ASPIRIN THERAPY

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Well over 100 years after aspirin was commercially introduced as a therapeutic agent, we have a much keener appreciation of how it achieves a potent cardioprotective effect. It is striking that only in recent years have we gained more insight about the mechanism for limiting major adverse vascular events and have understood the appropriate selection of patients, as well as dosing. In this brief review, I will highlight some of the progress that has been made in these 3 areas: mechanism, patient selection, and optimal dosing.

MECHANISM

The predominant effect of aspirin relies on its blockade of cyclooxygenase-1 (COX-1), which is achieved through irreversible acetylation of the serine-529 residue. COX-1 production in platelets leads to thromboxane A2, a key platelet aggregation agonist. In endothelial cells, COX-1 facilitates the genesis of prostacyclin, a vital vasodilator. The dynamic balance of thromboxane A2 and prostacyclin is modulated by aspirin, and the dosing can tip the favorable balance (less thromboxane A2, more prostacyclin) more or less optimally. Furthermore, gastrointestinal mucosal protection is influenced by these pathways. Of particular note, the production of a new class of potent anti-inflammatory natural omega-3 fatty acids (resolvins) is mediated through aspirin and not through other nonsteroidal anti-inflammatory agents, including COX-2 inhibitors.

Beyond the specific mechanism of aspirin's cardioprotective effect, we have come to understand the transformed role of platelets from sole hemostatic modulation to the combined role of governing inflammation and thrombosis. Within platelets are literally hundreds of constituents that influence arterial inflammation, such as CD40 ligand, P-selectin, and thrombospondin-1. Concurrent with the emergence of high-sensitivity C-reactive protein (hs-CRP) as a valuable test to track vascular inflammation is the demonstration that aspirin has had its most significant impact in primary prevention among patients with the highest levels of hs-CRP. Accordingly, major progress in the mechanistic benefit of aspirin has occurred at 2 levels—there are platelet-independent factors that aspirin generates, such as resolvins, and platelets themselves are a reservoir of inflammatory mediators that can be effectively suppressed by aspirin.

PATIENT SELECTION

Patient selection for aspirin use has been greatly advanced by the recent meta-analysis of the Antithrombotic Trialists' Collaboration (ATC), which summarized data in 287 randomized trials of over 212,000 patients, most of which involved aspirin. The results showed the marked benefit of aspirin among diabetic patients, a finding that has been reinforced by the recommendation from the American Diabetes Association for patients with type 1 and type 2 diabetes. The current recommendation for aspirin is for use in all patients with manifestations of arterial disease—coronary, cerebrovascular, or peripheral—as a secondary prevention agent. Reduction of death, myocardial infarction (MI), and stroke has been definitively shown for virtually all groups of patients with documented arterial disease.

Primary prevention with aspirin is recommended for all patients with an anticipated risk >1% per year of vascular events (ie, death, MI, stroke). The recent US Preventive Services Task Force reviewed the data from the 5 major aspirin primary prevention trials and concluded that the benefit of aspirin (predominantly reduction of MI) exceeded risk in patients with a >1% per year risk. Age older than 50 years with at least one traditional risk factor (ie, hypertension, smoking, hypercholesterolemia, family history) or with an hs-CRP level >3.0 mg/L should at least be considered for primary prevention with aspirin.

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can override this resistance. A single nucleotide polymorphism of Factor XIII (Val34Leu) has conferred a more pronounced delay in the activation of Factor XIII after aspirin in the Leu carriers. Ibuprofen appears to sterically impair the effect of aspirin (at the COX-529 residue) and detract from its cardioprotective effect. This is particularly important because a large proportion of patients take nonsteroidal anti-inflammatory drugs with low-dose aspirin thromboprophylaxis. The interaction has not been observed with diclofenac, acetaminophen, or COX-2 inhibitors but has not been assessed through dedicated randomized trials. A recent analysis of the putative interaction of aspirin with angiotensin-converting enzyme inhibitors suggests that there is not a meaningful interaction with this drug class, as was previously suspected. Nevertheless, it is abundantly clear that more clinical research needs to be undertaken to define the issues of aspirin resistance—both intrinsic due to genetic variants, and those that are drug related.

Summary

There have been recent multiple, major jumps forward in our understanding of how aspirin works and how it should be used to exploit its cardioprotective effects. The use of low-dose aspirin confers marked protective effects, and bleeding risk can be minimized with lower doses. With the use of routine protein assays, such as hs-CRP, to gauge vascular risk, we will be able to take advantage of the cardioprotective action of aspirin in a much broader population of asymptomatic individuals in the years ahead.

References