



Contents lists available at ScienceDirect

## International Journal of Infectious Diseases

journal homepage: [www.elsevier.com/locate/ijid](http://www.elsevier.com/locate/ijid)

## Letter to the Editor

## Suspected oseltamivir-induced bradycardia

Data from the ongoing influenza A(H1N1) pandemic have shown that early antiviral treatment is crucial to reduce morbidity and mortality.<sup>1</sup> The numbers likely to receive oseltamivir over future influenza seasons make it imperative to be aware of any oseltamivir-related severe adverse effects, given that the winter is by now long over. We report two patients with suspected oseltamivir-induced bradycardia.

A 39-year-old woman was admitted at 19 weeks of pregnancy for amnionitis confirmed by amniocentesis. Antibiotic treatment was initiated and termination of the pregnancy performed. The following evening, due to cough and suspected infiltrate on chest radiography, oseltamivir (75 mg twice daily) was started. Two days later, sinus bradycardia appeared, decreasing gradually to 40–45 bpm at rest (Figure 1). She was asymptomatic, with no additional dysrhythmias on electrocardiography and Holter monitoring two days later. Oseltamivir was discontinued for suspected oseltamivir-induced bradycardia; H1N1 PCR was subsequently negative.

An overweight 24-year-old woman, hypertensive and on fluoxetine for an eating disorder, was hospitalized with a presumptive diagnosis of H1N1 influenza, subsequently validated by PCR. Oseltamivir 75 mg twice daily was initiated, with roxithromycin and bronchodilator inhalations. The next day, the oseltamivir dose was doubled due to increasing dyspnea, then reduced one day later to the standard dose. The admission heart

rate was 79 bpm, decreasing to 45 bpm the following morning; she subsequently experienced repeated episodes of bradycardia, occasionally accompanied by dizziness or pre-syncope. Holter testing showed an average rate of 51 bpm, with multiple bradycardic episodes. Respiratory symptoms and fever had by then resolved; oseltamivir and fluoxetine were discontinued.

Of the patients' medications other than oseltamivir, none is known to be associated with bradycardia. Thyroid function, cardiac enzymes, and echocardiography were normal, and neither woman experienced hypoxia. While the Naranjo score<sup>2</sup> for both cases was 3 (possible adverse drug reaction), the appearance of bradycardia in conjunction with resolution of the admission diagnosis (amnionitis/influenza) in both women supports a drug reaction. Repeat cardiac Holter testing several weeks later was normal.

While both mild and severe adverse effects have been reported for oseltamivir,<sup>3,4</sup> we could find no published reports of oseltamivir-induced bradycardia. Roche prescribing information mentions cardiac arrhythmias in the post-marketing assessment, but gives no further information.<sup>5</sup> We consider it probable that oseltamivir can cause bradycardia, an adverse event with potentially severe consequences; however, the lack of previous reports would indicate that it is relatively rare. Awareness of the possibility of oseltamivir-induced bradycardia will improve diagnosis if such an adverse effect exists; further post-marketing studies focusing on cardiac dysrhythmias are needed to validate the possibility.

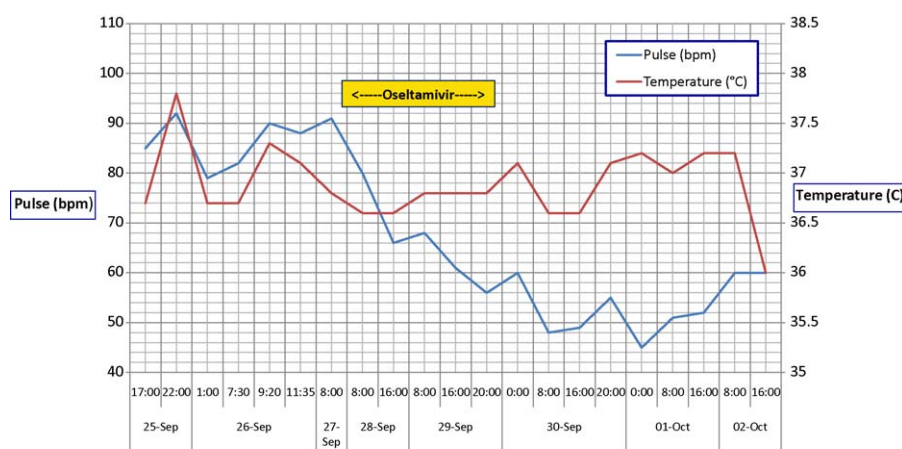


Figure 1. Temperature and pulse rate chart for patient 1.

*Conflict of interest:* No conflict of interest to declare.

## References

1. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al., for the 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* 2009;**361**(20):1935–44 [Epub 2009 Oct 8].
2. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–45.
3. Dutkowski R, Thakrar B, Froehlich E, Suter P, Oo C, Ward P. Safety and pharmacology of oseltamivir in clinical use. *Drug Saf* 2003;**26**:787–801.
4. Maxwell C. Tamiflu and neuropsychiatric disturbance in adolescents. *BMJ* 2007;**334**:1232–3.
5. Product information: Tamiflu® oseltamivir phosphate oral capsules, powder for oral suspension. Nutley, NJ: Roche Pharmaceuticals; 2008.

R. Karplus<sup>a,\*</sup>  
S. Sanset<sup>b</sup>  
R. Zaidenstein<sup>c</sup>  
D. Schneider<sup>d</sup>  
M. Berkovitch<sup>e</sup>

<sup>a</sup>Infectious Diseases Unit (Building 228), Assaf Harofeh Medical Center, 70300, Zerifin, Israel

<sup>b</sup>Internal Medicine Department B, Assaf Harofeh Medical Center, Zerifin, Israel

<sup>c</sup>Internal Medicine Department A, Assaf Harofeh Medical Center, Zerifin, Israel

<sup>d</sup>Department of Gynecology, Assaf Harofeh Medical Center, Zerifin, Israel

<sup>e</sup>Clinical Pharmacology and Toxicology Unit, Assaf Harofeh Medical Center, Zerifin, Israel

\*Corresponding author

E-mail address: [reba\\_vaca@hotmail.com](mailto:reba_vaca@hotmail.com)

(R. Karplus)

**Corresponding Editor:** William Cameron, Ottawa, Canada

10 February 2010

1 March 2010