

Selective serotonin reuptake inhibitors related bleeding risk: case report and review of literature

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Abstract

Gastrointestinal bleedings are relevant side effects in patients during anticoagulant therapy for atrial fibrillation. Direct oral anti-coagulants (DOACs) are less correlated with major bleeding events than vitamin K antagonists (VKAs), but concerns are present about the relative risk of gastrointestinal bleeding. Here we report the case of a patient with atrial fibrillation and dementia on DOAC treatment who developed a SSRI-associated thrombocy-

topenia with subsequent life-threatening bleeding. Physicians should be aware of the possible correlation between SSRI-induced thrombocytopenia and concomitant use of anticoagulant and/or antiplatelet drugs, thus preventing life-threatening bleedings.

Highlights

- Selective serotonin reuptake inhibitors (SSRIs) can interfere with platelet adhesion by approximately 50% or more at the highest concentration;
- SSRIs, in particular escitalopram, can induce and/or worsen thrombocytopenia as a major side effect, thus leading to an increased bleeding risk;
- SSRI prescription during hospitalization for an acute coronary syndrome is related to lower incidence of recurrent ischemia, heart failure or cardiac enzyme elevation;
- Physicians should be aware of the possible correlation between SSRI-linked thrombocytopenia and use of anticoagulant and/or antiplatelet drugs, thus preventing life-threatening bleedings.

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Introduction

Some data in literature reported that the use of selective serotonin reuptake inhibitors (SSRIs) can be related to an increase risk of bleeding.^{1,2} Bleedings correlated with SSRI use have been showed to occur mostly in the upper gastrointestinal tract and then intracranially.³ Patients taking those drugs suffering from depression often display comorbidities needing the use of antithrombotic drugs. Indeed, patients affected by atrial fibrillation (AF) display a higher incidence of affective disorders, and antidepressant use are correlated with a 34% and 36% higher risk of AF.^{4,5} Here we report the case of a life-threatening gastrointestinal bleeding linked to escitalopram therapy in the setting of direct oral anticoagulant (DOAC) ongoing treatment.

Case Report

A 84-year-old Caucasian man was referred to our ward for melena, loss of fluids and worsening of general conditions. His past medical history was characterized by severe cognitive impairment due to Alzheimer's disease, permanent atrial fibrillation on DOAC therapy and benign prostatic hypertrophy. The patient was taking home therapy with escitalopram, apixaban 5 mg 1 tablet twice a day and alfuzosin. Peripheral heart rate was 82 beats per minute (bpm), while central heart rate was 76 bpm and blood pressure 110/70 mmHg. His electrocardiogram showed atrial fibrilla-

tion, left axis deviation, intraventricular block and abnormalities of QRS profile. On physical examination, patient was stuporous with no neurologic deficits. Skin and mucous were dry and dehydrated. Vesicular murmur was diffusely reduced. Heart rate was arrhythmic. No peripheral edema was present. Abdomen examination was normal, apparently painless. At digital rectal examination there were soft stool black in color. Abdomen x-ray did not show intestinal perforation signs. No inflammatory parenchymal and pleural alterations were present on chest x-ray. Brain computed tomography demonstrated no bleeding lesions or edema, and no indirect signs of intra-cranial expansive lesions.

Anemia and thrombocytopenia (haemoglobin: 8.7 g/dL; platelet count: $66 \times 10^3/\text{mmc}$, Table 1) were evident on blood exams. Reticulocyte absolute count (reticulocytes %: 2.62) and reticulocyte index (2.56) were required to ascertain the cause of anemia and thrombocytopenia; the results did not support a possible hyporegenerative medullary disease. During hospitalization no platelet aggregation tests were performed due to their unavailability. All the remaining causes of thrombocytopenia, including those related to drugs, were considered. By reconsidering patient medical history, escitalopram treatment had been introduced for about a month, due to a form of depression linked to dementia. Some previous reports demonstrated SSRIs to be correlated with thrombocytopenia, as a side effect. Subsequently, escitalopram was with-

drawn with a progressive increase of platelet count, and the concurrent resolution of the gastrointestinal (GI) bleeding. Once the blood pressure was restored to normal level, a gastroscopy was performed showing a diffuse inflammation of the gastric mucosa and hemorrhagic suffusions.

The patient was discharged on the sixth day in good clinical conditions. The same home therapy was reintroduced, but with a halved dosage of apixaban and a standard dose of proton-pump inhibitor. No antidepressant drugs were prescribed at discharge. Therefore, a clinical and laboratory follow-up was set up for the prescription of DOAC for atrial fibrillation.

Informed consent was obtained from the patient regarding the reporting and publication of this case report.

Discussion and Review of literature

SSRIs effects on platelet aggregation and platelet count

SSRIs (e.g. citalopram and sertraline) do not significantly change plasma coagulation but can interfere with platelet adhesion by approximately 50% or more at the highest concentration.⁶

Table 1. Blood tests of the patient on admission and discharge.

Laboratory test	MU	Normal reference values	Admission	Discharge
Folic acid	ng/mL	3-17	2.8	
B12 Vitamin	pg/mL	200-950	1886.0	
Ferritin	ng/mL	15-300	486.8	
ESR	mm/h	0-19	40	38
Bilirubin total	mg/dL	0-1.2	0.9	0.8
INR	-	0.9-1.2	1.8	1.29
aPTT	sec	28-40	111	108
CRP	mg/dL	0,5-1	2.98	1.03
RBC	X $10^6/\text{mmc}$	4.7-6.1 (M) 4.2-5.4 (F)	3.03	2.99
HGB	g/dL	14.0-17.5 (M) 12.3-15.3 (F)	8.7	8.8
HCT	%	40-54	43.9	39.8
MCV	fL	78-98	85.5	87.6
MCH	pg	26.0-34.0	28.7	29.4
MCHC	g/dL	30.0-36.0	33.6	33.6
WBC	X $10^3/\text{uL}$	4.5-10.0	5.50	5.43
PLT	X $10^3/\text{mmc}$	150-400	66	144
Basophils	X $10^3/\text{uL}$	0.00-0.27	0.01	0.03
Neutrophils	X $10^3/\text{uL}$	1.35-8.10	4.06	4.10
Lymphocytes	X $10^3/\text{uL}$	1.57-7.43	0.88	0.99
Monocytes	X $10^3/\text{uL}$	0.05-1.62	0.43	0.67
Eosinophils	X $10^3/\text{uL}$	0.05-1.21	0.11	0.02
Reticulocytes	%	0.5-2.5	2.62	2.59
Fibrinogen	mg/dL	150-400	310	410
Creatinin	mg/dL	0.50-1.40	0.8	0.8
Aptoglobin	mg/dL	30-200	47	
LDH	U/L	80-300	711	
TSH	UI/mL	0.35-4.50	2.42	

Abbreviations: ESR, erythrocyte sedimentation rate; INR, International Normalized Ratio; aPTT, activated partial thromboplastin time; CRP, C reactive protein; RBC, red blood cells; HGB, haemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; WBC, white blood cells; PLT, platelets; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

SSRIs, in particular escitalopram, can induce and/or worsen thrombocytopenia as a major side effect⁷ and are associated with bleeding risk.^{3,8}

In the work of Ataoglu *et al.*, patients with depression on escitalopram treatment exhibited significant reduction in mean platelet volume (MPV) and a significant decline in platelet count.⁹ Moreover, a subsequent study enrolling 131 patients with depression showed a decrease in platelet count on escitalopram, while other antidepressants such as venlafaxine and bupropion did not exert the same effect.¹⁰ A work by Lopez-Vilchez demonstrated that escitalopram can inhibit platelet response to thrombin, measured as platelet aggregation and expression of activation markers CD62-P and CD63 from platelet granules, and interfer with signalling pathways mediated by thrombin (RhoA, PKC, Erk1/2 and PI3K/AKT). Escitalopram can dysregulate the polymerization of the actin cytoskeleton and association of contractile proteins during activation with thrombin. Resting platelets incubated with escitalopram became most spherical.¹¹

Moreover, an *in vitro* study showed how medium or high amount of escitalopram can significantly inhibit platelet aggregation induced by ADP and by collagen, together with a reduced expression of glycoprotein (GP)_{IIb/IIIa}, lysosome-associated membrane glycoprotein 3 (LAMP-3) and GP37 on platelet surface.¹²⁻¹⁵

Some SSRIs (*e.g.*, fluoxetine, paroxetine or citalopram) may decrease the secondary phase of aggregation in response to ADP, and significantly lower adenosine triphosphate¹⁶ and serotonin release in normal platelet rich plasma.^{13,14} SSRIs can block serotonin release from dense granule during platelet aggregation.¹⁷

Tseng *et al.* demonstrated that SSRIs can decrease the amplification of platelet aggregation secondary to the activation of purinergic receptor P2Y₁₂, thus reducing the activation of the downstream molecules of the ADP signaling pathways.¹³

Differences between citalopram and other SSRI

Citalopram displays a greater effect to inhibit platelet adhesion to both collagen and fibrinogen surfaces than sertraline.⁶ Moreover, citalopram, but not paroxetine, may significantly decrease P-selectin expression on platelets after ADP activation, thrombin receptor-activating peptides (TRAP) and cross-linked collagen-related peptide (CRP-XL).¹⁸ A recent *in vitro* study demonstrated two distinct inhibitory mechanisms on platelet for citalopram: i) inhibition of CalDAG-GEFI/Rap1 signaling, and ii) competitive antagonism of glycoprotein VI (GPVI) in platelets.¹⁹ Citalopram-related inhibition of GPVI-mediated platelet aggregation was instantaneous, reversible and displayed competitive characteristics, thus showing that those effects were not induced by GPVI decrease in surface expression, but by competitive binding.¹⁹

SSRIs-induced bleeding risk in patients undergoing anticoagulant therapy

As mentioned earlier in the background, SSRI treatment is related to a higher risk of upper GI bleeding, probably due to SSRI-induced increase in gastric acid secretion.^{20,21} SSRI-associated gastrointestinal bleeding incidence can be also increased by the concurrent use of nonsteroidal anti-inflammatory drug (NSAID)s, anticoagulants and antiplatelet agents.^{20,22} In our case, patient was on treatment with DOAC for a permanent AF, and the association between escitalopram-induced thrombocytopenia and anticoagulation may have exacerbated the gastrointestinal bleeding.

Moreover, DOACs are known to increase the potential risk for upper GI tract bleeding.²³

In the work of Wallerstedt *et al.*, the addition of SSRI to war-

farin-treated patients was correlated with an increased risk of clinically relevant bleeding.²⁴ These findings have been reinforced by a recent work by Quinn *et al* analyzing a cohort of 9,186 patients adults with atrial fibrillation.²⁵ SSRI utilization was related to higher incidence of bleedings in comparison with no antidepressants, and bleeding was more detected during periods of SSRI exposure than no antidepressants ones.²⁵

A recent work by Bakker *et al.* reinforced the concept that SSRIs are related to an increased risk of high INR and major bleeding in patients taking vitamin K antagonist therapy.^{2,26} Indeed, SSRI therapy versus non-use was related to a 2.41-fold (95% CI: 2.01-2.89) increased risk for a high INR, which was 3.14-fold (95% CI: 1.33-7.43) among CYP2C9-inhibiting SSRI users.² The adjusted HR of major bleeding was 1.22 (95% CI: 0.99-1.50) in all SSRI users and 1.31 (95% CI: 0.62-2.72) in CYP2C9-inhibiting SSRI users compared with non-users.² Therefore, SSRIs can increase the risk of major bleeding in patients on VKA therapy not only by decreasing platelet function but decreasing VKA metabolism through cytochrome CYP2C9 inhibition.

Some guidelines recommended to avoid SSRIs in DOAC users.^{27,28} However, a work by Bezabhe *et al.* analyzing data during 2018 demonstrated that SSRIs were co-prescribed with DOACs in 14.8% of users.²⁹ High rate of concomitant SSRIs and DOAC prescribing (22.9%) was also reported in an Australian study of elderly hospitalized patients.³⁰ A recent study by Zhang *et al.*, involving almost 24,000 new users of DOACs in the UK Clinical Practice Research Datalink, found a significant increase in the risk of major bleeding in patients co-prescribed an SSRI/SNRI (OR 1.68 95% CI, 1.10-2.59).³¹

A sub-analysis of the ROCKET AF trial was performed on 737 patients taking SSRIs.³² Authors found no significant increase in bleeding risk when SSRI s were combined with anticoagulant therapy, although there was a suggestion of increased bleeding risk with SSRI s added to warfarin than rivaroxaban (HR 1.58 vs. 1.13).³² Furthermore, SSRIs are more related to non-ulcer gastrointestinal bleeding after adjusting for age, gender and co-morbidity in comparison with aspirin.³³ The prescription of concurrent proton pump inhibitors therapy can be beneficial. Bleedings have been less commonly reported at other sites, especially those associated with surgical procedures.²⁰ A more recent work performed on 98863 patients with AF, demonstrated an increased risk of intracerebral hemorrhage (ICH) was associated with the combinations of DOACs with SSRIs (RR: 1.38, 95% CI: 1.08-1.76). In subgroup analyses stratified by individual DOACs, SSRIs increased the risk of ICH in the dabigatran-treated patients (RR: 1.55, 95% CI: 1.04-2.33). In our clinical case, time latency from SSRIs starting and bleeding event could confirm the possible association with SSRI and the involved mechanism related to impairment of platelet adhesion.

The 'beneficial' effect of SSRIs on cardiovascular disease

An increasing body of evidence is available about SSRIs and their possible protective effects against cardiovascular and ischemic heart disease events. SSRI effects on platelet reactivity, endothelial reactivity, and inflammatory molecules can be responsible for the beneficial effect on ischemic heart disease.³⁴⁻³⁷

A recent systematic review performed on 1148 patients showed that SSRIs were related to a significantly lower risk of myocardial infarction in patients with CAD and depression (RR 0.54, 95% CI 0.34-0.86), and in post-ACS patients with depression (RR 0.56, 95% CI 0.35-0.90). Authors found no statistically significant dif-

ference in all-cause mortality, cardiovascular mortality, hospitalizations, angina, congestive heart failure, or stroke incidence.³⁸

Iasella *et al.* performed a retrospective study with co-primary endpoints of bleeding and MACE in patients treated with clopidogrel-based DAPT within 1 year of percutaneous coronary intervention (PCI). SSRI patients had lower MACE risk than mirtazapine patients (HR 0.61, 95% CI 0.38-0.97, $p = 0.036$) but higher MACE risk than patients on neither agent (HR 1.21, 95% CI 1.02-1.43, $p = 0.030$) in adjusted analyses. No significant differences were associated with bleeding risk (SSRI vs. neither adjusted HR 1.07, 95% CI 0.93-1.24, $p = 0.36$).³⁹

Moreover, previous data demonstrated that sertraline can decrease inflammatory molecules, such as C-reactive protein and interleukin-6 (IL-6), after a 20-week administration, thus improving endothelium-mediated dilation.⁴⁰

Otherwise, other published works found no clear data in favor of the use of SSRIs in terms of cardiovascular risk reduction.⁴¹⁻⁴³ A work by Almuwaqqat *et al.* on 2027 participants treated with antidepressants at some time between 1987 and 2013. CVD risk was similar for SSRI and non-SSRI antidepressant users (hazard ratio, 1.10; 95% CI, 0.86-1.41 for AF; hazard ratio, 0.98; 95% CI, 0.77-1.25 for heart failure; hazard ratio, 0.91; 95% CI, 0.64-1.29 for myocardial infarction; and hazard ratio, 1.07; 95% CI, 0.70-1.63 for ischemic stroke).⁴¹

Conclusions

Since the absolute risk of GI bleedings due to SSRIs is low, precautions are needed in high-risk subjects only, like those referring peptic acid disease and previous events of bleeding.²⁰ Further studies are needed to ascertain the possible antiplatelet effect of escitalopram in people affected by ischemic cardiac diseases. Risk assessment by platelet function/aggregation tests in patients taking SSRIs could direct a tailored therapy. Proton-pump inhibitor should be recommended in patients taking SSRIs and concomitant anticoagulant therapy. SSRI prescription during hospitalization for an acute coronary syndrome is related to lower incidence of recurrent ischemia, heart failure or cardiac enzyme elevation at the expense of higher bleeding rates in patients taking high dose antiplatelet therapy and heparin. Physicians should be aware of the possible correlation between SSRI-linked thrombocytopenia and use of anticoagulant and/or antiplatelet drugs, thus preventing life-threatening bleedings.

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