Antiplatelet Effect of Aspirin in Patients With Cerebrovascular Disease

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Background and Purpose—Aspirin is used commonly to prevent ischemic strokes and other vascular events. Although aspirin is considered safe and effective, it has limited efficacy with a relative risk reduction of 20% to 25% for ischemic stroke. We sought to determine if aspirin as currently used is having its desired antiplatelet effects.

Methods—We ascertained patients with cerebrovascular disease who were taking only aspirin as an antiplatelet agent. Platelet function was evaluated using a platelet function analyzer (PFA-100). PFA test results were correlated with aspirin dose, formulation, and basic demographic factors.

Results—We ascertained 129 patients, of whom 32% were taking an enteric-coated aspirin preparation and 32% were taking low-dose (≤162 mg/d) aspirin. For the entire cohort, 37% of patients had normal PFA-100 results, indicating normal platelet function. For the patients taking low-dose aspirin, 56% had normal PFAs compared with 28% of those taking ≥325 mg/d of aspirin, while 65% of patients taking enteric-coated aspirin had normal PFAs compared with 25% taking an uncoated preparation (P<0.01 for both comparisons). Similar results were obtained if PFA results were analyzed using mean closure times (low-dose aspirin, 183 sec; high-dose aspirin, 233 sec; enteric-coated, 173 sec; uncoated, 235 sec; P<0.01 for comparisons). Older patients and women were less likely to have a therapeutic response to aspirin, independent of aspirin dose or formulation.

Conclusions—A significant proportion of patients taking low-dose aspirin or enteric-coated aspirin have normal platelet function as measured by the PFA-100 test. If these results correlate with clinical events, they have broad implications in determining how aspirin is used and monitored. (Stroke. 2004;35:175-178.)

Key Words: antiplatelet therapy ■ aspirin ■ cerebrovascular disorders ■ stroke, ischemic

Ischemic stroke is a common and serious disorder, as it accounts for approximately 80% of the 730,000 new or recurrent strokes each year in the United States.1 2 While there are now a number of antithrombotic medications used for preventing ischemic stroke, aspirin (ASA) remains the most widely used agent. Despite its wide use, general good safety profile, and low cost, there are concerns about the efficacy of ASA. Several large clinical trials have found that 30% to 40% of patients who had a stroke were taking ASA at the time of their event.3 4 Large meta-analyses have shown that the relative risk reduction of ASA for stroke in patients with a prior stroke or transient ischemic attack (TIA) was only 22%.5

Why does ASA fail in so many patients? There are several explanations, including poor patient compliance, drug interactions, stroke mechanisms that are not highly responsive to ASA, and ASA resistance. Past studies have found some degree of aspirin resistance or ASA unresponsiveness in 20% to 30% of patients.6–8 Most studies of aspirin resistance have focused on patients with coronary artery disease, although a few have identified aspirin resistance in patients with stroke or cerebrovascular disease.9 10 Most of these studies have examined patients who had an atherothrombotic event while receiving aspirin.

In the past, the measurement of platelet function and ASA effects has required platelet aggregometry, which is time-consuming, labor intensive, and expensive. Several years ago a new bench-top device, the PFA-100 (Dade-Behring), received FDA approval for analyzing platelet function.10 11 The PFA-100 test has several advantages for the assessment of platelet function: it is rapid (usually <10 minutes for a result), is not labor intensive, and has a low per-test cost. Prior studies have shown that the PFA-100 system has a sensitivity of 95% for detecting aspirin effects compared with platelet aggregometry.10 12 Other studies have found a mean coefficient of variance for duplicate
samples of 5% using this system, indicating a high degree of consistency and reliability.\textsuperscript{12}

We conducted a prospective observational study of ASA resistance in patients with cerebrovascular disease. Our goal was to assess how common ASA resistance was in patients with cerebrovascular disease, and to determine how it related to ASA dose, preparation, and demographic factors.

**Subjects and Methods**

Individuals were enrolled prospectively from 2 sources: the Northwestern Memorial Hospital inpatient neurology service, and the Northwestern Memorial Faculty Foundation clinic, which is an outpatient clinic where patients with cerebrovascular disease are seen. We attempted to ascertain consecutive patients who met our study criteria, although in some cases PFA testing was not performed as a result of clerical oversight or errors, inability to obtain a blood sample, misplaced blood sample, or patient discharge.

For inclusion, patients had to have clinical evidence of an ischemic stroke, TIA, or cerebrovascular disease (symptomatic or asymptomatic) involving intracranial or extracranial cerebral vessels. In all cases the diagnosis was made or confirmed by a board-certified neurologist with fellowship training in cerebrovascular disease and confirmed by standard diagnostic techniques such as head CT, MRI, MR angiography, CT angiography, carotid ultrasound, etc. As part of routine clinical care, information about sex, age, race, and medications was obtained from each patient and their relevant caregivers (in person or over the phone).

For inclusion into this study, patients must have been taking ASA with the last dose taken no more than 72 hours prior to their clinical evaluation and PFA blood test. Patients who did not regularly take ASA but took a dose on their way to the hospital or received ASA in the emergency department prior to PFA blood testing were excluded from this analysis. Information about ASA dose and preparation was obtained from the patient, caregivers, and medical records. Patients taking other antplatelet medications such as clopidogrel, ticlopidine, or Aggrenox (extended-release dipyridamole and aspirin), or those receiving warfarin or intravenous heparin were excluded from this analysis. Patients receiving nonsteroidal anti-inflammatory agents or cyclooxygenase-2 inhibitors were ascertained, as were patients receiving low-dose subcutaneous heparin or heparinoids for deep venous thrombosis prophylaxis.

Care was taken to determine if a patient was actually taking his or her medications by questioning the patient and his or her caregivers, spouse, and children, as well as review of medical records and medication dispensing logs, when appropriate. Information was also collected about concomitant medications, although we did not investigate in detail dosing and compliance with these other medications. If we could not reliably determine if the patient was taking ASA and when the last dose was received, the patient was excluded from this analysis.

Testing of antplatelet effects was done using the PFA-100 machine. Blood was obtained via venipuncture, then processed using the PFA-100 machine. 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. The PFA-100 part 1 tests for the ASA effect using 10 μg epinephrine and 2 μg fibrillar type I equine collagen as stimulants. Control samples are run at the hospital to determine normal values. The normal range for PFA-100 part 1 at our facility is 37 to 171 sec. All samples are processed within 2 hours of venipuncture. We considered any PFA-100 part 1 result >171 sec to be indicative of an antplatelet response. Further analyses were done using PFA-100 results as continuous variable.

The data and blood tests listed above are part of our routine clinical care for patients seen at Northwestern Memorial Hospital and the Outpatient Clinic. The study was reviewed by the local institutional review board, who agreed that it was exempt from needing informed consent since it did not involve any interventions beyond routine clinical care as practiced at this medical center. To conform with institutional review board regulations for exempt status, all individual data were de-identified for these analyses.

No attempt was made to determine a correlation between PFA-100 results and clinical events. As part of our routine clinical care, in some cases we did change ASA doses and formulations in an attempt to achieve a therapeutic antplatelet effect based on the PFA-100 results. For this report we did not analyze data about such changes.

Analyses were performed comparing aspirin dose and preparation with PFA-100 test results and other demographic variables. PFA results were analyzed as a dichotomous variable and as a continuous variable. Statistical analysis included chi-square and Fisher’s exact test for discrete variables, t test, analysis of variance, and linear and logistic regression. Statistical software used was S-PLUS (Insightful Corporation, 2000).

**Results**

We prospectively ascertained 129 patients with a diagnosis or hospital admission for stroke, TIA, or cerebrovascular disease of intracranial or extracranial vessel(s). Most patients were studied after the acute phase of their stroke or TIA. Basic demographic characteristics and data on ASA doses and preparations are shown in the Table.

Overall, 48 of 129 patients (37%) taking any dose or preparation of ASA had normal results on the PFA-100 test (indicating no antplatelet effect). A total of 39 patients were taking 81 mg of ASA a day or every other day, with 22 (56%) having normal PFA results (see Figure 1). Normal PFAs were...
found in 24 of 87 patients (28%) taking 325 mg/d of ASA. The rate of ASA resistance was higher in those taking 81 mg of ASA compared with 325 mg of ASA (56% versus 28%, chi-square $P=0.001$). Enteric-coated ASA was taken by 41 patients (32% of total population). The rate of ASA resistance was 65% for patients taking any enteric-coated ASA preparation compared with 25% for patients taking uncoated ASA (chi-square $P<0.001$, Figure 2).

We examined PFA results as a mean value with respect to ASA dose and preparation. The same trends seen above were again observed, with mean PFA values as follows: 81 or 126 mg/d, 183 sec; 325 mg/d, 233 sec; coated preparation, 173 sec; uncoated preparation, 235 sec (Figure 3) These differences were significantly different (analysis of variance, $P<0.001$). In general, the PFA-100 was more likely to show a therapeutic effect with higher doses of ASA and with an uncoated aspirin preparation.

We did find evidence for an age effect, with older individuals (>63 years) having a reduced therapeutic response to ASA, independent of ASA dose or preparation ($P=0.048$ and 0.034, respectively, linear bivariate regression analysis). Patients <63 years of age showed a stronger association between ASA dose and PFA results, with an odds ratio (OR) of 4.7 compared with an OR of 2.3 for those >63 years. Men showed a stronger association than women with ASA dose and a therapeutic PFA response (OR 5 versus 2.5, respectively). Although information was collected about concomitant medications (both number and type), the number of patients taking any single type of medication was too small for reliable statistical results.

As part of our routine clinical care, we had many patients who had normal PFA-100 results in whom we would either increase the ASA dose or change from an enteric-coated to an uncoated preparation. In many cases the PFA-100 showed a therapeutic effect when such changes were made. In about 15% of patients, the dose of ASA had to be increased to 325 mg bid or tid to achieve a therapeutic PFA-100 result. Approximately 7% of patients did not achieve a therapeutic PFA-100 result even on doses of 650 mg bid of uncoated ASA.

**Discussion**

ASA is the most widely used medication in patients with vascular disease or at risk for vascular disease and related atherothrombotic events. Despite its wide use, low cost, and good safety profile, ASA does have relatively limited efficacy for the prevention of ischemic stroke. The recent Antithrombotic Trialists’ Collaboration meta-analysis showed a 22% relative risk reduction for ASA in patients with prior stroke or TIA. Other studies have reported a relative risk reduction of only 16% for vascular events with ASA in patients with cerebrovascular disease.

ASA resistance may be one explanation for the relative lack of efficacy for ASA and high rate of ASA failures. ASA resistance may be caused by several factors, including poor absorption, inadequate dosing, genetic factors, and interactions with concomitant medications. For example, a recent study found that ibuprofen taken before an ASA dose significantly inhibits its antiplatelet effects. We collected data about concomitant medications, but the numbers in each group were too small for meaningful analyses and did not appear to explain our results. Patients taking nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors were not excluded since we wanted to evaluate ASA responsiveness in routine clinical practice.

The issue of ASA resistance in patients with stroke has been studied previously by Helgason et al. Their studies found rates of ASA resistance of 20% using platelet aggregometry. They also found that 23% of patients developed some degree of ASA resistance over about 6 months of observation. A recent study reported some degree of ASA resistance in 29% of patients with cardiovascular disease. Another study of ischemic stroke patients found that 16% had evidence of aspirin resistance using the PFA-100 device.

If ASA resistance is related to ASA dose and preparation as we found in our study, one would expect large clinical trials to show increased efficacy with higher ASA doses. The correlation between ASA dose and efficacy has been analyzed in several studies and meta-analyses. These studies failed to identify a significant dose-response effect for ASA on vascular events. However, several factors could mitigate such a result. An increased rate of patient drop-out with higher ASA doses may limit the power to detect a difference in efficacy with higher doses. In some patients, higher doses of ASA may inhibit the production of prostacyclin (as well as prostaglandin), which has intrinsic antiplatelet

![Figure 2](image2.png) An analysis of aspirin response and aspirin preparation. Therapeutic PFA (hatched bars) was defined as a value of $>171$ for part 1 of the test. The y axis refers to percentage of patients taking that preparation of aspirin. Coated refers to any enteric-coated preparation but excludes microcoated pills. The differences in response rates between the coated and uncoated group were significant ($P<0.01$). Black bars indicate normal PFA.

![Figure 3](image3.png) An analysis of mean PFA-100 part 1 by aspirin dose and preparation. The differences between the 2 aspirin doses and the 2 aspirin preparations were each significant ($P<0.01$).
and vasodilatory effects. However, higher doses of ASA may have a more significant anti-inflammatory effect in some cases, which may reduce vascular events. Therefore, within any population of patients taking a specific ASA dose, different effects and outcomes might be expected based on a variety of metabolic, genetic, physiological, and clinical factors.

Other studies have found that different markers of platelet function also correlate with ASA dosing and vascular events. Hart et al found that higher ASA doses were more effective in reducing serum and urinary thromboxane B2 in patients with vascular disease. Other studies in patients with cardiovascular disease have reported strong correlations between levels of urinary thromboxane B2 and vascular events. A prospective blinded study found that patients with aspirin resistance were more likely to have a vascular event (stroke, myocardial infarction, death) compared with aspirin responders.

Our study has found that some patients taking low-dose ASA or an enteric-coated ASA preparation may not have the desired antiplatelet effect. This implies that simply increasing the dose of ASA or changing the preparation may result in an enhanced therapeutic antiplatelet effect. Therefore, many patients labeled as having ASA resistance may simply be receiving too low a dose of ASA or an enteric-coated preparation that is not well absorbed. Due to the identification of our individual patient data, we could not track specific changes in PFA-100 results with changing ASA doses or formulation. However, our clinical observation is that the vast majority of patients with subtherapeutic PFA results who then increase their dose of ASA or change to an uncoated formulation then have therapeutic PFA results.

Our study included a somewhat heterogeneous patient population, which reflects a typical clinical practice. These findings should be confirmed by other researchers and in larger patient populations. Ongoing studies are evaluating the effects of concomitant medications and hematologic parameters on PFA results. If and how the PFA-100 results change over time in patients taking a stable dose of ASA is unclear but of great concern. At least 1 study found that 8% to 33% of patients receiving ASA develop some degree of resistance after 6 to 33 months of therapy. In summary, we found that a significant percentage of patients taking ASA have no detectable antiplatelet effect using the PFA-100 test. This lack of effect was most common in patients taking low-dose ASA or an enteric-coated ASA preparation. We do not yet know how PFA-100 results correlate with clinical events such as stroke, myocardial infarction, and vascular death. If subsequent studies find that PFA-100 results do correlate with clinical events, this could lead to ASA being utilized as a dose-adjusted medication. The use of dose-adjusted ASA might greatly increase the efficacy and safety of this commonly used medication. The public health implications of such a change would be significant in terms of routine medical care, improved efficacy and safety of ASA, and the prevention of vascular events.

References

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