Aspirin Resistance

To the Editor:

Aspirin resistance is a poorly defined term and could involve the clinical inability of aspirin to protect individuals from arterial thrombotic events or laboratory methods indicating the failure of aspirin to inhibit platelet aggregation, mainly platelet aggregation. Indeed, resistance to aspirin may be associated with an increase of arterial thrombotic events in spite of chronic aspirin intake.

Possible mechanisms of aspirin resistance were summarized by Cambria-Kiely and Gandhi,1 with Eikelboom et al2 contributing an additional observation. These authors believe that failure of suppression of thromboxane generation defines aspirin resistance. This hypothesis is based on a direct association between the urinary rise of a metabolite of thromboxane, the 11-dehydrothromboxane B2 levels, and the increment of vascular events (myocardial infarction, stroke, and cardiovascular death).

In 1983, through ex vivo aggregation experiments with platelet-rich plasma from volunteers taking aspirin, we showed that the inhibitory effect of aspirin on platelet aggregation induced by sodium arachidonate was overcome by the synergistic activity of a pair of agonists (sodium arachidonate and platelet activating factor, or ADP or collagen). We have employed a mixed agonist system in an attempt to better reflect the multiple stimuli that platelets encounter during in vivo activation. In these conditions, a normal platelet aggregation pattern was obtained although thromboxane levels measured in the stimulated platelet-rich plasma was <5% in all platelet aspirinized samples. Our study suggested that there is no correlation between platelet function and thromboxane level and that aspirin would not prevent an agonist potentiation effect when low doses or a daily high dose (500 mg) were administered. This fact could explain the erratic results obtained when this drug was used for anti-thrombotic therapy even if ex vivo inhibition of platelet aggregation was obtained. Thus, although a low concentration of thromboxane or its urinary metabolites were measured, aspirin could fail to prevent arterial thrombosis because several agonists acting conjointly in the site of endothelial injury will overcome aspirin inhibitory effect on platelet aggregation.

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To the Editor:

We are writing in response to the recent article by Eikelboom et al concerning aspirin-resistant thromboxane biosynthesis and risk of vascular events.1 The study clearly demonstrates, firstly, the variability of urinary levels of thromboxane A2 throughout the population and, secondly, the association between measured urinary levels of thromboxane A2 and risk of further vascular events. Although we agree that there will be variability in urinary thromboxane A2 levels in anatomically similar individuals, variability in this study will also exist because of variations in the extent of vascular disease and baseline intensity of platelet activation between patients. Patients with more atheroma will have increased background levels of platelet activation and hence thromboxane A2 generation because of this.2 It seems reasonable to hypothesize that individuals whose platelets have higher levels of activation because of these factors would be at increased risk of vascular events. In effect, Eikelboom and colleagues may have been performing an indirect assay of the amount of atheroma in the patients studied. What still remains unclear is whether this thromboxane generation comes from the endothelium, monocytes, or transiently from megakaryocytes as a consequence of once-daily dosing regimes.

This study adds valuable information to the literature and demonstrates the need for the development of simple and effective measures for assessing the effect of antiplatelet agents in individual patients. Future regimes of antiplatelet therapy may need to be tailored to the individual patient. However, this study cannot be taken as evidence that therapy targeted at lowering urinary thromboxane A2 will have any impact on future pathological events.

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Response

Dr Rouvier and colleagues highlight one of a number of other potential mechanisms of aspirin resistance, namely platelet activation that occurs through pathways that are not blocked by aspirin. Support for this mechanism comes from both laboratory and clinical studies, including the recently published Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial,1 which demonstrated the superiority of combined ADP-receptor blockade (with clopidogrel) plus aspirin over aspirin alone for the prevention of recurrent ischemic events and death in high-risk patients. However, unlike our study,2 which reported urinary levels of thromboxane B2 as an index of in vivo thromboxane generation, the laboratory study quoted by the correspondents3 measured ex vivo agonist-induced thromboxane generation by platelets collected from aspirin-treated volunteers, an approach that obviates examination of nonplatelet sources of thromboxane generation. Consequently, the lack of correlation between platelet aggregometry results and thromboxane generation observed in this laboratory study does not exclude the possibility that aspirin-resistant thromboxane generation contributes to platelet activation in patients treated with aspirin.

Dr Smout and colleagues suggest that the variation in urinary thromboxane B2 levels may simply reflect between-patient variability in the extent of vascular disease or the intensity of platelet activation. However, the association between urinary thromboxane excretion and risk of future clinical events in our study was independent of the presence of a history of symptomatic arterial vascular disease. Furthermore, on the basis of ex vivo thromboxane B2 production, studies have shown that low-dose aspirin produces >95% suppression of platelet cyclooxygenase-1 in the majority of patients.4 It is unlikely, therefore, that between-patient variability in the extent of platelet activation


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accounts for differences in urinary thromboxane excretion in aspirin-treated patients. Nevertheless, additional studies are needed to determine whether elevated urinary thromboxane levels provide a marker of aspirin resistance and whether more effective antiplatelet therapy in these individuals will reduce their risk of future arterial vascular events.

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