ADVANCES IN HEMATOLOGY

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Aspirin Resistance: Does It Exist and Is It an Important Clinical Problem?

John Eikelboom, MBBS, MSc
Associate Professor
Thrombosis Service, Hamilton General Hospital
Department of Medicine, McMaster University

H&O From a hematologist's perspective, why and in what populations is aspirin typically prescribed?

JE In the hematology populations, aspirin is primarily prescribed to patients at risk of arterial thrombosis. This includes patients who present with hematologic disorders who also have risk factors for cardiovascular disease or a past history of myocardial infarction, stroke, or peripheral arterial disease. Aspirin is also prescribed in the treatment of patients with myeloproliferative disorders.

H&O What is the mechanism of action of aspirin in hematologic patients?

JE The therapeutic effect of aspirin in preventing cardiovascular disease is believed to be mediated primarily through blocking platelet cyclooxygenase-1 (COX-1), which inhibits thromboxane production.

H&O What is aspirin resistance?

JE Aspirin resistance is a poorly defined term. Clinicians and researchers are essentially interested in whether aspirin exerts the expected inhibitory effect on platelets or whether some patients achieve less than expected inhibition of platelet function with aspirin. Patients who achieve less than expected inhibition of platelet function are often described as "aspirin resistant."

One way of further clarifying this concept is to consider cholesterol-lowering drugs. Just as antiplatelet drugs block platelet function, statins reduce cholesterol levels. If a particular drug reduces cholesterol levels by a certain amount in one patient and by a lesser amount in another patient, is the latter patient considered statin-resistant? The answer is probably no. The patient may be considered to have achieved less than the expected response, and this may lead the physician to increase the dose or switch to another drug. In the same way, aspirin may not inhibit platelet function to the extent expected. If not, clinicians may be led to consider whether it is necessary to increase the dose, switch to another antiplatelet drug, or add another antiplatelet drug to aspirin.

H&O What are the mechanisms behind aspirin resistance?

JE There are many possible mechanisms of aspirin resistance, including an inadequate dose of aspirin, lack of compliance, altered absorption due to a problem in the gastrointestinal tract, drug interactions, genetic polymorphisms of the COX-1 gene, or aspirin "bypass" due to generation of thromboxane from nonplatelet sources. The importance of these mechanisms, however, remains to be demonstrated.

As an example, one can consider the effects of altering the dose of aspirin. There is some evidence that higher doses of aspirin increase inhibition of platelet COX-1 as measured by greater inhibition of serum thromboxane production, as well as increasing inhibition of urinary thromboxane, possibly reflecting aspirin "bypass" pathways. However there is no evidence that increasing the dose of aspirin improves clinical outcomes. Ultimately the clinical relevance of aspirin resistance and the proposed mechanisms of aspirin resistance are determined in relation to clinical outcomes.

H&O What methods are most commonly used to test whether a patient is resistant to aspirin? Should tests be based on the clinical outcome?

JE Ideally, laboratory tests for aspirin resistance need to be linked with clinical outcome in order to establish their validity. Although many different assays have been used, there is currently no single laboratory test that has been shown to be superior for predicting clinical outcome. The historical gold-standard test for aspirin resistance is

optical platelet aggregation in response to arachidonic acid. Many other tests have been proposed, including whole-blood platelet aggregation using electrical impedance; point-of-care tests such as the VerifyNow Aspirin Assay (Accumetrics), Platelet Function Analyzer (Dade-Behring), and Plateletworks (Helena Laboratories); serum thromboxane; and AspirinWorks (AspirinWorks), a measure of urinary thromboxane.

H&O What are the known advantages and drawbacks of arachidonic acid–induced aggregation and the newer assays?

JE Each of the tests has strengths and limitations. While remaining the gold standard, the major drawback of arachidonic acid–induced aggregation is that it is time-consuming to perform (minimum of 1 hour) and requires particular expertise and equipment in the laboratory. Additionally, its reproducibility is unknown, and it may be affected by age or gender.

The immediate advantage of point-of-care tests is simplicity. After drawing the blood sample and placing the collection tube in the machine, the result is available within several minutes. The disadvantage of these newer assays is that it is uncertain whether they are any better or potentially worse than arachidonic acid–induced aggregation for predicting outcome. These tests are poorly correlated with each other; the Platelet Function Analyzer correlates poorly with arachidonic acid–induced aggregation and is affected by hematocrit and von Willebrand factor levels. Urinary thromboxane testing has been linked with outcome in epidemiologic studies, but its usefulness for individual patients is unknown.

An important question to ask is whether these tests should be used in clinical practice. Until it can be shown that patient outcomes are improved with these tests, it is debatable whether testing should be employed in clinical practice. Laboratory testing costs time and money, and when antiplatelet treatment is changed based on the results of the test we should be certain that the change in treatment improves patient outcome. Without appropriate studies to demonstrate benefit, it remains possible that we will harm patients by changing treatments. For example, if an assay shows that a patient is "resistant" and a physician decides to increase the dose of aspirin, this may "improve" the laboratory test result but increase the risk of bleeding without any benefit to the patient. Alternatively a clinician may decide to replace aspirin with an alternative antiplatelet drug, at increased cost to the patient and to the community but without any benefit in preventing cardiovascular events. Point-of-care tests are more affordable than standard aggregation but before they can be recommended for routine clinical use it is critically important that they are proven to be of benefit. Once it is proven that a test predicts outcome and that changes to treatment prevent adverse outcomes, testing may prove to be highly cost-effective.

On the other hand, taking a nihilistic view of laboratory testing for aspirin resistance based on the lack of evidence that testing improves clinical outcome may stifle the development of newer tests and may limit investment and innovation. Companies that are developing point-of-care assays to measure platelet function must be encouraged and supported, but the entry of such tests into routine clinical practice should be based on strong science and not simply on the potential to generate revenue.

H&O Does aspirin resistance result from the overprescription of aspirin?

JE There is no evidence that aspirin resistance is related to the overprescription of aspirin. There is a very large body of evidence to support the use of aspirin for prevention of cardiovascular disease. There is also an extensive body of randomized evidence to support the use of clopidogrel for preventing cardiovascular disease, either alone or in combination with aspirin. Clopidogrel is slightly more effective than aspirin but costs much more. While clopidogrel is probably cost-effective in terms of quality-adjusted life-years saved, there is general agreement that aspirin remains the front-line antiplatelet drug for the secondary prevention of cardiovascular disease unless patients are allergic, cannot tolerate aspirin, or experience cardiovascular events despite aspirin.

It is uncertain whether clinical outcomes would be improved if alternative antiplatelet drugs were used. There is also variability in the antiplatelet effect of clopidogrel, which has been termed "clopidogrel resistance." Less-than-expected inhibition of platelets by clopidogrel has been linked with an increased risk of cardiovascular events. It is possible that switching from aspirin to clopidogrel may improve clinical outcomes in those who are resistant to aspirin, but this remains to be demonstrated.

H&O What research has been undertaken regarding the similarities in resistance between clopidogrel and aspirin?

JE Several studies have explored whether people who are resistant to aspirin are more likely to respond to clopidogrel, and whether aspirin resistance can be overcome with clopidogrel. To date, however, there is no evidence that replacement of aspirin with clopidogrel improves clinical outcomes. One of the problems with this line of research is that there is currently no single global test of platelet function that reflects the antiplatelet effects of both aspirin and clopidogrel. The antiplatelet effect of aspirin is usually measured by arachidonic acid–induced

platelet aggregation and that of clopidogrel is measured by adenosine diphosphate–induced platelet aggregation; there is only limited overlap between these assays. Global tests of platelet function include bleeding time, platelet-dependent thrombin generation in the blood, or thromboelastography, but each of these tests has important limitations and remains to be validated for this purpose.

H&O Where do you see this field heading in the future?

JE In 10 or 20 years, I would hope to see platelet function routinely measured in the same way that blood pressure and blood cholesterol are routinely measured. It would be great to see a point-of-care device in every physician's office that allowed rapid measurement of platelet function using a simple, rapid, inexpensive, accurate, and validated assay that has been linked with clinical outcome. This would enable clinicians to optimize antiplatelet therapy for an individual patient by maximizing cardiovascular prevention while minimizing bleeding risk.

Suggested Reading

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