Short Communication

Low-Dose Aspirin for Atherothrombosis Prevention: Efficacy, Risks and Controversies

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ABSTRACT

Atherosclerosis is a chronic inflammatory illness in which immune systems work with metabolic risk factors to start, spread, and activate vascular lesions. It is the main cause of ischemic coronary artery disease and cerebrovascular disease. Myocardial infarction or ischemic stroke may result from arterial thrombosis, an acute complication that appears on the surface of a torn atheromatous plaque or as a result of endothelial erosion. The growth and advancement of atheromatous plaques may be aided by platelets, which are important biological elements of arterial occlusive thrombi. Additionally, essential to hemostasis, the physiological procedure that stops bleeding following tissue trauma and vascular injury, are platelets. Although the adhesion and activation of platelets can be seen as a repair-oriented response to sudden fissuring or rupture of an atheromatous plaque, unchecked progression of such a process through a series of self-sustaining amplification loops may result in intraluminal thrombus formation, vascular occlusion, and transient ischemia or infarction.

Due to their adhesive qualities and ability to quickly activate in response to a variety of stimuli, platelets can contribute in both healthy hemostasis and atherothrombosis. By selectively blocking important platelet enzymes or receptors, antiplatelet medications currently on the market interfere with specific steps in the activation process, lowering the risk of arterial thrombosis through mechanisms that cannot be separated from an increased risk of bleeding complications.

Keywords: Pharmacokinetics; Atherothrombosis; Aspirin; Atheromatous plaques

Introduction

In the stomach and upper small intestine, aspirin is quickly absorbed mostly through passive diffusion of nondissociated acetylsalicylic acid through gastrointestinal membranes. 30 to 40 minutes after ingesting uncoated aspirin, plasma levels reach their highest. Contrarily, enteric-coated formulations can take up to three or four hours after administration for plasma levels to peak; as a result, patients should chew these medications if a quick antiplatelet action is necessary [1]. In the liver and gastrointestinal mucosa, esterases hydrolyze aspirin to produce salicylic acid. Regular aspirin tablets have an oral bioavailability of between 40 and 50 percent over a range of doses, whereas enteric-coated tablets and sustained-release, microencapsulated formulations have far lower oral bioavailabilities. Platelets first come into touch with aspirin in the portal circulation, which exposes them to far higher drug levels than those found in the systemic circulation. In plasma, aspirin has a half-life of 15 to 20 minutes [2].

Despite aspirin's quick removal from the bloodstream, its antiplatelet effect lasts for the whole life of a platelet due to the irreversible inactivation of a crucial platelet enzyme. This effect can only be undone by producing new platelets. As a result, despite aspirin's extremely short half-life, its pharmacokinetics and pharmacodynamics are completely dissociated, allowing for the use of a once-daily regimen for antiplatelet therapy. The persistent inhibition of the cyclooxygenase (COX) activity of prostaglandin H (PGH) synthase 1 and synthase 2, often known as COX-1 and COX-2, respectively, is the most well-known mode of action of aspirin5. These isozymes catalyze the transformation of arachidonic acid into PGH2, the first committed step in prostanoid biosynthesis. PGH2 is an unstable metabolic intermediate and a source of at least five distinct bioactive prostanoids, including thromboxane A2 (TXA2) and prostacyclin, from numerous

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downstream isomerases (PGI2) [3]. Aspirin reaches the COX channel, a small hydrophobic passageway that connects the cell membrane to the enzyme's catalytic pocket, by diffusing through cell membranes. In order to block arachidonic acid from reaching the COX catalytic site of the enzyme, aspirin first binds to an arginine residue, which serves as a universal docking site for all nonsteroidal anti-inflammatory drugs (NSAIDs). It then acetylates a serine residue (serine 529 in human COX-1 and serine 516 in human COX-2) in the channel's narrowest part. Aspirin must be taken in higher doses to block COX-2 than COX-1.7. These variations may, at least in part, explain why antiplatelet effects can be attained daily dosages as low as 30 mg of aspirin, whereas analgesic and antiinflammatory benefits require much greater doses [4].

Although mature platelets exclusively express COX-1, newly generated platelets express both COX-1 and COX-2. Vascular endothelial cells, on the other hand, express both COX-1 and COX-2. The latter is the main source of PGI2 in both health and sickness and is up-regulated in response to physiologic hemodynamics. PGH2 is converted largely into TXA2 and PGI2 by platelets and vascular endothelial cells, respectively. In response to various stimuli (such as collagen, thrombin, and adenosine diphosphate), platelets produce and release TXA2, which then interacts with a G-protein-coupled receptor called the TXA2 receptor to cause irreversible platelet aggregation. TXA2 thus offers a way for enhancing platelet responses to various agonists [5]. TXA2 is also proatherogenic, a strong vasoconstrictor, and it stimulates the growth of vascular smooth muscle cells. In contrast, PGI2 interferes with platelet aggregation by interacting with the PGI2 receptor in response to all agonists.

Additionally, PGI2 causes vasodilation, prevents vascular smooth muscle cells from proliferating, shields the heart from oxidative stress, and is antiatherogenic. The significance of PGI2 in vascular thromboresistance is supported by the finding that deletion of the gene encoding the PGI2 receptor is linked to an increase in susceptibility to experimental thrombosis. While TXA2, a prostanoid primarily formed from COX-1 (primarily from platelets), is particularly sensitive to aspirin's ability to suppress its manufacture, vascular PGI2, which is primarily derived from COX2, is less so. Induced by aspirin, platelets develop a long-lasting functional impairment that can be identified clinically as an extended bleeding duration. Low-dose aspirin, on the other hand, has no detectable effects on PGI2-dependent vascular functions; as a result, it has no influence on blood pressure, renal function, or the antihypertensive properties of diuretics and ACE inhibitors. Although alternative pathways have been suggested, platelet COX-1 suppression alone is adequate to account for the antithrombotic properties of low-dose aspirin. Because platelet activation inhibition at sites of vascular injury may have indirect effects, such as reducing the release of inflammatory cytokines, oxygen radicals, growth factors, and other proteins, it is not necessarily implied that a single mediator, TXA2, is accountable for the 25% of major vascular events that can be prevented by lowdose aspirin in high-risk patients.

Additionally, the efficacy and security of low-dose aspirin are currently being studied in relation to other disease processes, which may be hampered, at least in part, by reduced release of these various platelet products. In fact, the idea that activated platelets cause the up-regulation of COX-2 in one or more types of cells implicated in early intestine carcinogenesis is compatible with the effectiveness of once-daily regimens of low-dose aspirin in preventing the recurrence of colorectal adenoma.

■ Drug interactions

Low-dose aspirin therapy (75 mg daily) has no effect on blood pressure management or the requirement for antihypertensive medicine in patients with intensively managed hypertension, in contrast to treatment with the vast majority of COX inhibitors. This finding is in line with the fact that low-dose aspirin has no impact on renal prostaglandin synthesis.

In humans, constitutively expressed COX-2 is necessary for renal prostaglandin production. The findings of a significant meta-analysis of myocardial infarction trials refute the hypothesis that aspirin may lessen the efficacy of ACE inhibitors after acute myocardial infarction. In patients with hypertension, there is no conflict between ACE inhibition and the cardioprotection provided by low-dose aspirin, and a meta-analysis of six long-term randomized trials comparing an ACE inhibitor with a placebo did not demonstrate that taking aspirin counteracted the positive effects of ACE inhibitors. Therefore, it would seem that ACE inhibitors are advantageous regardless of aspirin use.

The two-step method of COX-1 inactivation has a pharmacodynamic interaction that may prevent aspirin from having its intended antiplatelet effect. The irreversible acetylation of platelet COX-1 by low-dose aspirin may be avoided by concurrent administration of reversible COX-1 inhibitors such ibuprofen and naproxen. This is because these medications compete with aspirin for the same COX-1 channel docking site (arginine 120), which aspirin binds to with low affinity before acetylating serine 529. Coxibs and conventional nonsteroidal anti-inflammatory medications (NSAIDs), like diclofenac, which have some COX-2 selectivity, do not experience this pharmacodynamic interaction. Uncertainty exists on whether or not this interaction reduces or eliminates the cardioprotective effect of low-dose aspirin.

Upper gastrointestinal hemorrhage can result from aspirin therapy at low doses. Aspirin may lessen the gastrointestinal safety of selective COX-2 inhibitors, in comparison to standard NSAIDs, according to subgroup analysis from two large trials. However, studies that compare selective COX-2 inhibitors with conventional NSAIDs in individuals who have COPD need to investigate this potential interaction further. The inability of aspirin to decrease TXA2 production in vivo, to induce a meaningful response on ex vivo tests of platelet function, or to shield specific patients from thrombotic consequences has been referred to as "aspirin resistance."

Since we cannot be certain that a second vascular event in the same patient will share the same causative mechanisms as the first, there is no scientific justification for altering antiplatelet therapy in the face of such treatment failure. Furthermore, there isn't any solid proof that switching up the course of treatment is a better course of action than sticking with an antiplatelet regimen based on research. It may be possible to provide better patient care than requesting pointless tests of platelet function if there is a greater understanding of the elements that may conflict with the desirable antiplatelet effects of aspirin or clopidogrel, notably preventable medication interactions. To evaluate the antiplatelet effects of aspirin or clopidogrel in specific patients, no platelet function test is currently advised.

■ Efficacy and safety of low-dose aspirin in the prevention and treatment of atherothrombosis in high-risk patients

Aspirin's effectiveness and safety have been examined in a variety of populations, including individuals presenting with an acute myocardial infarction or an acute ischemic stroke and seemingly healthy people at low risk. According to individual studies and a metaanalysis of antiplatelet therapy trials, aspirin and other antiplatelet medications reduce the risk of a serious vascular event (nonfatal myocardial infarction, nonfatal stroke, or death from vascular causes) in patients with occlusive vascular disease by about 25%. This number reflects a combined 34 percent decrease in nonfatal myocardial infarction rates, a 25 percent decrease in nonfatal stroke rates, and a one-sixth decrease in nonfatal deaths from vascular or other causes. The absolute advantages of aspirin in specific patients can be assessed by lowering the projected absolute risk of nonfatal myocardial infarction by one because each of these proportional reductions applies uniformly to all groups of patients with vascular disease.

Third, the chance of a nonfatal stroke increased by a quarter, and the risk of vascular causes of death increased by a sixth. Aspirin normally avoids at least 10 to 20 fatal and nonfatal vascular events for every 1000 patients treated for a year among a variety of individuals with vascular disease, in which the annual risk of a serious vascular event varies from 4 to 8 percent. The risk of significant extracranial bleeding—most commonly upper gastrointestinal bleeding—roughly doubles with long-term therapy with low-dose aspirin, according to observational studies and a meta-analysis of randomized clinical trials in high-risk patients. This translates to an estimated absolute excess of 1 to 2 serious bleeding problems per 1000 patients receiving low-dose aspirin treatment for a year in middle-aged individuals. In addition, there are 1 to 2 hemorrhagic strokes per 10,000 patients in absolute excess.

Therefore, for the majority of high-risk patients taking low-dose aspirin, the likelihood of preventing a serious vascular event clearly outweighs the likelihood of preventing a major bleeding episode, unless a patient has an increased risk of bleeding due to advanced age, a history of ulcer, or concurrent treatment with other medications. Aspirin for patients at high risk for occlusive vascular disease has been approved by the Food and Drug Administration due to the aspirin's good risk-benefit ratio in high-risk patients, which led to level 1 recommendations. Cardiovascular registries and a recent survey suggest that aspirin use is not ideal despite this suggestion. A frequent justification for avoiding

long-term aspirin treatment in high-risk patients is a history of negative aspirin reactions.

In all clinical situations where antiplatelet prophylaxis has a good risk-benefit profile, aspirin is therefore advised. Considering that aspirin has the potential to reduce endothelial thromboresistance and gastric cytoprotection in a dosage-dependent manner, doctors are advised to take the lowest dose of aspirin that has been proven to be efficacious in each clinical situation. The evidence that is now available supports the use of daily aspirin doses between 75 and 100 mg for the long-term prevention of severe. Due to interindividual heterogeneity in the platelet turnover rate, which is a key factor in determining the intensity and duration of platelet inhibition on repeated low-dose aspirin administration, it is preferred to adopt a once-daily regimen rather than an every-other-day regimen. A loading dose of 160 to 200 mg should be administered at the time of diagnosis in clinical settings where an immediate antithrombotic effect is required (such as in the presence of acute coronary syndromes or acute ischemic stroke), in order to ensure rapid and complete inhibition of thromboxane-dependent platelet aggregation.

Discussion

Antiplatelet therapy could be enhanced in a number of ways to better prevent atherothrombosis. One crucial goal is to make sure that high-risk vascular disease patients utilize aspirin (or another effective antiplatelet regimen) as widely as is necessary. Many people who could benefit from low-dose aspirin are not routinely receiving it, according to several surveys; significant work is required to change these figures.

It is legitimate to wonder if an alternate antithrombotic regimen would be more successful than aspirin in high-risk individuals who are already taking aspirin. Adding a second antithrombotic agent (either an antiplatelet or an anticoagulant) to aspirin is likely to result in significantly higher reductions in risk than switching from aspirin to an alternative agent, even though clopidogrel may be slightly more efficacious than aspirin in some high-risk categories.

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