Reasons for Resistance to Aspirin in Cardiovascular Disease

To the Editor:

Aspirin effectively reduces the risk of myocardial infarction and stroke in patients with atherothrombosis. Yet, some patients have recurrent vascular events despite long-term aspirin therapy, raising the possibility that they are resistant to aspirin. The percentage of aspirin-resistance, estimated by platelet function tests, varies between 9% to 24% in stable cardiac patients. John Eikelboom and his colleagues reported on the association between urinary thromboxane excretion and risk of cardiovascular events in patients on long-term aspirin therapy. They concluded that resistance to aspirin increased the risk of cardiac death. The authors of this interesting article speculate about the role of nucleated cells (endothelium, monocytes) in resistance to aspirin; these cells could provide prostaglandin H₂, a precursor of thromboxane A₂ (TXA₂), even in the course of aspirin treatment, via cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2) pathways. We would like to point to two other possible explanations.

One is hypercholesterolemia and its treatment with statins. In hypercholesterolemic subjects, platelet aggregability is enhanced, TXA₂ production is increased, markers of thrombin generation are elevated in venous blood, and antithrombotic effects of aspirin are blunted. Treatment with statins depresses blood clotting, presumably through decreased expression of tissue factor. In the study of Eikelboom et al, percentage of subjects with hypercholesterolemia was similar among the cases and controls, but the former were significantly less often treated with lipid-lowering drugs. Because statins, with high probability, constituted the most common drugs used, this could explain, partly at least, differences both in the response to aspirin and the survival rate.

Another explanation could be a common genetic polymorphism of glycoprotein (GP) IIIa, a variable that has not been determined by Eikelboom et al. This polymorphism results in the Leu33 to Pro substitution, which defines PlA1 and PlA2 alleles, respectively. PlA2 allele is present in 20% to 30% of Caucasians and is associated with shortened bleeding time, enhanced thrombin formation, and impaired antithrombotic action of aspirin in vivo. Effects of aspirin on platelet aggregability in vitro might differ from those observed in vivo, and the issue has been discussed in detail recently. Apart from strictly antiplatelet effects, aspirin exerts additional anticoagulant actions, which clearly are coupled with inhibition of TXA₂ production by platelets, because only activated platelets are a source of the catalytic surface for the formation of prothrombinase and tenase complexes. It is not known to what extent these actions of aspirin, influenced by GPIIb/IIIa polymorphism, contribute to clinical efficacy of this drug and to the resistance to it.

How could a common genetic variation in β₃ integrins influence the anticoagulant effect of aspirin? Aspirin inhibits GPIIb/IIIa activation by interfering with intracellular signaling events and by acetylating GPIIb and GPIIIa molecules. Interestingly, the effects of aspirin on GPIIb/IIIa activation appear to be mediated by COX-dependent and COX-independent pathways (see references). The exact molecular mechanisms underlying these effects of aspirin remain to be elucidated.


Response

Dr Szczeklik and colleagues suggest differences in statin use or distribution of the platelet PlA₂ polymorphism between cases and controls as possible explanations for our findings of an association between aspirin-resistant thromboxane biosynthesis and risk of myocardial infarction, stroke, or cardiovascular death. However, we could not demonstrate an association between lipid-lowering therapy and urinary thromboxane B₂ concentrations, and our results remained unchanged even after adjusting for differences between cases and controls in the use of lipid-lowering therapy. Meanwhile, reports of an association between the PlA₂ polymorphism and atherosclerotic vascular disease have been conflicting, and we remain unaware of any convincing data demonstrating a significant clinical interaction between statin use or the PlA₂ polymorphism and aspirin therapy. Great interest remains in the possible role of platelet membrane glycoprotein or other (eg, COX-1) gene polymorphisms in determining an individual’s response to antiplatelet therapy. However, recent studies that have examined this question with respect to PlA₂ polymorphism and aspirin included only small numbers of healthy subjects, used nonspecific laboratory measures such as the bleeding time, platelet aggregation studies, or blood markers of thrombin generation to measure the inhibitory effect of aspirin, and did not correlate their findings with clinical outcomes. Future studies will require large sample sizes with sufficient numbers of clinical outcome events to reliably determine a possible interaction between the PlA₂ polymorphism and aspirin.

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