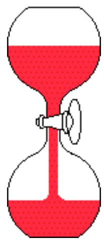

Orentreich
Foundation for the
Advancement of
Science, Inc.

VitaLongevity™

Logo: Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.

September 2006 www.orentreich.org

ANTI-PLATELET RESISTANCE

Aspirin was a remarkable drug in the 19th and 20th centuries, valued for its pain relieving actions without the stuporous effects of alcohol or opium. Yet the full value of aspirin (Figure 1) was not realized until the latter part of the 20th century when aspirin claimed its place in the pharmaceutical hall of fame as the single most important drug for the prevention of heart attack and stroke.

Today, although aspirin is a mainstay in the prevention of atherosclerotic events, physicians have other drugs available to replace or supplement aspirin, principal of these being clopidogrel (Plavix®). It is fortunate that there are aspirin alternatives because recent research indicates that there are patients who are resistant to aspirin, and even to clopidogrel.

The structure of aspirin

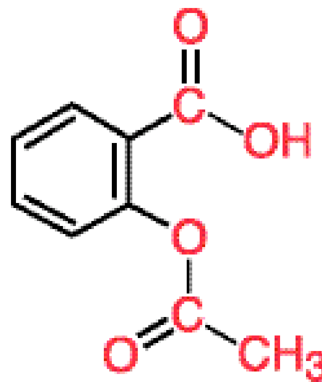

Figure 1.

How Anti-Platelet Therapy Works

Both aspirin and clopidogrel inhibit the ability of blood platelets to aggregate, or clump. Clumping is one of the early steps in producing a blood clot, which is, under ordinary circumstances, a beneficial effect. For example, clots prevent blood from leaking from vessels, and in their absence, in diseases such as hemophilia, survival is difficult. Nevertheless, inappropriate clot formation, for example, in the arteries supplying blood to the heart or brain, impairs blood flow, leading to damage or death of tissue.

Aspirin's anti-clotting action occurs because it binds to enzymes present in platelets, cyclooxygenases, or COX-1 and COX-2. These enzymes control the synthesis of thromboxane A_2, which increases the tendency of platelets to clump and of blood vessels to constrict. By irreversibly blocking COX, aspirin reduces blood's clotting ability, making harmful clot formation in the coronary or cerebral arteries less likely, hence reducing the probability of heart attack or stroke.

Clopidogrel acts by a different mechanism, blocking the ability of platelets to respond to molecules that initiate platelet aggregation. The end result is indistinguishable from that of aspirin: blood clots more slowly. In a study of 135,000 patients, aspirin therapy was associated with a 25-30% reduction in the risk of cardiovascular events, including heart attack, stroke, and death. Other studies have revealed similar benefits for clopidogrel therapy.

Aspirin Resistance

Despite aspirin's remarkable benefits, approximately 10-20% of aspirin-treated patients will have a cardiovascular event within 5 years of initiating therapy. This led to the concept that there is a subset of "aspirin resistant" patients who do not respond to anti-platelet clumping therapy and therefore are at persistent risk of future cardiovascular events. Of course, true biochemical aspirin resistance must be differentiated from non-compliance, not taking the drug as prescribed, a more common reason for therapy failure.

It is difficult to assess the clinical importance of aspirin resistance since there is currently no consensus on how to define, measure, and treat aspirin and clopidogrel resistance. Laboratory tests are just becoming available, and test results can vary depending on the laboratory performing the test and which test system is used. As a result, the incidence of 'resistance' has been estimated to be as low as 5% in some studies, and as high as 60% in others. This variation probably also reflects differences in treatment dosage and duration, as well as the existence of other conditions and/or medications that might influence drug action.

Aspirin resistance might be brought on by lifestyle, genetics, or other illnesses. Diabetes and hypertension, for example, increase the risk of aspirin resistance. Cigarette smoking and elevated cholesterol increase the tendency of platelets to aggregate and blood to clot by increasing the synthesis of other compounds that offset aspirin's reduction of thromboxane A_2, thereby restoring coaguability to the blood. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is also associated with aspirin resistance. NSAIDs include drugs such as indomethacin and common over-the-counter drugs such as ibuprofen (Motrin®). NSAIDs bind to the COX enzymes, briefly impairing their biological activity (8-50 hours); however, they also prevent aspirin from binding and impede its longer-term beneficial

action. Incomplete COX inhibition by aspirin might also reflect subtle genetic differences in the enzyme structure between individuals.

Another possible cause of aspirin resistance could be the production of COX-2 by macrophages, immune cells with nuclei and therefore capable of making more COX throughout the day. Platelets have no nuclei, and once all of their COX is irreversibly inhibited, they are essentially defeated. New platelets made each day have their COX enzymes irreversibly inhibited by the daily dose of aspirin; macrophages, however, can still be producing thromboxane A_2.

Clopidogrel, as a generally effective platelet inhibitor, has been used chronically to prevent cardiovascular events, as well as short-term at higher doses following coronary artery catherization to prevent the formation of blood clots. Combining clopidogrel and aspirin therapy has been reported to improve outcomes in patients who have had coronary artery stent implantation.

Blood-thinning foods/supplements that can interfere with test results.

Red wine
Fish (large amounts)
Fish oil supplements
Garlic
NSAIDs (*e.g.,* ibuprofen)
Ginger
Purple grape juice (large amounts)
Ginkgo biloba
Vitamin E
Ginseng

Table 1.

Clopidogrel Resistance

Recently there have been reports of decreased responsiveness to clopidogrel. Preliminary indications are that 5-10% of patients are clopidogrel-resistant, and up to 25% may be partially resistant. In one study of patients who had experienced heart attacks and were treated with stents and then clopidogrel, patients with clopidogrel resistance had a dramatically higher incidence of cardiovascular events during the ensuing 6 months.

Finally, some but not all studies found certain statins (Lipitor® and Zocor®) to interfere with clopidogrel because of competition for the same liver metabolizing enzymes.

Thus, there is a growing awareness in the research community and in clinical practice that resistance to anti-platelet therapy, while difficult to define or measure, is real and associated with increased risk of heart attack, stroke, or death. How can anti-platelet resistance be overcome?

What to Do

A first step for someone who wants to assess his or her anti-platelet therapy would be to have a laboratory test. However, testing is not simple. Many laboratories do not offer this testing, and those that do utilize a variety of technologies. Unfortunately, the varied technologies measure different components of platelet sensitivity or function and may not be directly comparable to each other. They also require fresh whole blood that must be tested promptly, possibly creating logistical problems.

The VerifyNow™ (Accumetrics) aspirin assay uses an optical detection system to measure turbidity, or thickening, of blood due to platelet aggregation in response to a chemical stimulus. Chances are that if you have a history of cardiovascular disease and are taking aspirin, your specialist has already ordered this test. A baseline test before beginning therapy is ideal.

The Platelet Function Analyzer (PFA-100®) (Dade Behring) records "closure time", the time it takes for a blood sample flowing under high shear stress to occlude a small aperture.

A simpler test, available in Canada but not yet in the US, measures a thromboxane A_2 metabolite in a casual urine sample.

Because certain foods or supplements (Table 1) can thin the blood and interfere with results, they should be avoided for several days before these tests.

There is, as yet, no clear consensus about how best to treat aspirin resistance. One approach is to increase the dosage of the agent, but there are risks associated with this. For example, a higher daily dose of aspirin (325 mg vs 81 mg) or taking 81 mg 3-4 times/day dramatically increases the likelihood of gastrointestinal bleeding. Enteric coated aspirin mitigates this risk. Alternatively, a different anti-platelet medication could be used — clopidogrel in place of aspirin, for example. Or, combination therapy utilizing both agents could be instituted.

Even if a patient is responding well to anti-platelet therapy, there is still reason to test annually, since anti-platelet resistance can develop over time. The same method of testing should be used each year for greater reliability.

Information for Donors

The Orentreich Foundation for the Advancement of Science, Inc., was founded in 1961. OFAS is a non-profit institution dedicated to biomedical research to prevent, halt, or reverse those disorders that decrease the quality or length of life. It is duly registered with the US Internal Revenue Service as an Operating Private Foundation under Section 4942(j)(3).

No accomplishment of OFAS is possible without your encouragement and generous support. Your tax-deductible contribution should be mailed to:
Orentreich Foundation for the Advancement of Science, Inc.
910 Fifth Avenue
New York, NY 10021-4187

© 2006, Orentreich Foundation for the Advancement of Science, Inc.