RESISTANCE TO ORAL ANTIPLATELET AGENTS: FACT OR FANTASY?

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INTRODUCTION

There is little question that oral antiplatelet agents have found a distinct and nearly universal role in the management of patients with atherosclerotic disease. Aspirin has proven to be an important drug that reduces the complications of virtually all manifestations of atherosclerosis in the cardiac and cerebral circulations.1 The thienopyridines, ticlopidine and clopidogrel, have been useful in managing patients who have undergone intracoronary stent placement[2] as well as those suffering from acute coronary syndromes[3] and ST segment elevation myocardial infarction.[4,5] However, a variety of publications over the past five years have reinforced the concept that the responses of individual patients to these drugs is heterogeneous, and that this heterogeneity may have important clinical consequences. This monograph will review the evidence that such variability not only exists but is also clinically meaningful.

An important point to recognize is that use of the term "resistance" is controversial and likely misleading for several reasons. First, a drug response must be defined in terms of biomarkers rather than clinical events; patients with atherosclerosis nearly always receive a variety of concomitant treatments, so a clinical event can be regarded as a failure of any or all of these treatments rather than simply an inadequate response to a specific drug. Second, a variety of in vitro tests are available to characterize the response to antiplatelet drugs. However, the responses reported by one test do not necessarily reflect responses reported by others, so categorizing a particular patient as either "responsive" or "resistant" is in part dependent on which test is used. Third, the basal reactivity of platelets before administering either drug may play a large role in determining the final degree of platelet activity after either drug is administered. Finally, relatively stringent criteria for a biomarker's adequacy have been expounded in recent years;[6] however, neither the in vitro responses to aspirin nor to clopidogrel have strictly met these requirements. In addition, almost no reports exist concerning the reproducibility of determinations made with any of the tests, and very few reports exist concerning the temporal stability of these estimates. For example, it is unknown whether a patient who is classified as aspirin "resistant" on day 1 will also be "resistant" at the end of a month or a year. In fact, there is reason to suspect that this may not be the case at all.

ASPIRIN

The primary action of aspirin occurs through its interdiction of prostaglandin G/H synthase (cyclooxygenase 1, or COX-I), although there is debate over whether aspirin also functions through alternative mechanisms. This enzyme is ultimately responsible for the formation of the vasoconscricror and proaggregam thromboxane A2 (TXA2) from arachidonic acid, an omega-6 fatty acid. Aspirin is absorbed from che proximal small intestine; when it enters the portal circulation, it acetylaces che serine 529 residue on COX-I and permanently inactivates the enzyme.7 As a resulr, measuring TXA2 formation (or its metabolite TXB2) in blood chat is allowed to clot provides the most pathway-specific measure of aspirin's activity. Given in doses above 75 mg daily, aspirin is able to inhibit >95% of TXA2 formation. Unfortunately, performing chis measurement is relatively difficult outside of experienced hands, so surrogate measures involving platelet aggregation in response co arachidonic acid, collagen, or ADP have been used. Three additional types of measurement have also been used: l) measurement of che urinary metabolite of TXA2 (ll-dehydro-TXB2); 2) global measures of platelet activity, such as the ability to seal a perforated membrane under flow conditions, or chromboelastography, which measures the tensile strength of a clot; and 3) a generation of point-of-care devices that measure platelet agglutination or formation of circulating platelet aggregates. There is controversy regarding which of these rests should be regarded as the standard for assessing the response to aspirin, as the findings between tests are not necessarily concordant. Although measurements of TXA2 or its metabolite are by far most specific for aspirin and possibly che most meaningful, more global tests of platelet accivi$_{cy}$ are more likely to indicate whether compensatory mechanisms are present char may attenuate the intracellular activity of aspirin.

When TXA2 formation is measured, approximately 1-2% of subjects who are

confirmed aspirin users are found to be "resistant." However, when turbidimetric (or "light transmittance") platelet aggregometry is used, 10-15% of patients have suboptimal responses to aspirin. As many as 40% of patients are found to be aspirin "resistant" when a device that measures the ability of activated blood to occlude a perforated membrane (PFA-100 device) is used for the assessment. The etiology of these responses *is* probably multifactorial. Drug-drug interactions account for some of them. The H2 blocker ranitidine has been shown to reduce the activity of aspirin in volunteers, probably because the higher stomach pH decreases absorption.[8] The nonsteroidal anti-inflammatory drugs (ibuprofen and naproxen) have been shown to interfere with aspirin's ability to acetylate COX-1.[9] Since this activity persists for several hours after the nonsteroidal is administered, patients who require both medications should take aspirin at least two hours before taking a nonsteroidal. Heparin also reduces the effect of aspirin on platelets through a mechanism that is not well understood.[10]

Other mechanisms have been postulated as well. Patients who undergo coronary artery bypass surgery have a markedly diminished response to aspirin for approximately a week after the surgery. This effect seems to parallel increased expression of COX-2,[11] an isoform of COX-1 that may provide an aspirin-insensitive alternate pathway of TXA2 production. We have also found that individuals with increased levels of circulating juvenile ("reticulated") platelets have a dramatically reduced response to aspirin, presumably because platelets express COX-2 during their formation and release in the bone marrow.[12] Another pathway independent of both COX-1 and COX-2 has also been described.[13]

The impact of aspirin "resistance" is also a matter of debate. A subsudy of the HOPE trial indicated that aspirin-treated patients whose urinary 11-dehydro-thromboxane 82 levels were in the upper quartile had nearly a two-fold increased risk of developing an ischemic event over the ensuing two years.[14] A study of patients with chronic coronary artery disease also indicated that the risk of myocardial infarction over nearly three years was elevated in those with evidence of aspirin resistance as defined using turbidimetric aggregation (in response to 5 µmol/L ADP) but not the PFA-100 device.15 Several smaller studies of patients undergoing percutaneous coronary intervention (PCI) have also indicated a higher risk of periprocedural myocardial infarction following Stent implantation in those with evidence of aspirin resistance detected using a point-of-care device.[16] However, it is worth noting that it is not clear whether or not aspirin resistance in these cases was simply a marker of clinical instability.

TREATMENT

While sensitivity to aspirin can arguably be viewed as an indicator of risk, there are no indications of specific treatment to rectify this. Several studies suggest that aspirin resistance is more common when lower doses are used;[16,17] however, randomized trials of various aspirin doses have not confirmed a clinical dose-response effect, and meta-analyses have also failed to reveal dose-dependent reduction in cardiac events.[1,18] Alternative TXA2 antagonises are currently undergoing evaluation, and a randomized trial is also being conducted of GP IIb-IIIa antagonise use in aspirin-resistant patients who undergo PCI.

CLOPIDOGREL

Unlike aspirin, clopidogrel is a pro-drug that is converted by members of the hepatic cytochrome P450 family to an active metabolite that binds the platelet "ADP receptor" P2Y12 and prevents platelets from becoming activated by ADP that is released at the site of red cell lysis or by other activated platelets. That the in vitro response is heterogeneous among individuals receiving clopidogrel is more firmly established than for aspirin. Multiple reports have implicated an impaired response to clopidogrel in a variety of ischemic outcomes, particularly after intracoronary stent implantation. Each of these studies is observational in nature, and most are retrospective. Thus, it is difficult to separate the effects of other states associated with increased platelet reactivity - such as prolonged or difficult stent procedures or acute coronary syndromes, which would be expected to have higher complication rates - from a biologic tendency to metabolize clopidogrel less effectively. In particular, assessing platelet reactivity shortly after a patient presents with an episode of stent thrombosis is more likely to reveal platelet function characteristics that have developed in response to the acute episode rather than a steady state defect.

As with aspirin, there are few estimates of the temporal stability of clopidogrel responses, and many commonly used drugs have been reported to interact with clopidogrel, most either inducing or suppressing the cytochrome P450 enzymes required to convert clopidogrel to its active metabolite. Nonetheless, several noteworthy studies suggest that use of clopidogrel is likely to be associated with an increased chance of developing a stent thrombosis after implantation. Hochholzer studied the platelet aggregation response to 5M ADP prospectively in 802 patients scheduled to undergo stent implantation. When the degree of suppression of aggregation was stratified into quartiles, the individuals in the highest two quartiles had the highest risk of stent thrombosis, and multivariable regression revealed that for every 10% increase in residual aggregation, the ischemic risk increased 1.32 fold.[19] Similar retrospective observations by Buonamici[20] and Price[21] support these observations.

A novel approach was recently studied by Bonello et al. using measurements of vasodilator-stimulated phosphoprotein (VASP). VASP, which plays a critical role in activating the platelet cyroskeleton and the aggregation receptor GP Ilb/Illa, becomes inactivated through phosphorylation by a cyclic AMP-dependent kinase. Activation of P2Yl2 by ADP decreases VASP phosphorylation while blockade of the receptor increases it. Increases in VASP phosphorylation provide a pathway-specific index of P2Yl2 blockade. When Bonello et al. observed responses of VASP phosphorylation to a 600 mg loading dose of clopidogrel prior to scent implantation, approximately 50% of patients had a suboptimal response to clopidogrel. When serial loading doses of clopidogrel were titrated to a VASP phosphorylation index, rhe authors noted a significant reduction in pose-procedural ischemic complications among patients who underwent clopidogrel titration compared with those who received a single loading dose.22 This srudy is the first to indicate that titrating a clopidogrel dose to an in vitro standard is likely to yield a beneficial clinical result.

Another line of evidence that indirectly confirms the clinical benefits of a more robust response to a P2Yl2 antagonise comes from the TRITON-TIMI 38 trial of a novel thienopyridine, prasugrel, which is metabolized more effectively than clopidogrel and inhibits platelet aggregacion to a greater and more consistent degree. In chis trial of 13,800 patients with acute coronary syndromes, prasugrel resulted in a 19% relative reduccion in a combined endpoint of cardiovascular deach, myocardial infarction, or ischemic stroke and was associated with a 50% relative reduction in scent thrombosis.23 These two studies provide the nexr important piece of evidence that adaptive drug dosing based on rhe response co clopidogrel or use of a more potent antagonist of P2Yl2 will reduce the risk of ischemic complications in patients with coronary artery disease. A large trial of clopidogrel titration, based on platelet aggregation as determined by a point-of-care device after coronary scene implantation, and a large trial of twice-daily rather than daily clopidogrel dosing are now underway.

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