

Measurement of the Antiplatelet Effects of Aspirin in Cerebrovascular Disease

To the Editor:

We read with interest the recent article on the use of the PFA-100 in measuring the ex vivo response to aspirin therapy in patients with cerebrovascular disease.1 Most patients were assessed in the acute phase after ischemic stroke or transient ischemic attack, although some patients with asymptomatic stenosis of an extracranial or intracranial artery were also studied. Thirty seven per cent of patients overall were “aspirin resistant” using the PFA-100, and the rate of aspirin resistance was higher in patients receiving 81 mg (56%) than in those receiving 325 mg daily (28%). However there are a number of issues that warrant further discussion.

The authors report that the “PFA-100 device uses a flow cytometry paradigm to determine the ability of whole blood to close an aperture after stimulation using collagen and epinephrine.”1 However, it must be emphasized to the readers that there are significant differences between flow cytometry techniques and the methodology used in the PFA-100 test system. Flow cytometry is a method used for sensing cells, including platelets, that aggregate to one another, thus forming a platelet plug that ultimately occludes the aperture. The time taken to occlude the aperture and aggregate to one another, thus forming a platelet plug that ultimately occludes the aperture. The time taken to occlude the aperture and aggregate to one another, thus forming a platelet plug that ultimately occludes the aperture.

The combination of high shear stress and biochemical stimulation activates the platelets and they adhere to the membrane and aggregate to one another, thus forming a platelet plug that ultimately occludes the aperture. The time taken to occlude the aperture is called the closure time and this provides a measure of platelet function in the sample. However, the device does not directly assess platelet activation status in the sample.

The authors included in their analysis an unspecified proportion of patients who were taking nonsteroidal antiinflammatory drugs (NSAIDs) or cyclooxygenase-2 inhibitors in combination with aspirin, because they wanted “to evaluate aspirin responsiveness in routine clinical practice.”1 This is a very important issue that was mentioned in the discussion.1 Although it has been shown that the administration of ibuprofen before aspirin may interfere with the ability of aspirin to maximally inhibit cyclooxygenase-1 in platelets, other NSAIDs such as diclofenac do not appear to have a similar effect.6 We agree with the authors’ suggestion that the use of ibuprofen in combination with aspirin could contribute to the phenomenon of aspirin resistance using the PFA-100. However, in theory, the use of a reversible cyclooxygenase-1 inhibitor (eg, diclofenac) in combination with an irreversible cyclooxygenase-2 inhibitor (aspirin) could also enhance the antiplatelet effects of aspirin and prolong the C-EPI closure time to a greater degree than that seen with either agent alone. Because of the potential confounding effects of concomitant medications on the results of the PFA-100, we would like to know the prevalence of aspirin resistance in patients who were on aspirin monotherapy. Furthermore, because it is possible that upregulation of cyclooxygenase-2 in platelets may contribute to the phenomenon of aspirin resistance,7 did the authors observe any patients who were aspirin resistant on aspirin monotherapy and subsequently had significant prolongation of their C-EPI closure times after the addition of a cyclooxygenase-2 inhibitor to their treatment regimen?

The maximum closure time recorded by the PFA-100 is 300 s. In our experience, many patients on aspirin have prolonged C-EPI closure times greater than 300 s. In the results section, Alberts et al compared mean C-EPI closure times between patients on different aspirin doses and formulations. However, if a proportion of patients in their study also had C-EPI closure times >300 s, one can never assume that the data are normally distributed. Therefore, it is more appropriate to use nonparametric statistics to compare median closure times between groups.

Do the results differ if nonparametric statistics are used? In addition, if one cannot assume that the PFA-100 data are normally distributed, do the authors consider it justified to use linear regression analysis to investigate the effect of age, aspirin dose, and preparation on the results obtained?

Finally, the authors implied that many patients who were aspirin resistant on the PFA-100 exhibited a “therapeutic effect” when the aspirin dose or formulation were changed. However, they stated that “we do not yet know how PFA-100 results correlate with clinical events such as stroke, myocardial infarction, and vascular death.” Despite the potential usefulness of this device in monitoring and predicting the response to aspirin, should one await data regarding its “clinical usefulness” before justifying the use of higher aspirin doses (>325 mg daily) to achieve an ex vivo response on the PFA-100?

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Response

My colleagues and I appreciate the thoughtful comments by Dr McCabe et al and Drs Varanasi and Steinhubl. Clearly the issue of aspirin resistance and its clinical relevance is an emerging and important area of medical research.

There are several devices currently available for the testing of platelet function. McCabe and colleagues nicely describe the testing paradigm used by the platelet function analyzer (PFA)-100 device. The PFA-100 uses flowing blood (via vacuum aspiration) to occlude a small aperture in a membrane. This is similar to what happens when platelets aggregate on a vascular lesion leading to vessel occlusion and an ischemic vascular event. This paradigm may be more representative of actual in vivo platelet activation and vessel occlusion than precipitating a platelet-rich solution in a test tube. Using the PFA-100 we have found very high rates of aspirin resistance in patients with acute cerebrovascular events. These results will be reported in a future publication. There are certainly many factors that affect platelet function as well as aspirin’s ability to inhibit platelet function.1,3,4 But the clinically relevant issue is whether a clot forms and occludes a vessel.

We analyzed our PFA results as both a continuous variable and as a dichotomous variable. Both analyses yielded the same conclusions, namely that many patients taking 81 mg/d of aspirin or using an enteric-coated preparation had normal PFAs by the PFA-100 test. Interestingly, we recently reported that adding clopidogrel to aspirin tended to ameliorate much of the dose effect and coating effect of the aspirin resistance.4 Therefore, 81 mg/d of aspirin appeared as effective as 325 mg/d when both were combined with clopidogrel. The same was true with coated versus uncoated aspirin. In both cases the rates of aspirin resistance were only 26% to 30%. These in vitro findings mirror what was seen clinically in the CURE study, where adding clopidogrel to aspirin produced enhanced efficacy with fewer ischemic vascular events in patients with acute coronary syndromes.5

We collected data about concomitant medication usage in our study of aspirin resistance. Most patients were taking other medications in various combinations and doses. We did not see any clear effect or trend of a specific type or class of medication on our results. There was no indication that ibuprofen or cyclooxygenase-2 (COX-2) inhibitors were responsible for the lack of an antiplatelet effect in our patient population.

The issue of a lack of a clear dose-response effect of aspirin in prior studies and meta-analyses deserves comment. Those studies examined large populations of patients and often compared aspirin to placebo.6 In such a setting, almost any dose of aspirin will show evidence of efficacy. However, cross-comparisons of efficacy for aspirin dose using diverse studies with different patient populations and event rates are fraught with the potential for erroneous conclusions. Few studies have directly compared aspirin doses in patients with cerebrovascular disease.7 These issues were nicely reviewed by Dyken et al more than 10 years ago.7 We must remember that overall the efficacy of aspirin for stroke prevention is quite modest, in the range of 15% to 20% relative risk reduction.5,8 There is certainly room for enhanced efficacy of aspirin for stroke prevention.

Studies by Hart et al and others have clearly shown that individual patients may have a differential effect to different doses of aspirin.9,10 Such individual effects will not be seen in large studies or pooled analyses. Since we treat individual patients, the issue of how a specific patient responds to a medication would seem to be of importance. This is particularly true when we consider the consequences of aspirin failure, which in many cases is a devastating stroke.

When a patient has a stroke while taking aspirin (a common occurrence) there are several possible courses of action in terms of medical therapies.11,12 Increasing the aspirin dose or changing from a coated to an uncoated preparation is likely the easiest and least expensive option. However, my colleagues are correct in stating that we do not know whether adjusting the dose of aspirin (or other antiplatelet agents) based on the results of PFA or other testing is currently warranted. Higher doses of aspirin and other agents may increase the risk of complications as well as offering enhanced protection against ischemic vascular events for some patients. This is clearly an area in need of further investigation. Ultimately this issue will only be answered definitively by a prospective randomized study of dose-adjusted antiplatelet therapy versus standard therapy. Until then the issue of dose-adjusted antiplatelet therapy will remain a large question in need of answers.

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