2003; 58:28-35.
3. Horlocker TT et al. Regional anesthesia in the anticoagulated patient: defining the risks (Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesthes Pain Med* 2003; 28: 172-197.
4. Kovesi T, Royston D. Is there a bleeding problem with platelet-active drugs? *Brit J Anaesthes* 2002; 88: 159-163.
5. Bosch X, Marrugat J. Platelet glycoprotein IIb/IIIa blockers ... Cochrane Database of Systematic Reviews, 2004; 4:4.
6. Bizzarri F et al, Perioperative use of tirofiban hydrochloride (Aggrastat) does not increase surgical bleeding after emergency or urgent coronary artery bypass grafting. *J Thor Cardiovasc Surg* 2001; 122: 1181-1185.

7. Anonymous, Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *New Eng J Med* 1994; 330:956-061.
8. Steinhubl SR et al. Ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events: data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) Trial. *Circulation* 2001; 103:1403-1409.
9. Mehta SR et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; 358: 527-533.
10. Yende S et al. Effect of clopidogrel (Plavix) on bleeding after coronary artery bypass graft surgery. *Chest* 2000; 118:S123.