Effects of Nonsteroidal Antiinflammatory Drugs on Platelet Function and Systemic Hemostasis

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Aspirin and nonaspirin nonsteroidal antiinflammatory drugs (NSAIDs) inhibit platelet cyclooxygenase, thereby blocking the formation of thromboxane A_2. These drugs produce a systemic bleeding tendency by impairing thromboxane-dependent platelet aggregation and consequently prolonging the bleeding time. Aspirin exerts these effects by irreversibly blocking cyclooxygenase and, therefore, its actions persist for the circulating lifetime of the platelet. Nonaspirin NSAIDs inhibit cyclooxygenase reversibly and, therefore, the duration of their action depends on specific drug dose, serum level, and half-life. The clinical risks of bleeding with aspirin or nonaspirin NSAIDs are enhanced by the concomitant use of alcohol or anticoagulants and by associated conditions, including advanced age, liver disease, and other coexisting coagulopathies.

Nonsteroidal antiinflammatory drugs (NSAIDs) provide effective relief of pain and inflammation caused by a variety of clinical disorders, including different types of arthritis, nonarthritic musculoskeletal conditions, headache, and dysmenorrhea. More than 70 million prescriptions for NSAIDs (excluding aspirin) were written in the United States in 1991, predominantly for these disorders, thus generating a per capita consumption of 278.6 prescriptions per 1,000 people and a retail cost exceeding $2.2 billion.[1]

Because of increased physician awareness of adverse gastrointestinal events among NSAID users,[2] a stabilization of NSAID usage and an increased use of gastroprotective and anti-ulcer drugs have occurred. Whereas most physicians find NSAIDs to be safe and effective, gastroenterologists have been increasingly concerned about their toxic effects on the gut, the most significant of which is gastrointestinal hemorrhage.[3-5] The risk of gastrointestinal bleeding from NSAIDs is compounded by their adverse effects on systemic coagulation resulting in a qualitative abnormality in platelets. This paper reviews effects of NSAIDs on platelet function and compares and contrasts actions of aspirin and nonaspirin NSAIDs. In addition, guidelines for identifying patients at risk of bleeding from aspirin and nonaspirin NSAIDs and suggestions for alternative analgesics are provided.

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PLATELET-VESSEL WALL INTERACTIONS

A monolayer of endothelial cells lines the intimal surface of blood vessels throughout the circulatory tree, and under normal circumstances, these cells maintain blood fluidity by providing a thromboresistant surface. Anticoagulant factors of endothelial cells include prostacyclin (PGI_2), an eicosanoid product of arachidonic acid metabolism, and nitric oxide, a component of endothelium-derived relaxing factor (EDRF).[6,7] Prostacyclin and nitric oxide maintain blood cells in a quiescent state by inducing vasorelaxation and inhibiting platelets. Prostacyclin stimulates adenylyl cyclase and raises the level of cyclic AMP in vascular smooth muscle cells and platelets. Nitric oxide stimulates guanylyl cyclase and raises levels of cyclic GMP in the same cell types.

At a site of vascular injury, thromboresistant properties of endothelial cells are lost or impaired, and thrombogenic subendothelial components of the vessel wall (e.g., collagen) become exposed to blood. Platelets attach to the damaged vessel wall through a

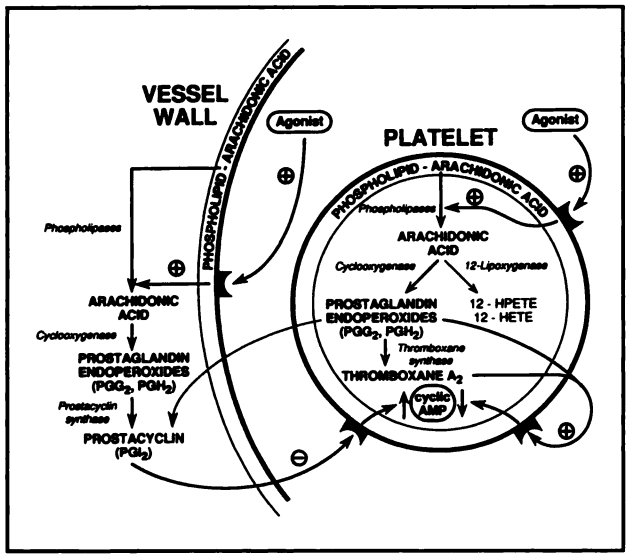

Figure 1. Platelet and vessel wall eicosanoid metabolism. Platelets and vascular endothelial cells are stimulated by a variety of positive stimuli (agonists) to activate phospholipases, which hydrolyze free arachidonic acid from their membrane phospholipid pools. Free arachidonic acid is then oxygenated to prostaglandin endoperoxides in both cell types by cyclooxygenase, an enzyme that is irreversibly inhibited by aspirin and reversibly inhibited by nonaspirin NSAIDs. (In platelets, arachidonic acid is also metabolized to 12-HPETE and 12-HETE by a 12-lipoxygenase, but the physiological significance of this pathway is unclear.) The labile endoperoxides, PGG_2 and PGH_2, are then metabolized by thromboxane synthase to thromboxane A_2 in platelets, and by prostacyclin synthase to prostacyclin (PGI_2) in endothelial cells. Activated platelets can also divert their endoperoxides to endothelial cells and augment prostacyclin formation. Prostacyclin is a potent platelet inhibitor (and vasodilator) that exerts this action by raising platelet intracellular cyclic AMP levels. Thromboxane A_2 is a potent platelet activator (and vasoconstrictor) that exerts this action by decreasing (or preventing the elevation of) intracellular cyclic AMP levels.

process of platelet "adhesion" mediated by the binding of von Willebrand factor to its platelet receptors on membrane glycoprotein (Gp) Ib. Binding of von Willebrand factor to platelet Gp Ib initiates a cascade of intracellular signals[8] that stimulates the "release reaction." Major products of this platelet release reaction are prepackaged contents (e.g., ADP) of specific granules and thromboxane A_2, which is synthesized *de novo* from arachidonic acid in response to platelet activation. Products of the platelet release reaction then act in concert to promote platelet aggregation, which results in formation of an occlusive platelet plug at the vascular injury site.

The principal cyclooxygenase metabolites of arachidonic acid are thromboxane A_2 in platelets and PGI_2 in endothelial cells[9] (Figure 1). The rate-limiting step in production of these metabolites is hydrolysis of free arachidonic acid from membrane phospholipid pools by phospholipases (phospholipase A_2 or the sequential actions of phospholipase C and diglyceride lipase), which are activated by various extracellular stimuli. Cyclooxygenases then catalyze the oxygenation of free arachidonic acid to cyclic endoperoxide prostaglandin G_2 (PGG_2), which is subsequently converted by hydroperoxidase to PGH_2. (In platelets, arachidonic acid is also oxygenated by a 12-lipoxygenase to form 12-hydroperoxy- and 12-hydroxy-fatty acids, which have uncertain biologic roles.) Subsequently, cells selectively differentiate in their metabolism of cyclic endoperoxides to biologically active products (e.g., via thromboxane synthase to thromboxane A_2 in platelets, or via prostacyclin synthase to prostacyclin in endothelial cells).

Platelet-derived thromboxane A_2 and endothelium-derived prostacyclin and nitric oxide have directly opposing actions on platelets and the vessel wall. Platelet-derived thromboxane A_2 is a potent platelet activator and vasoconstrictor, and endothelium-derived prostacyclin and nitric acid are platelet inhibitors and vasodilators. The balance of their production represents an important determinant of the state of platelet-vessel wall interactions, blood fluidity, and hemostasis. Both *in vitro*[10–13] and *in vivo*[14–16] studies demonstrate that activated platelets unidirectionally divert endoperoxides to vascular cells (termed "endoperoxide steal") to serve as substrates for prostacyclin synthase (Figure 1). This endoperoxide rediversion increases prostacyclin production at the platelet-vascular interface presumably as a thromboresistant response to activated platelets.

INHIBITION OF CYCLOOXYGENASE BY ASPIRIN AND NONASPIRIN NSAIDs

Aspirin covalently acetylates the active site Ser529 of cyclooxygenase and irreversibly inhibits the enzyme.[17–23] It might be expected that simultaneous inactivation of platelet and endothelial cyclooxygenase by aspirin would have deleterious effects on hemostasis by blocking thromboxane A_2 and prostacyclin formation. However, to enhance selectivity of aspirin inhibition on platelet thromboxane A_2 synthesis, several therapeutic strategies have been proposed to exploit pharmacokinetic differences between effects of aspirin on platelet and endothelial cyclooxygenase. First, cyclooxygenase acetylation by aspirin permanently inactivates the enzyme in anucleate platelets, which normally have a circulating lifetime of 7 to 10 days. Recovery of platelet thromboxane A_2 synthesis in an individual exposed to aspirin requires that senescent, cyclooxygenase-inhibited platelets be replaced in the circulation with new, uninhibited platelets from bone marrow

megakaryocytes not exposed to the drug. In contrast, vascular endothelial cells recover rapidly after aspirin exposure because they can continuously synthesize new, unacetylated cyclooxygenase.[24] This difference in protein synthetic capacities of the two cell types has led to suggestions that alternate-day administration may optimize the antithrombotic potential of aspirin by maintaining essentially continuous suppression of platelet thromboxane A_2 production while permitting intermittent recovery of endothelial prostacyclin production. A second difference between cyclooxygenases of the two cell types is increased sensitivity of platelet cyclooxygenase to aspirin.[25,26] Consistent with *in vitro* observations is the finding that administration of very low doses of aspirin to healthy subjects results in cumulative inhibition of platelet thromboxane production.[27,28] However, long-term administration of conventionally formulated aspirin at low doses partially suppresses vascular prostacyclin formation.[29,30] Therefore, biochemical selectivity of this regimen for platelets is at best relative, not absolute.[31,32] Finally, strategies with low-dose, controlled-release, and enteric-coated preparations of aspirin provide a drug delivery rate that does not exceed the threshold for hepatic extraction of aspirin, thus leading to first-pass metabolism of aspirin to salicylate, a very weak and reversible inhibitor of cyclooxygenase.[33] This permits cumulative inhibition of platelet cyclooxygenase in the prehepatic circulation while sparing the systemic vascular endothelium exposure to aspirin.[34-37] Salicylate released into the peripheral blood may block effects of residual circulating aspirin on vascular endothelium.

Whereas aspirin covalently acetylates and irreversibly inhibits cyclooxygenase, other NSAIDs (e.g., indomethacin, flurbiprofen, ibuprofen, naproxen) reversibly inhibit cyclooxygenase.[38,39] Additionally, ibuprofen and other nonaspirin NSAIDs protect platelets from irreversible inactivation by aspirin, presumably by blocking access of aspirin to the active site of cyclooxygenase.[40] All nonaspirin NSAIDs interfere with platelet function by essentially the same mechanism; the *in vivo* differences among these agents are primarily related to extent and duration of their effects on platelet function.

PLATELET AGGREGATION AND BLEEDING TIME: CLINICAL TESTS OF PLATELET FUNCTION

Platelet aggregation can be measured *in vitro* using an optical instrument.[41] This test is performed by adding standardized concentrations of substances that cause platelet aggregation to suspensions of platelet-rich plasma prepared from freshly drawn blood. Aggregation in the stirred samples of platelet-rich plasma is then measured by monitoring the increase in light transmission that occurs as platelets clump. Tracings of normal aggregation responses to various platelet agonists are shown in the top row of Figure 2. An initial depression in the baseline that is caused by a transient decrease in light transmission is often present. This reflects the initial platelet shape change that follows platelet stimulation. Next, a rapid increase in light transmission occurs as platelets aggregate. When a weak stimulus such as ADP or epinephrine is used as an aggregating agent, a biphasic pattern of platelet aggregation is characteristically observed; with strong stimuli, such as collagen and arachidonic acid, a single wave of platelet aggregation is noted. The plateau between first (primary) and second (secondary) waves of ADP- and epinephrine-induced aggregation corresponds to the platelet release reaction (see above) that follows initial platelet activation. Products released during this event, including thromboxane A_2 and ADP, mediate the second (and irreversible) wave of platelet aggregation. The plateau phase between first- and second-wave aggregation is undetectable when platelets are activated by strong stimuli such as collagen and arachidonic acid. Because NSAIDs inhibit thromboxane A_2 synthesis, and thereby block the release reaction, only primary-wave aggregation in response to ADP and epinephrine is seen in platelets prepared from subjects taking these drugs (as shown in the bottom row of Figure 2). Collagen-induced aggregation is markedly inhibited by NSAID use because aggregation in response to this stimulus is dependent on thromboxane A_2 formation. Arachidonate-induced platelet aggregation is entirely mediated by its con-

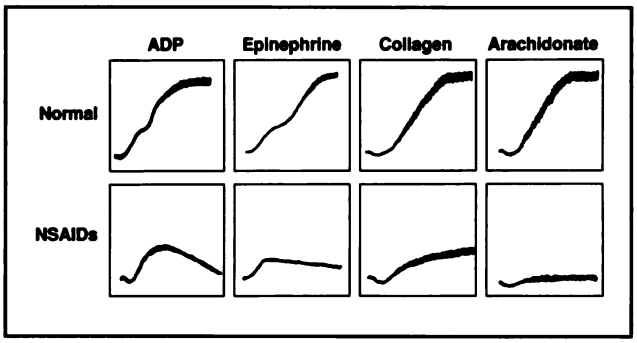

Figure 2. Patterns of platelet aggregation in vitro induced by ADP, epinephrine, collagen, and arachidonate. The upper series of tracings depicts normal aggregation patterns; the lower series shows changes in aggregation in response to the corresponding stimuli in individuals taking aspirin and nonaspirin NSAIDs.

version to thromboxane A_2 and, therefore, this response is abolished by NSAIDs.

The bleeding time is considered to be the best clinical screening test of *in vivo* primary hemostasis.[42–44] Prolongation of the bleeding time can be because of (a) a qualitative abnormality of platelets (e.g., secondary to NSAIDs), (b) thrombocytopenia, (c) an abnormality of platelet-vessel wall interactions, and/or (d) a primary vascular disorder. The standard Ivy method[45] has been modified to improve sensitivity and reproducibility. Semiautomatic template devices[46] have been largely supplanted by newer disposable automated products.[47–49] The test is performed by making a standardized incision over the volar aspect of the forearm while a blood pressure cuff (proximal to the incision) is inflated to 40 mm Hg. The bleeding time is taken as the time to complete cessation of free blood flow from the incision.

Although the bleeding time remains an important clinical screening test for evaluation of patients with suspected bleeding disorders, it has important limitations. First, it is fraught with potential technical artifact. Despite improvements in standardization, it is operator-dependent, and reproducibility is affected by several variables, including direction, size, and depth of incision; skin temperature and vascularity at the wound site; and interindividual variability of age, sex, ethnic origin, skinfold thickness, and anxiety.[44] Second, its role as a routine preoperative screening test to predict surgical hemorrhage has been critically challenged.[50–52] Finally, it cannot be extrapolated that skin bleeding time reflects bleeding time elsewhere in the body.[53] For example, prolongation of the skin bleeding time produced by aspirin use may not be associated with prolonged gastric bleeding time, as determined by endoscopic biopsy of the stomach.[54]

EFFECTS OF ASPIRIN ON PLATELET FUNCTION AND BLEEDING TIME

Aspirin affects both platelet aggregation and bleeding time. However, these two clinical tests are not necessarily equated. Aspirin has a more prolonged effect on platelet aggregation than on the bleeding time. Conversely, the bleeding time may be prolonged with defects of platelet function other than those involving the aggregation process (e.g., adhesion).

Platelet Function

Aspirin inhibits the second wave of ADP- or epinephrine-induced platelet aggregation *ex vivo* by blocking thromboxane A_2 formation.[55,56] Aspirin also abolishes arachidonate-induced aggregation, which is mediated entirely by its conversion to thromboxane A_2,[57,58] and may partially block aggregation induced by strong agonists (e.g., collagen, thrombin), depending on the concentration of stimulus applied. Long-term administration of very low-dose aspirin (20 mg/d) is sufficient to inhibit both *ex vivo* and *in vivo* thromboxane formation by more than 95%, an effect that blocks platelet aggregation by a variety of stimuli.[32] Chronic aspirin therapy at the lowest dose causing near-complete blockade of thromboxane synthase (40 mg/day) is associated with the same degree of platelet function inhibition as seen with a higher dose (325 mg/day).[59] After a single dose of aspirin, inhibitory effects on *ex vivo* platelet aggregation are maximal within 2 hours and persist for 4 to 7 days, which is long after blood salicylate levels become undetectable. This is consistent with the lifespan of irreversibly inhibited platelets.[55,60]

Bleeding Time

By virtue of its ability to inhibit platelet aggregation, aspirin prolongs the bleeding time in many normal individuals, and the effect is dose-dependent. Although it is not a consistent finding, a paradoxically greater bleeding time prolongation has occurred with lower doses.[61–63] This may be because of the relatively selective effect of low-dose aspirin on platelet thromboxane synthesis compared with vascular prostacyclin synthesis. With higher doses of aspirin, the simultaneous suppression of prostacyclin synthesis may offset the platelet inhibitory action of the drug. Bleeding times of healthy subjects typically increase to about two times baseline values 12 hours after ingestion of aspirin (325 mg) and return to normal within 24 to 48 hours.[60] After cessation of aspirin, the observation that prolonged bleeding time *in vivo* normalizes earlier than abnormal *ex vivo* platelet aggregation (see above) reflects the emergence of a large number of uninhibited platelets from the bone marrow into the circulation to achieve normal *in vivo* primary hemostasis (as measured by the bleeding time) but not *ex vivo* platelet activation (as measured by aggregometry).

EFFECTS OF NONASPIRIN NSAIDS ON PLATELET FUNCTION AND BLEEDING TIME

Platelet Function

Unlike aspirin, the effect of nonaspirin NSAIDs on platelets is reversible. Because these drugs reversibly inhibit platelet cyclooxygenase, function of the enzyme is restored as the drugs are cleared from circulation. Therefore, normal platelet function returns

more rapidly after discontinuation of NSAIDs with shorter half-lives.[64] Platelet effects of long-acting NSAIDs such as piroxicam may persist several days after the drug is discontinued.[65]

A study comparing ten commercially available NSAIDs administered to healthy human volunteers demonstrated considerable variability in extent and duration of their inhibitory effects on *ex vivo* platelet aggregation.[66] As predicted, a single oral dose of aspirin abolished the second wave of aggregation in response to ADP and epinephrine, and it produced a long-lasting effect that persisted for 5 to 8 days. Additionally, piroxicam, naproxen, diclofenac, and indomethacin blocked ADP- or epinephrine-induced second-wave aggregation, and the abnormality persisted 3 days after piroxicam was discontinued and 2 days after naproxen, diclofenac, and indomethacin were discontinued. Ibuprofen and diflunisal produced a weaker but definite effect, which normalized within 24 hours of ingestion. Results from a more detailed study in subjects taking diflunisal for 8 days showed that its platelet inhibitory effects were dose-dependent. Although no changes in ADP- and collagen-induced platelet aggregation were found with daily doses of 250 mg or 500 mg, respectively, 1,000 mg daily of diflunisal caused impaired platelet aggregability equivalent to that seen with aspirin (1,300 mg daily). The changes on day 8 tended to be greater than on day 1, and they diminished within 24 hours of the last dose for most subjects.[67] Effects of indomethacin, which is as potent an inhibitor of platelet thromboxane production as aspirin, occur within 2 hours of drug ingestion and persist for up to 8 hours. Restoration of normal platelet aggregability after administration of indomethacin is related to dose and plasma concentration.[68] Sulindac likewise produces transient changes in platelet aggregation that are lost 24 hours after the last dose.[69]

The effect of ibuprofen on platelet function has been well studied. Ibuprofen inhibits platelet aggregation and thromboxane A_2 synthesis.[66,70–76] Ibuprofen inhibited platelet aggregation at 1.5, 3, and 6 hours after a single 800-mg oral dose.[66] A single dose of ibuprofen between 300 mg and 900 mg blocked platelet aggregation 2 hours after administration; however, the effect was lost within 24 hours.[38,72]

The relationship between platelet aggregability, thromboxane production, and serum concentrations of ibuprofen has been examined. After ibuprofen administration of 200 mg, 400 mg, and 800 mg to healthy subjects, arachidonate-induced platelet aggregation was inhibited for 6, 8, and 11 hours, respectively.[75] This study developed a pharmacodynamic model to relate platelet aggregation parameters to serum drug levels, but ibuprofen concentrations were measured as total (bound plus unbound) unresolved drug. Results of a subsequent study showed intensity and duration of the antiplatelet effect to be dose-dependent, and the antiplatelet effect was related to plasma unbound concentration of S(+)-ibuprofen, which is the enantiomer responsible for cyclooxygenase inhibition.[76] Although these studies indicate that platelet function usually returns to normal within 12 hours after administration of ibuprofen, the time for disappearance of antiplatelet effects after cessation of chronic therapy is less predictable. The S(+)-enantiomer of ibuprofen potentially accumulates in adipose tissue, and its leaching from these stores may result in prolonged platelet inhibition after chronic therapy.[77]

Bleeding Time

Although ibuprofen inhibits platelet function like aspirin, its effects on the bleeding time are less well established. Results of an early study with low doses of ibuprofen (200 mg three times daily) showed that it did not prolong the bleeding time;[78] however, one study demonstrated a slightly but significantly prolonged bleeding time 2 hours after a single, 600-mg dose of ibuprofen.[72] Additionally, significant prolongations of the bleeding time have been reported 90 minutes and 1 week after ibuprofen dosed at 600 mg three times daily; however, the bleeding times typically do not become abnormally prolonged.[79] In a study of HIV(+) hemophiliac patients taking ibuprofen 400 mg every 6 hours concomitantly with zidovudine, the mean bleeding time was prolonged above normal limits at 1 hour, and this prolongation continued through the fourth hour after the dose.[80] Bleeding times at later time points were not determined.

In addition to ibuprofen, which shows a general correlation between serum levels and bleeding time,[72,79] other nonaspirin NSAIDs, including diflunisal,[67] indomethacin,[81] and ketorolac,[82–84] cause a prolongation of bleeding time. Nonaspirin NSAIDs cause transient, dose-dependent, and modest bleeding time abnormalities; however, abnormalities often do not exceed the upper limit of normal.

EFFECTS OF ASPIRIN ON CLINICAL BLEEDING

Aspirin has been associated with clinically significant spontaneous bleeding complications. For example, results from two randomized trials for the primary prevention of cardiovascular disease demonstrated that regular aspirin (325 mg every other day or 75 mg/day) use among healthy male physicians

was associated with an increase in disabling hemorrhagic stroke.[85,86] This complication has been attributed to the interference of primary hemostasis by aspirin. However, these results were not supported by a meta-analysis of 31 randomized secondary prevention trials.[87] Aspirin use is also a risk factor for development of chronic subdural hematoma after head injury.[88]

Regular administration of aspirin (75–250 mg/day) predisposes patients to overt gastrointestinal hemorrhage.[89,90] Although a suggested relationship exists between the dose of aspirin and risk of gastrointestinal bleeding, doses as low as 75 mg per day increase the frequency of gastrointestinal bleeding episodes.[91] Risk of such adverse effects from low-dose aspirin may be particularly pronounced in elderly patients, a population expected to derive greatest benefit from regular aspirin administration for prevention of vascular complications. In a 12-month, double-blind, randomized, placebo-controlled trial of 400 subjects older than 70 years, clinically evident gastrointestinal bleeding occurred in 3% of those receiving low-dose enteric-coated aspirin (100 mg daily); no such events occurred in the placebo group.[92] Aspirin-treated subjects also had a significantly greater decrease in hemoglobin levels as compared with placebo-treated subjects.

In addition to overt gastrointestinal bleeding, aspirin is associated with fecal blood loss. Whereas normal subjects lose approximately 0.5 mL of blood per day, there is a dose-related increase in blood loss from the gastrointestinal tract in aspirin users.[93] In an 8-day study of normal subjects, administration of aspirin (1,300 mg twice daily) was associated with a 6.6 mL blood loss, which was a sixfold increase over that in control subjects.[67]

Numerous reports provide conflicting results regarding the relationship between aspirin use and surgical bleeding complications. Results from one study[94] demonstrated that patients taking aspirin had a significant increase in perioperative blood loss during total hip arthroplasty; however, the clinical significance of this finding was questioned. Aspirin-treated patients undergoing cholecystectomies have prolonged bleeding times and a high incidence of postoperative bleeding.[95] In contrast, results from another study showed no difference in perioperative blood loss between patients taking and those not taking aspirin preoperatively.[96] There has been considerably more published literature concerning the risk of bleeding when aspirin is used before cardiac surgery. Patients taking aspirin before undergoing coronary artery bypass graft (CABG) surgeries have increased operative blood loss[97–101] and increased risk of reoperation for bleeding.[100–102] Aspirin use (of unreported doses) within 7 days before CABG was associated with an almost twofold increase in the likelihood of reoperation because of bleeding; however, no correlation could be demonstrated between risk of reoperation for bleeding and proximity of aspirin exposure before surgery.[101] Results of other studies have not shown increased CABG surgical bleeding with preoperative aspirin use.[103–105] Ingestion of aspirin during pregnancy may also be associated with excessive bleeding in both mother and neonate during the peripartum period.[106–108]

It can be concluded from these studies that if preoperative aspirin ingestion causes excessive intraoperative or postoperative bleeding it is of marginal clinical significance in most patients. History of preoperative aspirin use should not cause emergency surgery to be delayed. Many patients requiring cardiac surgery will be on chronic aspirin therapy for preventing secondary coronary events. Delaying surgery in these patients until discontinuation of aspirin to allow for the restoration of normal platelet function would not only increase cost but also carry a potentially undesirable clinical result.[105] The decision whether to delay surgery for up to 1 week after discontinuing aspirin should be individually evaluated for each patient, weighing the risks of excessive bleeding against the urgency of the operation and the type of surgery contemplated. However, two exceptions should be noted. First, aspirin should be discontinued for at least 7 days before elective surgery involving sites where even small amounts of bleeding are potentially dangerous (e.g., neurosurgery). Second, aspirin should be stopped before any elective surgery in patients with coexisting systemic coagulopathies (e.g., von Willebrand's disease) because aspirin-induced impairment of platelet function may provoke serious clinical bleeding.

EFFECTS OF NONASPIRIN NSAIDS ON CLINICAL BLEEDING

Although nonaspirin NSAIDs also increase bleeding times, effects of these drugs on clinical bleeding are less clear.[109] The incidence of gastrointestinal bleeding is higher with high-dose aspirin than with nonaspirin NSAIDs.[110–116] Endoscopic studies suggest that the degree of gastric mucosal injury and gastrointestinal bleeding may vary depending on NSAID and dose used.[117–119]

Conflicting results have been reported regarding effects of nonaspirin NSAIDs on perioperative blood loss. An increased frequency of bleeding episodes was found following abdominal surgery in patients treated with indomethacin 100 mg every 8 hours as compared with placebo.[120] Increased blood loss with

indomethacin has also been found in patients undergoing hysterectomies.[121] In contrast, no significant increase in blood loss was noted in patients who had received a continuous infusions of indomethacin before undergoing emergency surgeries of the lower extremities; however, bleeding times were prolonged.[122] Compared with placebo, no significant increase in blood loss was found in patients receiving diclofenac before undergoing hip replacements,[123] transurethral resections of the prostate,[124] or gynecologic laparotomies.[125] Another nonaspirin NSAID, ketorolac, was not associated with increased perioperative blood loss in patients undergoing transurethral prostatectomies.[109]

As is the case for aspirin, surgery does not need to be delayed in most patients taking NSAIDs. NSAIDs should be discontinued before surgery involving sites that require critical hemostasis or in patients with a coexisting coagulopathy. The delay in these cases should involve only a matter of hours, rather than days, because of the reversible nature of the platelet inhibitory effect of nonaspirin NSAIDs.

CONDITIONS COMPOUNDING THE RISK OF BLEEDING WITH NSAIDS

Alcohol ingestion by itself does not prolong the bleeding time. However, alcohol potentiates bleeding time prolongation produced by aspirin and nonaspirin NSAIDs;[126,127] this can range from a slight increase to a marked, sustained elevation, which is potentially sufficient to provoke spontaneous bleeding in otherwise normal individuals.[126,128] The magnitude of the augmentation varies independently from response with aspirin alone and, therefore, it is not possible to predict individual sensitivity to simultaneous ingestion. This interaction with alcohol has been found not only with aspirin but also with other NSAIDs, including ibuprofen and indomethacin.[126]

The mechanism of the alcohol-NSAID interaction has not been completely elucidated. *In vitro* studies have shown that low concentrations of alcohol reverse the inhibition of vascular prostacyclin synthesis but not the inhibition of platelet thromboxane synthesis mediated by aspirin.[129] Furthermore, alcohol (at doses achieved through consumption of alcoholic beverages) potentiates the inhibitory effect of prostacyclin on platelet aggregation.[130] The risk of alcoholic patients bleeding from NSAIDs may be compounded by coexisting factors, such as coagulopathy from liver failure, thrombocytopenia because of hypersplenism and toxic effects of alcohol on the bone marrow, and potential anatomic sites of hemorrhage (e.g., esophageal varices, ulcers, hemorrhoids). In addition to alcohol ingestion, patients with underlying platelet function disorders (e.g., von Willebrand's disease) exhibit a marked exaggeration of aspirin-induced prolonged bleeding time.[131–133]

Interaction of NSAIDs with other drugs may increase the risk of bleeding. Most NSAIDs potentiate the activity of oral anticoagulants[134,135] by displacing protein-bound drug[136] or inhibiting metabolism by hepatic microsomal enzymes.[137] Results of one study showed that aspirin, but not nonaspirin NSAIDs, is associated with an increased risk of bleeding from all sites in patients simultaneously treated with warfarin.[138] In contrast, a large retrospective cohort study of Medicaid enrollees aged 65 years or older who were taking nonaspirin NSAIDs revealed a nearly 13-fold increase in risk of developing hemorrhagic peptic ulcer disease in concurrent users of oral anticoagulants.[139] Furthermore, approximately 10% of hospitalizations for hemorrhagic peptic ulcer disease in users of anticoagulants were attributed to NSAID exposure. This study concluded that NSAIDs should be used with extreme caution in elderly patients receiving anticoagulants. NSAID use in patients with coexisting coagulopathies (e.g., liver failure, inherited coagulation factor deficiencies) may also increase bleeding risk. Lastly, use of ibuprofen and zidovudine in HIV(+) hemophiliacs is associated with defects in platelet function[80] and an increased frequency and severity of hemarthroses and hematomas.[140]

RECOMMENDATIONS

With the widespread use of aspirin and nonaspirin NSAIDs for a variety of clinical indications, physicians must be aware of their potential to cause bleeding complications. The chronic use of even very low-dose aspirin (the equivalent of 1 "baby" aspirin daily) can produce maximal inhibition of platelet function and primary hemostasis. Easy bruising, particularly in young and otherwise healthy women, is not uncommonly encountered with the use of aspirin and nonaspirin NSAIDs. Nevertheless, serious bleeding problems rarely occur spontaneously as a result of the use of these platelet inhibitory drugs. Even major surgery is not usually complicated by clinically significant bleeding in patients taking these drugs. Therefore, it is usually not necessary to delay surgery to restore normal hemostasis after discontinuation of these agents. An exception to this generalization should be considered in patients undergoing surgery at sites where normal hemostasis is critical. The most important bleeding problems that occur with the use of aspirin and nonaspirin NSAIDs are encountered in patients who have coexisting coagulopathies. Particular care should be taken with the

use of these drugs in patients with inherited coagulation disorders (e.g., hemophilia, von Willebrand's disease), severe thrombocytopenia (platelet count less than 50,000/mm^3), liver disease, or in those who are concomitantly using alcohol or anticoagulants.

Considerations should be given to alternate therapy in patients at risk of excessive bleeding because of aspirin and nonaspirin NSAIDs use. Because it has no effect on hemostatic mechanisms, acetaminophen is commonly used in patients with coexisting coagulopathies or other risk factors.[141]

CONCLUSIONS

Nonaspirin NSAIDs produce a systemic bleeding tendency by reversibly inhibiting platelet cyclooxygenase, thereby blocking formation of thromboxane A_2. Effects of individual NSAIDs on *ex vivo* platelet function, bleeding time, and clinical bleeding depend at least in part on dose, serum level, and drug half-life. Additionally, their systemic effect on platelets compounds the gastrointestinal bleeding potential created by their actions on gastric mucosa. Furthermore, the risk of systemic bleeding with NSAIDs is enhanced by concomitant use of alcohol or anticoagulants, and by associated conditions, including advanced age, liver disease, and other hemorrhagic diatheses (e.g., hemophilia, von Willebrand's disease). Because of the increased risk of bleeding in such patients, acetaminophen or other analgesics that do not affect platelet function should be substituted for NSAIDs whenever possible.

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