ASPIRIN RESISTANCE? *by Ann Gerhardt, MD*

Subscribe at algerhardt@sbcglobal.net 11/28/07

Published by

Healthy Choices for Mind and Body

Written by Ann Gerhardt, MD

Bottom Line at the Top: If you are at risk for stroke or heart or vascular disease, take your low-dose aspirin every day. Resistance may exist in diabetics, the elderly and women, but higher aspirin doses don't work better.

Daily low-dose aspirin prevents many heart attacks and strokes. But artery-clogging is a complex process and patients taking aspirin continue to suffer recurrent events. Not even aspirin is simple. **Scientists have recognized between-individual aspirin responsiveness for over 40 years.** A flurry of recent research activity concerning platelets, aspirin and other 'blood thinners,' attempt to sort out why, but many questions remain unanswered.

Blood thinners do not really thin blood flowing through arteries and veins. They prevent the process by which blood changes from a flowing slurry of cells, proteins and nutrients into a congealed solid clot. Clots may stop blood flow in veins, such as a leg clot that may travel to the lungs and kill. Or they clog arteries, cutting off the blood supply to the brain, causing a stroke, the heart, causing a heart attack, or other organs, killing whatever tissue no longer receives blood.

We don't really know how "thin" most people's flowing blood is. As long as it moves quickly along, coursing through arteries and veins without dallying along the way, we can presume that few micro-clots exist. Some people with a genetic predisposition to clotting may experience intermittent, devastating loss of a tissue when random clots close off its blood supply. For most of us, problems don't occur until blood flow slows and stagnates. This occurs when the heart pumps poorly (as in aneurysm or atrial fibrillation), or when part or all of the body is immobilized (as in long airplane flights or bedridden patients). Exercise and muscular activity produce the opposite effect, pushing blood along through blood vessels.

A clot typically contains platelets, stuck together in an aggregated clump, and fibrin, an insoluble protein that forms a type of scar tissue in clot. More than one stimulus can set off a variety of types of reactions that lead to clot. **"Blood-thinning" drugs come in two types: Those that act on platelets and those that prevent fibrin activation. Each of the drugs acts on a slightly different step in the process, and their effects are often additive.** Certain supplements and herbs, including garlic, ginseng, ginger and ginkgo and high doses of vitamin E and fish oil, have anti-coagulant or anti-platelet activity.

Aspirin blocks platelet aggregation and clot by inhibiting cyclooxygenase-1 (COX-1). Platelet COX-1 converts arachidonic acid to thromboxaneA2, which stimulates platelets to clot. Aspirin permanently inactivates COX-1 of platelets, rendering them useless for blood clotting. Once blocked by aspirin, the effect lasts the lifetime of the platelet (8-10 days) and recovers only by making new ones.

When taken by mouth, aspirin starts inactivating platelets as soon as it is absorbed into the portal vein (the blood vessel from the intestine to the liver), long before any reaches the rest of the body. It takes 60 minutes for maximal effect after swallowing a pill whole. Chewable or liquid aspirin is absorbed much more quickly, with maximal platelet inhibition within 30 minutes.

A single, chewed, 162 mg dose quickly inactivates most of the body's platelets. **This is why a person with a heart attack or stroke should immediately take 162 mg aspirin even before arrival in the emergency room. Higher or multiple doses are unnecessary and incur greater bleeding risk.**

To sustain the effect requires only 81 mg per day… At least in most people. Doctors have identified a phenomenon of 'aspirin resistance,' in which patients have a second heart attack or stroke even while on aspirin, and their platelets seem to be immune to aspirin's effect. Depending on the study and assay method, as few as 5% and as many as 65% of people are at least mildly aspirin-resistant.

This phenomenon has upset the apple cart concerning understanding aspirin dosing. If people can be resistant to aspirin's effects, one would expect large population trials to have shown that higher doses work better. This is unequivocally not the case. **No one has found any evidence that increasing aspirin dose confers more platelet inactivation or fewer heart attacks. Almost all trials favor a low, 50 - 81 mg dose for optimal effect.**

So how can aspirin resistance and low-dose-works-best coexist? Possible explanations are: 1) Aspirin-resistance is not really a significant problem; 2) There is more to platelet inhibition than the COX-1 pathway; and 3) High dose aspirin is somehow harmful. The answer relates to all three.

First: **Careful study of aspirin resistant people shows that most of them are not taking it every day or even at all.** It is hard for the drug to work if someone doesn't take it. Some people use enteric-coated aspirin, which blocks aspirin absorption to some extent, so it doesn't work as well. Others are taking other anti-inflammatories, which sit on COX-1 in such a way that they block aspirin's effect. True aspirin resistance is very rare.

Second: The COX-1-mediated, aspirin -sensitive path is not the only way to get platelets to aggregate. Platelets can be stimulated to clot by mechanisms other than COX-1-dependent thromboxane production, so someone taking aspirin may have a heart attack even if the aspirin is working perfectly well. Genetics influence platelet reactivity, with some people's platelets clotting much more easily than others. **Those who have the most readily clottable blood prior to any blood thinners have the greatest risk of a recurrent heart attack while on them.**

Third: Aspirin has more than one effect on blood vessels – In addition to blocking platelet COX-, it affects arterial walls by inhibiting COX-2. Normally COX-2 in blood vessel walls makes a good substance, prostacyclin, that opens the vessel and blocks clogging. By blocking COX-2, aspirin cuts off prostacyclin production, leading to blood vessel constriction and clot. It takes much higher amounts of aspirin to block COX-2 than COX-1. **So *low* dose aspirin is much more likely to inhibit COX-1-induced platelet clotting and leave the beneficial COX-2 prostacyclin alone, which prevents heart attacks.**

Genetic factors control how likely a person is to clot while on aspirin. These genetic factors seem to affect non-aspirin-sensitive pathways to platelet clotting. No single genetic factor affecting platelets, including response to aspirin, determines whether or not an individual is likely to have a heart attack.

Some believe that diabetics as a group are less responsive and have more heart and vascular disease because the disease increases all pathways to clot, not just the one affected by aspirin. Differential aspirin sensitivity probably also makes a difference in the elderly and females. Aspirin inactivates their platelets less effectively compared to young males. The elderly incur many more strokes and vascular events. Platelet reactivity may be part of the problem.

Most trials proving that aspirin protects against heart attack and stroke studied men and doctors extrapolated those results to women. Subsequent studies suggest that women are not men who happen to have an X chromosome: Regular aspirin use by women seems to protect against stroke, but not as well against heart attack.

Heart attack and stroke prevention trials have used anywhere from 50 to 1500 mg aspirin daily and the US Food and Drug Administration recommends doses up to 1300 mg. Analysis of trials done through 2007 found that doses above 81 mg (a baby aspirin) confer no extra benefit, but induce many more bleeding complications.

Aspirin and other blood thinners are not innocuous. They not only inhibit the clots we don't want, but they prevent good clots, like when you don't want to bleed to death from a paper cut. In some, aspirin causes life-threatening bleeding from the stomach, bowel or bladder, a rather obvious inconvenience. The balancing act of clot vs. no clot has to be finely tuned to prevent both heart attacks and excessive bleeding.

Higher aspirin dose makes bleeding more likely, but some aspirin-sensitive people will bleed with baby aspirin. Extrapolating one trial's results to the 50 million U.S. people who take aspirin daily predicts that 900,000 more people would experience major bleeding episodes per year on 325 mg daily, compared to 81 mg.

Combining two blood thinners, like aspirin and warfarin or aspirin and clopidogrel, leads to many more episodes of serious bleeding. Studies comparing a combination with either alone show that each regimen cause the same number of deaths, just for different reasons.

Companies have capitalized on aspirin-resistance fear by developing tests to measure it. None of them are validated and none accurately and conclusively assesses a person's aspirin sensitivity and propensity to clot. The ability of these tests to predict cardiac events is entirely unknown. It follows that scientists have been unable to formulate diagnostic criteria for aspirin resistance and appropriate therapeutic response.

There is no way to predict aspirin sensitivity. The tests for it are fraught with problems and studies uniformly favor low dose aspirin to prevent heart attack and stroke. So why do doctors continue to prescribe 325 mg (the standard aspirin pill size) daily for vascular disease prevention? For some it is habit, while others can't believe that less is more. Others fear that a patient who 'failed' low dose aspirin and had another stroke or heart attack must be aspirin resistant and need more. What we need is more information from the ongoing research, and for high risk patients to take their 81 mg aspirin every day.