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P-selectin in Major Depression: Preliminary Findings with Venlafaxine Treatment

John E. Piletz[1], Angelos Halaris[1], Omer Iqbal[2], Debra Hoppensteadt[2], Jawed Fareed[2], He Zhu[2], James Sinacore[3], and C. Lindsay DeVane[4]

Departments of Psychiatry[1], Pathology[2], and Epidemiology[3],

Loyola University Chicago, Stritch School of Medicine, 2160 South First Ave., Maywood, Illinois 60153;

Department of Psychiatry[4], Medical University of South Carolina, 173 Ashley Ave., Charleston, South Carolina 29425-0742

ABSTRACT

Background

Disturbances in affective state are known to cause platelet activation, which may relate to evidence linking major depression and coronary artery disease. The platelet activation biomarker, P-selectin, exists in various blood fractions that demarcate steps of platelet activation. If circulating platelets are more activated in depressed patients, the literature suggests that amongst antidepressant classes, the Serotonin-Selective Reuptake Inhibitors (SSRIs) are best able to normalize this abnormality. Serotonin/ Norepinephrine Reuptake Inhibitors (SNRIs), like venlafaxine, have not been studied in this regard.

Aim of the Study

To determine the status of activated P-selectin (platelet surface-bound and/or released forms) in depressed patients before and after 8 weeks of treatment with the SNRI, venlafaxine.

Methods

Baseline (untreated) subjects were major depressives (n= 23) and age/sex-matched healthy controls (n= 17) with no evidence of coronary artery disease. A subgroup of the depressed cohort (n= 15) was restudied after 4 and 8 weeks on venlafaxine. P-selectin levels were compared to two biomarkers not known to change during platelet activation: the membranous fibronectin-signaling protein, IRAS, and the antigen of the GPIIb/IIIa receptor, CD61.

Results

At baseline, both activated forms of P-Selectin were high in the depressives, but only the soluble form showed statistical significance (p= 0.03) versus healthy controls. Venlafaxine treatment led to mood normalization based on reduced Hamilton Depression scores (p< 0.0001), while the level of soluble P-selectin was non-significantly lowered (p= 0.13). Platelet membranous IRAS and CD61 levels were normal at baseline but down-regulated after 4 and 8 weeks of treatment (p = 0.01 each).

Conclusion

High levels of soluble P-selectin were identified in depression, indicative of platelet activation. Venlafaxine treatment had minimal effect on soluble P-selectin but had clear effects on platelet IRAS and CD61. Therefore, platelet activation does not readily normalize with mood correction after 8 weeks on venlafaxine, but other platelet effects seem to occur.

Keywords: P-selectin, IRAS, CD61, Platelets, Cardiovascular Disease, Depression, Venlafaxine

INTRODUCTION

A large body of evidence indicates that major depressive disorder (MDD) imparts a substantial lifetime risk for developing coronary artery disease (CAD).[1] Prospective epidemiological studies have repeatedly produced relative risk values (RRs) associated with depression in the 1.3 - 4.5 range for future cardiac disease, stroke, and/or death.[2] The greatest RRs are found in patients exhibiting clinical depression within 6 months post-myocardial infarction.[3, 4] No exact mechanism has been established linking depression to CAD, but there are findings of sympathoadrenal activation and hypothalamic-pituitary-adrenal axis dysregulation in depressed patients.[5] Another finding is that platelets are more activated (sticky) in depression [6-8], which is thought to predispose to atherosclerosis.

Unfortunately, not all studies agree that platelets are more activated in depression.[9-12] Part of the discrepancy may owe to different methods for assessing platelet activation. To clarify this, we have focused on the most frequently studied biomarker of platelet activation, P-selectin, and have analyzed its three activated forms: the soluble form in unperturbed plasma (sP-selectin), the unstimulated form detected by flow cytometry (platelet basal P-selectin), and the agonist-stimulated form detected by flow cytometry (platelet stimulated P-selectin). To anchor these measurements, we have added two unrelated platelet biomarkers: the integrin beta-3 protein antigen (CD61) and the integrin alpha-5 accessory protein, IRAS, on unperturbed platelets. These biomarkers are not associated with

Corresponding author: Angelos Halaris, MD, Ph.D.
Department of Psychiatry
Loyola Stritch School of Medicine,
2160 South First Ave.
Building 105
Maywood, Il 60153 USA
E-mail: jpiletz@lumc.edu
Tel.: 708-216-3276
Fax.: 708-216-5885