

UKMi Q&A 66.4

Is there an interaction between warfarin and proton pump inhibitors?

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Background

Warfarin is the anticoagulant of choice in the UK for a number of conditions including prophylaxis of deep vein thrombosis (DVT), treatment of DVT and pulmonary embolism, atrial fibrillation, cardioversion and dilated cardiomyopathy (1). Patients taking warfarin are monitored regularly to check prothrombin times and INRs (international normalised ratio).

Warfarin is a mixture of 2 active isomers – the R-isomer and the S-isomer. The S-isomer is more potent. The R- and S-isomers are both metabolised in the liver. The S-isomer is metabolised more rapidly than the R-isomer, mainly by the cytochrome P450 isoenzyme CYP2C9. The R-isomer is metabolised mainly by CYP1A2 and partly by CYP3A4 and CYP2C19 (2, 3, 4, 5). Therefore, concomitant use of other drugs that are also metabolised by the liver or have an effect on the liver, may need careful monitoring.

There are 5 proton pump inhibitors (PPIs) available in the UK – esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole (1). These are all metabolised by the liver by CYP2C19 and CYP3A4 so may affect the activity of warfarin (6-37).

Answer

Esomeprazole

Esomeprazole is metabolised by the liver enzymes CYP2C19 and CYP3A4. The Summaries of Product Characteristics (SPC) for esomeprazole preparations, state that concomitant administration of 40mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment (6-9, 38).

In practice, there is no reason for avoiding concurrent use of esomeprazole with warfarin although monitoring is recommended when initiating, modifying or ending concomitant treatment (4, 6-9, 39).

Lansoprazole

The SPCs for lansoprazole preparations indicate that lansoprazole is metabolised mainly by the liver enzyme CYP2C19 and to a lesser extent, CYP3A4 (10-12). Two isolated reports of elevations in prothrombin time and INR following co-administration of warfarin and lansoprazole have been highlighted (39).

In clinical practice, lansoprazole does not normally interact with warfarin. It would be prudent to monitor prothrombin time or INR when lansoprazole is added to, changed during, or discontinued from concomitant treatment with warfarin. If any increase in the INR is seen, the dose of warfarin should be adjusted as necessary to maintain the desired level of anticoagulation (4, 38, 39).

Omeprazole

The product literature for omeprazole reports that as omeprazole is metabolised in the liver through cytochrome P450 it can prolong the elimination of warfarin. The metabolism is mainly dependent on CYP2C19. Monitoring of patients receiving warfarin is recommended and a reduction of warfarin dose may be necessary (13-24).

The current standard reference source on drug interactions has identified two studies that have shown that omeprazole causes a small and clinically insignificant change in the anticoagulant effects of warfarin by decreasing its clearance, although in an isolated case report of one patient on warfarin

given omeprazole, developed a prolonged prothrombin time and bled (4, 38, 39). The effect of the interaction between warfarin and omeprazole is small and has been described as having minor, doubtful or limited clinical significance (4, 5, 39).

A systematic overview of warfarin and its drug and food interactions published in 2005 concluded that potentiation of the effect of warfarin by omeprazole was highly probable. The authors of the review concluded that use of omeprazole with warfarin should be avoided (3). It is interesting to note that the systematic overview only referenced one of the two studies highlighted by the other reference sources and came to a different conclusion regarding the severity of the interaction and subsequent recommendation (3).

In practice, the response of patients should be monitored when omeprazole is added to, changed during or discontinued from concomitant treatment with warfarin and a reduction in warfarin dose may be necessary (4, 13-24, 39).

Pantoprazole

Pantoprazole is metabolised by CYP2C19 and CYP3A4 (38). Although no interaction has been observed during concomitant administration of pantoprazole and warfarin in clinical pharmacokinetic studies, a few isolated changes in INR have been reported in the post-marketing period (25-36).

A systematic overview has highlighted one study with pantoprazole and warfarin that classed the probability of the reaction as high but concluded that there was no effect on the activity of warfarin (3).

In practice, patients given pantoprazole and warfarin concurrently should have monitoring of prothrombin time/INR after initiation, termination or during regular use of pantoprazole (4, 25-36).

Rabeprazole

The UK SPC for rabeprazole states that the drug is metabolised by CYP2C19 and CYP3A4. The SPC does not list an interaction between rabeprazole and warfarin (37). No significant change in the pharmacokinetics of warfarin was observed after single dose administration to healthy subjects who had been receiving rabeprazole 20mg daily for 7 days (4, 39).

The American product literature says there have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly (4, 39).

In practice, there is no reason for avoiding concurrent use of rabeprazole with warfarin. It would be prudent to monitor prothrombin time or INR at close intervals if the 2 medicines are given together (4, 39).

Summary

- Generally, the evidence for an interaction between warfarin and proton pump inhibitors is poor, but rarely and unpredictably raised INRs and bleeding may occur.
- In practice, whilst there is no reason for avoiding concurrent use of any proton pump inhibitor with warfarin, close monitoring of the prothrombin time or INR may be required.
- If any increase in the INR is seen, the dose of warfarin should be adjusted as necessary to maintain the desired level of anticoagulation.

Limitations

This answer has been constructed from general information sources as well as specific drug interaction resources. Both American and British resources were used. While information was generally similar for most PPIs, the opinions on the use of omeprazole and rabeprazole differed slightly. The summary was based on the consensus of the majority of the resources available at the time the answer was prepared.

References

1. Martin J (Ed). British National Formulary 61st Edition, March 2011. Coumarins and phenindione. London: Pharmaceutical Press. Electronic version, 2011. Accessed via www.bnf.org on 11/07/11.

2. Sweetman SC (Ed). Martindale: The Complete Drug Reference. Warfarin Sodium (monograph last revised and modified 14 May 2011). London: Pharmaceutical Press. Electronic version, 2011. Accessed via www.medicinescomplete.com on 11/07/11.
3. Holbrook AM, Pereira JA et al. Systematic overview of warfarin and its drug and food interactions. Archives of Internal Medicine 2005; 165: 1095-1106.
4. Klasco RK (Ed): DRUGDEX® Drug Evaluation – warfarin. Last modified 23/06/11 MICROMEDEX(R) Healthcare Series. Accessed via <http://www.thomsonhc.com/home/dispatch> on 11/07/11.
5. Uno T, Sugimoto K et al. The role of cytochrome P2C19 in R-warfarin pharmacokinetics and its interaction with omeprazole. Therapeutic Drug Monitoring 2008; 30: 276-81.
6. Summary of Product Characteristics - Nexium 10mg gastroresistant granules for oral suspension, sachet. AstraZeneca UK Limited, last updated 22/06/11.
7. Summary of Product Characteristics - Nexium 20mg Tablets. AstraZeneca UK Limited, last updated 07/07/11.
8. Summary of Product Characteristics - Nexium 40mg Tablets. AstraZeneca UK Limited, last updated 07/07/11.
9. Summary of Product Characteristics - Nexium IV 40mg powder for solution for injection/infusion. AstraZeneca UK Limited, last updated 13/06/11.
10. Summary of Product Characteristics - Zoton Fastab. Wyeth Pharmaceuticals, last updated 27/06/11.
11. Summary of Product Characteristics – Lansoprazole 15mg Gastro-resistant Capsules. Winthrop Pharmaceuticals UK Ltd, last updated 24/01/11.
12. Summary of Product Characteristics – Lansoprazole 30mg Gastro-resistant Capsules. Winthrop Pharmaceuticals UK Ltd, last updated 24/01/11.
13. Summary of Product Characteristics - Losec MUPS Tablets 10mg, 20mg & 40mg. AstraZeneca UK Limited, last updated 29/03/11.
14. Summary of Product Characteristics - Losec Capsules 10mg, 20mg & 40mg. AstraZeneca UK Limited, last updated 29/03/11.
15. Summary of Product Characteristics - Losec IV Injection 40mg. AstraZeneca UK Limited, last updated 29/03/11.
16. Summary of Product Characteristics - Losec Infusion 40mg. AstraZeneca UK Limited, last updated 29/03/11.
17. Summary of Product Characteristics - Mepradec 10mg gastroresistant capsules. Discovery Pharmaceuticals Ltd, last updated 16/02/10
18. Summary of Product Characteristics - Mepradec 20mg gastroresistant capsules. Discovery Pharmaceuticals Ltd, last updated 16/02/10.
19. Summary of Product Characteristics - Mezzopram 10mg dispersible gastroresistant tablets. Sandoz Ltd, last updated 04/05/11.
20. Summary of Product Characteristics - Mezzopram 20mg dispersible gastroresistant tablets. Sandoz Ltd, last updated 04/05/11.
21. Summary of Product Characteristics - Mezzopram 40mg dispersible gastroresistant tablets. Sandoz Ltd, last updated 04/05/11.
22. Summary of Product Characteristics - Omeprazole 10mg capsules. Actavis UK Ltd, last updated 18/03/11.
23. Summary of Product Characteristics - Omeprazole 20mg capsules. Actavis UK Ltd, last updated 18/03/11.
24. Summary of Product Characteristics - Omeprazole 20mg capsules. Winthrop Pharmaceuticals UK Ltd, last updated 20/06/10.
25. Summary of Product Characteristics – Pantoloc Control 20mg gastroresistant tablets. Novartis Consumer Health, last updated 23/03/10.
26. Summary of Product Characteristics – Pantoprazole 20mg gastro-resistant tablets. Wockhardt UK Ltd, last updated 04/03/11.
27. Summary of Product Characteristics – Pantoprazole 40mg gastro-resistant tablets. Wockhardt UK Ltd, last updated 07/03/11.
28. Summary of Product Characteristics – Pantoprazole 20mg gastro-resistant tablets. Nycomed UK Ltd, last updated 07/04/11.
29. Summary of Product Characteristics – Pantoprazole 40mg gastro-resistant tablets. Nycomed UK Ltd, last updated 07/04/11.

30. Summary of Product Characteristics – Pantoprazole 20mg gastro-resistant tablets. Winthrop Pharmaceuticals UK Ltd, last updated 06/05/11.
31. Summary of Product Characteristics – Pantoprazole 40mg gastro-resistant tablets. Winthrop Pharmaceuticals UK Ltd, last updated 06/05/11.
32. Summary of Product Characteristics – Pantoprazole 20mg gastro-resistant tablets. Sandoz Ltd, last updated 14/03/11.
33. Summary of Product Characteristics – Pantoprazole 40mg gastro-resistant tablets. Sandoz Ltd, last updated 14/03/11.
34. Summary of Product Characteristics – Pantoprazole 40mg powder for solution for injection. Sandoz Ltd, last updated 25/02/11.
35. Summary of Product Characteristics – Pantoprazole 40mg powder for solution for injection. Actavis UK Ltd, last updated 19/05/11.
36. Summary of Product Characteristics - Protium 40mg IV Powder for Solution for Injection. Nycomed UK Ltd, last updated 06/09/10.
37. Summary of Product Characteristics - Pariet 10mg & 20mg. Eisai Ltd, last updated 24/11/10.
38. Blume H, Donmath F et al. Pharmacokinetic drug interaction profiles of proton pump inhibitors. Drug Safety 2006; 29 (9): 769-784.
39. Baxter K (Ed). Stockley's Drug Interactions. Coumarins + Proton Pump Inhibitors (Updated 27 January 2011). London: Pharmaceutical Press. Electronic version, 2011. Accessed via www.medicinescomplete.com on 11/07/11.

All Summaries of Product Characteristics accessed via <http://emc.medicines.org.uk> on 11/07/11.

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Search strategy

- Embase: 1980 to Present; WARFARIN/it [it=Drug Interaction] AND [[ESOMEPRAZOLE/it [it=Drug Interaction] OR LANSOPRAZOLE/it [it=Drug Interaction] OR OMEPRAZOLE/it [it=Drug Interaction] OR PANTOPRAZOLE/it [it=Drug Interaction] OR RABEPRAZOLE/it [it=Drug Interaction]] OR PROTON PUMP INHIBITOR/it [it=Drug Interaction]] [Limit to: Publication Year 2009-2011 and Human and English Language]
- Medline: 1950 to Present; search terms = WARFARIN/ AND DRUG INTERACTIONS/ AND [[OMEPRAZOLE/ OR esomeprazole.af OR lansoprazole.af OR pantoprazole.af OR rabeprazole.af] OR PROTON PUMP INHIBITORS/] [Limit to: Publication Year 2009-2011 and Humans and English Language]
- In-house database/resources: BNF, Martindale, Drug Interactions
- Electronic Medicines Compendium: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- MICROMEDEX(R) Healthcare Series – DrugDex: warfarin monograph
- IDIS: "WARFARIN 20120208" and "ANTIULCER-PROTON PUMP INHIB 56260600" or "ESOMEPRAZOLE 56260605" or "LANSOPRAZOLE 56260603" or "OMEPRAZOLE 56260602" or "PANTOPRAZOLE 56260606" or "RABEPRAZOLE 56260604" and Descriptor(s): "DRUG INTERACTION 50" Years: 2009-2011