1.1. Omeprazole and coumarine interactions

Introduction

Omeprazole (Losec®) is a proton pump inhibitor (PPI) which has been registered in the Netherlands since November 1988. It is indicated for use in *gastroduodenal ulcerative disease*, *acid relate dyspepsia, reflux-oesophagitis or reflux symptoms and in Zollinger-Ellison's syndrome* [1]. Furthermore omeprazole is used as prophylactic treatment in people at risk for drug related erosive or ulcerative gastric disorders. With 1,025,000 users in 2007 omeprazole is the most frequently used PPI [1]. Among its most common adverse reaction are headache and gastro-intestinal symptoms [2].
In the Netherlands both acenocoumarol and phenprocoumon (Marcoumar®) are coumarine 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. VKAs have a narrow therapeutic range. 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. Internationally, warfarin is more commonly used. Differences in these three preparations are predominantly limited to pharmokinetic properties. As warfarin, acenocoumarol and phenprocoumon are racemates.
No information on effects of omeprazole on coumarine treatment is mentioned in the product information texts of the brand preparations involved [1,3,4]. In SmPCs of some generic preparations the possibility of coumarine interactions is addressed, however only addressing the possibility of interaction with warfarin, a drug very rarely used in the Netherlands. Coumarin interactions are addressed in the Dutch SmPC for esomeprazole [5].
This report describes possible coumarine potentiating effects associated with omeprazole use.

Reports

Until April 1st 2009 the Netherlands' Pharmacovigilance Centre Lareb received nine reports of potentiation of coumarine-induced coagulation effects associated with use of omeprazole (table 1). Eight cases were reported by physicians from thrombosis services. In four reports INR increase was such that bleeding risks may have posed a real threat with reported INRs above six. Increases in INR occurred predominantly within days after onset of PPI therapy, with a maximum of eleven days. No cases that led to lowering of INR and upward adjustment of coumarin treatment after start of omeprazole treatment were reported. Lareb received seven cases of potentiation of VKA anticoagulatory effect after start of esomeprazole. Cases of coumarin potentiation by other PPIs have not been reported.

Table 1. Reports of possible interaction of omeprazole and a coumarine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction Maximum INR	Time to onset, Action with drug outcome
A 78206 F, 73 Fed. Dutch Thromb. Services	acenocoumarol atrial fibrillation, omeprazole capsule 20mg shoulder pain	ibuprofen 400mg	drug interaction potentiation, INR increased INR >9.0	1 week discontinued recovered

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction Maximum INR	Time to onset, Action with drug outcome
B 70891 M, 56 Fed. Dutch Thromb. Services	acenocoumarol coronary artery disorder, omeprazole tablet 10mg	pravastatin 10mg gemfibrozil 600mg bisoprolol 5mg	drug interaction potentiation, INR increased INR 8.5	1 week discontinued recovered
C 82911 M, 72 general practitioner	acenocoumarol paroxysmal atrial fibrillation, omeprazole capsule 40mg gastroesophageal reflux	valsartan 80mg digoxin 0,25mg flecainide 200mg psyllium	drug interaction potentiation, blistering of mouth, haematoma, INR increased INR 7.3	5 days discontinued recovered
D 78208 F, 63 Fed. Dutch Thromb. Services	acenocoumarol atrial fibrillation, omeprazole capsule 20mg	metformin non specified insulin diclofenac 50mg	drug interaction potentiation, INR increased INR 7.1	5 day no change unknown
E 73971 F, 79 Fed. Dutch Thromb. Services	phenprocoumon vascular disorder, omeprazole tablet 10mg	nebivolol 5mg, isosorbide mononitrate 10mg digoxin 0,125mg triamterene 50mg captopril 12,5mg bumetanide 1mg	drug interaction potentiation, INR increased INR 5.2	1 day unknown not yet recovered
F 73970 M, 57 Fed. Dutch Thromb. Services	acenocoumarol atrial fibrillation, futicasone 50mcg omeprazole tablet 10mg	perindopril 2mg amlodipine 5mg	drug interaction potentiation, INR increased INR 5.1	1 day unknown unknown
G 78207 F, 54 Fed. Dutch Thromb. Services	phenprocoumon atherosclerosis of arteries of the extremities, omeprazole capsule 20mg	-	drug interaction potentiation, INR increased INR 5.0	11 days no change recovered
H 73972 M, 82 Fed. Dutch Thromb. Services	acenocoumarol deep venous thrombosis femoral, omeprazole tablet 10mg	-	drug interaction potentiation, INR increased INR 5.0	1 day unknown recovered

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction Maximum INR	Time to onset, Action with drug outcome
I 73973 M, 60 Fed. Dutch Thromb. Services	acenocoumarol coronary artery bypass, omeprazole tablet 10mg not specified glimerpiride not specified	metoprolol retard 47,5mg metformin 500m spironolactol 25mg ramipril 2,5mg furosemide 40mg retardor 10mg, mono cedocard 25mg	drug interaction potentiation, INR increased INR 4.8	1 day no change unknown

Other Sources

Literature

Information on omeprazole interactions with acenocoumarol or phenprocoumon is limited. Enderle, Mueller and Grass present two cases of potentiation of phenprocoumon induced by omeprazole [6], whereas Garcia *et al* present one case of acenocoumarol potentiation by omeprazole use [7]. Given its wider use internationally, more information on warfarin reactions is present. In several review articles [8-10], guidelines [11] and in the FDA drug information [12] it is warned to use omeprazole with caution in people using warfarin.
In two studies, the effect of omeprazole on anticoagulatory effects have been studied. The first, a retrospective observational database study, compared INRs in 118 acenocoumarol using patients, five to seven days, after start of omeprazole. Omeprazole users were compared with subjects that did not use concomitant therapy [13]. The second study concerns a small placebo-controlled trial (n=8) of three days duration [14]. Both studies concluded that omeprazole has no effect on coumarine anticoagulatory therapy.

Databases

The nine cases of INR increase for omeprazole result in disproportionality in the database of the Netherlands Pharmacovigilance Centre Lareb, Reporting Odds Ratio (ROR) 8.2, 95% confidence interval 4.1 - 16.3).

Eudravigilance database

On April 15 the Eudravigilance database contained 32 reports of increases in INR in omeprazole users. The reaction was rated serious in 31 cases. Sixteen male patients were involved and fifteen female patients. Sex was not specified in one case. Age ranged from 29 to 91 years. Reportedly six reactions led to decease, seven to life threatening symptoms. Hospitalisation was required in fifteen cases, in no reports disability was reported.

WHO:
The WHO Collaborating Centre database contained eighteen reports of omeprazole-associated INR increases.

Mechanism

Omeprazole has CYP 2C19 inhibitory effects, progressing in the first week of use and more limited effects on other CYP systems (CYP 2C9 and CYP3A4). By the effect on CYP2C19, it may slow the metabolism of the R-enantiomer of acenocoumarol, which is the active component of this drug due to its longer half time, compared to the very short half time of the S-enantiomer. Especially in poor CYP 2C19 metabolisers, using acenocoumarol this may lead to increases of acenocoumarol plasma values and increases in INR.
This mechanism does not explain INR increases in phenprocoumon and warfarin users. In these two drugs, half-times differ less between both enantiomers than in acenocoumarol. Subsequently, in phenprocoumon and warfarin, the more potent S-enantiomere acts as most effective component. The S-enantiomeres of coumarines are metabolised by CYP2C9, which is inhibited to a lesser degree than CYP2C19 by omeprazole. One of the mechanisms postulated is competition between omeprazole and phenprocoumon for CYP 2C9 binding sites in CYP2C19 deficient individuals [6].
Effects of omeprazole on action of coumarins through other systems, like VKORC1, cannot be excluded. However these are not supported by findings published in literature [15].

Discussion

The potentiating effect of omeprazole on acenocoumarol and phenprocoumon is demonstrated in nine generally well documented cases. Furthermore this association is supported by known effects of esomeprazole on VKA anticoagulation. Since maintaining a strict control of vitamin K-inhibition is vital, both reports of potentiation and inhibition of coumarines are clinically highly relevant. Through coumarine monitoring programs, patients' coumarine use is strictly regulated and reports of INR lowering might be expected to be reported. The absence of these reports may be considered as a support for the association described in this report. In all reports the PPI was added to the coumarin, which excludes instability of anticoagulation in the initial phase of coumarin treatment. In literature, two studies are presented in which evidence for coumarine potentiating effects of omeprazole is lacking [13,14].
Compared to the use of VKAs and omeprazole, the number of reports is relatively small, fitting in polymorphism affecting only a minor part of the general population.
In two studies, it was concluded that omeprazole has no effects on coumarine action. However these studies either had a short duration, or were limited in size. This may hamper detection of averse effects of omeprazole in subgroups of patients with impaired metabolism due to CYP polymorphisms.

Conclusion

Lareb received nine reports of increases in INR after start of omeprazole, possibly related to CY2C19 interaction. In almost half of the cases involved serious increases of coagulability (INR greater than six). The possibility of this interaction should be mentioned in sections 4.4., 4.5 and 4.8 of the product information of omeprazole, esomeprazole, acenocoumarol and phenprocoumon.

References

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This signal has been raised on July 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).