Published in final edited form as:
Transl Res. 2008 March ; 151(3): 168–172.

Selective Serotonin Reuptake Inhibitors (SSRIs): Measurement of Effect on Platelet Function

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Abstract

Selective serotonin reuptake inhibitors (SSRIs) reduce platelet serotonin and are associated with increased gastrointestinal bleeding, an effect that is enhanced when taken with NSAIDs or aspirin. The best method to evaluate hemorrhagic events in patients taking SSRIs has not been determined. Platelet aggregation, not widely available, shows SSRI inhibition of platelet function; we tested whether a platelet function analyzer could detect SSRI inhibition of platelet function. Two groups of out-patients with mood disorders were recruited; each was taking a stable dose of either an SSRI or bupropion for at least 6 weeks. They were tested using the platelet function analyzer-100 (PFA-100) concomitantly with platelet aggregation. 58 patients were analyzed. We detected significant differences between the groups using aggregation methods with arachidonic acid (aggregation, $p = .00001$; release, $p = .009$); and collagen, (aggregation, $p = .016$; release, $p = .006$). The PFA-100 did not detect differences between the groups or results outside the reference range. The PFA-100 does not detect the inhibitory effects of SSRIs on platelet function, but can be used to direct evaluation of bleeding in a patient taking an SSRI: Abnormal PFA-100 results suggest further evaluation for von Willebrand disease, other platelet inhibitory medications, or underlying intrinsic platelet dysfunction.

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Key Findings: Abnormalities in platelet function due to SSRIs are not detected in patients by the PFA-100. Patients placed on SSRIs should be followed at intervals, be informed about the possible bleeding risks, and be cautioned about the use of anti-platelet agents, particularly non-steroidal anti-inflammatory medications and aspirin.. While not indicated for routine follow-up of patients on SSRIs, the PFA-100 can be a useful instrument to direct further evaluation of the etiology of the bleeding in a patient taking an SSRI who has a bleeding episode.

Keywords

SSRI; Platelets; PFA-100; Platelet Aggregation

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are used to treat depression, obsessive-compulsive disorder, social anxiety disorder, and a variety of additional psychiatric conditions[1]. These commonly used medications have been advertised widely and are among the most frequently prescribed medications worldwide due to their efficacy and generally mild adverse side effects[2,3]. Recent epidemiological studies have also shown that the risk of gastrointestinal bleeding is increased in patients receiving SSRIs[4–9]. Additional studies indicate that bleeding episodes requiring hospital admission are more frequent and that transfusion requirements during orthopedic surgery are increased in patients taking SSRIs[10, 11].

The bleeding diathesis that is seen after SSRI administration is linked to a decrease in platelet function that occurs when serotonin reuptake into platelets is inhibited. Platelets contain approximately 99% of whole blood serotonin and release it at sites of vascular injury, causing amplification of platelet aggregation that is vital to hemostatic thrombus formation[12,13]. Cellular serotonin is decreased by more than 80% in subjects given paroxetine, and the reduction leads to decreased exposure of activation proteins at the surface of platelets and to impairment of platelet aggregation, effects that can be measured using flow cytometry and platelet aggregation techniques[14]. These tests are time consuming, not widely available, and require technologists skilled in their use.

The best method to evaluate hemorrhagic events in patients taking SSRIs has not been determined. The purpose of this study was to compare platelet function in patients treated with an SSRI vs. bupropion, a non-SSRI antidepressant, using the platelet function analyzer-100™ (PFA-100), a more accessible instrument. Platelet aggregation studies were performed concomitantly for comparison, assuming that this sensitive method would demonstrate abnormalities.

Methods

The study used a descriptive design comparing two groups of out-patients recruited from the National Center for the Treatment of Phobias, Anxiety, and Depression and from the National Institutes of Health (NIH). Each group was taking a stable dose of either an SSRI medication or buproprion for at least 6 weeks. The SSRI medications included citalopram (Celexa®, n=1), fluoxetine (Prozac®, n=10), venlafaxine (Effexor®, n=2), paroxetine (Paxil®, n=3, and sertraline (Zoloft® n=16). The NIH National Heart, Lung, and Blood Institute Institutional Review Board approved the study in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained.

Sample

A pre-study power calculation indicated that at least 26 evaluable subjects in each group were required to detect a difference of 40% in the platelet aggregation between the groups; an additional 3 to 5 were recruited into each group, assuming there would be attrition. Table 1 illustrates the inclusion and exclusion criteria. Subjects were paid $20.00 for their participation. Each subject underwent a medical history, including specific questions regarding use of over-the-counter medications that can interfere with platelet function, and laboratory testing. Subjects taking medications that caused platelet dysfunction were asked to discontinue them

for 7–10 days prior to testing. If subjects were unable to discontinue medications that caused platelet dysfunction, they were not eligible for the study. Laboratory tests (Table 1) were performed according to routine procedures.

Platelet Instruments and Assays

PFA-100—Platelet Function Analyzer-100™ (Dade International Inc, Miami, FL) assays were carried out using the directions provided by the manufacturer. Briefly, the instrument aspirates citrated whole blood under constant negative pressure to a collagen coated membrane with a standard-sized aperture; either epinephrine or adenosine diphosphate is also added. Collagen plus either epinephrine or ADP initiates platelet activation, resulting in adhesion and aggregation. The platelet plug occludes the aperture and registers a drop in pressure. The time required for occlusion of the aperture (closure time) is recorded in seconds. The instrument is simple to use from a technical standpoint, results are easy to interpret, and it is applicable to general hematology laboratories[15]. Initial studies with the PFA-100 showed a good correlation of results in subjects with platelet dysfunction using the PFA-100 and platelet aggregation (sensitivity of 94.9% and specificity of 88.3%)[15]; additional studies have shown a number of false negative results in patients with mild platelet defects such as storage pool and release defects, macrothrombocytopenia, and Hermansky Pudlak syndrome[16]. The PFA-100 assesses the combination of both platelet adhesion and aggregation in whole blood. It differs from platelet aggregation and release studies by using whole blood and fewer agonists and by not measuring platelet granule release; it has been considered less sensitive than platelet aggregation and release.

Platelet Aggregation and Release—Platelet aggregation and release assays utilizing platelet rich plasma were performed on a lumi-aggregometer (Chrono-Log Corp), with measurement of ATP release according to the manufacturer's methods. Platelet rich plasma (PRP) was prepared from citrated blood (3.2%) by centrifugation. The PRP was removed, and the remainder of the sample was spun to obtain platelet poor plasma. Platelets in the PRP were adjusted to 200,000/μL using this platelet poor plasma. A fresh laboratory control sample was prepared and run in the same manner. 400μL PRP were equilibrated with 50μL luciferase in a stirred cuvette at 37°; each agonist was then added separately to PRP samples. Aggregation was measured as the percent change in light transmission. Platelet release was measured in nanomolar ATP release by fluorescence emitted from the luciferin-luciferase reaction. Interpretation of aggregation was done by one author (MER) who was blinded to the subject's medication group.

Statistical Methods

Results of platelet assays were compared using standard independent-sample t-tests; 2-tailed P-values are reported with the value of the t-statistic and its degrees of freedom. A value of $P \leq 0.05$ was considered statistically significant. Descriptive statistics and all formal statistical tests were calculated using commercially available software (SPSS 11.5, SPSS Inc., Chicago, IL).

Results

Enrollment

We enrolled a sample of 61 subjects, 12 males and 49 females (Table **2**). The groups consisted of 29 patients taking buproprion and 32 patients taking SSRIs. Three individuals with prolonged aPTTs were excluded from further analysis. An increase in thyroid stimulating hormone (TSH) levels (5.1 and 5.4 mU/L [normal range 0.4–4.2 mU/L]) was found in 2 subjects who had normal free T4 levels, and they are included in the analysis.

Platelet Function Analyzer-100

The PFA-100 assays did not show results outside the laboratory reference range (Table 3). There were no significant differences between the SSRI and buproprion groups (epinephrine-collagen, $t = -1.55$, $df = 56$, $p = .127$; ADP-collagen, $t = -.557$, $df = 56$, $p = .580$).

Platelet Aggregation and Release Studies

Arachidonic acid—Platelet aggregation was significantly decreased in the SSRI group compared with the buproprion group ($t = 4.84$, df 56, p=0.00001), and there was no aggregation in 14 of 32 SSRI subjects. The platelet release reaction was also significantly decreased in the SSRI subjects (mean 0.27 nM) compared to the buproprion subjects (mean = 0.50 nM) (t =2.71, $df = 56$, $p = 0.009$) (Table 4), and the ATP release was below the normal reference range in 16 of 32 patients taking SSRIs.

Collagen—Aggregation was significantly decreased using collagen in the SSRI group compared to the bupropion group ($t = 2.52$, $df = 39$, $p = .016$). Release of ATP was also significantly decreased in the SSRI compared to the buproprion patients, SSRI mean = 0.45 nM vs. bupropion mean = 0.67 nM ($t = 2.82$, $df = 56$, p=0.006) (Table 4), and the ATP release was below the normal reference range for collagen in 25 of the 32 SSRI subjects.

Epinephrine and ADP—Aggregation and release responses to the weaker agonists, epinephrine and ADP, were decreased in the SSRI patients compared to the buproprion patients, but they were not significantly different (Table **4**).

Thrombin—There was no difference in the aggregation or release responses to thrombin between the two sets of patients (data not shown).

Discussion

The PFA-100 closure times were not significantly different between SSRI and bupropion patients. Additionally, no results were outside the normal reference range. However, platelet aggregation methods detected significant abnormalities in the SSRI patients; arachidonic acid, which initiates aggregation via the prostaglandin pathway, is most abnormal. There is also a significant decrease in aggregation using collagen as agonist.

Studies using PFA-100 closure times to evaluate platelet function in normal volunteers given SSRI medications have been contradictory. A crossover protocol using paroxetine and placebo showed no significant difference in closure times while subjects were taking paroxetine[17]. Another investigation showed a prolongation in closure times of 31% in normal subjects receiving 20 mg of paroxetine daily compared to placebo ($p<.02$)[18].

Our results confirm the platelet dysfunction resulting from SSRI use as assessed by platelet aggregation, and they show that the PFA-100 does not detect the mild abnormalities brought about by SSRIs. This is the largest study assessing platelet aggregation in patients taking SSRIs and the first study comparing platelet function in patients taking an SSRI vs a non-SSRI antidepressant. The selection of patients from an outpatient setting may have reduced the effect of differences in platelet reactivity that can be present in depressed subjects compared with normal volunteers[19]. Limitations of the study include its small size, the variety of SSRIs that are included, and the lack of documented correlation between clinical bleeding and platelet aggregation abnormalities[20].

The abnormalities of platelet aggregation did not correlate with clinical bleeding in our SSRI patients, indicating that platelet aggregation using arachidonic acid or collagen agonists is too

sensitive to evaluate bleeding episodes in patients taking SSRIs. While none of our patients had clinical bleeding during the study, the literature demonstrates an increase in bleeding, particularly gastrointestinal blood loss, in patients on SSRIs[4–9]. The absence of PFA-100 abnormalities in patients taking SSRIs allows use of the PFA-100 to evaluate patients presenting with a bleeding problem: if PFA-100 results are abnormal, testing for von Willebrand disease, other platelet inhibitory medications, or underlying intrinsic platelet abnormalities should be carried out.

Speculations

Health care providers and patients should be aware of bleeding risks with SSRIs, particularly when taking aspirin or NSAIDs, or if a history of gastrointestinal bleeding is present. Patients should be evaluated with history and physical examination at intervals, and the use of tests for detecting occult blood in the stool might be applied appropriately in these patients. While not indicated for routine follow-up of patients on SSRIs, the PFA-100 can be a useful instrument to direct further evaluation of the etiology of the bleeding. Thorough bleeding histories, education of the patient, and careful follow-up remain the major tools for preventing a bleeding diathesis that is caused or aggravated by SSRI medications.

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Table 1

Inclusion and Exclusion Criteria

Inclusion Criteria

- Male or female subjects with a diagnosis of depression over the age of 18 years
- Subjects currently prescribed and taking a stable dose of SSRI for at least 6 weeks or
- Subjects currently prescribed and taking a stable dose of buproprion for at least 6 weeks

Exclusion Criteria

- Inherited or acquired coagulopathies or platelet disorders
- Patients receiving comadin or heparin, non-steroidal antiinflammatory drugs (NSAIDs), acetylsalicylic acid (Aspirin), corticosteroids, chemotherapy, alternative medications, or other medications known to interfere with platelet function studies. (Patients taking NSAIDS and aspirin or other medications known to interfere with platelet function studies were eligible if they discontinued these medications for an appropriate interval prior to testing)
- Patients receiving the following psychotropic medications: valproic acid, carbamazepine, buspiron, atypical antipsychotics
- Abnormal thyroid function
- Severe depression
- Abnormal laboratory tests: complete blood count, coagulation profile (prothrombin time, aPTT, thrombin time, fibrinogen), liver function tests, serum lipids, cobalamin level, folate level, C-reactive protein, TSH, and free T_4

Table 2

Demographic Information

	SSRI (n = 32)	Buproprion (n = 26)
Gender		
Male	7	6
Female	25	20
Age		
mean (range)	42 (20–66)	41 (19–75)
Ethnic group		
Caucasian	27	24
African American	3	2
Hispanic	1	0
Asian	1	0

Table 3

PFA-100 Closure Times

Agonist	*Mean*[*]	*SD*	*p*
Epinephrine-collagen			
SSRI	118 sec	28	.127
Buproprion	132 sec	38	
ADP-collagen			
SSRI	79 sec	18	.580
Buproprion	82 sec	18	

[*] Normal mean closure time for epinephrine-collagen is 86–154 sec and for ADP-collagen is 73–129 sec

Table 4

Platelet Aggregation and Release Responses

Agonist	Mean Aggregation (%)*	*SD*	*p* (aggregation)	Mean Release (nM/L)	*SD*	*p* (release)
Arachidonic acid (0.87mM)						
SSRI	18.9	33.2	0.00001	0.27	.29	0.009
Bupropion	59.3	29.5		0.50	.36	
Collagen (2.2 and 4.4μg/mL)						
SSRI	62.5	19.9	0.016	0.45	.28	0.006
Bupropion	71.1	6.8		0.67	.30	
Epinephrine (7.5μM)						
SSRI	33.1	21.8	0.104	0.25	.29	0.166
Bupropion	43.3	24.9		0.38	.41	
ADP (5.5μM)						
SSRI	54.8	12.9	.452	0.15	.20	0.294
Bupropion	58.6	22.3		0.23	.33	

* Mean aggregation % - average percent change in light transmission for each group.