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Severe Thrombocytopenia with Oseltamivir Treatment for Viral Fever–A Case Study

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ABSTRACT: The possibility of an avian flu pandemic has spurred interest in preventive treatments with anti-virals such as oseltamivir. A previously conducted pharmacokinetic study of oseltamivir plus probenecid among healthy volunteers indicated a sudden decrease in the platelet count in few patients. In this study a 23-year-old woman who developed severe thrombocytopenia 2 days after starting oseltamivir treatment for Viral fever is described. She was receiving no other drug therapy at the time. Her platelet count decreased from 3.9 to 1.3 lakh cells/mm^3, although no clinically evident bleeding abnormalities were noted. The drug was discontinued. 2 days later, without any therapeutic intervention, her platelet count returned to normal. By using the Naranjo adverse drug reaction probability scale to assess the strength of the association between the drug and the adverse event, a score of 6 was derived, indicating that the association was probable. However, a review of the United States Food and Drug Administration's Adverse Event Reporting System database found 93 cases of thrombocytopenia and/or decreased platelet counts associated with oseltamivir. Clinicians should be aware that the use of oseltamivir has been reported to be associated with thrombocytopenia.
KEYWORDS: Thrombocytopenia, Oseltamivir, Viral fever.

I. INTRODUCTION:

Due to the possibility of an avian flu (Bird flu) pandemic has spurred interest in preventive treatments with anti-virals such as oseltamivir. Oseltamivir is generally indicated for treatment and post-exposure prophylaxis of influenza infection for adults and children. It is an antiviral drug that acts against neuraminidase, which is the targeted catalytic site to prevent virus replication. Oseltamivir is approved for use in the treatment of or prophylaxis against influenza virus A and B, including avian influenza.[1]

Oseltamivir shortens the duration of the usual influenza-related illness and reduces hospitalization if given within 48 hours after illness onset.[2] Oseltamivir treatment should be started immediately in any case in which viral infection is suspected. Although there is no documented benefit from any antiviral therapy initiated later in the course of illness, oseltamivir has been used regardless of the time of the illness for very sick patients, because neuraminidase inhibitors are the only potentially effective anti-influenza drugs.[3]

In this report, we present the case of a patient who developed severe thrombocytopenia after the initiation of oseltamivir treatment.We also analyzed the platelet counts to identify changes from baseline. We assessed causality of relationships between drugs and the adverse event by using the Naranjo adverse drug reaction probability scale.

II. 2.CASE PRESENTATION:

A 24 year old female patient who permitted and gave consent in writing this report, was bought to the emergency department with complaints of fever, headache and myalgia since two days and also had right side neck pain since a day. The patient had a history of vomiting since one day. She had no significant past medical history or hematologic disorder. The patient was not taking any prescription or over-the-counter drugs or herbal products.

On admission her physical examination was unremarkable as she was conscious and oriented. The patient was febrile with an elevated body temperature of 102◦F. Her platelet count on the day of admission was 3.9 lakh cells/mm^3. The patient was tested negative for Dengue NS1, Dengue IGG Antibodies, Dengue IMM Antibodies,

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Typidot-IGM and SARS-cov-2 (Covid-19). The patient was diagnosed with Viral fever and was given antiviral treatment.

NORMAL RANGE	
PLATELET COUNT = 1.5- 4.5 lakh cells /mm^3	
DAY	**PLATELET COUNT**
1	3.9 lakh cells /mm^3
2	1.47 lakh cells /mm^3
3	1.33 lakh cells /mm^3
4	0.97 lakh cells /mm^3
5	0.51 lakh cells /mm^3
6	0.96 lakh cells /mm^3
7	2.4 lakh cells /mm^3

Table 2.1.,Platelet count progression chart.

The patient was treated with Tab. Fluvir (Oseltamivir) – 75 mg twice daily. Her blood count after the initiation of the antiviral therapy revealed severe thrombocytopenia with a platelet count of 1.3 lakh cells/mm^3 (Normal range of Platelet is 15-45 x 10^3/mm^3). The subject's platelet counts decreased to 0.51 lakh cells/mm^3 on day 5 of the antiviral treatment. This confirmed severe thrombocytopenia. All other hematologic blood values were within their normal ranges. Her platelet count increased to 0.96 lakh cells/mm^3 by 48 hours and was within the normal ranges 3.2 lakh cells/mm^3 on Day 7after the cessation of the antiviral treatment (Tab.Fluvir – Oseltamivir). According to the Naranjo algorithm, a score of 7 was derived for the drug. A score of 5–8 is considered probably related to the drug under consideration.

III. DISCUSSION:

We report a case of severe, reversible thrombocytopenia during administration of oseltamivir. The platelet count of the patient was normal on admission but eventually decreased with the initiation of oseltamivir treatment. For this report, we conducted a thorough literature search. There were very few relevant articles.

There was study conducted that reported a case of thrombocytopenia during administration of oseltamivir and probenecid. This event was seen in only one study participant Since there was no evidence of significant thrombocytopenia in any other older subject, age itself was unlikely a major factor. No other effects on red or white bloods cell counts were seen.[5]The only relevant oseltamivir article other than the clinical trial study article was a case report of a child with avian influenza who developed thrombocytopenia while taking oseltamivir; however, the authors did not suggest oseltamivir as a potential cause.[6]

The only report of thrombocytopenia with probenecid was a case where probenecid was used concomitantly with methotrexate and was not considered a primary suspect as a cause for thrombocytopenia.[7]A proposed mechanism for probenecid- or oseltamivir-induced thrombocytopenia is not known. Probenecid is an inhibitor of organic anion transporter 1 and inhibits platelet aggregation by affecting platelet cytosolic calcium levels and blocking leukotriene C4 efflux.[8,9]

Oseltamivir inhibits the neuraminidase activity of influenza virus. Viral neuraminidase cleaves sialic acid residues on the cell surface to allow effective release of viral progeny during infection. Whether oseltamivir affects platelet surface sialic acid residue cleavage resulting in thrombocytopenia through rapid hepatocyte clearance of platelets is unknown.[10]The incidence of above reaction was assessed with the Adverse Drug Reaction Probability Scale - Naranjo causality ADR assessment scale.

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Table 3.2.,Naranjo causality ADR assessment scale

Question	Yes	No	Do Not Know	Score
1.Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	+1
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
	Total Score			**6**

Score	Interpretation of Scores
Total Score ≥9	**Definite**. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.
Total Score 5 to 8	**Probable**. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	**Possible**. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	**Doubtful**. The reaction was likely related to factors other than a drug.

By using the Naranjo adverse drug reaction probability scale to assess the strength of the association between the drug and the adverse event, a score of 6 was derived, indicating that the association was PROBALE - The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal

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but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

IV. CONCLUSION:

Oseltamivir is useful for influenza treatment and prophylaxis. However, practitioners should be aware of the possibility of thrombocytopenia with either oseltamivir drug alone or in combination. A continuous monitoring of platelet count is essential while administration of oseltamivir. Further studies are needed to clarify a potential mechanism.

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