Patient Case Report

Pantoprazole-induced Thrombocytopenia: Unresponsive to Corticosteroid and Thrombocyte Concentrate Transfusion

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Abstract

Introduction: Pantoprazole is a proton pump inhibitor (PPI) class drug that is widely used in the treatment of SRMD (stress-related mucosal disease in critical ill patients. PPI are one class of drugs used commonly both for treatment and prophylactic therapy for stress ulcers in intensive care unit (ICU).

Case: We report a case of a 51-year old male who was referred to PKU Hospital. He was admitted to ICU with diagnosis of Hyperosmolar Hyperglymic State and bronchopneumonia. Thrombocytopenia was noted in admission. There was more than 70% decrease in platelet count after initiation of pantoprazole. Patient received Thrombocyte Concentrate (TC) transfusion and corticosteroid iv for several days, but only had minor increase in platelet count. The platelets recovered after stopping pantoprazole.

Discussion: In the present case report, another exposures to parenteral pantoprazole in a dose of 40 mg once daily re-produced the same adverse drug reaction. In comparison to lansoprazole, thrombocytopenia from pantoprazole is more severe that necessitate TC transfusion and corticosteroid trial. However, in the present case, TC transfusion and corticosteroid fail to escalate platelet count. This finding suggests probability of non-immune mechanism of pantoprazole-induced thrombocytopenia.

Conclusion: Pantoprazole may induce thrombocytopenia with new features that were immediately developed, resulting a decrease in platelet count >70%. The mechanism found in this case may be non-immune. Drug-induced thrombocytopenia is one of the rare complications that has to be kept in mind with the use of pantoprazole.

Keywords

pantoprazole, drug-induced thrombocytopenia, proton pump inhibitors, adverse drug reaction

Introduction

Pantoprazole is a proton pump inhibitor (PPI) class drug that is widely used in the treatment of gastric and duodenal ulcers, moderate-severe inflammation of the esophagus, symptoms of gastroesophageal reflux disease, acute gastrointestinal bleeding, and gastric acid hypersecretion disorders.[1] In critical ill patients, there is a risk of developing stress-related ulcers in the upper gastrointestinal tract, which can develop into acute upper gastrointestinal tract bleeding.[1] Several studies have recommended pharmacological therapy to reduce the incidence of upper gastrointestinal bleeding that can affect the clinical condition of the patient.[2] PPIs, especially pantoprazole, have good efficacy as stress ulcer prophylaxis.[3]

Pantoprazole is generally well tolerated, and the most commonly reported side effects include headache and mild gastrointestinal symptoms.[4,5] Rarely reported side effects consist of hematologic abnormalities including thrombocytopenia. The literature study shows that starting from 2005 to 2021, only 10 articles has been published as a case report or retrospective study related to pantoprazole. Drug-induced thrombocytopenia was defined as a decrease in platelet count below $100 \times 10^3/\mu L$ that resolved with discontinuation of the causative agent and no other cause was identified.[6] This article describes a case of

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Table 1. Medications Received During Hospitalization.

	Day								
Nama Obat/Dosis	PH	1	2	3	4	5	6	7	8
Continuous novorapid, iv	✓	✓	✓	✓	✓	✓	✓		
Paracetamol, 1g, iv, thrice daily	✓	✓	✓	✓	✓	✓	✓		
Ondansetron, 4 mg, iv	✓	✓	✓	✓					
Meropenem 1g, iv, thrice daily	✓								
Pantoprazole 40 mg, iv, once daily	✓	✓	✓	✓	✓	✓	✓	✓	
NaCl 3%	✓	✓	✓	✓	✓	✓	✓	✓	
Dobutamin	✓	✓	✓	✓	✓	✓	✓	✓	
NaCl .9%	✓	✓	✓						
Ceftazidim 2g, iv, twice daily		✓	✓	✓	✓	✓	✓	✓	
Mecobalamin iv, once daily				✓	✓	✓	✓	✓	
Lisinopril 10 mg, po, once daily	✓	✓	✓	✓	✓	✓	✓	✓	✓
Methyl prednisolon 62.5 mg, iv, twice daily		✓	✓	✓	32,5	32,5	32,5	32,5	
TC transfusion 5 bags				✓					

Abbreviation: PH, previous hospital.

drug-induced thrombocytopenia that may have been caused by taking pantoprazole.

Case

We present a case of 51-year old male patient admitted to intensive care unit for decreased consciousness and fever since 4 days ago. The doctor diagnosed the patient with Hyperosmolar Hyperglycemic State (HHS), sepsis, acute kidney injury, and thrombocytopenia. Past medication history was diabetes mellitus, and he routinely inject insulin subcutaneously, but the type and dose was unknown. The patient was referred from private hospital and has received intravenous fluid therapy of .9% NaCl, continuous rapid acting insulin infusion, 1 g of paracetamol infusion, ondansetron 4 mg iv injection, meropenem, pantoprazole 40 mg, 3% NaCl because the patient has hyponatremia, and dobutamine for his hypotension with tachycardia from the previous hospital.

On admission, his blood pressure was 126/80 mmHg, pulse was 122 bpm, and there was oral mucosa bleeding. His laboratory result at admission were as follows: random blood sugar 458 mg/dL, urea 194 mg/dL, serum creatinine 3.95 mg/dL, hemoglobin 10.9 g/dL, leukocytes 22.58 × 10^3/μL, and platelets 42 × 10^3/μL. On day 2 of hospitalization, his creatinine dropped to 1.5 mg/dL and urea decreased to 117 mg/dL, indicating Acute Kidney Injury was resolved. However, his platelet continued to drop until 18 ×10^3/μL. Double check of platelet count at the same day resulted 21 ×10^3/μL. Therefore, it was planned to give 250 mL of Thrombocyte Concentrate (TC) transfusion. Since the patient's condition was not stable, the transfusion was postponed to the next day. After transfusion, platelet count increased slightly to 29 × 10^3/μL.

Patients received .9% NaCl therapy, rapid acting insulin, ceftazidime 2 g/12 hours, pantoprazole 40 mg/24 hours, mecobalamin 500 μg/12 hours, lisinopril 5 mg, paracetamol infusion 1 gram/8 hours, and injection methylprednisolone 62.5 mg/12 hours to treat thrombocytopenia. His full list of medications was shown in Table 1. The dose of methylprednisolone was tapered down to 31.25 mg/12 hours since the effect on platelet were negative. On day 4, the platelets count slightly increased to 39 × 10^3/μL then to 40 × 10^3/μL on day 5. After analyzing the possibility of Drug-induce Thrombocytopenia (DIT), we decided to stop pantoprazole on day 5. 2 days later, the platelet count was increased to 100 × 10^3/μL. The next day patients was sent home.

Discussion

Several cases and retrospective study have been reported the incidence of thrombocytopenia due to the administration of pantoprazole since 2006. In the present case report, the patient developed thrombocytopenia after the first injection (immediately developed) in the previous hospital. This reaction was similar to previous report.[7] Platelet counts continued to drop until day 3 when we ran TC transfusion. There was slight increase in platelet count after transfusion as seen in Figure 1. This finding suggested no benefit of transfusion. Moreover, co-administration of methyl prednisolone also contributed slight improvement.

There was more than 70% decrease in platelet count in our case after initiation of pantoprazole. In comparison to other PPI,[8,9] pantoprazole resulted in more severe thrombocytopenia.[7,10] The severity level of this case was moderate, whereas the platelet count dropped to 18,000/mm^3 without the appearance of symptoms such as ecchymosis, hematuria, purpura, and petechiae. Since DIT is a diagnosis of exclusion, therefore, other causes of thrombocytopenia should be excluded before DIT was diagnosed. We ruled out the

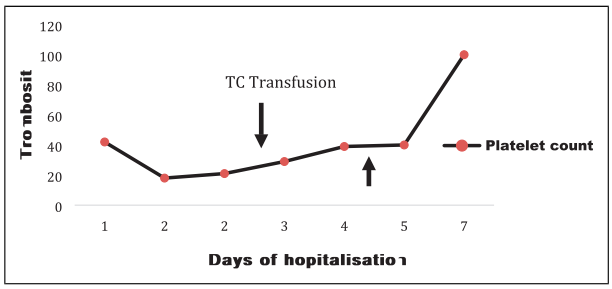

Figure 1. Trend of platelet count during hospital stay.

incidence of Idiopathic thrombocytopenic purpura (ITP) because no diagnosis of ITP was confirmed. Besides, thrombocytopenia was unresponsive to corticoteroid.

Another possibility that we have ruled out is dilution thrombocytopenia. The patient's condition was dehydrated due to his HSS in the days preceding the thrombocytopenia event. This finding excluded dilution thrombocytopenia.

We conduct causality analysis using Naranjo Scale and Liverpool algorithm to assess the suspicion of an unwanted drug reaction and the results were probable, Appendices 1 and 2. These results suggested that the manifestation of side effects or laboratory results changes after drug use, changes in laboratory data do not appear to be disease progression, and the response to clinical drug discontinuation is acceptable.

Summarizing previous study and reported pantoprazole-induced thrombocytopenia cases, the platelet started to drop after 3 days on pantoprazole,[5] whereas in previously reported case[7] and in the present case, the onset of thrombocytopenia appeared immediately. Another interesting finding from other case report was thrombocytopenia with PPIs might be an individual drug effect rather than a class effect, also there was no cross reactivity among PPI.[10]

Thrombocytopenia is defined as a decrease in the platelet count of $<150 \times 10^3/\mu L$. A sudden decrease in the number of platelets after the first dose indicates an acute destructive process. The mechanism of drug-induced thrombocytopenia is often poorly understood, and whether this is a PPI class effect.[4] However, the next case report by Kallam hypothesized that this adverse effect may be immune mediated.[10] There are 2 kinds of mechanism which are an immune or non-immune process or autoimmune mechanisms.[11,12] However, from the present case, the use of methyl prednisolone injection show no benefit. This finding highlights the possibility of non-immune mechanism for thrombocytopenia.[13] Besides, the addition of TC transfusion also resulted in minimal increase of platelet count. This finding may indicate direct destruction from offending agent.

Since the first report, thrombocytopenia has been reported more severe in nature. This is like every new drug features. The longer duration in the market, the more adverse drug reaction emerge.

To conclude, drug-induced thrombocytopenia is one of the rare complications that has to be kept in mind with the use of pantoprazole. Pantoprazole induced thrombocytopenia with new features that were immediately developed, resulting a decrease in platelet count >70%. Non-immune mechanism is suspected from present case.

Appendix 1

Table A1. Causality Assessment Using Naranjo S#.

Question	Yes	No	Do not know or not done	Score
Are there previous conclusive reports on this reaction?	+1	0	0	1
Did the adverse event appear after the suspected drug was given?	+2	−1	0	2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	1
Did the adverse reaction appear when the drug was readministered?	+2	−1	0	0
Are there alternative causes that could have caused the reaction?	−1	+2	0	2
Did the reaction reappear when a placebo was given?	−1	+1	0	0
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total score				**7**

Appendix 2

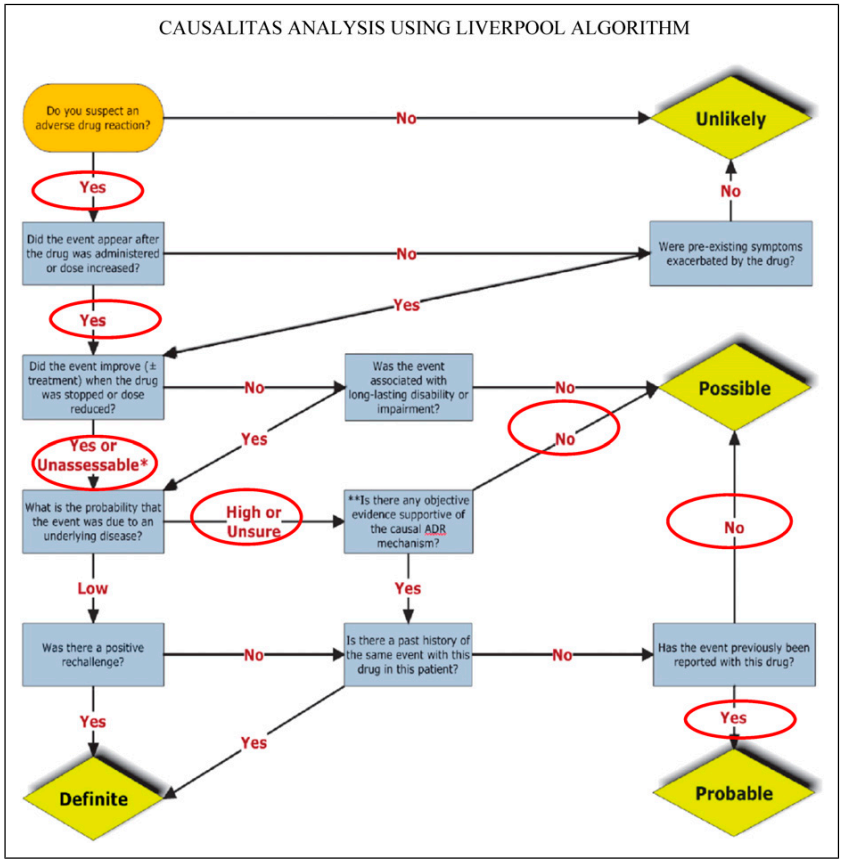

Figure A1. Causality assessment using Liverpool Algorithm.

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Declaration of Conflicting Interests

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References

1. Hoogerwerf WA, Pasricha PJ. Agents used for control of gastric acidity and treatment of peptic ulcers and gastroesophageal reflux disease. In: L Brunton, J Lazo, K Parker, eds. *Goodman and Gilman's the pharma- cological basis of therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001:1007-1009.
2. Alhazzani W, Alshahrani M, Moayyedi P, Jaeschke R. Stress ulcer prophylaxis in critically ill patients: review of the evidence. *Pol Arch Med Wewn*. 2012;122(3):107-114. doi:10.20452/pamw.1173.
3. Young PJ, Bagshaw SM, Andrew FB, The PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group, et al.. Effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among icu patients receiving invasive mechanical ventilation: The PEPTIC randomized clinical trial. *JAMA*. 2020;323(7):616-626. doi:10.1001/jama.2019.22190.
4. Watson TD, Stark JE, Vesta KS. Pantoprazole-induced thrombocytopenia. *Ann Pharmacother*. 2006;40(4):758-761. doi:10.1345/aph.1G384.

5. Binnetoğlu E, Akbal E, Şen H, et al. Pantoprazole-induced thrombocytopenia in patients with upper gastrointestinal bleeding. *Platelets*. 2015;26(1):10-12. doi:10.3109/09537104.2014.880108.
6. Dotan E, Katz R, Bratcher J, et al. The prevalence of pantoprazole associated thrombocytopenia in a community hospital. *Expet Opin Pharmacother*. 2007;8(13):2025-2028. doi:10.1517/14656566.8.13.2025.
7. Mukherjee S, Jana T, Pan JJ. Adverse effects of proton pump inhibitors on platelet count: a case report and review of the literature. *Case Rep Gastrointest Med* 2018;2018:5, 4294805. doi:10.1155/2018/4294805.
8. Zlabek JA, Anderson CG. Lansoprazole-induced thrombocytopenia. *Ann Pharmacother*. 2002;36:809-811.
9. Saad M, Mitwally H. Lansoprazole-induced thrombocytopenia in a critically Ill patient: A case report. *J Pharm Pract*. 2020;33(5):700-704.
10. Kallam A, Abhishek Singla A, Silberstein P. Proton pump induced thrombocytopenia: A case report and review of literature. *Platelets*. 2015;26(6):598-601. doi:10.3109/09537104.2014.953045.
11. Danese E, Montagnana M, Favaloro EJ, Lippi G. Drug-induced thrombocytopenia: mechanisms and laboratory diagnostics. *Semin Thromb Hemost*. 2020;46(3):264-274. doi:10.1055/s-0039-1697930.
12. George JN, Aster RH. Drug-induced thrombocytopenia: Pathogenesis, evaluation, and management. *Hematol Am Soc Hematol Educ Progr* 2009;(1):153-158.
13. Neunert C, Lim W, Crowther M, et al. The American society of hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117:4190-4207.