Depression, Alterations in Platelet Function, and Ischemic Heart Disease

ERICA C. BRUCE, BSA, AND DOMINIQUE L. MUSSELMAN, MD

Platelets, the smallest corpuscular component of human blood, are central to various crucial biologic pathways in the human body. Diminished platelet function is thought to contribute to the increased risk of ischemic heart disease in patients with major depressive disorder, and to the increased morbidity and diminished survival of depressed patients after an index myocardial infarction. We reviewed both recent studies that evaluated platelet function in various patient groups and recent information regarding the potential beneficial effects of selective serotonin reuptake inhibitors on platelet reactivity. Key words: depression, platelet dysfunction, ischemic heart disease.

IHD = ischemic heart disease; SSRI = selective serotonin reuptake inhibitor.

INTRODUCTION

Platelets are central to hemostasis, atherosclerosis, thrombosis, and acute coronary syndromes. As the smallest corpuscular component of human blood, platelets are thought to contribute to the increased risk of patients with depressive disorders to the development of ischemic heart disease (IHD), and the increased morbidity and diminished survival of depressed patients after an index myocardial infarction. Markovitz and Matthews first proposed that enhanced platelet responses to psychologic stress might trigger adverse coronary artery ischemic events (1).

The basic platelet response begins with binding of agonists such as collagen or thrombin to receptors on the platelet surface. Platelets then become activated, converting platelet membrane GPIIb/IIIa complexes into functional receptors for fibrinogen, increasing so-called “platelet stickiness.” Activation is accompanied by change in platelet shape, degranulation, secretion of intraplatelet contents, and aggregation. Platelet aggregation occurs when activated platelets bind together. Early platelet events that occur after platelet activation by primary agonists and prior to platelet aggregation can be detected by fluorescence-activated flow cytometry (FAFC). Changes at the activated platelet surface, which occur before platelet aggregation, may be detected with murine monoclonal antibodies (mAbs) as the platelet proceeds from activation to aggregation (2). Enzyme-linked immunosorbent assay (ELISA) may be used to measure plasma concentrations of the platelet-specific proteins secreted from storage granules during degranulation in vivo, i.e., beta-thromboglobulin (β-TG) and platelet factor 4 (PF4) (3). Dose–response platelet aggregation is induced by platelet agonists such as adenosine diphosphate (ADP) and collagen. Aggregation results are expressed as the agonist concentration producing half-maximal aggregation (AC_{50}).

As summarized in Table 1, studies with differing methodologies have shown that depressed patients with risk factors for IHD or clinically evident IHD exhibit evidence showing circulating platelets that have proceeded through the platelet response cascade to irreversible secretion. The extent of the increased platelet “stickiness,” increased numbers of functional GPIIb/IIIa receptor, or platelet degranulation (as reflected by increased plasma concentrations of β-thromboglobulin [β-TG] and platelet factor 4 [PF4]) appears to be as great (4), or greater (5,6), than comparison groups of patients with atherosclerotic thrombovascular disease, respectively.

More recently, interest has been growing about whether treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants exerts beneficial effects on platelet reactivity. Significantly decreased platelet secretion in response to collagen stimulation has been reported after 6 weeks of open-label treatment with sertraline.6 In patients with major depression, significant reduction in the number of functional GPIIb/IIIa receptors and diminished secretion of PF4 has been observed after short-term, open-label treatment with the SSRI paroxetine (7). In a double-blind, randomized trial of depressed IHD patients comparing paroxetine with the nonselective tricyclic antidepressant (TCA) nortriptyline, paroxetine, but not nortriptyline, significantly decreased PF4 and β-TG plasma concentrations after 6 weeks of treatment (8). Inhibition of serotonin transport into the platelet by SSRI antidepressants, with subsequent depletion of intraplatelet serotonin, may impair platelet activation, thereby impeding potentially therapeutic benefit to depressed patients with atherosclerotic heart disease. For example, in the SADHART study, plasma samples were collected from patients randomized to sertraline (n = 28) or placebo (n = 36). In comparison to the placebo, treatment with sertraline was associated with substantially less release of β-TG, as well as significantly diminished plasma concentrations of E-selectin, which is a component of the inflammatory response that can be released from both platelets and vascular endothelium. That is, sertraline treatment of these depressed patients was associated with greater reductions in platelet/endothelial activation even with the presence of traditional cardiac antiplatelet regimens such as aspirin and clopidogrel (9). Congruent with the SADHART platelet substudy results are reports of the “antiplatelet” effects of SSRI treatment. Indeed, retrospective examinations of

DOI: 10.1097/01.psy.0000164227.63647.d9
large-scale prescription medication databases reveal an increased risk of upper gastrointestinal bleeding with SSRI antidepressants (10,11), especially when coprescribed with nonsteroidal antiinflammatory drugs (10,12), although discordant reports exist (13). In a related, double-blind, placebo-controlled, randomized trial, prophylactic administration of sertraline to poststroke survivors significantly reduced the incidence of poststroke depression; serious adverse events and hospital admissions related to cardiovascular causes were significantly reduced in sertraline-treated patients (14).

Although SSRIs are potentially cardioprotective in patients who exhibit increased platelet activation, e.g., smokers (15), a critical question is whether antidepressant-induced inhibition of platelet function contributes to IHD-related morbidity and/or mortality, e.g., bleeding. Certainly, future prospective, double-blind trials using “antiplatelet” SSRIs will reveal whether these agents confer an added advantage in patients with depression and comorbid coronary artery disease.

**REFERENCES**


23. Deleted in proof.

