Review

Aspirin Resistance, an Emerging, Often Overlooked, Factor in the Management of Patients with Coronary Artery Disease

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Summary: Aspirin is the most widely used medication in patients with cardiovascular disease. It has had a greater effect on patients with cardiovascular disease than any other drug. With the importance of aspirin now known for decades, it is recently becoming clearer that some patients do not derive as great a benefit from this “wonder drug” secondary to their resistance to its effects. Aspirin resistance, its prevalence, its identification, and how to overcome or avert it with other medications then becomes a central topic of discussion as important, if not more so, than the importance of aspirin itself as a cornerstone in the treatment of patients with cardiovascular disease. This review explores the current understanding of the mechanism of aspirin resistance with regard to its prevalence and the magnitude of its clinical significance. It also examines the therapeutic implications of a diagnosis of aspirin resistance.

Key words: aspirin, clopidogrel, resistance, nonresponder, risk factor, coronary artery disease

Introduction

Aspirin has long been and continues to be the central medication in the treatment armamentarium of patients with cardiovascular disease. Ever since it was first commercially developed in 1897 by Felix Hoffman,¹ aspirin has been used by millions for everything from headaches to fever, and most no-

tably over the past 30 years as the cornerstone of antiplatelet therapy in patients with cardiovascular disease.

The Antithrombotic Trialists' Collaboration has shown us that aspirin is an effective agent for the prevention of cardiovascular events in a wide variety of patients with heart and vascular disease. The risk of these cardiovascular events is reduced by about 25% in patients receiving aspirin, irrespective of the territory of the vascular disease, whether it be cardiac, cerebral, or peripheral vascular. Despite this impressive effect, it is now increasingly realized that certain “resistant” patients will have events despite regular daily aspirin therapy. It is estimated that one in eight high-risk patients will suffer from the recurrence of a vascular event within the subsequent 2 years despite receiving aspirin therapy.^{2–4}

Aspirin exerts its antithrombotic effect by irreversibly acetylating platelet cyclooxygenase-1 (COX-1), resulting in inhibition of platelet-dependent synthesis of thromboxane-A₂. Cyclooxygenase-1 is the isoenzyme expressed in mature human platelets, and the therapeutic efficacy of aspirin in atherothrombotic disease has been attributed to its effect on this isoenzyme. The anti-inflammatory effect of aspirin has been ascribed to its effect at higher doses on COX-2, the other isoenzyme that plays a dominant role in inflammation.⁵

Although much is currently known about the effect of aspirin on platelets, the mechanism by which some patients are resistant to aspirin, the proper diagnostic modality to use to determine this resistance, the clinical significance of this resistance, and the proper way to deal with this resistance therapeutically all remain elusive topics that have emerged and caught the attention of the medical community. This review examines these issues by taking a comprehensive view of the established data in the literature and by exploring some of the as of yet unanswered areas in the field of aspirin resistance.

Discussion

The entity of aspirin resistance has been examined by numerous small studies in the literature, with each of these studies examining a varying aspect of this complex field. Some study the prevalence of aspirin resistance and how to achieve defining its presence,^{6–8} some study the mechanisms for aspirin resistance,^{9–12} and yet others examine the impact or clin-

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Received: September 25, 2005

Accepted: October 20, 2005

ical significance of aspirin resistance on the presence or development of cardiovascular disease^{13–21} (Table I). There is no consensus on the ideal technique for the assessment of the presence of aspirin resistance and therefore no agreement about a standardized definition. There are also no large randomized trials delineating the mechanism or the proper and effective way to treat aspirin resistance. This lack of a uniform definition has led to a lack of appreciation of the true clinical significance of aspirin resistance.

Defining Aspirin Resistance

Aspirin resistance has been defined in many different ways; different studies have used everything from clinical findings to laboratory studies. In some reports, patients with thrombotic events during aspirin therapy were labeled as resistant or non-responders; other studies based resistance upon laboratory studies. Platelet function has traditionally been assessed by platelet-aggregation studies using an optical aggregometer; this method, however, is variable and not easy to perform.^{10,22}

More recently, easier techniques employing whole blood optical aggregometry have been used. Another method is the platelet function analyzer (PFA)-100, which is a semiautomated analyzer using whole blood for the assessment of platelet function. The PFA-100 produces results that are easily reproducible and correlate well with optical aggregometry.²³ Recently, Eikelboom *et al.*¹⁷ used urinary 11-dehydrothromboxane B₂ levels as a marker of suppression of thromboxane formation with aspirin therapy. These levels, however, reflect both platelet and nonplatelet sources of thromboxane formation and are therefore less specific. All of these techniques identify a decreased response to aspirin that falls within a wide range of variation from 5–60%.²³

Weber *et al.*⁸ sought to classify patients with aspirin resistance. Aspirin responders were defined as those in whom aspirin treatment of 100 mg/day for 5 days resulted in more than 95% inhibition in thromboxane formation and collagen-induced platelet aggregation. They further characterized three stages of resistance: In “type I resistance,” oral treatment with the above regimen was ineffective, but the *in vitro* addition of 100 μ M of aspirin resulted in complete inhibition; in “type II resistance,” neither oral treatment, nor *in vitro* aspirin addition resulted in a response; in “type III resistance,” which was labeled “pseudoresistance,” oral treatment resulted in inhibition of thromboxane synthesis, but did not inhibit the collagen-induced platelet aggregation.⁸ The clinical relevance of this last category or of the overall classification has yet to be tested. Further prospective studies need to be performed to validate this schema or to devise a new system of standardized classification for aspirin resistance.

Mechanisms of Aspirin Resistance

Aspirin resistance likely stems from a variable response to aspirin in a diversity of pathways that all have the same effect of altering platelet aggregation. Some studies have suggested that aspirin resistance is due to an increased reactivity to the

various inducers of platelet activation, including collagen and platelet activating factor (PAF). Along with this increased reactivity to induction of aggregation usually comes decreased response to the antiaggregatory effects of substances such as prostaglandin I₂.^{24,25}

Gum *et al.*¹⁴ speculate that cytokine induction of COX-2 in patients with vascular disease may provide an alternative pathway for prostaglandin H₂ production, which may lead to thromboxane production even in the presence of aspirin. This is because aspirin is 170 times less potent against COX-2 compared with COX-1. Because more than 90% of the thromboxane A₂ needs to be inhibited for aspirin to exert its effect, even small amounts of induction of the production of thromboxane can have a great impact.^{14,24}

Another postulated mechanism for aspirin resistance involves a polymorphism in platelet glycoprotein IIIa. Since the glycoprotein IIb/IIIa receptor serves as the final step in platelet aggregation, it is important to aspirin resistance. Three reports^{14,26,27} cite the presence of a P1A2 polymorphism affecting the glycoprotein IIIa subunit as a risk in patients who are homozygotes for increased platelet activation with agonists and decreased inhibition with aspirin.

A final mechanism suggested by Cipollone *et al.*²⁸ points to increased thromboxane production by oxidative stress through mechanisms not inhibited by aspirin. Increased amounts of isoprostanes that are prostaglandin F₂-like compounds have been identified in the urine of patients with unstable angina. These prostaglandins may promote aspirin resistance through platelet aggregation and vasoconstriction.^{24,28}

Clinical Implications of Aspirin Resistance

Few long-term clinical studies have examined the clinical significance of aspirin resistance (Table I)^{13,15–17,19–21} Mueller *et al.*¹³ studied 100 patients undergoing peripheral balloon angioplasty and found that aspirin-resistant patients had an 87% higher risk of vascular reocclusion after 18 months. Sane *et al.*¹⁶ found an increased prevalence of aspirin resistance in patients post coronary artery bypass during their most vulnerable period, which was the first 5–10 days post surgery. Grundmann *et al.*¹⁹ studied aspirin resistance with relation to cerebrovascular disease and noted that 34% of patients with aspirin resistance suffered recurrence of an ischemic stroke or a transient ischemic attack over a follow-up period of over 5 years.

Two large trials have studied the risk of adverse outcomes in patients with aspirin resistance. In a subgroup analysis of the patient population of the Heart Outcomes Prevention Evaluation (HOPE) trial, Eikelboom *et al.*¹⁷ studied 976 patients over a period of 5 years. In this investigation, 11-dehydrothromboxane B₂ was used as a marker of thromboxane generation, and patients were divided into quartiles based upon the levels of 11-dehydrothromboxane B₂ measured in their urine. The composite endpoint was myocardial infarction (MI), stroke, or cardiovascular death. Patients in the highest quartile (indicating greatest aspirin resistance) had a 1.8-fold higher risk of the endpoint than those in the lowest quartile. Those in the highest quartile also had double the risk of MI and 3.5

TABLE I Aspirin resistance

Reference (no.)	Patient population	Aspirin dose (mg/day)	Determination of resistance (test used)	Prevalence of resistance	Endpoint(s)/follow-up	Conclusions
Mueller <i>et al.</i> (13) (1997)	100 patients with PVD	100	Whole blood aggregation	—	Peripheral vascular arterial reocclusion over 1½ years	Aspirin-resistant patients had an 87% higher risk
Gum <i>et al.</i> (14) (2001)	325 patients with stable cardiovascular disease	325	Optical platelet aggregation or PFA-100	5.5% were resistant and 23.8% were non-responders	Profile and prevalence of aspirin resistance	Aspirin resistance or nonresponse was more likely in women and the elderly, and less likely in smokers. There were no differences in aspirin sensitivity by race, diabetes, platelet count, renal disease, or liver disease
Zimmerman <i>et al.</i> (15) (2001)	24 patients post CABG	100	Collagen-induced aggregation and thromboxane formation	—	Resistance at Days 1, 5, and 10	Patients post CABG are more likely to display the presence of aspirin resistance in the postoperative period compared with controls and this might be related to increased platelet levels
Sane <i>et al.</i> (16) (2002)	88 patients with CHF	325	Conventional platelet aggregometry, PFA-100, and expression of major surface receptors using flow cytometry	56.8%	Frequency of aspirin resistance in patients with CHF	“Until definitive clinical trials are completed, physicians should be aware of the high rate of resistance in patients with heart failure...”
Eikelboom <i>et al.</i> (17) (2002)	976 patients from the HOPE study population	75–325	Urinary 11-dehydrothromboxane B ₂	—	Composite of myocardial infarction stroke/ cardiovascular death over a 5-year period	1.8 times the risk of endpoint in patients in the highest quartile versus the lowest quartile of urinary 11-dehydrothromboxane B ₂ levels
Grundmann <i>et al.</i> (19) (2003)	53 patients with cerebrovascular/peripheral vascular or cardiovascular diseases	100	PFA-100	—	Recurrence of CVA/TIA during > 5 years	34% recurrence of CVA/TIA in aspirin nonresponders
Gum <i>et al.</i> (20) (2003)	326 patients with stable cardiovascular disease	325	Optical platelet aggregation	—	Composite of death/MI/CVA over 679 ± 185 days	24% risk of composite endpoint in aspirin-resistant versus 10% in aspirin-sensitive (hazard ratio = 3.12) patients
Chen <i>et al.</i> (21) (2004)	151 patients undergoing elective PCI	80–325	PFA: defined ASA resistance as aspirin resistance units ≥ 550	19.2%	Myonecrosis as assessed by a CK-MB rise after PCI	“Despite adequate pretreatment with clopidogrel, patients with aspirin resistance as measured by a point-of-care assay have an increased risk (2.9 fold) of myonecrosis following non-urgent PCI”

Abbreviations: PVD = peripheral vascular disease, CABG = coronary artery bypass graft, PFA = platelet function analyzer, CHF = congestive heart failure, HOPE = Heart Outcomes Prevention Evaluation, CVA = cardiovascular accident, TIA = transient ischemic attack, MI = myocardial infarction, PCI = percutaneous coronary intervention, ASA = aspirin, CK = creatine kinase.

times the risk of cardiovascular death than those in the lowest quartile. The second study is that of Gum *et al.*,²⁰ which looked at stable patients with cardiovascular disease over a period of > 2 years. This prospective study of 326 patients found an increased risk (24 vs. 10%, $p < 0.03$) of the composite end-point of death, MI, or cerebrovascular accident in aspirin-resistant patients. This study identified platelet count, age, heart failure, and especially aspirin resistance to be independent predictors of major adverse long-term outcomes (hazard ratio for aspirin resistance = 4.14, 95% confidence interval 1.42–12.06, $p = 0.009$).^{17, 20}

Management of Aspirin Resistance

No specific guidelines for the treatment of aspirin resistance have been recommended in the literature. Certain strategies, however, when followed, may minimize thrombotic risks in the presence of possible aspirin resistance. Basic strategies of assessing and assuring patient compliance play a major role in management. Aspirin dosing does not appear to affect a reduction in the incidence of vascular events in high-risk patients.^{3, 22}

Newer antiplatelet agents are now becoming available, and it has been questioned whether patients who are aspirin resistant may benefit from either substitution of these new agents for aspirin or the combination of these new agents with aspirin. One agent of importance is the thienopyridine clopidogrel. Recent large trials using clopidogrel, Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (CURE),²⁹ Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE),³⁰ and Clopidogrel (PlavixTM) for the Reduction of Events During Observation (CREDO),³¹ have shown a superior clinical benefit of clopidogrel, either alone, or in combination with aspirin, compared with aspirin alone. What is not clear, however, is whether this benefit is related to the compensation for aspirin resistance with the addition of clopidogrel, and whether adding clopidogrel to a patient with aspirin resistance will help overcome the observed adverse outcomes. It is hoped that an ongoing trial, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA),³² will add some guidance to this area by comparing the combination of aspirin plus clopidogrel versus aspirin alone in both secondary prevention and high-risk primary prevention.^{22, 32} Chen *et al.*²¹ found that despite pretreatment with clopidogrel (300 mg loading dose of clopidogrel > 12 h before and a 75 mg maintenance dose in the morning of the coronary intervention), patients with aspirin resistance still have an increased risk of myonecrosis assessed by creatine kinase (CK)-MB rise following nonurgent percutaneous coronary intervention.

Unanswered Questions and Future Directions

Many areas in the field of aspirin resistance remain unstudied and unexplained. The literature shows that aspirin resistance does exist, but it does not agree how to define it. Should we screen all patients for aspirin resistance or should we only

screen high-risk patients who have recurrent events despite aspirin therapy? Is there gender or racial variation in the presence of aspirin resistance? Do we add clopidogrel to all patients in whom we note aspirin resistance, or do we simply use higher doses of aspirin in these patients? Should we look for new agents that directly inhibit thromboxane or have greater effects against COX-2?

All of these questions have great clinical implications for the management of patients with cardiovascular disease. Further studies to evaluate possible treatments and to elucidate the exact mechanism of aspirin resistance need to be performed. Many of the answers to these questions are currently on the horizon and will be arriving as we further study the nature of this complex yet simple “wonder” drug we call aspirin.

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