Is there an interaction between warfarin and proton pump inhibitors?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Background

Warfarin is an anticoagulant licensed 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 (2-6). 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 (7-11).

Answer

Esomeprazole

The Summaries of Product Characteristics (SPC) for esomeprazole states 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 (7, 12).

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, 7, 12-14).

Lansoprazole

Two isolated reports of elevations in prothrombin time and INR following co-administration of warfarin and lansoprazole have been highlighted (13).

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, 8, 12-14).

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 (9).

Two studies 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, one patient on warfarin developed a prolonged prothrombin time and bled when given omeprazole (4, 12,

13). 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, 13).

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. 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, 9, 13, 14).

Pantoprazole

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 (10).

A systematic overview has highlighted one study with pantoprazole and warfarin that classed the probability of the interaction 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, 10, 13, 14).

Rabeprazole

The SPC for rabeprazole does not list an interaction with warfarin (11). 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, 13).

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, 13).

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, 13, 14).

Other information

An article on pharmacokinetic drug interaction profiles of PPIs first produced in 2006 and updated in 2014 indicated that there has been no new information on an interaction between esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole and warfarin (15).

An observational study published in 2015 investigated the effects of INR in patients prescribed a PPI (n = 305) and found no effect on the INR. The mean INR 70 days before PPI initiation was 2.6 (95% CI: 2.5 – 2.8) and INR measured 1-3 weeks after PPI initiation was also 2.6 (95% CI: 2.5-2.7; p = 0.67). Analyses of all individual PPIs were consistent with the pooled main analysis (16).

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. The answer has only addressed the interaction between oral proton pump inhibitors and warfarin, intravenous products have not been considered.

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Quality Assurance

Prepared by
Tim Meadows, East Anglia Medicines Information Service

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Checked by
Abigail Scott, East Anglia Medicines Information Service

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Search strategy

- In-house database/resources: BNF, Martindale, American Hospital Formulary Service, Stockleys Drug Interactions, Micromedex
- Electronic Medicines Compendium: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, warfarin
- Embase: 1974 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 2017-2019]
- Medline: 1946 to Present; search terms = exp WARFARIN/ AND exp DRUG INTERACTIONS/ AND [exp OMEPRAZOLE/ OR exp ESOMEPRAZOLE OR exp LANSOPRAZOLE OR pantoprazole.af OR exp RABEPRAZOLE] [Limit to: Publication Year 2017-2019]