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Acta Haematologica Polonica

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DOI: 10.5603/AHP.a2022.2050

Article type: Original research article

Submitted: 2022-06-22

Accepted: 2022-07-29

Published online: 2022-10-18

Effect of psychotropics on bleeding and clotting factors

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Received: 22.06.2022 Accepted: 29.07.2022

Abstract

Introduction: Coagulopathies are rare side effects with psychotropics and are thus frequently overlooked while prescribing. Selective serotonin reuptake inhibitors are more commonly associated with deranged bleeding parameters, the most frequent being decreased platelet aggregability and activity, and the prolongation of bleeding time. Thrombocytopenia as a side effect of valproate administration often goes unnoticed, and olanzapine has been associated with a higher risk of venous thromboembolism.

The aim of our study was to determine what percentage of patients on psychotropics develop changes in bleeding parameters, and whether these changes are significant enough to warrant routine monitoring of these parameters.

Material and methods: This was a prospective observational, single-center study which included 100 patients newly started on psychotropics. Those on medications affecting bleeding parameters or having an acute illness like sepsis were excluded. Patients were only on a single psychotropic agent, and their bleeding parameters — prothrombin time, international normalized ratio (INR), bleeding time, clotting time (CT) and platelet count — were assessed at baseline and after 15 and 30 days.

Results: Mean values of prothrombin time (PT), INR, bleeding time and CT increased over time while the mean value of platelet count showed a decreasing trend but no clinical manifestations

were noted. Olanzapine was the only drug causing a reduction of PT, INR and CT and valproate was the only drug affecting platelet count. Paroxetine affected the bleeding parameters the most among the antidepressants. Sertraline, fluoxetine, amitriptyline and haloperidol were the other drugs affecting various bleeding parameters, though the effects were less compared to the other drugs in the study.

Conclusions: Routine monitoring of bleeding parameters in patients receiving psychotropics is not warranted, but caution must be taken while prescribing these drugs, especially in groups such as patients with known blood dyscrasias or peri-operative patients.

Key words: psychotropics, bleeding parameters, coagulopathies, prothrombin time

Introduction

Antidepressants, antipsychotics and mood stabilizers constitute a large proportion of all the psychotropic medications routinely prescribed. Each has its unique side effects such as: headache, sedation, insomnia, nausea, sexual dysfunction, and hyponatremia for selective serotonin reuptake inhibitors (SSRIs) [1]; dry mouth, constipation, sedation, orthostatic hypotension, and arrythmias for tricyclic antidepressants (TCAs) [2]; weight gain and sedation for mirtazapine [3], extra pyramidal symptoms seen in first generation antipsychotics (FGAs) [4]; metabolic side effects of second generation antipsychotics (SGAs) [5]; weight gain, hepatic dysfunction, pancreatitis, and alopecia as seen with valproate [6]; tremors, hypothyroidism, polyuria, and cognitive dulling as seen with lithium [7].

Coagulopathies are side effects which, although rarely seen, are frequently overlooked while prescribing psychotropic medications.

Certain psychotropic medications such as SSRIs, especially paroxetine, fluoxetine and sertraline, are more commonly associated with deranged bleeding parameters, the most frequent being decreased platelet aggregability and activity, the prolongation of bleeding, and in rare instances hemorrhagic manifestations [8]. Although rare, these side effects can have life-threatening outcomes if not detected and treated in time. Similarly, thrombocytopenia as a side effect of valproate administration often goes unnoticed and can suddenly manifest with life-threatening events such as hemorrhagic stroke. Olanzapine, a second-generation antipsychotic,

has been associated with a higher risk of venous thromboembolism (VTE), especially in the elderly [9].

Although only limited studies with equivocal results exist, there is a sense of caution in clinical practice, particularly in patients with hematological disorders and patients on psychotropics especially the SSRIs and valproate undergoing major surgical procedures.

Therefore, the present study was undertaken to investigate the effects of these psychotropic medications on bleeding parameters.

As a tertiary care center, we routinely prescribe different classes of psychotropic medications to our patients, and this study aimed to establish what percentage of patients on psychotropics in a naturalistic condition develop changes in their blood parameters and whether these changes are significant enough to warrant routine monitoring of these parameters.

Material and methods

This was a prospective observational study done in a tertiary care hospital after approval from the institutional ethics committee. Convenient continuous sampling method was used. After receiving written consent, 100 patients were enrolled, with the inclusion criteria being age >18 and newly started on psychotropics. Those already on psychotropics, those on medicines affecting bleeding parameters like aspirin, warfarin etc, and those having acute illness like sepsis or febrile illness were excluded. Patients were only on a single psychotropic agent, and benzodiazepines and trihexyphenidyl were given as required.

A semi-structured proforma was used to collect demographic and phenomenological details. The following blood parameters were checked:

- **prothrombin time (PT)/international normalized ratio (INR):** done in central lab using a coagulation analyzer;
- **bleeding time (BT):** done in the open phase detection (OPD) using the Duke method (finger of subject is sterilized with spirit and pricked with sterilized needle using a prick gun, time of pricking is noted, stain of punctured point taken on a filter paper after 30 s, and repeated at 30 s intervals until bleeding stops; the time of no stain is noted properly which is the bleeding time of the subject);

- **clotting time (CT):** done in the OPD using the capillary tube method (two capillary tubes are filled with free flowing blood from the puncture after wiping the first drip of blood, the tubes are then kept at body temperature. After 2 min, the capillary tubes are broken at 1 cm distance to see whether a thin fibrin stand is formed between the two broken ends, the watch is stopped and the time calculated from the average of the two capillary tubes);
- **platelet count:** done in the Central Lab using Automated Hematology analyzer.

Baseline investigations of blood parameters were done prior to starting medications. Patients were started on psychotropic medications at an appropriate dose. On follow up 15 and 30 days later, patients were evaluated again for their blood parameters.

Data thus obtained was pooled and analyzed using computerized software and appropriate statistical tests were applied.

Results

100 patients were included in our study, having a mean age of 32.93 ± 10.41 years (range 18–55). 49 were male and 51 were female. Table I shows the diagnosis distribution of the sample population. The patients were on various drugs, with the most frequently used being valproate, olanzapine and escitalopram. Table II shows the bleeding parameters: PT, INR, bleeding time, clotting time and platelet count over the three serial observations; day zero, day 15, and day 30. The mean values of PT, INR, bleeding time and clotting time increased over time, while the mean value of platelet count showed a decreasing trend. It should also be noted that although the mean values changed, all of them fell within the normal range. The *p* value however was <0.01 for all five parameters, signifying that the change was statistically significant. No clinical manifestations of the changes were noted however, signifying that the above changes were statistically significant but not clinically significant.

Table I. Diagnosis of sample population

Diagnosis	**Frequency (n = 100)**
Schizophrenia	30
BMD	24
MDD	23
Anxiety disorders:	23
• GAD	6
• panic disorder	6
• OCD	5
• conversion disorder	3
• agoraphobia	1
• illness anxiety	1
• social anxiety	1

BMD — bipolar mood disorder; MDD — major depressive disorder; GAD — generalized anxiety disorder; OCD — obsessive-compulsive disorder

Table II. Change in bleeding parameters (in seconds)

Parameter	Day 0 Mean ± SD (min–max)	Day 15 Mean ± SD (min–max.)	Day 30 Mean ± SD (min–max.)	F value	*p* value
PT (normal value 10–13.5 s)	10.81 ± 0.42 (10–12.4)	11.06 ± 0.73 (10–12)	11.47 ± 1.25 (9.8–15.5)	15.72	**<0.01**
INR (range) (normal value 0.8–1.2 s)	0.85 ± 0.07 (0.8–1.1)	0.86 ± 0.09 (0.7–1.2)	0.9 ± 0.14 (0.7–1.3)	8.65	**<0.01**
Bleeding time (range) (normal value 2–9 s)	5.05 ± 1.4 (3–9)	5.58 ± 1.36 (3–9)	6.25 ± 2.01 (2–10.8)	14.66	**<0.01**
Clotting time (range) (normal value 3–8 s)	4.76 ± 1.17 (3–8)	5.1 ± 1.16 (2–8)	5.42 ± 1.35 (2–8.5)	11.79	**<0.01**
Platelet count (range) (normal value 1.5–4 s)	2.61 ± 0.51 (1.65–3.9)	2.5 ± 0.5 (1.56–3.76)	2.36 ± 0.52 (1.22–3.69)	24.35	**<0.01**

SD — standard deviation; PT — prothrombin time; INR — international normalized ratio

Table III. Drugs causing deranged bleeding parameters

Drug	Deranged PT	Deranged INR	Deranged BT	Deranged CT	Deranged platelet count	Total

	↓	↑	↓	↑	↓	↑	↓	↑	↓	↑	
Olanzapine	2	0	9	0	0	0	7	0	0	0	18
Paroxetine	0	6	0	2	0	4	0	1	0	0	13
Valproate	0	0	0	0	0	0	0	3	6	0	9
Sertraline	0	2	0	2	0	2	0	1	0	0	7
Fluoxetine	0	2	0	0	0	2	0	0	0	0	4
Amitriptyline	0	1	0	0	0	1	0	0	0	0	2
Haloperidol	0	0	0	0	0	0	0	1	0	0	1

PT — prothrombin time; INR — international normalized ratio; BT — bleeding time; CT — clotting time

Table III shows the drugs causing derangement in bleeding parameters. Of the 13 drugs used in our study, seven caused derangement in bleeding parameters, and these are arranged in descending order in the above Table.

Olanzapine caused deranged bleeding parameters on 18 occasions. On nine occasions it affected INR, on seven occasions it affected CT, and two occasions it affected PT. It is to be noted that olanzapine caused an elevation of the above parameters. Furthermore it is seen that all cases of reduction of PT, INR and CT were due to olanzapine alone.

Paroxetine was the second most common drug causing a derangement in bleeding parameters. It caused abnormalities in PT on six occasions, BT on four occasions, INR on two occasions, and CT on one occasion, prolonging each one of them.

Valproate was the third most common drug causing a derangement in bleeding parameters. On six occasions it caused a fall in platelet count, and on three occasions it caused prolonged CT. Valproate was the only drug in our study that affected the platelet count.

Sertraline, fluoxetine, amitriptyline and haloperidol were the other drugs affecting various bleeding parameters. Looking further into our study reveals a female predominance of aberrations of bleeding parameters on psychotropics. 25% of the sample population had an aberration in one or more bleeding parameters, with prothrombin time and bleeding time the most affected parameters.

Discussion

Our study was a naturalistic study i.e. patients irrespective of their diagnosis were assessed. Our patients had an almost equal distribution among schizophrenia, major depressive disorder (MDD), bipolar mood disorder (BMD), and anxiety disorders. Our study thus was unique in this respect, as earlier studies conducted considered a single diagnosis or medication group, as in Halperin and Reber [10], Tham et al. [11], Demet et al. [12], and Tielens et al. [13], which all assessed only patients suffering from MDD.

Our study assessed the effect of 13 medications, distributed among antidepressants, antipsychotics and mood stabilizers. Among antidepressants, SSRIs were the most widely used with escitalopram being the most widely given, closely followed by paroxetine and sertraline. In antipsychotics, olanzapine was the most widely used, and valproate was the most widely used mood stabilizer in our study. This again was unique to our study as previous studies had assessed a single drug or a drug group, as in the studies by Tham et al. [11], Demet et al. [12], and Tielens et al. [13], which studied the effect of venlafaxine, mirtazapine and paroxetine respectively.

The dosages of the various medications used in our study were within the FDA approved dose range.

Our study further depicted a change in all five bleeding parameters (PT, INR, BT, CT and platelet count) over 30 days. Although the changes were statistically significant, none of the mean values went beyond the normal range. We further noted that the change was more pronounced from day 15 to day 30 than from day zero to day 15. However, the changes did not have any clinical manifestations, as was seen in studies by Dall et al. [14], Dalton et al. [15], Turner et al. [16], and Andrade et al. [17], where upper gastrointestinal (GI) bleed was seen with SSRIs.

Of 13 drugs used, seven caused an aberration of bleeding parameters in our study, causing derangement of at least one parameter in 25 out of the 100 patients.

Three drugs belonged to the class of SSRIs, the probable mechanism being impairment in the platelet hemostatic response by inhibiting serotonin uptake into platelets [18]. SSRIs also have broad antiplatelet effects by decreasing platelet binding affinity, inhibiting calcium mobilization, and reducing platelet secretion in response to collagen [19]. Other mechanisms leading to an increased bleeding diathesis are inhibition of nitric oxide synthase and serotonin's important role in hemostasis, mainly through an enhancing effect on adenosine diphosphate (ADP) and thrombin. SSRIs inhibit the platelet secretory response as well as platelet aggregation stimulated by ADP, collagen and thrombin [20]. It has been shown that long-term treatment with SSRIs upregulates the expression of glycogen synthase kinase 3β on platelets [21]. Further, low levels of fibrinogen and plasminogen activator inhibitor (PAP) are seen in patients treated with SSRIs [22], which could be another possible explanation of their role in abnormal hemostasis. Among the SSRIs, paroxetine affected the bleeding parameters the most, deranging all four parameters: PT, INR, BT, CT in two patients, followed by sertraline and fluoxetine. Escitalopram, although the most widely used SSRI in our study, did not lead to any derangement of bleeding parameters. The probable reason for this is the higher affinity of paroxetine towards serotonin transporter, as discussed by Meijer et al. in their study [23].

Amitriptyline showed aberration in PT and BT in only one patient, derangement being much lower compared to SSRIs which is in accordance with the study by Schaffer et al. Valproate was the drug responsible for a fall in platelet count in all the six patients who had deranged platelet count. Six patients out of 16 (37.5%) who were administered valproate had thrombocytopenia which is in accordance with the study by May and Sunder [24]. The mechanism of valproate-induced thrombocytopenia is increased disruption of platelets or formation of autoantibodies destroying platelets or by decreased production due to a direct toxic effect on bone marrow [25]. Laboratory studies have shown that valproate disrupts hematopoietic homeostasis by inhibiting erythroid differentiation and by activating the myelo-monocytic pathway [25]. The most common clinical manifestations are represented by prolonged bleeding time, or petechial bleeding.

Olanzapine was the only drug responsible for lowering PT, INR and CT. This might explain the prothrombotic properties of olanzapine and the risk associated with olanzapine

therapy like DVT and pulmonary thromboembolism [26, 27]. Although the exact mechanism for this aberration is not available in the literature, possible mechanisms include sedation, obesity, elevation of antiphospholipid antibodies, increased platelet activation and aggregation, hyperhomocysteinemia, and hyperprolactinemia [28]. Furthermore, recent research suggests increased overall coagulation potential and impaired overall fibrinolysis potential in patients with schizophrenia receiving long-term antipsychotics, which is substantiated by a statistically significant rise in overall hemostatic potential (OHP) [28].

Haloperidol caused elevation of CT in one patient, although studies such as those by Storrie et al., Ananth et al., Ekblom et al. and Swett et al. suggest that first generation antipsychotics such as haloperidol may cause a drop in platelet count on rare occasions [29–32]. We also observed that patients who were having an aberration in their bleeding parameters were predominantly female (17 females vs. 8 males), although the gender distribution was almost equal in our study population. This is in accordance with most of the studies conducted, although an explanation for this difference is not available and needs research.

Thus, to conclude, our study demonstrates that although statistical differences in bleeding parameters were seen in some of our patients, none of them had any clinical manifestations. So routine monitoring of bleeding parameters may not be warranted in patients on psychotropics. Nevertheless, pharmacokinetic interactions between SSRIs and anticoagulants are possible, both at the plasma protein binding level and at the CYP450 isoenzymes level, and therefore monitoring of the main coagulation parameters is recommended in patients who undergo serotoninergic antidepressant and anticoagulant treatment simultaneously.

Conclusions

None of the patients in our study had any statistically significant clinical manifestations of the changes in their bleeding parameters. Therefore it may be concluded that routine monitoring of bleeding parameters in patients receiving psychotropic medications is not warranted.

However, caution must be taken while prescribing drugs such as SSRIs, valproate and olanzapine in special population groups like the elderly, patients with known blood dyscrasias or peri-operative patients, as they caused significant changes in bleeding parameters in our study.

Limitations

Our study was conducted in a tertiary care center and hence the results cannot be generalized. The patients were followed up for only 30 days, meaning that any changes beyond that could not be assessed. Since the patients were on a single drug, the pattern of changes in cases of polypharmacy and drug-drug interaction could not be assessed.

Conflicts of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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