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Metronidazole causes an unexpected rise in INR in anticoagulated patients even after warfarin has been stopped

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Interaction between metronidazole and warfarin is thought to potentiate the anticoagulant effect of warfarin. In this article, the authors propose mechanisms for this interaction, based on three case studies

In the 1970s an interaction between metronidazole and warfarin was described in healthy volunteers.¹ Subsequently, there have been few reports describing the interaction during the concurrent administration of warfarin and metronidazole. A critical analysis of warfarin interactions concluded that the metronidazole-warfarin interaction is "highly probable", with metronidazole potentiating the anticoagulant effect of warfarin.^{2,3}

We propose mechanisms for this interaction, based on three patients in a surgical emergency unit whose international normalised ratios (INR) rose despite the cessation of warfarin some days previously.

Informed patient consent has been obtained for publication of these studies.

Case 1 An 80-year-old Caucasian male was referred by his dental practitioner for correction of an INR of 4.6 and a tooth extraction. His regular medicines were: warfarin (for a previous axillary vein thrombosis), levothyroxine 125µg *od*, ferrous sulphate 400mg *od* and lisinopril 5mg *od*. Routine blood investigations were within the normal range, except for the patient's haemoglobin level, which was 10.2g/dl (reference range 12–16g/dl).

On admission, intravenous cefuroxime (750mg *tds*), metronidazole (500mg *tds*) and oral paracetamol (as required for pain relief) were started. Warfarin was stopped one day after admission and metronidazole was stopped on day two. On day four, the patient's INR rose from 5.6 to 10.3. He had a vasovagal attack and his haemoglobin level dropped to 6.6g/dl. The patient was treated with 1mg of intravenous vitamin K followed by three units of blood and four units of fresh frozen plasma (FFP). His INR fell to 1.8 and his haemoglobin increased to 11.1. On day nine, the patient was discharged. Figure 1 (p66) summarises the temporal relationship between warfarin and metronidazole administration and the patient's INR.

Case 2 A 71-year-old Caucasian female was referred by her GP with a one-day history of generalised abdominal pain. She was taking

warfarin for a mitral valve prosthesis. Her INR on admission was 4.9. Her regular medicines were: amiloride 5mg *bd*, furosemide 80mg *bd*, lisinopril 20mg *on*, long-term allopurinol 300mg *od*, atorvastatin 10mg *on*, salbutamol as required and Seretide two puffs *bd*. She had known renal impairment (creatinine clearance 20ml/min) which remained stable before and during admission. The patient's white cell count (WCC) was $17.7 \times 10^9/L$ (reference range $4-10 \times 10^9/L$).

On admission, warfarin was stopped and intravenous cefuroxime 1.5g *tds* and metronidazole 500mg *tds* were started. Emergency intestinal surgery was performed after correcting her INR to 1.7 with three units of FFP, after which an infusion of unfractionated heparin was started. The patient made good progress and the antibiotics were stopped on the morning of day three, after a total of five doses had been administered.

The patient's heparin infusion was changed to low molecular weight heparin (7,500 units *od* of dalteparin, subcutaneously). On day four, her INR started to rise, and on day five it was 6.0. Figure 2 (p66) summarises the temporal relationship between warfarin and metronidazole administration and the patient's INR.

Case 3 A 75-year-old female was referred by her GP with a three-day history of abdominal pain, nausea and vomiting. Her regular medicines were: warfarin (started 20 years previously for atrial flutter), sotalol 40mg *bd*, losartan 50mg *od*, long-term, regular ibuprofen 200mg *tds*, bendroflumethiazide 2.5mg *od* and paracetamol 1g *tds* or *qds*. On admission the patient's INR was 4.0 and her WCC was $17 \times 10^9/L$.

Warfarin was stopped and intravenous cefuroxime 1.5g *tds* and metronidazole 500mg *tds* were started to treat a possible intra-abdominal infection from small bowel perforation. The patient was given four units of FFP and a Hartman's procedure was performed, at which time her INR was 2.1. She was given a morphine infusion and was started on dalteparin (7,500 units daily). The patient's INR continued to rise, reaching 4.1 on day four and 10 on day six.

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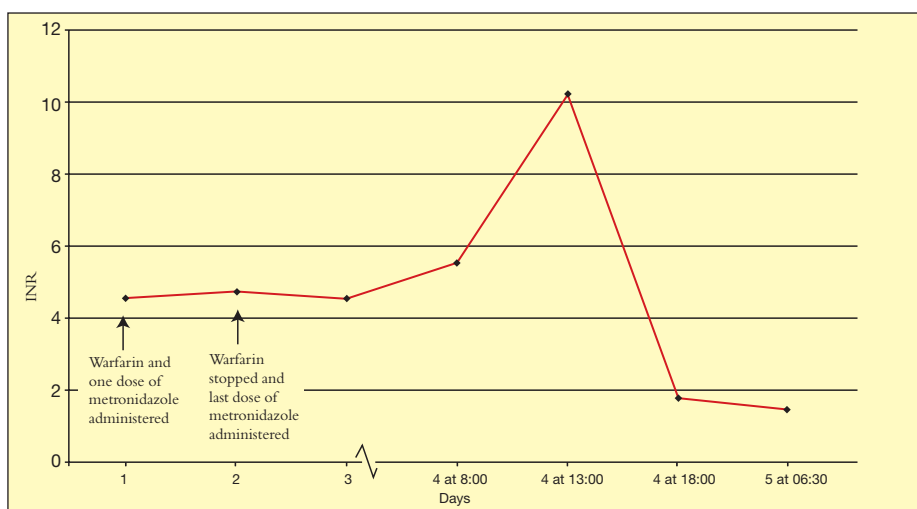


Figure 1: Temporal relationship between warfarin/metronidazole administration and INR values in Case 1

There was no evidence of bleeding and the patient was given 1.5mg intravenous vitamin K. The dalteparin was reduced to 2,500 units *od*. Due to her persistently high WCC and C-reactive protein level, she was maintained on antibiotic treatment. Figure 3 (p67) summarises the temporal relationship between warfarin and metronidazole administration and the patient's INR.

Discussion

Approximately 1 per cent of the UK population is on a long-term oral anticoagulant.⁴ Many drugs interact with warfarin, and over-anticoagulation with antibiotic use is probably one of the major causes of bleeds with antithrombotic therapy.^{4,5}

Two case reports^{6,7} describe excessive bleeding requiring admission to hospital due to an interaction between warfarin and metronidazole, administered concurrently. Furthermore, a two-year retrospective analysis of drug interactions recorded in a hospital database found that warfarin-metronidazole was the main interaction to involve inhibition of cytochrome P450 (CYP) enzyme 2C9⁸. INRs reached a maximum after eight days of co-administration with a change in mean INR from 2.2 at baseline to 4.3 during coadministration.

In contrast, in the three cases we report, the change in INR occurred several days after stopping warfarin and INR rose to levels well above those seen while the patient was taking warfarin regularly. All patients had their warfarin stopped on admission (or one day later) and were started on intravenous metronidazole and cefuroxime. There were no other significant changes in medication that might explain the INR rise and there were no significant changes in serum biochemistry, including serum proteins, liver function tests and renal function markers.

INRs at baseline were all above the expected target (mean INR was 4.4) and

were corrected with FFP in Cases 2 and 3 before emergency surgery (mean INR following FFP was 1.9). A "watch and wait" policy was adopted in Case 1, where the hospital admission was not related to a life-threatening condition. About 48 hours after cefuroxime and metronidazole were started, a rise in INR to a mean peak of 8.8 (range 6–10.3) was observed in all patients, despite the fact that warfarin had been stopped. Metronidazole had also been stopped 24 hours before the rise in Cases 1 and 2. We believe that the rises in INR were due to an interaction between warfarin and metronidazole, but the nature of this interaction needs clarification.

There is little evidence to suggest any direct effect of metronidazole on vitamin K metabolism or on regulation of clotting. However, reports by Yacobi *et al*⁹ indicate that rats treated with high doses of metronidazole had a decrease in prothrombin complex activity (PCA) coupled with an increase in the endogenous PCA elimination rate constant. Whether this is significant in humans still needs to be investigated —

we could not find any reports on humans in the literature or in the Medicines and Healthcare products Regulatory Agency yellow card database.

Warfarin acts on vitamin K-dependent clotting factors and two variables may alter vitamin K levels in the body: dietary intake or any factors associated with malabsorption, and changes in gastrointestinal flora that produce vitamin K. The recommended daily dietary intake of vitamin K is 1 µg/kg of body weight, easily exceeded by a normal Western diet of around 300–500µg daily.¹⁰ Vitamin K stores in the body may be rapidly depleted following a low intake of food for a week or longer¹¹ but this is not likely to be the case in our patients, who were suffering from acute conditions not linked to fat malabsorption. Cases 2 and 3 were on a "nil by mouth" regimen prior to surgical intervention, but were on complete enteral feeds after surgery when oral intake was tolerated.

Impaired production of vitamin K by antibiotic-induced changes in gastrointestinal flora cannot be eliminated, but this appears to be more significant with prolonged use of antibiotics¹⁰ and in the absence of dietary intake. Cephalosporins linked with inhibition of gastrointestinal flora include those with high Gram-negative activity and excretion in bile, and have not included cefuroxime.¹¹ No reports have been found related to metronidazole.

Warfarin is administered as a racemic mixture of S(-) and R(+) isomers. Altered synthesis of clotting factors has a delayed effect on INR as pre-formed clotting factors are metabolised; changes in INR are typically seen two days after a change in dose. The stereoselective interaction of warfarin and metronidazole in humans has been established in a study involving eight volunteers administered either racemic warfarin, the S(-) isomer or the R(+) isomer, with or without metronidazole. In patients taking S-warfarin alone, metronidazole increased the

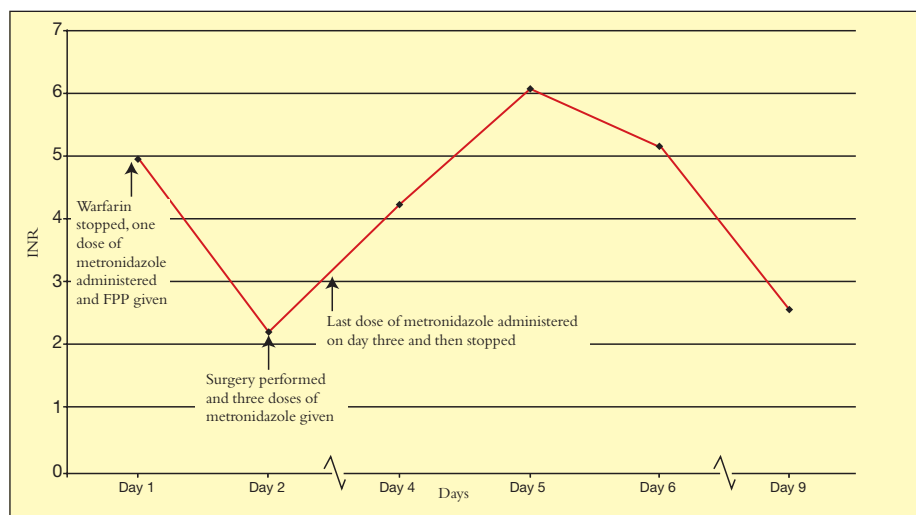


Figure 2: Temporal relationship between warfarin/metronidazole administration and INR values in Case 2. "FFP" means fresh frozen plasma.

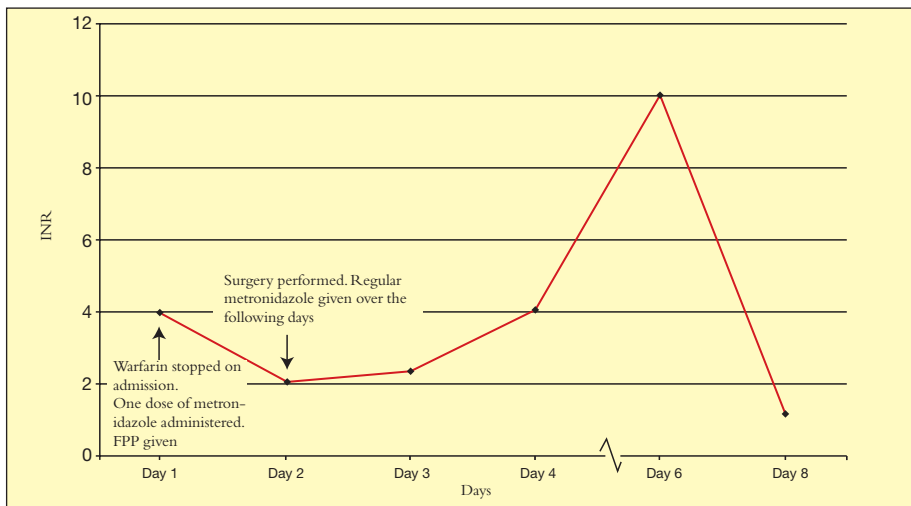


Figure 3: Temporal relationship between warfarin/metronidazole administration and INR values in Case 3. "FPP" means fresh frozen plasma.

half-life from 32 to 50 hours, reduced warfarin clearance and increased the prothrombin time.¹ Since the S-isomer is the more potent, this interaction is more important clinically. It occurs due to metronidazole's inhibition of CYP2C9¹³. The R-isomer is metabolised by CYP1A2, CYP2C19 and CYP3A4.¹⁰

The interaction was further investigated in rats where observations were made following administration of warfarin with no, low dose or high dose metronidazole.⁹ Higher doses of metronidazole reduced plasma protein binding and plasma clearance of the free drug with a more marked effect on S-warfarin, confirming the stereoselectivity of the inhibitory effect of metronidazole. If metabolism were the sole mechanism of interaction, one would expect that the effect of warfarin might be prolonged, but not that it would be increased well above the baseline values as in our patients.

The clinical significance of reductions in plasma protein binding by interacting drugs has been debated. Protein-bound warfarin is in equilibrium with free warfarin such that around 99 per cent is bound. Displacement of warfarin from serum proteins will result in an increased amount of free drug, making it available to move to the intracellular sites of action and to be excreted. The effect is usually described as transitory and said only rarely to require warfarin dosage adjustment^{10,13} because the increased free drug is metabolised or excreted and a new equilibrium established.

Yacobi *et al*⁹ have reported that metronidazole displaces warfarin from albumin in rats, but only *in vivo*, suggesting that it may be a metabolite rather than the parent drug which is responsible. Our patients had normal albumin levels that did not change throughout their hospital stay. If metronidazole or a metabolite did cause a substantial displacement of bound drug then the free warfarin could have passed into cells and affected clotting factor synthesis. If the effect

were indeed transitory then we would expect to see a rise and fall in INR similar to that seen about two days after a single large dose of warfarin. If, in addition, the free drug were eliminated more slowly because of CYP inhibition, then the effect would be more pronounced.

Other medicines may also interfere with warfarin but, in all three cases reported here, the medicines taken before admission were continued. Paracetamol, the analgesic used in all cases, has been linked to potentiation of warfarin by an unknown mechanism, though there have been inconsistencies in case reports and no randomised controlled trials.^{13,14} However, since all three patients were taking regular paracetamol before admission, it is unlikely that this caused the rise in INRs. There is evidence of increased bleeding with some second and third generation cephalosporins, linked to the presence of an N-methylthiotetrazole side chain believed to interfere with the gamma-carboxylation of clotting factors.^{13,15} There is no evidence of such an effect by cefuroxime¹³ which does not have that side-chain.

The potentiation of the warfarin effect we describe differs from that in published reports⁸ in that we report a larger and earlier rise in INR despite warfarin being stopped. The peak INR occurred after a mean of five days after stopping the warfarin and around 48 hours after starting metronidazole. In healthy volunteers, S-warfarin has a half-life of 32 to 50 hours and as much as 50 per cent may have remained when metronidazole was administered. A potentiation of the anticoagulant effect may therefore have occurred due to displacement of warfarin from albumin and inhibition of metabolism by metronidazole. This effect is especially evident in Cases 2 and 3, where the anticoagulant effect was reversed using FFP.

After the infused coagulation factors have been eliminated from the body, one would expect a maximum rise to baseline INR.

However, this was not the case, with the INR reaching a peak of 10 and 6, respectively, several days after administering FFP.

We propose that the most likely explanation for these observations is a combination of metronidazole-induced displacement of warfarin and inhibition of warfarin metabolism. Whatever the mechanisms involved, this is a clinically serious interaction that warrants further investigation.

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