Bleeding Attributed to the use of Paroxetine

Mete Şaylan[1], Raşit Tükel[2]

ÖZET:

Paroksetin Kullanımına Bağlı Kanama

Seratonin geri alınım inhibitör (SSRI)'leri psikiyatrik bozuklukların büyük bir kısmında tedavide kullanılmaktadır. Literatürde SSRI kullanımına bağlı kanama, sık bildirilmesine rağmen; sıklığı ve etyolojisi tam olarak bilinmemektedir. Bu yazıdaki amaç 20 mgr/gün paroksetin alan bir hastada oluşan ekimoz tarzındaki kanamayı rapor etmek ve mevcut literatürü gözden geçirerek bu yan etkinin muhtemel oluşum mekanizmalarını tartışmaktır. Ayaktan tedavi kliniğine başvuran, major depresif bozukluk tanısı alan, bayan, 25 yaşında hasta. Dört hafta süreyle 20 mgr/gün paroksetin kullanmış. Hastanın semptomları ikinci haftada iyileşirken, 4. haftada bacağının üst kısmında ekimoz şeklinde yakınması olmuş. Biyokimyasal analizler, trombosit fonksiyon testleri, pıhtılaşma ve kanama testleri ve fiziksel muayenede bir anormallik ortaya çıkmadı. Kanama ile ilgili bilinen diğer riskler tıbbi geçmişi sorgulanarak dışlandı. Kanama paroksetin tedavisine bağlandı. İlaç kesildikten sonra yeni ekimozlar oluşmadı ve 2 hafta içinde kendiliğinden kayboldu. Literatürde SSRI'larla oluşan kanamaların etyolojisiyle ilgili ileri sürülen en yaygın neden, nöronlardakine benzer mekanizmayla plateletlerden granüler serotonin boşalmasıdır. Gözden geçirme ve olgu çalışmaları SSRI tedavisi alan hastalarda, özellikle de kanama için multipl risk faktörüne sahip olanlarda dikkatli olmanın gerekliliğini önermektedir.

Anahtar sözcükler: kanama, SSRI, paroksetin, depresyon

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ABSTRACT:

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Abstract: Selective serotonin reuptake inhibitors are used for the treatment of a wide range of psychiatric disorders spectrum. Although bleeding attributed to the use of serotonin reuptake inhibitors is reported frequently in the literature, its exact frequency and etiology are unknown. The aim of this manuscript is to report a patient who experienced bruises while having 20mg/day paroxetine and to discuss possible mechanisms of this side effect while reviewing the current literature. 25 years old female patient admitted to our outpatient clinics and was diagnosed with major depressive disorder. She was given paroxetine 20mg/day for four weeks. While her depressive symptomatology improved by the second week of the treatment, she complained of bruises appearing on her upper legs at the fourth week. The biochemistry analysis, platelet function tests, clotting and bleeding tests and physical examination revealed no abnormality. Other known risk associated bleeding were also excluded in her medical history. The bruises were attributed to paroxetine treatment. No new spontaneous ecchymosis occurred after the drug was discontinued and they disappeared spontaneously within two weeks.Depleted granular serotonin in platelets by the same mechanism as in neurons is the commonly suggested cause for the etiology of bleeding attributed to SSRIs in the literature. Reviews and case studies urged the need for caution in patients receiving SSRI therapy, particularly for those with multiple risk factors of bleeding.

Key words: bleeding, SSRI, paroxetine, depression

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INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are widely used for psychiatric and psychosomatic disorders. SSRIs are preferred to tricyclic antidepressants because of their effectiveness, low side effect profiles and ease of administration (1). However, case reports linked SSRI treatment, including paroxetine, with bleeding complications (2-7). Despite this side effect, which is frequently described in the recent literature as case reports and retrospective analysis, its real incidence and its mechanism are still unknown (8-11).

Retrospective case control studies are not appropriate type of studies because of their methodological weaknesses to assess the correct incidence and the risks for this side effect. For some studies, the primary outcome measure was an admission related to a specific organ or system bleeding and for others related to any abnormal bleeding (10,12,13). Possible confounding factors might also contribute to inconsistent findings in these studies (12-14). Although some cohort studies tried also to classify the

[1]Psychiatrist, M.D., [2]Professor, M.D., Istanbul Medical Faculty Psychiatry Department, İstanbul-Turkey

Yazışma Adresi / Address reprint requests to: Şaylan Mete M.D, Istanbul Medical Faculty, Psychiatry Department, 34390 Sehremin Istanbul-Turkey

Telefon / Phone: +90-216-554-0182
Faks / Fax: +90-216-554-0184

Elektronik posta adresi / E-mail address: saglayan_mete@lilly.com

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antidepressants based on their affinity for serotonin transporter affinity and found higher risk for relatively higher degrees of inhibitiors, because of their methodological constraints, it is not possible to determine the relative risk of each SSRI and to clarify the underlying mechanism of bleeding associated with SSRI treatment. Only theoretical approaches such as "depleted serotonin in the platelet" are made to explain the patophysiology of this event (9).

Although its severity may vary from mild to very severe cases, the need for caution is stressed particularly for patients with multiple risks for bleeding. Old age, a history of gastrointestinal problems and concomitant use of other drugs that may cause bleeding are the identified risk factors for bleeding associated with SSRIs (10).

Here we present a patient with bleeding disorder occurring after four weeks of paroxetine administration and we discuss possible mechanisms of this side effect with detailed literature data.

Case Report

A 25-years-old female patient admitted to Istanbul University Istanbul Medical Faculty outpatient clinic on August 1999, with the complaints of insomnia, anhedonia, avolition, and difficulty in concentrating and working since last month. She was diagnosed with major depression and treated with paroxetine (Seroxat) 20mg one tablet every day for four weeks. In the second week of the treatment, her complaints ameliorated and no side effect was observed.

In the fourth week of treatment, she applied to the outpatient clinic with the complaint of spontaneously appearing bruises reaching to a maximum diameter of 8 mm. She had not any personal or family history of a bleeding disorder. She did not take any drug that might cause/contribute to bleeding except for paroxetine taken in the last 4 weeks and she did not have any trauma history. In the physical examination no abnormality other than ecchymosis was observed. Although it is reported rarely, we thought that these bruises may be attributed to paroxetine intake and the drug was discontinued.

Hepatic function tests, urine analyses, erythrocyte sedimentation rate, hemoglobin level, and complete blood count results were all in normal ranges. No change in blood cell formulation was noticed. Bleeding time, protrombine time, partial protrombine time, activated partial protrombine time, INR, clotting time and fibrinogen level were also normal. Platelet function tests could not be performed immediately after paroxetine discontinuation because of technical reasons.

No new spontaneous ecchymosis occurred after the cessation of paroxetine and old ones disappeared gradually within two weeks. One week later, we started nefazadone (Serzone) 400mg for its significantly less serotonin reducing effect in platelets (15). We performed ADP, collagen, ristocetine tests, and platelet aggregation response to epinephrine test, in order to exclude any subclinical platelet functional disorder, 4 weeks after drug cessation. The results of all laboratory examinations were normal.

Discussion

Ecchymoses of our patient are attributed to SSRIs, after excluding other etiologies for bleeding. In literature, ecchymosis and severe complications like epistaxis, internal hemorrhoidal bleeding, menorrhagia, hemorrhagic ulcerations are reported (7,16,17). It is known that SSRIs deplete granular serotonin stores in platelets by the same mechanism in neurons (18,19). In vitro and in vivo studies demonstrated that fluoxetine inhibits serotonin reuptake in platelets by 65% and 80%, respectively (20). More than 99% of total blood serotonin is stored in platelets (21). Serotonin, under normal circumstances, mediates platelets aggregation and haemostasis, by acting on 5HT2 receptors when there is a tear on vascular tissue (22). Since platelets are unable to synthesize serotonin, decrease of serotonin concentration in platelets during SSRI administration might be the cause of impaired platelet function and prolonged bleeding time (9,15). However, the thrombopathy associated with SSRI use is difficult to detect with routine laboratory tests. Hergovich et al. investigated the potency of paroxetine to inhibit platelet plug formation under shear stress and its potential inhibition of platelet responsiveness to thrombin receptor-activating peptide in 16 healthy

volunteers (23). They demonstrated that paroxetine decreases platelet plug formation under shear stress as well as platelet activation in response to thrombin receptor-activating peptide. Their findings were also helpful to gain insight into the underlying mechanism of bruises, petechia and bleedings.

Another viewpoint is enhancement of the underlying subclinical disorder by the same way (24). Shen and his colleagues elucidated a different mechanism and propose the hypothesis that SSRIs induce bleeding by inhibition of nitric oxide synthase (25). A reduced level of nitric oxide sequentially leads to decreased production of cyclic guanosine monophosphate (cGMP), which acts to relax smooth muscle and regulate platelet aggregation. Laine-Cessac et al. focused on failure of primary haemostasis in order to explain a possible pharmacological effect of fluoxetine. The single statistically significant difference observed in laboratory test was a decreased velocity in platelet aggregation stimulated by epinephrine. This result was interpreted as a possible effect of fluoxetine on platelet adrenoreceptors (26).

Weinrieb et al systematically reviewed the Medline for "SSRI related bleeding" literature and supplemented it with a case report of an HCV-infected patient who had a fatal gastrointestinal bleed while taking 20mg/day paroxetine (11). They found 6 retrospective studies, 5 of which were case control studies and 18 case reports of bleeding in 37 people between the years 1996 and 2002. We additionally identified 6 casereports in the Medline search (7,27-31).

In one study, estimated incidence rate of upper gastrointestinal bleeding was 1 case per 1300 SSRI users (12). Approximately three times higher risk of upper gastrointestinal bleeding with SSRI use was justified by two retrospective case control studies (10,12). Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) increases further the risk for bleeding. Most of the cases reported in the literature were using SSRIs within the dosage range as indicated on the product label. Multiple potential confounding factors such as NSAIDs or aspirin use, coagulopathies, recent trauma, multiple systemic illnesses, or recent alcohol or drug use were present in some of these cases. Bleeding sites were diverse: from arm and leg petechiae (24) in mild cases to subhyaloid

Table 1: Studies reporting antidepressant associated bleeding rates

Study	Study Design	Index Case	Bleeding Rates	Main Conclusion
De Abajo et al. (12)	Population based case-control	Upper gastrointestinal bleeding	1 case per 8000 prescriptions	SSRIs increase the risk of upper gastrointestinal bleeding. The absolute effect is moderate
Layton et al. (13)	Observational cohort	Abnormal bleeding reported during treatment for SSRIs	2.77 per 1000 patient-months	Weak evidence to support an increase in the rate of bleeding level
Van Walraven et al. (14)	Retrospective cohort	Admission to hospital for upper gastrointestinal bleeding	7.3 per 1000 patient years	Antidepressants with high inhibition of serotonin reuptake increased the risk of upper gastrointestinal bleeding
Bak et al. (38)	Nested case-control	Hemorrhagic stroke	Odds ratio of hemorrhagic stroke in current SSRI users compared with never users was 1.0 [95% (CI), 0.6 to 1.6]	Current exposure to SSRIs is not associated with increased risk of intracerebral hemorrhage
Dalton et al. (10)	Retrospective cohort of current and former SSRI users	Upper gastrointestinal tract bleeding	3.1 per 1000 treatment-years	SSRIs increase the risk of upper GI bleeding
Meijer et al. (34)	Nested case control	Hospitalization for a primary diagnosis of abnormal bleeding	4.9 per 1000 person-years	An increased risk of abnormal bleeding was strongly associated with the degree of serotonin reuptake inhibition

(17) and intracerebral hemorrhage (31) in severe ones. Table 1 summarizes antidepressant associated bleeding rates reported in different studies.

The majority of the bleeding events occurred within a few weeks of the start of antidepressant therapy (13). The adverse events generally diminished after discontinuation of the drug and reappeared when rechallenged with the same or other SSRIs. This hematological adverse event that aroused in the first month of the treatment did not reoccur when we substitute the current treatment with an antidepressant from a different class.

Studies with restricted number of subjects could not show any laboratory changes related to bleeding or coagulation with this group of drug (32-34). We could not find any abnormal laboratory results in our case.

Even though this side effect appears more frequently with fluoxetine, this can be explained by its prevalent use and their time differences in entering the market. Paroxetine has a higher potency compared with fluvoxamine, fluoxetine and sertraline (35). It can therefore be speculated that paroxetine should produce bleeding disorder more frequently by doing more diminution of serotonin in platelets. On the other hand, SSRIs cannot be directly classified for their potency to inhibit serotonin reuptake. As serotonin inhibition for different SSRIs is measured based on equilibrium dissociation constants in human cell cultures, factors such as dosage, blood drug level, protein binding and the activity of metabolites are not considered.

A more recent case control study investigated the risk of all types of abnormal bleeding associated with the use of antidepressants and aimed to establish the relationship between degree of serotonin reuptake inhibition and risk (36). A significant association is found between degree of serotonin reuptake inhibition and risk of hospital admission for abnormal bleeding. They identify 196 patients who were hospitalized with a primary diagnosis of abnormal bleeding which corresponds to an incidence of 4.9 per 1000 person a year. The adjusted odds ratio of high affinity antidepressants was 2.6, compared with low affinity antidepressants. As the index event was hospitalization for abnormal bleeding during antidepressant use, this may cause to fail to notice bleeding events that did not result in hospitalization or that resulted in death before admission to hospital.

This rare side effect has an important place in consultation and liaison psychiatry. It is recommended to discontinue the drug before elective surgery for patient with documented bleeding time prolongation and to manage clotting by administering fresh frozen plasma or clotting factors (37).

Controlled and broader prospective studies are necessary to better understand the bleeding disorders related to SSRIs use. This side effect should be considered particularly for its use in Consultation-Liaison Psychiatry. SSRIs should be used carefully, for the treatment of patient with underlying functional or constitutional bleeding disorder and with concomitant drug use that may cause bleeding disorders. More detailed examination, routine complete blood count and platelet function tests have to be performed in patients with symptoms and signs related to a bleeding disorder.

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