Interactions with warfarin are many and varied and, because of warfarin’s narrow therapeutic index, are often clinically significant. Here a potential interaction between iloprost and warfarin is discussed.

Did the concomitant use of iloprost and warfarin cause increased INR?

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Iloprost is a prostacyclin analogue that is licensed for the treatment of patients with pulmonary hypertension. At Royal Liverpool and Broadgreen University Hospitals NHS Trust (RLBUHT) it is also used off label for the treatment of peripheral vascular disease (see adjacent Box). Here we present a case of a man who was taking warfarin and received iloprost for critical limb ischaemia, and who subsequently developed an elevated international normalised ratio (INR).

Presentation
An 89-year-old Afro-Caribbean man weighing 54kg presented to RLBUHT with bilateral burning leg pain at rest, which was worse at night. His past medical history included Paget’s disease, glaucoma, deep vein thrombosis and pulmonary embolism. On admission he was taking:

- Warfarin 4mg/5mg on alternate days (target INR of 2.5)
- Alfacalcidol 250ng three times a day
- Furosemide 40mg once daily
- Calcium plus ergocalciferol one tablet twice daily
- Timolol 0.25% eye drops twice daily

On examination no pulses were palpable below both knees. He had an ischaemic ulcer to the base of his right first toe and a necrotic left fifth toe. He was diagnosed with bilateral critical limb ischaemia and was admitted under the care of the vascular surgeons.

Due to the severity of calcification and stenosis in the arteries at and below the knee, the treatment options for his bilateral critical limb ischaemia were either bilateral above-knee amputation or a course of iloprost.

Treatment
The patient was started immediately on analgesia — regular paracetamol 1g four times a day and codeine phosphate 60mg four times a day.

On day 2 he was started on iloprost 50μg daily (infused over six hours), continued for 10 days. He tolerated the iloprost infusion well and reported no side effects despite receiving the maximum dose.

All other medicines were unchanged except for warfarin, which was dose-adjusted according to INR. His INR started to rise — increasing from 2 to 3 within 24 hours of starting iloprost — and reached a peak at day 4 of iloprost treatment (INR = 4.7). The dramatic rise in the INR required reduction and withholding of warfarin doses (see Figure, p126). On day 7 his INR

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Iloprost

Prostacyclin is an endogenous compound produced by the vascular endothelium. Iloprost is a synthetic prostacyclin analogue that is licensed for the treatment of patients with primary pulmonary hypertension. It has been shown to:

- Inhibit platelet aggregation, adhesion and release
- Dilate arterioles and venules
- Increase capillary density and reduce the response of increased vascular permeability caused by the mediators serotonin and histamine
- Stimulate endogenous fibrinolysis

Because of these effects iloprost is used at the North West Regional Vascular Unit, which is based at Royal Liverpool and Broadgreen University Hospitals NHS Trust (RLBUHT), for the treatment of peripheral vascular disease, specifically:

- Critical limb ischaemia when surgical revascularisation is not possible
- Severe Raynaud’s disease
- Thromboangiitis obliterans (Buerger’s syndrome)

Such “off label” use of iloprost has taken place at RLBUHT since 2004 for over 50 patient episodes using an intravenous preparation licensed for this indication, which is imported from Germany.

The evidence base for the use of iloprost for peripheral vascular disease dates back to the mid 1980s. Several large studies have demonstrated the following benefits with a 2ng/kg/min infusion:

- Improved ulcer healing rate by 60% at 28 days, which was maintained for six months
- Reduced need for amputation at six months and one year
- Increased maximal walking distance and time to claudication for up to 60 days after infusion
- Reduced pain scores in Buerger’s syndrome
- Decreased number, duration and severity of attacks of Raynaud’s syndrome

Side effects of iloprost are dose-related and common. Up to 70% of patients will experience minor vascular reactions (flushing and headache) and gastrointestinal symptoms are also common. Hypotension associated with the use of iloprost can be profound, but this side effect can be minimised by carefully titrating the dose upwards with regular monitoring of pulse and blood pressure.

The complexities in the administration of this drug have led to the development of a standardised prescription and monitoring chart for use at RLBUHT.
was 2.7 and he was prescribed 3mg of warfarin, which was inadvertently omitted. He had no bleeding complications from his warfarin treatment.

During this period of iloprost treatment his leg pain improved substantially and he stopped taking all analgesics on day 7. It is worth noting that his left fifth toe auto-amputated.

**Discussion**

Iloprost is a vasodilator that also inhibits platelet aggregation. It is theorised that it may increase the potential for bleeding when given with anticoagulants. An EMBASE and MEDLINE search did not reveal any relevant articles that discussed this drug interaction.

Iloprost is metabolised extensively by the liver, with the plasma levels of the active substance influenced by changes in hepatic function. Iloprost is metabolised predominantly via beta-oxidation; the cytochrome P450 system plays only a minor role in its metabolism. It is cleared rapidly, with a terminal half-life of 30 minutes when given intravenously, hence the need for a continuous infusion. Iloprost is highly protein-bound (>60%).

Like iloprost, warfarin is extensively bound to plasma proteins. The plasma half-life of warfarin is about 37 hours. Warfarin’s S-isomer is metabolised more rapidly than its R-isomer, mainly by CYP2C9; the R-isomer is cleared mainly by CYP1A2. Iloprost is not known to affect these isoenzymes, therefore we speculate that the mechanism of this drug interaction is via drug displacement from protein binding sites.

### Paracetamol

Paracetamol may have played a role in this interaction, but it is debatable whether or not paracetamol can increase INR. Some studies have shown an increase in INR with co-administration of warfarin and paracetamol, but this effect generally takes between four and seven days to develop. Moreover, the interaction is generally classified as mild (increasing the INR by an average of 1.2).^5^ In this case, the patient’s INR increased from 2 to 3 within 24 hours of starting iloprost and within 48 hours of starting paracetamol, reaching a peak at more than double its baseline level on day 3 of iloprost; this would have been unlikely to occur with paracetamol alone.

### Protein binding interactions

The binding of drugs to plasma proteins is reversible and equilibrium is established between the drug molecules that are bound and those that are unbound. The bound molecules form a pharmacologically inactive reservoir. As the free molecules are metabolised some of the bound molecules unbind and pass into solution to exert their normal pharmacological actions before they, too, are cleared.

Competition can occur if two drugs that bind to similar sites on blood proteins are used concurrently — the net result is one drug displacing the other from its binding site and hence raising its free concentration. For example, a drug that reduces the binding of another from 99% to 98% increases the free fraction from 1% to 2% (hence doubling its potential effects). Warfarin is 99% protein-bound and is known to be particularly susceptible to this type of drug interaction. Small reductions in its protein binding have a relatively large affect on its free fraction and therefore its pharmacological action (as demonstrated in this case). This protein binding interaction is likely to be important only for drugs that are given intravenously and have a:

- High hepatic extraction ratio
- Short half-life
- Narrow therapeutic index

Most medicines do not fit these criteria. However, iloprost, when given intravenously for peripheral vascular disease, has all the above properties.

### References