

Oseltamivir induced sinus bradycardia: an area of potential concern**Karan B. Shah¹, Bhavesh S. Shah², Supriya D. Malhotra^{3*}, Pankaj R. Patel⁴**

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ABSTRACT

Oseltamivir was approved for the prevention and treatment of influenza in 1999 by the USFDA (US Food and Drug Administration). The use of Oseltamivir is increasing rapidly all over the world, especially after the 2009 “Swine Flu” pandemic. Less data is published as far as the cardiovascular side effects of Oseltamivir are concerned, but it could be associated with some serious cardiovascular side effects. This study presented a case series of 5 cases suspected to be suffering from seasonal influenza H1N1 (“Swine Flu”), who developed sinus bradycardia while they were on Oseltamivir therapy.

Keywords: Bradycardia, H1N1, Oseltamivir, Swine flu

INTRODUCTION

Oseltamivir, the first neuraminidase inhibitor available orally was approved in 1999 by the USFDA (US Food and Drug Administration) for the prevention and treatment of

influenza in adults.¹ It is also in the WHO (World Health Organization) list of essential medicines. The use of Oseltamivir has increased tremendously since the first pandemic of H1N1 influenza virus in 2009 (the “Swine Flu”) and has reached at its peak especially in India

because of the ease in the restrictions by DCGI (Drug Controller General of India) (change in category from ‘X’ to ‘H1’). Today, India is facing a major outbreak of the seasonal H1N1 influenza (“Swine flu”) with the total 22,186 diagnosed cases and around 1100 deaths till August 2017 according to the Central Health Ministry data.^{2,3} Other neuraminidase inhibitors approved for the treatment of Influenza by the USFDA are Zanamivir (via inhalational route) and Peramivir (via Intravenous route). Oseltamivir is the most commonly used drug for influenza due to its oral route of administration. The risk/benefit ratio of Oseltamivir is still unclear and many studies conducted in different parts of the world have raised questions regarding the safety of this antiviral agent.⁴ One of the major safety concerns of Oseltamivir use is its potential to cause cardiac rhythm abnormalities.⁵ Post marketing reports have also included abnormal cardiac rhythms as a side effect of Oseltamivir.⁶ Bradycardia as an adverse drug reaction of Oseltamivir was observed in animal studies as well as human trials. When we checked on VigiAccess™, 13 cases of bradycardia have been reported out of total 12141 ADRs of Oseltamivir (0.10%), and in eHealthMe™ Database by FDA, out of 14220 ADRs of Oseltamivir, 122 people (0.86%) had bradycardia.^{7,8} So, this is an underreported ADR. Keeping this background in mind here we report 5 cases of sinus bradycardia in the patients of suspected seasonal H1N1 influenza on Oseltamivir therapy.

CASE REPORT

Here we have reported 5 cases suspected to be suffering from seasonal influenza H1N1 (“Swine Flu”), who developed sinus bradycardia while they were on Oseltamivir therapy. For the sake of simplicity, we have extracted the common findings of all the cases and

described them collectively. As far as the individual data/parameters are concerned we have tabulated the same (Table 1).

All of the patients had similar chief complaints of sore throat, cough, cold, runny nose and 3 of them were having fever since 12-24 hours. All patients were put under observation for next 24 hours for their symptoms and oxygen saturation. None of them improved even after 24 hours and two of them showed relative fall in the oxygen saturation (checked using fingertip pulse oximeter). All of them were put under the B (i) category of seasonal H1N1 influenza (“Swine Flu”) as per the “ABC guidelines for Seasonal H1N1 influenza” provided by the Government of India.⁹ All the patients were started Oseltamivir Phosphate 75mg BD for 5 days as prescribed by their treating physician. Following are the parameters before and after the initiation of Oseltamivir treatment. The ECG findings are shown (Figure 1).

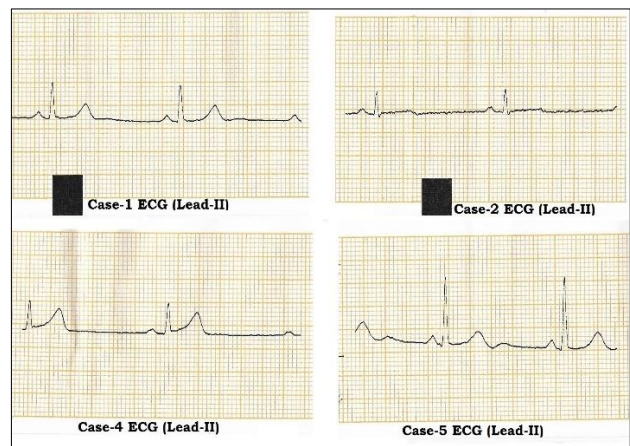


Figure 1: ECG readings.

Table 1: Individual case details.

Case no.	Age	Sex	Pulse* before starting the Oseltamivir therapy	Bradycardia observed after these many days of starting the drug	Pulse* at the time of bradycardia	Bradycardia resolved/ Pulse* returned to pre therapy levels after these many days of stopping the drug	Approx. Heart beats per minute as calculated by ECG reading (Large block method) (Figure 1)
1	39	M	70	3	50	4	50
2	42	F	110	4	59	6	50
3#	24	M	85	2	53	3	-NA-
4	35	M	76	2	55	4	48
5	35	F	72	2	57	3	57

*Measured using fingertip pulse oximeter M=Male, F=Female #ECG not available

From data presented in Table 1, it is evident that all the patients developed Sinus Bradycardia within 2-4 days (Mean=2.6 days) after starting the treatment with

Oseltamivir which resolved within 3-6 days (Mean=4 days) of stopping the treatment. All the above suspected

ADRs were reported to the nearest ADR Monitoring Centre and were uploaded to the Vigiflow™.

According to the WHO-UMC causality assessment scale, all these ADRs were categorized as Probable/Likely because of several reasons. None of the above patients had any history of comorbid conditions. All were otherwise healthy patients. The time relationship between the administration of a drug and development of the ADR explains the same. None of the above patients were taking any other medications which are known to cause bradycardia. In past also there were few reported cases of the similar ADR suspected to be caused by Oseltamivir administration (VigiFlow Report IDs: 2017-48185, 2017-48186, 2017-46579, 2017-48212, 2017-48199 for Case 1, Case 2, Case 3, Case 4 and Case 5 Respectively).

DISCUSSION

Scientific literature pertaining to occurrence of sinus bradycardia with Oseltamivir is scarce. Less data is published as far as the cardiovascular side effects of Oseltamivir are concerned, but it could be associated with some serious cardiovascular side effects. These side effects may range from arrhythmia, bradycardia, tachycardia, cardiac arrest, torsade de pointes to even myocardial infarction in some cases.⁷ Despite this physician are not aware of these side effects.

Although the bradycardia which we have reported were all sinus bradycardia and was not associated with any rhythm disturbances, it is important to note that in past there were few reports of extreme bradycardia leading to atrial standstill because of Oseltamivir.¹⁰ This becomes more important when the patient has pre-existing heart disease and/or is on any medication which produces bradycardia e.g. various cardiovascular medications (Beta blockers, Calcium Channel Blockers of Non-dihydropyridines). Concomitant administration of Oseltamivir with these drugs can lead to cardiac arrest and may require vigorous efforts to revive the patients like defibrillation.

The temporal relationship of this ADR can also be explained. Oseltamivir is converted into its active metabolite Oseltamivir carboxylate in GI tract and liver. Steady-state plasma concentrations of Oseltamivir carboxylate are achieved within 2-3 days of twice-daily administration. This active metabolite has a plasma half-life ($t_{1/2}$) of 6-10 hours. The bradycardia as an ADR was observed within 2-3 days of the beginning of the therapy which coincided with the steady state concentration of Oseltamivir in the body. Abatement of ADR was seen after 3-6 days coinciding with the time to elimination of the drug from the body.¹¹

According to a recent study done by Frommeyer et al, when whole-heart rabbit model was infused with a combination of acetylcholine and isoproterenol it resulted in a significant reduction of aAPD₉₀ (atrial action potential duration) and aERP (atrial effective refractory period)

leading to atrial fibrillation. Then, it was infused with Oseltamivir which resulted in increase in both aAPD and aERP leading to an increase of atrial post-repolarization refractoriness (aPRR). It also induced a significant increase of ventricular ERP. So, basically it slows the conduction of the heart and increases the time taken by the heart to complete one contraction (heart beat).¹²

CONCLUSION

Monitoring of pulse and heart rate in patients receiving Oseltamivir should also be an area of focus for the prescribing physician. In all the cases stated above the sinus bradycardia recovered uneventfully but this could assume dangerous proportions in patients with concomitant cardiac rhythm disturbances or patients taking medications known to cause bradycardia.

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