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Editorial

Aspirin resistance and ischemic stroke outcome: Fact or fiction?

Stroke is a major cause of morbidity and mortality in Taiwan, where it is the leading cause of disability[1] and the third leading cause of death.[2] Close to a quarter of the nearly 800,000 strokes that occur annually in the United States are recurrent events.[3] Thus, it is important to reduce the risk of recurrent stroke in patients that have suffered a prior stroke event.

Platelet activation plays a vital role in arterial thrombosis, such as in cardiovascular disease, peripheral arterial disease, and ischemic stroke, for which such thrombosis accounts for 70% of the strokes in Taiwan.[4] Arterial thrombosis is commonly treated and prevented by administration of antiplatelet agents. Of these, aspirin remains the most widely used agent for the prevention of noncardioembolic ischemic stroke.[5] The relative risk reduction for recurrent stroke is 22%, leaving some patients (30–40%) to develop new strokes despite taking aspirin.[6] Such recurrent events in aspirin-treated patients represent a significant treatment challenge.

Aspirin works by irreversibly acetylating the cyclooxygenase (COX)-1 enzyme, thus suppressing the formation of thromboxane A_2 (TXA_2), a potent agonist of platelet aggregation.[7] The term "aspirin resistance" (AR) has been used to describe the various manifestations of aspirin's insufficient inhibitory effects on platelet function, due to AR or persistently high platelet reactivity in laboratory tests, such as short bleeding time and/or persistently high levels of TXA_2 production.[8,9] Patients are considered to have biochemical (laboratory-defined) AR when their *in vitro* platelet reactivity is not properly blocked despite the use of aspirin, and are considered to have clinical AR or "treatment failure" when thrombotic events occur even while they are taking aspirin.

The mechanisms underlying AR are uncertain. Several pharmacodynamic and pharmacokinetic factors are likely to play a role in the variability of platelet inhibition observed with aspirin treatment, including bioavailability, patient compliance, genetic polymorphisms, activation of alternate platelet-stimulation pathways, accelerated platelet turnover, and factors associated with antiplatelet resistance.[8–10]

The prevalence of biochemical AR in stroke patients is highly variable, ranging from 3% to 85% in different studies.[8] This high variance can be attributed, at least in part, to the use of noncorrelated measurement techniques, such as the Platelet Function Analyzer (PFA)-100 assay, the VerifyNowAspirin assay, and light transmittance aggregometry (LTA).[8] In theory, assays that are directly related to COX-1 functionality—such as the generation of thromboxane B_2 (TXB_2, a stable metabolite of TXA_2) in serum and arachidonic acid (AA)-induced platelet aggregation—should enable more accurate assessment of aspirin efficacy.[9]

Serum TXB_2 levels reflect the total capacity of platelets to synthesize TXA_2 *ex vivo* in response to various stimuli. The rate of clinically significant residual TXB_2 production is extremely low in healthy individuals and cardiovascular disease patients who are taking aspirin. Levels of the urinary thromboxane metabolite (i.e., 11-dehydroTXB_2) reflect *in vivo* time-integrated TXA_2 biosynthesis.[11] Assays of the urinary metabolite are less specific than assays of COX-1-generated TXA_2, as about 30% of the urinary metabolite is derived from COX-2 generated sources, which are independent of platelets.

Other COX-1 activity-dependent tests of platelet function measure changes in the light transmission of a platelet suspension during aggregation in *vitro*.[9,10] However, these tests may not be specific for the effects of aspirin as platelets can be activated by other factors besides stimulation of the TXA_2 receptor. In LTA, the most thoroughly evaluated light transmission method for testing platelet function, changes in light transmission produced by AA agonist-induced platelet aggregation are measured. Although LTA is the historical gold standard for examining the antiplatelet effects of aspirin and remains the most widely used test for assessing platelet function, it is labor-intensive and has yet to be strongly correlated and standardized with other tests.

Several "point-of-care" assays have been developed to reduce the laboratory requirement for LTA, including the PFA-100, which uses less whole blood than LTA and has a quick enough analysis time to be amenable to outpatient use. The PFA-100 could be regarded as an *in vitro* bleeding time recorder.[12] It simulates an artificial vessel with a thrombogenic membrane coated with collagen and either epinephrine or adenosine diphosphate. A constant negative pressure aspirates anticoagulated blood through this faux-vessel until a platelet plug forms. The time needed for blood flow to be interrupted (closure time) is recorded. Although the PFA-100 is easy to use, it is sensitive to many variables, including platelet count and presence of the von Willebrand factor, which hinders its specificity as a tool with which to assess aspirin efficacy.

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Clinical studies using various platelet function tests have linked low platelet inhibition in patients exhibiting biochemical AR to an increased risk for ischemic events. Two meta-analyses focused on aspirin nonresponders identified by the PFA-100 method showed that PFA-100-defined aspirin nonresponders were more likely to have vascular events than responders.[13,14]

In the current issue of the *Journal of the Chinese Medical Association,* Lai et al report a relationship between biochemical AR and functional outcome following an acute ischemic stroke.[15] Demographic data, vascular risk factors, and inflammatory biomarkers were analyzed prospectively in 269 patients. Biochemical AR after 5 days of aspirin use was assessed using a PFA-100 instrument equipped with an epinephrine/collagen cartridge. Patients classified as having biochemical AR ($n = 83$; 30.9%) had poorer 30-day and 90-day functional outcomes (as defined by modified Rankin Scale scores >2) than non-AR patients. However, the effect did not remain significant when the analysis was adjusted in consideration of other risk factors. This seemingly contradictory result was explained by the concomitant presence of inflammation/infection in acute ischemic stroke overriding the AR effect. However, it is also important to note that only short-term outcome data were available, leaving the long-term effect of AR unknown.

A total of 1,276 acute ischemic stroke patients were registered in the Taipei Veterans General Hospital stroke databank from February 2009 to February 2011. Of these, 180 (14.1%) died within 1 year. Use of antiplatelet drugs after discharge was associated with a better outcome (Yang et al, unpublished data). Furthermore, in a population of over 20,000 registered stroke patients in the Taiwan Stroke Registry, use of antithrombotic agents was associated with a better 6-month functional outcome.[4] Although AR was not tested in these studies, it is clear that antiplatelet medication is a good predictor of a better outcome after stroke. Well-defined, large-scale prospective long-term follow-up trials are needed to establish the role of AR in ischemic stroke in Taiwan and elsewhere.

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