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Special Issue

New antiplatelet drugs and new oral anticoagulants

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Abstract

In our daily anaesthetic practice, we are confronted with an increasing number of patients treated with either antiplatelet or anticoagulant agents. During the last decade, changes have occurred that make the handling of antithrombotic medication a challenging part of anaesthetic perioperative management. In this review, the authors discuss the most important antiplatelet and anticoagulant drugs, the perioperative management, the handling of bleeding complications, and the interpretation of some laboratory analyses related to these agents.

Key words: antiplatelet agents; anticoagulants and haemorrhage; blood coagulation tests

Editor's key points

- Antiplatelet agents significantly increase the risk of bleeding in high-risk surgery.
- A number of anticoagulant drugs that either inactivate factor Xa or directly inhibit thrombin have become available in recent years.
- Current data do not support the use of periperative bridging therapy to cover the withdrawal of oral anticoagulants in patients at low risk of thromboembolism.
- Standard coagulation tests together with assay of factor Xa activity can be used to guide the managment of new anticoagulant drugs in the perioperative setting.

Arterial and venous thrombosis have an important impact on worldwide morbidity and mortality. Worldwide, >10 million deaths per annum are caused by arterial thrombotic events (ischaemic stroke, heart disease, and peripheral gangrene).[1 2] Platelets are the key prothrombotic element in arterial thrombosis, forming aggregates interconnected by fibrin. Antiplatelet treatment can counteract this process. For decades, aspirin has been the first-line antiplatelet drug of choice; recently, however, alternative antiplatelet substances have been introduced.

Half a million deaths related to venous thromboembolism occur in the European Union per year.[1] Venous thrombi consist primarily of fibrin with some cells trapped in between. Anticoagulants are the drugs of choice to prevent or treat these conditions. For decades, warfarin and heparin were the mainstay of treatment, but the development of new anticoagulant drugs is constantly enlarging the pharmaceutical armamentarium.

In this review, the pharmacological properties of the new antiplatelet and new oral anticoagulant drugs, their usage in the perioperative setting, and the management of bleeding complications are discussed.

Antiplatelet agents (Table 1)

Platelet adhesion, activation, and aggregation are mediated by numerous adhesive proteins. The reactions of these proteins underpin the physiological responses to endothelial damage or rupture of atherosclerotic plaques. Amplification of these mechanisms and excessive thrombus formation endanger vascular flow, leading to occlusion of arteries and temporary or persistent ischaemia.[3] Blocking such thrombus formation can prevent ischaemic events.

Treatment strategies for prevention or therapy of arterial thrombosis are changing constantly. The duration of treatment,

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Table 1 Summary of the characteristics of currently available antiplatelet drugs

Characteristic	Aspirin	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Abciximab	Eptifibatide	Tirofiban
Route of administration	Oral once daily, (i.v.)	Oral once daily, (i.v. under investigation)	Oral once daily	Oral twice daily	i.v.	i.v.	i.v.	i.v.
Bioavailability	68%	50%	80%	36%				
Plasma peak concentration	30–40 min	1 h	30 min	1.5 h	Seconds	Dose dependent	Dose dependent	Dose dependent
Time to plasma steady state		2–8 h	30 min to 4 h	30 min to 2 h	Seconds	Initial bolus and continuous application	Initial bolus and continuous application 4–6 h	Initial bolus and continuous application 10 min
Plasma half-life	15–30 min	8 h	7 h	7 h	2–5 min	10–15 min	2.5 h	2 h
Plasma protein binding	Strong	Strong	Strong	Strong				
Time from last dose to offset	7–10 days	7–10 days	7–10 days	5 days	60 min	12 h	2–4 h	2–4 h
Reversibility of platelet inhibition	No	No	No	Yes	Yes	Yes	Yes	Yes
Recommended period of discontinuation before surgical intervention (see Fig. 2)	0–5 days	7 days	10 days	7 days	1–6 h	48 h	8 h	8 h

especially of dual or triple antiplatelet therapy, is highly dependent on the indication for treatment and, for percutaneous coronary intervention, the chemical constitution of any coronary stents (Table 2).[4–6]

Acetylsalicylic acid (aspirin)

For >50 yr, aspirin has been known to have antithrombotic and anti-inflammatory properties.[7] Aspirin is a cyclooxygenase (COX) inhibitor that irreversibly inhibits COX1 and, in higher doses, COX2. Inhibition of COX1 is the main antithrombotic mechanism; the formation of prostaglandin H_2 is blocked, thus thromboxane A2 cannot be synthesized. Thromboxane A2 activates platelets and stimulates their aggregation.[8] The irreversibility of the effect of aspirin causes inhibition for the lifespan of a platelet (7–10 days). After the discontinuation of aspirin intake by a patient, their platelet function can be expected to increase by 10–15% per day as a result of new platelet formation.[8 9] Aspirin is a key component of antiplatelet treatment to reduce death attributable to myocardial infarction or stroke.[10] Bleeding risk is smaller with low doses (75–100 mg), which deliver an equivalent antithrombotic impact to higher doses (300 mg).[11] Drug interactions with aspirin are scarce, but co-administration of non-selective COX1 inhibitors may impair its efficacy. Owing to potential aggravation of ischaemic heart diseases attributable to selective COX2 inhibitors, these drugs should be avoided in patients with coronary artery disease. About one-third of patients receiving aspirin manifest treatment failure (thrombotic complication or death). Non-compliance is a substantial problem but difficult to quantify, with estimates ranging between 3 and 40%. Adverse events resulting from rebound thrombocyte activation after aspirin withdrawal are frequent. Some patients show biochemical resistance or high platelet reactivity, detected by platelet function assays. Diabetes, cardiac surgery, or acute coronary syndromes, all of which are associated with an inflammatory response, are associated with high platelet reactivity. In addition, genetic polymorphisms (COX1, COX2 alleles, platelet glycoprotein receptors), or increased platelet turnover (bone marrow diseases) can reduce the effect of aspirin. The fact that aspirin has only a single binding site and does not influence

Table 2 Treatment recommendations for antiplatelet agents.[4–6] BMS, bare metal stent; DES, drug-eluting stent; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease

Condition	Treatment recommendations
Primary prevention	Aspirin Risk *vs* benefit evaluation
Acute coronary syndrome	PCI: aspirin lifelong plus ticagrelor, prasugrel, or clopidogrel ≥12 months Non-PCI: aspirin lifelong plus clopidogrel or ticagrelor ≥12 months
Stable angina or former myocardial infarction	Aspirin lifelong plus clopidogrel BMS ≥1 month DES ≥6 months
Recent stroke	Aspirin in high-risk situation plus clopidogrel 90 days
Past stroke	Aspirin or clopidogrel
PVD	Aspirin or clopidogrel

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