The Ultimate Solution to the Problem of Aspirin Resistance

In their State-of-the-Art paper, Gasparyan et al. (1) provide an excellent review of the potential factors responsible for aspirin resistance. As they point out, a major problem is the lack of an accurate, reproducible, and practical quantitative test for measuring platelet activation. All commercially available tests use the measurement of the transmission of light through a suspension of platelets or the passage of cells through a narrow aperture. Both of these techniques are limited in that they detect macroaggregates but not microaggregates of platelets. This limitation is easily demonstrated by performing a dose-response test by adding linearly increasing doses of a glycoprotein IIb/IIIa inhibitor such as abciximab, epifibatide, or tirofiban to the sample before measuring the percent inhibition produced by the addition. When this is done with any of the commercially available tests and the dose is plotted against the percent inhibition, the response is not linear, but flattens out at approximately 80% inhibition, which is close to the degree of inhibition that is likely to be clinically desirable. This problem can be overcome if, instead of using the commercial tests, one uses an automatic cell counter to count individual platelets before and after the addition of the agonist. The percent inhibition is the difference between the before and after counts divided by the before count. When a dose-response test with a glycoprotein IIb/IIIa inhibitor is performed by using this technique, the response is linear throughout the entire range of inhibition. An ideal test for platelet activation would eliminate the need for an agonist. Such a test would reflect in vivo activation at the time the sample was drawn. To avoid use of an agonist, it would need to be extremely sensitive. To allow for establishment of its specificity, it would need to be quantitative. When platelets become activated, one of the first effects is the release of platelet microparticles that can be identified by flow cytometry. These microparticles have all of the surface markers of platelets that can be detected with fluorescent-labeled antibodies. Because each activated platelet releases large numbers of microparticles, each with multiple markers, a modified flow cytometer could be developed specifically to detect these markers on microparticles and, thus, be a very sensitive measure of platelet activation. Such a machine would have great utility as a tool for adjusting the doses of antiplatelet agents such as aspirin and clopidogrel, and in detecting early acute cardiac events.

Enteric Coating Is a Possible Cause of Aspirin Resistance

The observation that aspirin does not inhibit platelet function as expected in some patients has been referred to as “aspirin resistance.” The reported increased incidence of cardiovascular events in patients exhibiting aspirin resistance is indeed concerning (1,2) and highlights the importance of eliminating modifiable etiologies. In a recent issue of the Journal, Gasparyan et al. (3) discussed several of these causes, including poor compliance, nonsteroidal anti-inflammatory agents, and proton pump inhibitors. It is also important to take note of recent reports of incomplete suppression of platelet aggregation with enteric-coated aspirin (4,5). In a randomized, open-label, crossover study of healthy volunteers, incomplete thromboxane (TX) B₂ inhibition was found to occur in 8% of the aspirin group and 54.3% of the enteric-coated aspirin group (p = 0.0004) (4). In another study of 131 stable cardiovascular patients treated with enteric-coated aspirin (75 mg/d), 44% of patients failed to attain optimal inhibition of serum TX, indicating suboptimal inhibition of platelet COX-1 activity, and those with an incomplete aspirin response were more likely to demonstrate platelet aggregation to arachidonic acid (21% vs. 3%; p = 0.004) (5). These data are of increasing importance when considering aspirin resistance because many patients now receive low-dose enteric-coated aspirin preparations for primary and secondary prevention of cardiovascular events.

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We thank the 2 authors for their interest in our review (1), in which a number of issues were raised regarding definition, possible causes, detection, and treatment of “aspirin resistance.” The emergence of the latter requires, first of all, the selection of specific, reproducible, simple, and standardized platelet function tests that could distinguish patients responding to COX-1–related aspirin effects from those patients in whom the administration of aspirin fails to inhibit production of thromboxane A₂ through COX-1–related pathway(s). The latter is viewed by us as a true incident of “laboratory aspirin resistance.”

The most specific test for the assessment of aspirin effects is light transmission platelet aggregometry with low concentrations of arachidonic acid and adenosine diphosphate. This method is widely used in almost all large prospective studies of aspirin resistance and is closely associated with occurrence of cardiovascular events. Its use allows the clinician to assess platelet function by forming macroaggregates of platelets and is characterized by more serious limitations. First and foremost, platelet aggregometry requires the use of different agonists at different concentrations and their (ex vivo) addition to platelet-rich plasma. A frequently used agonist, arachidonic acid, has been criticized for its possible lytic effects on platelets, resulting in an increase of the light transmission through platelets suspension without an increase in the level of macroaggregates (2). Another frequently used agonist, adenosine diphosphate at low concentrations, can partly activate the arachidonic acid cascade, but its main effect is not specific for the COX-1 pathway. Also, the adjustment of platelet count in platelet-rich plasma by adding autologous platelet-poor plasma, which is mandatory for platelet aggregometry, can itself suppress platelet function (3). Thus, laboratory preparation and the use of agonists for platelet aggregometry can cause unpredictable results, far from reflecting true platelet function per se in cardiovascular disease patients taking aspirin.

Thus, we would agree with the comments that we should avoid the use of agonists for the “ideal test” of aspirin resistance, but this suggestion probably requires the revision of the current definition of “laboratory aspirin resistance.” From the physiological point of view, platelet aggregometry in platelet-rich plasma is also an in vitro time-consuming test that neglects interactions of platelets with leukocytes and erythrocytes at the time of blood sampling. This problem is partly overcome with the use of whole blood aggregometry and semiautomated point-of-care platelet function assays that use whole blood (e.g., the PFA-100 test, Siemens Health Diagnostics, Newark, Delaware), which again exhibits a number of other limitations.

It was thought that the use of light transmission aggregometry in combination with other platelet function tests could avoid the limitations of different tests and provide a comprehensive assessment of platelet function. However, this alternative approach raises another important question as to how interpret different, and sometimes polarized, results of different tests. One of the latest studies (4) assessing the prevalence of aspirin resistance with several major platelet function tests (e.g., light transmission aggregometry, whole blood aggregometry, PFA-100, VerifyNow-Aspirin [Accumetrics, San Diego, California], and urinary 11-dehydrothromboxane B₂) yielded a prevalence ranging from 6.7% (by VerifyNow-Aspirin) to 59.5% (by PFA-100). These results again confirm the lack of correlation between laboratory tests of aspirin resistance.

We would agree with the comments that flow cytometry is an in vivo quantitative test for the detection of activated platelets and release of microparticles with the surface markers specific for thromboxane A₂ pathway at an early stage of platelet activation, and that it may be viewed as an important tool for future studies on true prevalence of “laboratory aspirin resistance.” Nonetheless, the expense of flow cytometry and the need to assay samples in highly-specialized laboratory centers would make it difficult to employ flow cytometry in large-scale prospective studies.

Finally, we agree with Kapoor on the suggestion that there is incomplete suppression of platelet aggregation with enteric-coated aspirin. Nonetheless, we should not lose sight of the fact that one common explanation for aspirin resistance, whether defined as laboratory resistance or clinical resistance (i.e., increased thrombotic events), is noncompliance (5).

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IIb or Not IIb

White et al. (1) present an interesting case for the ability to switch to bivalirudin therapy from heparin (unfractionated heparin or enoxaparin) in non-ST-segment elevation acute coronary syndrome. The baseline characteristics of the 2 groups (consistent vs.