1.1. Oseltamivir and coumarin potentiation

Introduction

Oseltamivir (Tamfilu®) is a neuraminidase inhibitor indicated for use in early phases of influenza illness or for prophylactic use in this disease [1]. Oseltamivir is a pro-drug which eventually exerts its clinical effect by selective inhibition of neuraminidase which is essential for influenza virus replication. Given recent recommendations for oseltamivir use in H1N1 novel type I influenza a marked increase in its use can be expected in novel outbreaks of this infection.

Acenocoumarol and phenprocoumon (Marcoumar®) are coumarin derivates registered for *prophylactic use to reduce thromboembolic events*. Both drugs act as vitamin-K antagonists (VKA), leading to inhibition of coagulation factor II, VII, IX and X synthesis [2,3]. VKAs have a narrow therapeutic range and are substrate of many drug interactions. Low concentrations lead to insufficient thromboembolic risk reduction whereas high serum levels may result in life-threatening bleeding. In 2008 approximately 350,000 patients used acenocoumarol or phenprocoumon in the Netherlands [4]. Internationally, warfarin is more commonly used.

In this report, two cases with significant increases in international normalised ratio (INR) in patients using oseltamivir for prophylaxis are presented. Furthermore an overview of reports in the Eudravigilance and WHO-UMC databases will be provided.

Reports

On September 15, 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports of marked increases in INR.

Report A, presented by a pharmacist, concerns a 54-year-old female who used phenprocoumon for an unspecified indication. Concomitantly used medication consisted of levothyroxine, inhaled salmeterole and fluticasone, vitamin B12, calcium, Vitamin D3 and vitamin B12. Days after start of oseltamivir for prophylactic use, INR rose from 3.5 to 14.0. Withdrawal led to recovery. No information on vitamin K administration or phenprocoumon dose adjustment was provided.

The patient in case B, reported by a hospital pharmacist, is an 82-year-old female with atrial fibrillation and a suspected M. Parkinson. No signs of an active infection were present. Acenocoumarol was used over a year leading to stable anticoagulation. No changes in drug use were performed over an unspecified prolonged period. Three days after oseltamivir use for influenza prophylaxis, INR rose to over 15. Withdrawal of acenocoumarol and vitamin K administration led to recovery. No information of duration of oseltamivir use was provided. Co-medication consisted of spironolactone, digoxin, furosemide, levodopa/carbidopa, folic acid and silver sulfadiazine for topical use.

Table 1. Cases of possible coumarin interactions associated with oseltamivir use reported to Lareb.

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 42969 F, 54 years	oseltamivir prophylaxis phenprocoumon atrial fibrillation	fluticasone fluticasone/ salmeterole hydrochloro-thiazide hydrocobalamin levothyroxine	coagulation time increased (INR 14 from 3.5 before oseltamivir start)	days, withdrawn, no information on phenprocouomon dose adjustment or vitamin K administration recovered
B, 56482 F, 82 years	oseltamivir prophylaxis acenocoumarol atrial fibrillation	spironolactone, levodopa/ carbidopa digoxin furosemide lactulose folic acid dermal silver sulfadiazine	INR increased to >15 in stable patient	days, one year of coumarin use vitamin K administration, dose adjustment no indications for an active infection, no recent modifications in concomitant medication.

Other sources of information

SmPC

The possibility of oseltamivir-coumarin interactions is not addressed in the SmPCs of the products involved [1-3].

Literature

To the best of our knowledge, no case reports or further information is published in peer-reviewed medical journals. However both the Canadian (2006) and British (September 2009) regulatory agencies have issued signals addressing the possibility of coumarin interactions associated with use of oseltamivir [5,6]. Neither of these two reports claim to be conclusive, because of lack of mechanisms known to cause oseltamivir coumarine interactions and potential reporting bias.

Databases

Given the limited number of reports in the database of the Netherlands Pharmacovigilance Centre Lareb, disproportionality could not be assessed.

The database of the World Health Organization (WHO) contained 37 reports of increased PT or INR associated with oseltamivir use (ROR 5.8). A decreased anticoagulatory effect after oseltamivir use was reported four times.

On the 15th of September 2009, the Eudravigilance database contained 42 reports of increased PT or INRs, all rated serious. (Proportionate risk ratio 5.2, CI= 3.8-7.1). No cases of decrease of coumarin effects were reported. Ten cases were poorly documented, lacking essential clinical information and these cases will not be taken into account. Of the remaining 32 better documented cases, clinical significance was the most common reason for rating the reports as serious cases. Decease of patient and disability were both reported once. Life threatening aspects were indicated four times, hospital admission or prolongation of a stay in hospital were reported three times. Reactions occurred both in prophylactic setting (n=13) and therapeutic use (n=13). In six reports no information on indication was provided. Eleven cases of significant increases (INR>6 occurred in both groups), were reported. In an additional three cases INR increased to just below six. In one case, no INR was specified. However in this report a fourfold increase was mentioned.
In Eudravigilance, eleven reports concerned minor increases (INR increase less than two). Information on co medication is limited. Twenty-one patients were aged more than eighty years.

Mechanism
The mechanism for coumarin potentiation by oseltamivir is unclear. No effects of oseltamivir on the Cytochrome P-450 enzyme system, which could explain effects on coumarin metabolism, are known [8]. Excretion occurs predominantly renal in all drugs involved, although to a different extent.

Discussion and conclusion

This signal is based on two cases presented to the Netherland's Pharmacovigilance Centre Lareb of marked INR increases, leading to a substantial risk for potentially life-threatening bleeding. Internationally 42 cases were presented to the Eudravigilance, while the WHO-UMC database contains 37 reports. In both databases these numbers lead to a marked disproportionality. Signals concerning this association were issued by the Canadian and British regulatory agencies.

Although the number of Dutch reports is limited, the reports are remarkable because the reaction occurred in prophylactic setting and because of the clinical significance of the reported INR increases.

The number of reports in the international databases, its disproportionality and especially the thirteen cases that occurred in a prophylactic setting may support an association between oseltamivir use and coumarine potentiation. However causality assessment on these reports is hampered by the following factors leaving significant space for biases affecting the association of this report. First, it must be noticed that the international cases, concern an older population, 21 patients were older than 80 years at the time of INR increases. Unfortunately, no information was provided on anticoagulatory history or previous INR values.
Furthermore, information on concomitant medication is limited and not always in line with reported co morbidity. Ciprofloxacin, for which cases of coumarine potentiation are known [7], was used by one patient (INR increased to 4.8). Besides effects of this drug, also the infection for which it was used could have been causative for the increased INR.
With respect to the Canadian signal , it must be noticed that a significant number of the Canadian reports (eleven of a total nineteen reports) originated from a single source.

However, given the cases presented in this quarterly report and the issued signals from British and Canadian regulatory agencies, an interaction cannot be excluded and attention for the possibility of an oseltamivir-induced coumarin potentiation is especially warranted in the present setting of expected increases in oseltamivir use.

References

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This signal has been raised on October 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).