Does warfarin interact with oseltamivir or zanamivir?

Background
During previous Swine Influenza (influenza A H1N1v) pandemics, a number of cases have been seen of a significantly increased International Normalised Ratio (INR) in people taking warfarin whilst they have been treated with oseltamivir. This has raised the question of whether there is a drug interaction between oseltamivir and warfarin.

Answer
Manufacturers’ information (1,2) and the standard drug interactions texts (3,4) do not highlight any risk of a drug interaction between warfarin and oseltamivir or zanamivir.

A cross-over study in 20 volunteers taking warfarin (INR 2-3.5) who were given oseltamivir 75mg twice daily for 4.5 days demonstrated no significant changes in INR or Factor VIIa compared to placebo (5). It was concluded that oseltamivir had little or no effect on pharmacokinetics or pharmacodynamics of warfarin.

A retrospective review of patients on anticoagulation therapy who took oseltamivir identified 15 patients who were tested for international normalized ration (INR) within 10 days of starting oseltamivir therapy (6). These patients had previously stable INR values. Seven patients had an increase in INR levels and eight patients remained stable. In the seven patients affected, the mean (SD) INR value was 2.08 (0.46) prior to the administration of oseltamivir and 5.15 (2.00) after a mean of 5.7 days after their first dose of oseltamivir. Bleeding events (e.g. blood-tinged sputum and bloody ascites) occurred in three of the seven patients.

An observational retrospective cohort study looked at Medicare beneficiaries who received warfarin for at least one month prior to a prescription for oseltamivir, ampicillin, trimethoprim-sulfamethoxazole (TMS), or an angiotensin converting enzyme (ACE) inhibitor (7). New bleeding events (gastrointestinal hemorrhage, epistaxis, hematuria, and intracranial bleeding) occurring within 14 days of a new prescription for the one of the above medicines were identified. Using ACE inhibitors as the reference, adjusted odds ratios (OR) and 95% confidence limits for any bleeding events within 14 days were

- Oseltamivir 1.20 (0.94, 1.50),
- Ampicillin 1.43 (1.11, 1.82),
- TMS 2.67 (2.46, 2.89),

Bleeding with oseltamivir and warfarin was not significantly increased.

Warfarin is susceptible to drug interactions via the following mechanisms (8)

- an effect on the absorption of warfarin
- the inhibition of intestinal bacterial production and absorption of vitamin K2
- the inhibition of the absorption of vitamin K1 present in food
- an alteration of the plasma protein binding of warfarin
- an alteration of the metabolism of warfarin by liver microsomes

It does not seem likely that either zanamivir or oseltamivir would interact with warfarin by one of these mechanisms. They are protein bound to only a relatively small extent and they are neither substrates, inducers nor inhibitors of cytochrome P450 enzymes (1,2,9)
One of the key clinical features of the H1N1 virus is that it causes a sudden fever (a high body temperature of 38°C/100.4°F or above) (10) It is known that acute febrile illness can lead to an increase in the effects of warfarin. This is thought to be due to an increased catabolism of clotting factors (11,12).

In 2006, the Canadian Adverse Drug Reactions Newsletter reported that 19 cases of increased INR in patients taking oseltamivir concurrently with warfarin were received between 1999 and 2005. The report (13) includes the comment that “Causality assessment of these cases is difficult because some of the reports presented conflicting or insufficient clinical information, and numerous factors (e.g., diet, medical conditions, fever) are known to influence a patient’s response to anticoagulants”. It goes on to discuss the low potential for oseltamivir to interact with warfarin by currently understood mechanisms.

The MHRA commented on this issue in February 2010 (14)

**Possible Drug Interaction between Tamiflu and Warfarin**

We continue to keep under review reports suggestive of a possible drug interaction between Tamiflu and warfarin (a drug used to prevent blood clotting) resulting in prolonged blood clotting time. Blood clotting control can be affected by flu and associated symptoms (e.g. decreased appetite and anorexia). Therefore it is very difficult to establish whether these cases represent a true drug interaction between Tamiflu and warfarin or whether blood clotting control in these patients may have been affected by underlying infection and associated symptoms.

Other data from clinical trials conducted by the Marketing Authorisation holder do not support the existence of an interaction between Tamiflu and warfarin. Currently there is no strong evidence of an interaction between the two drugs. Patients should continue to take Tamiflu and warfarin as advised by their healthcare provider. All reports of a possible interaction with warfarin remain under close review by the MHRA.

**Summary**

- There is no evidence of an interaction between warfarin and zanamivir
- There are conflicting reports of an increased bleeding risk in people taking oseltamivir and warfarin from spontaneous reporting systems and observational, retrospective studies.
- Whilst reports exist of increases in the INR of people taking warfarin and oseltamivir, the mechanism for a possible interaction has not been proposed.
- Whilst a specific interaction between warfarin and oseltamivir cannot be ruled out, it may be that the fever associated with swine flu is a more likely cause or contributory factor in these cases of raised INRs in people on warfarin.
- Further well designed prospective studies and genetic evaluations are needed to determine the exact nature of the interaction between warfarin and oseltamivir
- Until then, caution is advised if these agents are co-prescribed and more frequent monitoring of INR is probably justified.

**Limitations**

There are a number of other potentially interacting medicines that may be co-prescribed for people with swine flu (e.g. antibiotics) and a number of co-morbidities that may be aggravated and alter the pharmacokinetics and pharmacodynamics of warfarin (e.g. heart failure). These other potential contributory factors have not been reviewed here.

**References**


Available through NICE Evidence Search at [www.evidence.nhs.uk](http://www.evidence.nhs.uk)
24/7/2013
7. Roccoosi JA et al Hemorrhage following concurrent use of warfarin and oseltamivir by medi care beneficiaries. Pharmacoeconomics Drug Safety 2011;20:S147

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Search strategy
- Medline and Embase 24/7/2013
  1 EMBASE OSELTAMIVIR/
  2 EMBASE ZANAMIVIR/
  3 EMBASE WARFARIN/
  4 EMBASE 1 OR 2
  5 EMBASE 3 AND 4
  6 MEDLINE OSELTAMIVIR/
  7 MEDLINE ZANAMIVIR/
  8 MEDLINE WARFARIN/
9 MEDLINE 6 OR 7
10 MEDLINE 8 AND 9

- In-house database/ resources – previous enquiries
- Drugdex accessed 24/7/2013
  - “Oseltamivir”
  - “Zanamivir”
- Clinical experts
  - Anticoagulant Pharmacist University Hospitals Bristol