Antiplatelet Drugs : Is There a Surgical Risk?

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Abstract

Acetylsalicylic acid has long been the only nonsteroidal anti-inflammatory drug recommended for the treatment and prevention of thromboembolic diseases. More recently, new compounds have been used in patients with vascular diseases. However, these drugs are often associated with longer bleeding times and greater operative risk. In most surgical specialties, the question always arises as to whether antiplatelet therapy should be stopped before elective surgery. If so, for how long? If not, what are the risks? This article reviews the various antiplatelet drugs in use today, focusing on their mode of action, their effects on platelet function and the associated operative risks. It also proposes an algorithm for decision making in this setting, based on the literature and an understanding of the mechanisms of action of this class of drugs.

MeSH Key Words: *hemorrhage/chemically induced; platelet aggregation inhibitors/adverse effects; perioperative care*

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Hemostasis is a process encompassing the various mechanisms that stop the bleeding when the vascular wall is ruptured. A number of factors, including the endothelial wall, the platelets, and the proteins of the coagulation cascade and of fibrinolysis, play essential roles in this function. A congenital or acquired anomaly involving one or more of these factors predisposes a patient to hemorrhagic accidents[1] (Table 1).

Hemostasis consists of a vascular phase, a platelet phase and a coagulation phase. The first 2 phases constitute primary hemostasis, in which the vessel wall, platelets and plasma proteins, including von Willebrand factor and fibrinogen, participate. Reflex vasoconstriction of the blood vessel facilitates platelet adhesion and aggregation needed for formation of the hemostatic clot (see Fig. 1, Platelet activation and aggregation mechanisms, at the end of the article. The coagulation phase, also known as secondary hemostasis, allows consolidation of the platelet clot by formation of a fibrin clot. Finally, fibrinolysi rids the organism of fibrinous deposits.

Abnormal platelet aggregation plays an important role in the pathogenesis of thromboembolic diseases such as myocardial infarction, cerebral ischemia and peripheral arterial insufficiency.[3] Although several antiplatelet agents have been developed in recent years, acetylsalicylic acid (ASA) is still the standard for preventing vascular diseases.[4–6] Of the newer agents, ticlopidine,[7] clopidogrel[8] and dipyridamole[9] have an effectiveness comparable to that of ASA. Each of these drugs has its own mechanism of action and pharmacokinetics (Table 2). Their effects on primary hemostasis also differ. This article reviews the various drugs in use today, focusing on their mode of action, their effects on platelet function and the associated operative risks.

Evaluation of Platelet Function

The preoperative assessment of all dental patients should include a targeted medical questionnaire aimed at identifying any personal or family history of hemostatic anomalies. It is important to note the circumstances (traumatic vs. spontaneous), duration (a few minutes vs. several hours or days), severity (whether a blood transfusion was needed) and type of bleeding reported. Platelet disorders are evidenced mainly by epistaxis, bleeding gums or mucocutaneous bleeding in the form of ecchymoses or petechiae, whereas coagulopathies are associated more with deep

Table 1 **Systemic diseases associated with hemostatic disorders**

Type of hemostatic disorder	Systemic diseases
Platelet anomalies	
Quantitative	Hemolytic anemia Megaloblastic anemia Hepatic cirrhosis and hypersplenism Ethylism Leukemias Systemic lupus erythematosus Idiopathic thrombocytopenic purpura AIDS
Qualitative	Megaloblastic anemia Kidney failure and uremic syndrome von Willebrand's disease Bernard-Soulier syndrome Chediak-Higashi syndrome Hermansky-Pudlak syndrome Wiskott-Aldrich syndrome Glanzmann's disease
Coagulopathies	
Congenital	Factor VII deficiency Factor VIII deficiency (hemophilia A) Factor IX deficiency (hemophilia B)
Acquired	Hepatic cirrhosis Vitamin K deficiency Ethylism

bleeding and hence risk of hemarthrosis. Although the bleeding associated with vascular malformations is similar to the bleeding encountered in platelet disorders, the latter occurs more at the level of the affected vessels. A number of systemic diseases, including kidney[10] and liver failure, myeloproliferative syndromes,[11] collagenoses[12] and certain neoplasias,[13] are associated with platelet dysfunction. Finally, it is imperative that the medication history be well known. Many drugs, natural products and foods cause various platelet dysfunctions (Table 3), which can in turn affect primary hemostasis.[2,14]

The platelet count is the main laboratory test used in the evaluation of hemostasis (normal range $150–400 \times 10^9$/L). Values higher than normal indicate thrombocytosis, whereas values lower than normal indicate thrombocytopenia. Minor elective procedures are generally contraindicated if the platelet count is less than 50×10^9/L. Spontaneous bleeding may occur in patients whose platelet count is less than $10–20 \times 10^9$/L.

The bleeding time (BT) test is also used in evaluating primary hemostasis. In 1951, O'Brien defined BT as the time between the making of a small cut on the skin and the cessation of bleeding (normally 4–8 minutes). Because of the wide variability and lack of specificity of this test, its use in the detection of blood dyscrasia is limited. Nevertheless, the BT test remains useful in the preoperative assessment of patients with hemostatic disorders. In addition to the BT test, most medical laboratories perform a platelet aggregation test. This in vitro test evaluates the platelet aggregation capacity of a blood sample in response to specific inducers such as epinephrine, adenosine diphosphate (ADP), collagen, serotonin, arachidonic acid and ristocetine. The level of response to these various substances pinpoints the nature of the platelet dysfunction. A recently developed fast, sensitive diagnostic test, the PFA-100 (Dade-Behring, Mississauga, Ont.), is now being used to quantify platelet activation and aggregation capacity.[14]

Acetylsalicylic Acid

ASA is still the only nonsteroidal anti-inflammatory drug (NSAID) used in the treatment and prevention of thromboembolic diseases.[15] ASA acts by irreversibly inactivating (for the life of the platelet) the enzyme cyclooxygenase (COX). This enzyme is responsible for the formation of prostaglandins and thromboxane A_2, which are involved in platelet activation and aggregation mechanisms[16,17] (Fig. 1).

ASA therapy has long been associated with an increase in BT and risk of postoperative hemorrhage. For most elective surgeries, it has typically been recommended that the patient stop taking ASA 7 to 10 days before the procedure. This recommendation was based on general surgical studies, which reported an increase in intraoperative and postoperative bleeding in patients taking ASA.[18–21] Other studies, mainly related to general and cardiovascular surgery, did not show any significant increase in blood loss or any need for postoperative transfusions.[22–26] Several factors might explain this discrepancy, including the heterogeneity of the populations studied, improvements in surgical techniques, and use of local and systemic means to control bleeding.

Ardekian and others[27] maintained that a daily dose of 100 mg of ASA did not significantly increase intraoperative and postoperative bleeding during tooth extractions. Moreover, Sonksen and others[28] showed that the increase in BT caused by daily ASA in doses of up to 300 mg did not exceed normal limits in most patients. Thus, patients need not stop taking ASA before dental surgery, provided the hemorrhagic risk is not greater than the thromboembolic risk associated with interrupting use of the drug. When intraoperative or postoperative bleeding does occur, local hemostatic methods are generally very effective (Table 4).[29]

However, a high hemorrhagic risk has been documented in patients with qualitative or quantitative platelet anomalies,[30] those with congenital or acquired coagulopathies,[31] those presenting with chronic kidney[32,33] or liver[34] failure, and alcoholic patients[35,36] (Table 1). In these situations, a medical consultation should be requested and ASA should be stopped 7 days before surgery to minimize the hemorrhagic complications. If interruption of ASA therapy is contraindicated, the patient should receive specialized treatment in hospital.

Table 2 **Pharmacological properties of and therapeutic indications for antiplatelet drugs**

Drug	Mechanism of action	Duration of antiplatelet effect	Indications
ASA	Irreversible inactivation of cyclooxygenase (COX-1 and COX-2)	7–10 days	- Secondary prevention of myocardial infarction, peripheral arterial insufficiency and certain forms of CVA - Inflammatory and degenerative arthritis - Chronic moderate pain
Nonselective NSAIDs	Reversible inactivation of cyclooxygenase (COX-1 and COX-2)	Depends on half-life of the drug	- Slight to moderate pain - Inflammatory and degenerative arthritis
Ticlopidine or clopidogrel	Blocking of ADP receptor on platelets	7–14 days	- Secondary prevention of myocardial infarction and CVA - Secondary prevention of peripheral arterial insufficiency (clopidogrel only)
Dipyridamole[a]	Increase in concentration of cAMP	24 hours (half-life = 12 hours)	- Secondary prevention of CVA

ASA = acetylsalicylic acid, CVA = cerebrovascular accident, NSAID = nonsteroidal anti-inflammatory drug, ADP = adenosine diphosphate, cAMP = cyclic adenosine monophosphate.
[a] In combination with ASA (Aggrenox)

Table 3 **Drugs, natural products and foods that may alter platelet function[15,16]**

Drugs
Nonsteroidal anti-inflammatory drugs • ASA, ibuprofen, diclofenac, naproxen, indomethacin, diflunisal, phenylbutazone, meclofenamic acid
Antiplatelet drugs • ticlopidine, dipyridamole, clopidogrel, GP IIb/IIIa receptor blockers
Anticoagulants, fibrinolytics and antifibrinolytics • aminocaproic acid, heparin, protamine
Antibiotics • penicillins and derivatives • cephalosporins and derivatives
Cardiovascular agents • diltiazem, propranolol, nitroprusside, nifedipine, nitroglycerin, quinidine, furosemide
Psychotropic, anesthetic and narcotic agents • fluoxetine and other SSRIs • amitriptyline, nortriptyline, promazine, chlorpromazine • lidocaine • heroin, cocaine
Other • diphenhydramine, cyclophosphamide, chlorpheniramine
Natural products • *Ginkgo biloba,* ginseng
Foods and beverages • ginger, garlic, cumin, onion, alcohol

ASA = acetylsalicylic acid, GP = glycoprotein, SSRI = selective serotonin reuptake inhibitor.

Other Nonsteroidal Anti-inflammatory Drugs

Unlike ASA, the other NSAIDs inactivate the enzyme COX transitorily. Their effect on primary hemostasis depends on their plasma half-life.[37] Long-acting NSAIDs, such as piroxicam, have a prolonged effect that lasts for several days after the patient stops taking them.[38] Conversely, short-acting NSAIDs, such as ibuprofen, lose their antiplatelet effect in a few hours.

BT generally increases with NSAIDs but remains within normal limits.[39] It is therefore unnecessary for the patient to stop taking NSAIDs before elective surgery. However, as with ASA, the antiplatelet effect may be exaggerated in patients with hemostatic disorders (Table 1). In these cases, it is recommended that the patient stop taking the NSAID 2 to 3 days before surgery to minimize the risk of hemorrhage.

Finally, COX-2-specific NSAIDs, such as meloxicam, rofecoxib and celecoxib, do not alter hemostatic factors. Therefore, it is not necessary to interrupt their use before elective dental surgery.[40]

ADP Receptor Blockers

Ticlopidine and clopidogrel are members of the thienopyridine family. This class of antiplatelet drugs acts on the ADP receptors implicated in platelet aggregation[41] (Fig. 1). Both are recommended for the secondary prevention of thromboembolic diseases in ASA-resistant or ASA-intolerant patients and when a greater risk of cerebral ischemia is identified.[7,8,42]

Ticlopidine seems more effective than ASA in preventing cerebrovascular accidents (CVAs), but its use is associated with major side effects such as diarrhea, anemia and neutropenia.[42,43]

The antiplatelet activity of clopidogrel is greater than that of ASA and ticlopidine. The CAPRIE study[8] confirmed the superiority of clopidogrel over ASA in the secondary prevention of CVA, myocardial infarction and peripheral arterial insufficiency. Moreover, clopidogrel has

Table 4 Methods of local hemostasis

Agent	Composition	Mechanism of action
Vasoconstrictor	Epinephrine or levonordefrin	Arterial vasoconstriction
Bone wax	Beeswax and salicyclic acid	Mechanical blocking of osseous bleeding
Suture	Various materials	Tissular compression
Gelfoam (Pharmacia, Mississauga, Ont.)	Animal gelatin	Scaffold for formation of the platelet clot
Surgicel (Johnson & Johnson, Guelph, Ont.)	Oxidized cellulose	Stabilization of the platelet clot
Collagen	Bovine collagen	Platelet activation
Fibrinous glue	Plasma rich in platelets and thrombin	Formation of fibrin clot
Thrombostat (Pfizer, Toronto, Ont.)	Thrombin	Fibrinogen activation
Electrocautery	Electrical current	Tissular coagulation
Laser	Ionized unipolar current	Tissular coagulation

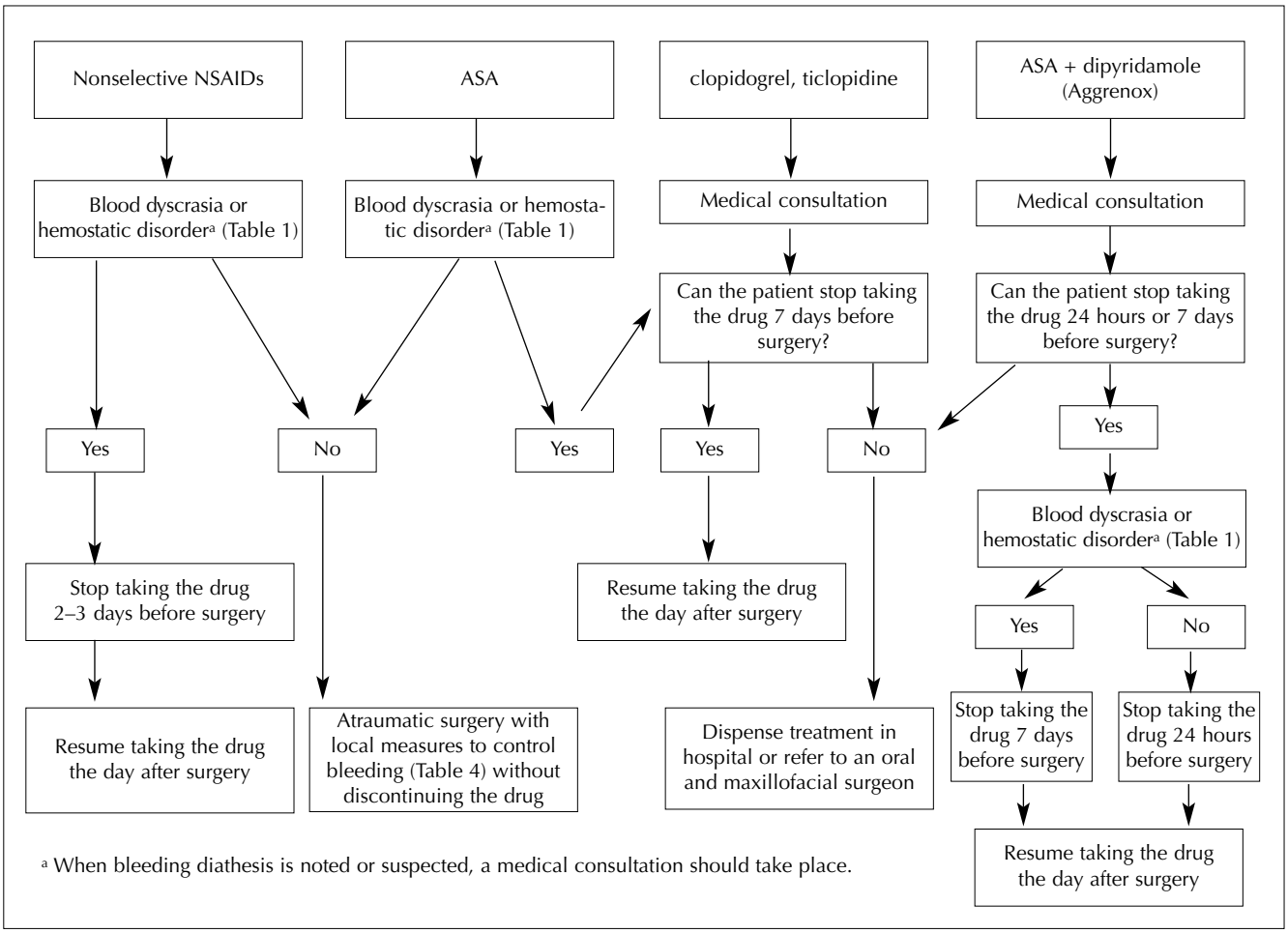

Figure 2: *Algorithm for surgical preparation of patients who are taking antiplatelet drugs*
NSAID = nonsteroidal anti-inflammatory drug, ASA = acetylsalicylic acid

fewer side effects than ticlopidine.[44] Despite its growing popularity, clopidogrel is very expensive, so it is used only selectively in patients resistant to treatment with ASA.

The antiplatelet effect of clopidogrel and ticlopidine is irreversible and lasts for the life of the platelet (7 to 10 days).[41] The use of these drugs is associated with a significant increase in postoperative bleeding in patients who have undergone cardiovascular surgery.[45,46] Although the risk of postoperative hemorrhage in dental surgery has not been studied, the clinical experience of the authors of this article (with specific consideration of the higher risk of hemorrhage and the irreversible effect of these drugs) suggests that patients should stop taking them 7 to 10 days before elective surgery.[47] When the thrombotic risk exceeds the

hemorrhagic risk and interruption of the drug cannot be considered, the patient should be referred to a hospital, where the surgical procedure can be performed under medical supervision and where systemic measures can be taken if necessary.[48,49]

Phosphodiesterase Inhibitor

Dipyridamole is one of the antiplatelet drugs that acts by inhibiting phosphodiesterase, an enzyme involved in the breakdown of cyclic adenosine monophosphate (cAMP). The resulting increase in cAMP inhibits platelet activation and aggregation.[6] However, the antiplatelet activity of dipyridamole is less than that of ASA and the ADP receptor blockers. Moreover, its action on phosphodiesterase is wholly reversible and ceases about 24 hours after the drug is discontinued.[50] According to the European Stroke Prevention Study,[51] dipyridamole seems as effective as ASA in secondary prevention of CVA and transient cerebral ischemia (TCI). The ASA–dipyridamole combination, however, proved twice as effective as each of these 2 drugs taken alone. This combination, marketed under the name Aggrenox (Boehringer Ingelheim, Vancouver, B.C.), is used for certain patients who have had TCI or CVA.

Few studies have measured the hemorrhagic complications related to Aggrenox. Daily use of dipyridamole does not appear to increase blood loss significantly during surgical procedures.[52] However, cases of uncontrollable bleeding have been reported with Aggrenox, where bleeding could only be controlled by stopping the drug.[53,54] The increased hemorrhagic risk associated with Aggrenox is probably attributable to the additive effects of ASA and dipyridamole, which alter platelet function through independent mechanisms.

Because of the operative risk associated with Aggrenox, it is recommended that the patient undergo a medical consultation and stop taking it before surgery. The antiplatelet activity of the dipyridamole in Aggrenox is eliminated from the body within 24 hours.[50] Dental procedures can then be performed, provided proper hemostasis is ensured, as described for patients taking ASA.

Conclusions

All antiplatelet drugs used in the secondary prevention of thromboembolic diseases can cause intraoperative and postoperative hemorrhagic complications. However, stopping these drugs before a procedure exposes the patient to vascular problems with the potential for significant morbidity. An algorithm for decision making (Fig. 2) has been developed that takes into account the pharmacological properties of antiplatelet drugs, their effects on hemostasis and the patient's health. ➧

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Figure 1: *Platelet activation and aggregation mechanisms*
The platelet phase of hemostasis is divided into 3 stages: adhesion, secretion and aggregation. During trauma, surface receptors, such as the glycoprotein (GP) Ib/IX complex, ensure adhesion of the platelets to the subendothelial collagen fibres by means of von Willebrand factor (vWF). The platelets then undergo morphological changes (mainly the appearance of pseudopodia) and biochemical changes leading to secretion of the contents of the cytoplasmic granules into the extracellular environment. There are 2 different types of granules: dense granules, which contain adenosine triphosphate (ATP), adenosine diphosphate (ADP), serotonin and calcium; and alpha granules, which contain proteins, such as fibrinogen (Fg) and vWF. The ADP molecules secreted into the extracellular environment help trigger platelet aggregation by altering the configuration of the GP IIb/IIIa receptors. These changes enable the GP IIb/IIIa receptors to bind to the circulating fibrinogen or vWF molecules. Platelet cohesion and aggregation are thus assured by the formation of Fg or vWF bridges between the GP IIb/IIIa surface receptors of the platelets. The enzyme cyclooxygenase (COX) enables arachidonic acid (AA) to be converted into thromboxane A_2 (TXA_2). The role of TXA_2 is similar to that of ADP. The platelets also help to trigger the coagulation cascade necessary for formation of a fibrin clot, by activating factor X and prothrombin. 1 = site of action of nonsteroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid (ASA); 2 = site of action of dipyridamole; 3 = site of action of clopidogrel and ticlopidine. Figure adapted from George and Shatil.[2]