

Unexpected outcome (positive or negative) including adverse drug reactions

Tongue swelling in association with oseltamivir (Tamiflu)

Tania Kalsi, Jennifer Stevenson, Paul Wade, Mark Kinirons

Guys & St Thomas' NHS Foundation Trust, London, UK

Correspondence to Dr Tania Kalsi, tania.kalsi@gstt.nhs.uk**Summary**

A 29-year-old lady presented with an increasingly swollen tongue 3 days after commencing oseltamivir (Tamiflu) for flu-like symptoms. Once identified as the cause, her symptoms rapidly improved with antihistamines and discontinuing the Tamiflu. The authors find only one other case in the literature reporting this very rare side effect.

BACKGROUND

The use of oseltamivir (Tamiflu) has become common in both primary and secondary care in the UK. As with any medication, side effects are not uncommon. Clinicians should be familiar with its side effects in order to appropriately consider the potential for serious adverse events. We report a rare case of tongue swelling associated with the use of Tamiflu.

CASE PRESENTATION

A 29-year-old lady presented to accident and emergency with a 1 day history of an increasingly swollen tongue. No other part of her face or body had any swelling. There was no history of any associated rash. She had not been exposed to any common allergens, for example new pets or peanuts, and this had never happened to her before. She had no abdominal pains, had no history of allergies or eczema and no family history of angioedema.

She had been commenced on Tamiflu 75 mg twice daily capsules 3 days prior to the swelling commencing, having attended her general practitioner with a sore throat, myalgia and fever. She had a mild frontal headache and photophobia. These symptoms had continued while on Tamiflu. She had a medical history of systemic lupus erythematosus (SLE) and pansinusitis. She had a previous admission in June 2010 with pneumococcal meningitis. Her regular medications included prednisolone, hydroxychloroquine and Adcal D3.

On examination she was febrile at 37.9°C, had a markedly swollen tongue and tender cervical lymphadenopathy. There was no rash and Kernig's sign was negative. The remainder of the clinical examination was unremarkable, in particular there was no wheeze and no stidor.

INVESTIGATIONS

White cell count and C-reactive protein levels were normal, erythrocyte sedimentation rate remained unchanged from previous. C3 level was 0.4 and C4 was 0.07 which was similar to previous measurements in lupus clinic. CT brain and lumbar puncture were entirely normal successfully excluding meningitis. IgE measured outside the acute event was normal.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis was an adverse reaction to Tamiflu (either allergic or an idiosyncratic drug reaction) and angioedema. Acquired angioedema has been observed in association with SLE.

TREATMENT

Her Tamiflu was discontinued and she was treated with antihistamines. Her symptoms and signs resolved within 24 h of treatment after which she was discharged home. The reaction was reported to the Medicines and Healthcare Products Regulatory Agency through the British National Formulary Yellow Card Scheme.

DISCUSSION

This case reports a rare case of tongue swelling in association with Tamiflu. The differential diagnosis was of course angioedema. Certainly the related drug, zanamivir, is known to be associated with angioedema in its side effect profile. She had no additional facial swelling with the tongue swelling to suggest this. Angioedema is typically not responsive to antihistamines. Her symptoms responded rapidly to antihistamines. Her C3 and C4 levels were low but similarly to her previous results taken for her SLE. If this reaction was angioedema, one might expect her C4 levels to drop further acutely. It did not. To estimate the probability of this being a true adverse drug reaction (ADR), the Naranjo algorithm was used and scored as a possible ADR.

We performed literature searches using conventional medical databases (EMBASE, MEDLINE, PubMed, AMED, BNI and CINAHL). Only one other case was found in the literature reporting this adverse effect of Tamiflu in New Zealand.¹ This case developed tongue swelling while on mechanical ventilation in the intensive care unit. The timing of the tongue swelling in this patient was similar to our patient, 3 days after commencing Tamiflu. This rare side effect has otherwise only been observed in post marketing surveillance.²⁻⁵ These were reported during clinical practice therefore it is difficult to establish a causal relationship.⁶ We found no evidence linking tongue swelling and

the influenza virus, nor any association with prednisolone, hydroxychloroquine or Adcal D3⁷⁻¹⁰.

Her reaction to Tamiflu is likely to be an idiosyncratic drug reaction. An IgE mediated allergic reactions (type 1 hypersensitivity) is also possible. However, her IgE levels were normal and she did not have a history of atopy. The rarity of this reaction to Tamiflu would also make this less likely but not impossible.

Idiosyncratic drug reactions are unpredictable¹¹ and are not completely understood. The reactions are thought to probably be an immune-mediated reaction to metabolites. There are different hypotheses to how these reactions occur, but one hypothesis is unlikely to explain all reactions as the type of reaction can vary immensely for different drugs.¹² By nature, these reactions occur rarely, thus making them difficult to study.

This patient also has SLE, an autoimmune disorder with immune complex formation (type 3 hypersensitivity reaction). C3 and C4 levels are typically depressed in active SLE due to consumption by immune complex induced inflammation, as they were in this case. There are similarities between the pathogenesis of SLE and the hypothesised mechanism involved in idiosyncratic drug reactions.

She was also already on corticosteroids for her SLE. By its immunosuppressive properties, this may have dampened down both an idiosyncratic drug reaction or an IgE mediated reaction, making her presentation less florid than it might have been.

Learning points

- ▶ Be alert to rarer potentially serious side effects of commonly used drugs such as Tamiflu.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Scott A**, More R, Freebairn RC. Tongue swelling complicating management of a ventilated patient with acute respiratory distress syndrome secondary to novel influenza A (H1N1). *Anaesth Intensive Care* 2010;**38**:370–2.
2. Summary of Product Characteristics. Tamiflu 75mg capsules, Roche Products Limited. Date of revision of text 26 Nov 2010. <http://www.medicines.org.uk/EMC/medicine/10446/SPC/Tamiflu+75mg+hard+capsule/> (accessed on 11 Jan 2011).
3. Micromedex (Drugdex). <http://www.thomsonhc.com> (accessed on 11 Jan 2011).
4. AHFS Drug Information <http://www.medicinescomplete.com> (accessed on 11 Jan 2011).
5. **Tullu MS**. Oseltamivir. *J Postgrad Med* 2009;**55**:225–30.
6. Drug Safety Information: Tamiflu (oseltamivir phosphate) capsules and for oral suspension, US Food & Drug Administration (FDA), Jan 2008. <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM147992.pdf> (accessed on 29th May 2011).
7. Summary of Product Characteristics. Prednisolone 5mg tablets, Actavis UK Ltd., Date of revision of text 17 Jan 2011. <http://www.medicines.org.uk/EMC/medicine/24128/SPC/Prednisolone+5mg+Tablets/> (accessed on 27 Jan 2011).
8. Summary of Product Characteristics. Plaquenil tablets, Sanofi-Aventis, Date of revision of text 17 Aug 2010. <http://www.medicines.org.uk/EMC/medicine/6977/SPC/Plaquenil+Tablets/> (accessed on 27 Jan 2011).
9. Summary of Product Characteristics. Adcal D3 chewable tablets, ProStrakan, Date of revision of text 10 Sept 2009. <http://www.medicines.org.uk/EMC/medicine/5336/SPC/Adcal+D3+chewable+tablets/> (accessed on 27 Jan 2011).
10. Aronson JK, Editor. *Meylers Side Effects of Drugs, The International Encyclopedia of Adverse Drug Reactions and Interactions*, 15th edition. Oxford, Elsevier, 2006.
11. **Knowles SR**, Uetrecht J, Shear NH. Idiosyncratic drug reactions: the reactive metabolite syndromes. *Lancet* 2000;**356**:1587–91.
12. **Zhang X**, Liu F, Chen X, *et al*. Involvement of the immune system in idiosyncratic drug reactions. *Drug Metab Pharmacokinet* 2011;**26**:47–59.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Kalsi T, Stevenson J, Wade P, Kinirons M. Tongue swelling in association with oseltamivir (Tamiflu). *BMJ Case Reports* 2011; 10.1136/bcr.06.2011.4396, date of publication

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow