Unexpected outcome (positive or negative) including adverse drug reactions

Clinically significant interaction between warfarin and popular cough lozenges 'Fisherman's Friend'

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The authors report a highly probable and clinically relevant interaction between warfarin and the popular cough lozenges 'Fisherman's Friends' in a 67-year-old man, whereby ingestion of these lozenges for approximately 1 month was associated with a significant reduction in international normalised ratio to subtherapeutic levels.

BACKGROUND

This case highlights a probable and clinically relevant drug interaction between warfarin and a freely available commercial cough remedy and could conceivably have implications for other patients who take warfarin.

CASE PRESENTATION

A 67-year-old man with no significant medical history presented to hospital on 19 May 2011 with visual disturbance which started abruptly earlier that day. On confrontation testing, he was found to have a left homonymous hemianopia and an electrocardiograph revealed atrial fibrillation. Brain imaging with CT confirmed right occipital infarct. He was commenced on warfarin together with amlodipine, atorvastatin and bisoprolol. On discharge 11 days later, his international normalised ratio (INR) was stable at 2.7, having been between 2 and 3 (his target range) for 4 days beforehand.

Five days after discharge in early June, he presented to the anticoagulant clinic where his INR was 3.0 and he continued on 4 mg of warfarin daily during this and a subsequent two visits (each 1 week apart) where his INR was 2.6 then 2.4, respectively.

On his next visit 14 days later, however, his INR was found to be subtherapeutic at 1.7. He had started to take around four to six 'Fisherman's Friend' cough lozenges every day in the week prior to this clinic visit for a dry cough which he did not mention to the nurse at this stage. He had not been unwell with other coryzal symptoms over this time period. He took no other over the counter remedies, nor was there any change in his diet or prescribed drug regimen during this time. He was advised therefore to take an extra dose of 7 mg in clinic that day then continue daily on 4 mg as before and return in 2 weeks for another check-up. At this stage, his INR was found to be 1.9 and he was advised to increase his warfarin dose to 4 mg Monday–Friday and 5 mg Saturday–Sunday which he did.

On recheck 2 weeks later, however, his INR remained subtherapeutic at 1.6 despite the increased dose of warfarin and he was told to begin taking 4 mg/5 mg of warfarin

on alternate days. He also took it upon himself to stop using the 'Fisherman's Friend' cough lozenges which he had been continuing to consume at a rate of around four to six lozenges per day up to this point and been using for around 1 month.

On checking his INR a week later on the 8th August it had come up to 2.3 and a subsequent check 2 weeks after this showed that it remained therapeutic at 2.4 (figure 1).

OUTCOME AND FOLLOW-UP

Patient's INR has remained stable at two separate clinic visits 2 weeks apart since ceasing his consumption of 'Fisherman's Friend'.

DISCUSSION

'Fisherman's Friend' are a popular brand of cough lozenges worldwide, retailing in over 100 countries and selling over 500 000 packets of lozenges per day. Each lozenge contains, among other ingredients, eucalyptus oil, menthol and liquorice, each of which has at least a theoretical potential to interact with drugs metabolised by cytochrome P450 and therefore warfarin.¹ What's more, from a clinical perspective, the sequence of events reported here would be classified as being a 'probable' drug interaction on the Naranjo scoring system for likelihood of drug interactions.²

Despite the popularity of the cough drops, there are no case studies to date describing a possible interaction between 'Fisherman's Friend' and warfarin specifically. There are however two recently published reports claiming a probable interaction between warfarin and separate other brands of menthol-containing cough drops.^{3 4} In both cases, a drop in INR was observed soon after the patient began to consume the menthol drops regularly and the INR recovered back to the previous level on cessation of the drops, with the dose of warfarin subsequently being able to be lowered to the dose that was previously being taken to maintain a therapeutic INR.

Both authors suggest that there may be an interaction occurring between menthol and warfarin, which seems likely as the potential ability of menthol to affect the pharmacokinetics and pharmacodynamics of many drugs

Figure 1 Time course of events.

is significant⁵ and the compound is present in significant quantity in many commercially available cough drops.

It is not the only potentially active compound in most cough drops however and both 'Fisherman's Friend' and the brand of cough drop cited as causing a potential reaction by Kassebaum *et al*⁶ contain other potentially active substances, among them eucalyptus oil. Eucalyptus oil is present in many cough remedies, sweets, shampoos and herbal remedies in greatly varying concentrations and has in vitro at least the capacity to interact with P450 isoenzymes⁴ and therefore theoretically with the metabolism of warfarin in humans.

The third potentially active compound in 'Fisherman's Friend' lozenges is liquorice—a natural plant substance which contains significant amounts of glycyrrhizin and glabridin, compounds which may theoretically interact with warfarin in a number of ways including inhibition of P450 isoenzymes^{6,7} and competition for binding sites on albumin.⁸ Indeed, the US National Institute of Health's website states as 'major' the potential for interaction between warfarin and liquorice in its assessment of the substance.⁹

The potential for interaction between all three of the primary ingredients in 'Fisherman's Friend' lozenges is significant then and well-studied in vitro, but reports of clinically significant in vivo interactions between warfarin and menthol, liquorice or eucalyptus oil compounds such as cough sweets are scarce.

This case is interesting as it highlights a likely and highly clinically relevant drug interaction between a widely sold cough sweet and warfarin—a widely used anticoagulant drug. The number of people taking both at any one time in the UK is likely to be significant and many instances of interactions between warfarin and over the counter drugs, cough/cold remedies and herbal medicines are probably missed each year as most patients are unlikely to see a link between these remedies and conventional medicines and anticoagulant clinic staff, general practitioners (GPs) and medical teams may not ask specifically. Under-reporting of herbal remedy and complementary medicine use by patients is a well-known problem indeed¹⁰ and it is likely that reporting of the use of commercial cough/cold remedies without specifically being asked will be even lower. In this case however, it was the patient who first acknowledged that the cough lozenges may be interacting with his warfarin and not his GP, medical team nor the anticoagulant clinic staff.

Increased awareness of the numerous potential interactions between warfarin and widely used cough/cold remedies and herbal products on the part of medical staff and patients themselves may help to reduce the number of such interactions occurring and presumably therefore the number of adverse events occurring as a result.

Learning points

- ▶ Taking a good dietary history and specifically asking about recent over the counter drug use, herbal remedy use or use of commercial cough or cold remedies in a patient with erratic INRs may help to elicit a cause
- ▶ Clear warnings on the side of packets of sweets and cough and cold remedies that have the potential to interact with warfarin should be considered.
- ▶ Lifelong regular INR monitoring is essential in all patients on warfarin therapy due to the unpredictability of potential interactions of the drug with other substances and its narrow therapeutic window.
- ▶ Making patients aware of the possibility of interaction between warfarin and commercially available products such as cough and cold remedies is a duty of the medical team and the anticoagulant clinic staff and patients should be informed or reminded of this on commencement of warfarin and at each anticoagulant clinic visit.

Competing interests None.

Patient consent Obtained.

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