**A warfarin -antibiotic drug-drug interaction: A podiatric surgical case report**

**Level of Evidence: IV**

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**Authors:**

* Ms Sally Feeney MSc FRCPodS - (Consultant Podiatric Surgeon)
* Dr Sharon Rees MSc MSc PhD SRPharmS (Associate Professor Therapeutics & Prescribing)
* Mr Ravi Krishān Modha MSc FRCPodS - (Podiatric Surgeon)

**Address correspondence to:** Mr Ravi Krishān Modha, Podiatric Surgeon, Department of Podiatric Surgery, West Middlesex University Hospital, London, United Kingdom.

E-mail: info@osteogait.com

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List of abbreviations -

IM - Intermetatarsal

FBC - Full Blood Count

ESR - Erythrocyte Sedimentation Rate

INR - International Normalized Ratio

DDI - drug-drug interaction

APTT -Activated Partial Thromboplastin Time

ADE - Adverse Drug Event

# Introduction

Worldwide, the most commonly prescribed drug for treatment and prevention of thromboembolism in patients with deep vein thrombosis, pulmonary embolism, atrial fibrillation and mechanical heart valves is the oral anticoagulant known as warfarin [1].

Warfarin is a vitamin K antagonist, inhibiting the formation of pro-coagulation factors II, VII, IX and X, as well as the anticoagulant proteins C and S [2]. The drug has a narrow therapeutic range, requiring frequent monitoring via the international normalized ratio (INR) in order to avoid potentially life-threatening complications from both under-and-over coagulation [3].

Many dietary variations and co-prescribed medications can alter the INR, by interfering with haemostasis, or affecting warfarin levels. This is further complicated because most warfarinised patients have comorbidities, are of an older age, and there may be polypharmacy [4].

Several groups of antibiotics are known to interact with warfarin, presenting a challenge to the prescriber trying to manage underlying clinical infection, whilst mitigating the risk coagulopathy [3, 5, 6]. The authors present a case report of a 64-year old warfarinised patient undergoing forefoot surgery for a painful neuroma. Management of a subsequent infection with combinations of antibiotics, led to excessive anti-coagulation and an adverse drug event.

# Case Report

Patient A presented in 2016 with pain in both feet across the lesser metatarsal-phalangeal joints (MTPJs). On clinical examination, she had pain in both 3rd/4th intermetatarsal (IM) spaces suggesting a neuroma or bursa. An ultrasound scan confirmed an intermetatarsal (IM) neuroma/bursa complex in both 3rd/4th IM spaces. Options were discussed and verbal and written information provided regarding the available treatments.

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| **Medical history** | **Drug history**  |
| Aortic valve replacement (metal) 2004 | Warfarin regime - 7mg Tuesday to Thursday and 6mg Friday to Monday |
| Hypothyroidism | Levothyroxine 100mcg once daily |
| Hypercholesterolemia  | Atorvastatin 20mg once daily |
| Pruritis | Hydroxyzine 25mg once daily |
| Heart failure | Bisoprolol 1.25mg  |
| Pain post-surgery | Paracetamol 1000mg four times daily |
| Pain post-surgery | Codeine phosphate 30mg four times daily |
| Pre-operative bridging therapy  | Tinzaparin 15,000iu daily subcutaneously  |

Table 1: Medical and Drug History for Patient A

Patient A consented to undergo a steroid injection into both IM spaces, and she was monitored post injection. She reported pain relief for seven months, after which her symptoms returned with an additional pain in the 2nd /3rd space on the right foot. A repeat ultrasound scan was requested, revealing a soft tissue mass in the right? 2nd/3rd space. The patient decided to proceed with surgery to remove the soft tissue mass from both the 2nd/3rd and 3rd/4th IM spaces on the right foot.

Verbal and written information on the risks and benefits of surgery was provided and consent obtained to the procedure being performed under a local anaesthetic via a popliteal nerve block. The patient took warfarin 6 mg or 7 mg daily (post heart valve replacement), which she stopped five days prior to surgery and then restarted in the evening after the procedure. Due to her metal heart valve, she required bridging with low molecular weight heparin until after the surgery when she could restart her warfarin.

Patient A was prescribed four days of tinzaparin 15,000iu to be administered every morning at 10am. She was advised to return to her normal warfarin regime in the evening on the day of her surgery. The surgery took place in March and was uneventful. The two soft tissue masses were excised from the second/third and third/fourth intermetatarsal spaces and sent to histopathology for analysis which is the standard hospital procedure.

Following surgery, a haematoma formed at the base of the 3rd toe, which was observed ather first review 5 days following the procedure. The 3rd digit appeared dusky and showed signs of vascular compromise. The patient was taken back to theatres to remove the haematoma. She was placed on a course of flucloxacillin, (previously known to be tolerated) to offset the risk of infection from the haematoma and a second surgery within one week.

The patient was monitored closely, as her foot remained painful. She continued to take 1000mg of paracetamol four times a day which she found sufficient to manage her symptoms without the additional need for opioid based analgesia. Blood tests were requested at her first appointment 5 days following the second procedure, consistent with CKS advice to ‘measure INR 4-7 days after any antibiotic is initiated’ (CKS 2021this ref is not in list and needs a number). This revealed: a normal full blood count (FBC), her ESR was 47mg/L and her INR was 2.3 which was within her therapeutic range.

Patient A was seen twice weekly for dressing changes and to monitor the third toe. Although the circulation appeared to be returning slowly, the digit still looked dusky with signs of vascular compromise. At each review, sterile dressings were applied, and the patient remained on flucloxacillin which she tolerated well. Her INR was checked weekly and three weeks after the initial surgery, it was consistent at 2.3. In addition, her inflammatory markers were monitored to ensure her CRP remained under 5mg/L and her neutrophils were checked to ensure they also remained within normal limits.

Five-weeks after the initial surgery, the skin degloved, which exposed a small area of the proximal phalanx. The patient remained in sterile dressings (changed twice weekly) and the microbiology team suggested changing the antibiotics to co-amoxiclav 500/125 to improve bone penetration. To manage the discomfort, she continued on the 1000mg paracetamol four times daily.

Two weeks later, the head of the proximal phalanx was visible as the ulcer had increased in size. A swab was taken from the exudate which grew anaerobes (main pathogens) and *Staphylococcus aureus*. The anaerobes were sensitive to metronidazole, and the S. aureus was resistant to penicillin, but sensitive to flucloxacillin. Microbiology recommended two to three weeks of 2g once daily i.v ceftriaxone plus oral metronidazole 400mg three times daily for 10 days, with a plan to extend the course if progress was not seen.

Patient A continued to monitor her INR weekly either be attending the hospital or her GP nurse. One week after commencing the ceftriaxone and metronidazole, the INR was 2.9, APTT 38.5 seconds (normal range 30-40) and prothrombin time 44.7 seconds (normal range <20). As the INR remained at a stable level, attention was not focused on the elevated prothrombin time. Patient A was progressing well on the antibiotic regimen and therefore remained on the medication with the above monitoring in place.

Four days later, the patient attended A&E with a painful swollen knee unable to weight bear. An ultrasound scan found the swelling was caused by a bleed behind her knee. On review of her INR and prothrombin time, they had risen to 8.3mg/L and 139.5 seconds respectively in just four days.She was admitted on to the ward and treated with 2mg i.v Vitamin K. Her prothrombin time reduced to 31.2 after six hours and her INR returned to 2.4 within the first 2 days of hospitalisation. The patient remained in hospital for a total of 13 days while her knee and foot were monitored. The ulcer on the 3rd toe was reviewed daily and the dressings changed.

The antibiotics were continued but altered in her second week in hospital to a one-week course of 2g i.v ceftriaxone. After discussion with patient A, the decision was taken to remove the exposed head of the proximal phalanx as the ulcer failed to show any signs of improvement and osteomyelitis was suspected as the bone was visible. Once the bone was removed and the wound closed, she went on to heal successfully and the circulation returned fully to the 3rd toe.

# Discussion

In the case outlined, Patient A was warfarinised at the time of infection management. There was a clear requirement for antibiotic use to manage her post-operative infection and the expectation was for short term duration. This was a calculated risk, based upon the counsel of both the microbiology and antimicrobial pharmacy teams. With the development of haemarthrosis of the knee, this case demonstrates a hypocoagulation effect, probably because of a drug-drug interaction(s) (DDI). However, patient A was on a mixture of antibiotics, making it difficult to determine which drug or combination(s) of drugs provoked the DDI.

Warfarin is a drug with a narrow therapeutic index and small changes to plasma concentrations can result in bleeding or a compromised therapeutic action. Effects of antibiotics on warfarin are poorly defined, but all antibiotics can potentially affect gut flora, which synthesise vitamin K. Lower levels of this vitamin can enhance warfarin action. The other route is via changes to metabolizing enzymes.

Metronidazole is mooted to inhibit the liver metabolizing enzyme family CYP2C9, which could impair the breakdown of warfarin and enhance anti-coagulant effects (Table 1). Ceftriaxone is not metabolized, but is broken down into inactive metabolites by gut flora. This is thought to lower vitamin K levels and increase bleeding risk, because there is reduced opposition to warfarin action.

Flucloxacillin acts in the opposite direction, that is to cause sub-therapeutic levels of warfarin. The mechanism (theoretical) is thought to be increased expression of CYP3A4, as induced by flucloxacillin. This could lead to the increased metabolism of warfarin in the liver and lower circulating levels [7].

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|  | **Flucloxacillin**  | **Metronidazole**  | **Ceftriaxone**  |
| Warfarin 6-7mg/day | Decreased warfarin efficacy.  | Theory: inhibits breakdown;increases anti-coagulation effects | Enhances warfarin action |
| Drug-drug-interaction information | BNF: ‘severe’ ‘potentially alters the anticoagulant effect. Manufacturer advises monitor INR and adjust doseSPC; ‘rare’ cases of altered INR | BNF ‘severe’ & ‘increases the anti-coagulant effect’. Manufacturer advises monitor INR and adjust doseSPC some potentiation of anticoagulant therapy with warfarin | BNF ‘severe’; potentially increases the risk of bleeding events when given with warfarin. Manufacturer makes no recommendation SPC; may increase the anti-vitamin K effect and risk of bleeding |

Table 2: Drug-drug interactions warfarin and the antibiotics used [8] [9] [10] [11] [12] [13].

Although the warfarin-metronidazole interaction is well documented, clinicians continue to prescribe the medications concurrently [12]. An analysis of an electronic decision support system in an outpatient setting revealed that of nearly 10,000 patients receiving warfarin, almost one third were co-prescribed an interacting medication, including both metronidazole and cephalosporins [14].

Zhang et al found a frequency of up to 20% concurrent prescribing for either metronidazole or cephalosporins with warfarin. The combination(s) was also associated with significantly increased likelihood of haemorrhage over warfarin use alone [13]. Further, it has been documented that use of any antibiotic with warfarin in older patients can increase risk of bleeding requiring hospitalization two-fold [3].

Since concomitant prescribing of these drugs may alter INR levels and cause ADEs, it is imperative to appreciate the risks and attempt to minimize them accordingly. Clearly, if alternatives are clinically appropriate, then there may be other options. Otherwise, counselling patients on the risks of bleeding or a thrombotic episode, as well as close monitoring of INR levels are key safety measures.

Increased bleeding is likely to be seen within one to two weeks of initiating antibiotic therapy [13], therefore more intensive INR testing should be instigated within 72 hours and for a period covering the therapy [3]. The CKS states 4-7 days after the start (add REF)- PLEASE ADD IN PROTOCL BEING USEDWhile careful monitoring is mandatory, dosing adjustments might also be needed. Some studies have demonstrated that a reduction of around 30% preemptively was effective in both reducing hemorrhagic event and maintaining therapeutic anticoagulation when antibiotic co-prescription was required [15] [16] [17]. However, there is no standard protocol for this in the UK. Consultation with the medical team e.g cardiology or haematology will be central to decision making.

# Conclusion

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Prescribing antibiotics in conjunction with warfarin is complicated by pharmacokinetic and dynamic variables. The process warrants consideration regarding choice, duration and additional safety netting measures. From this perioperative case report we highlight the following learning points

The INR of Patient A should have been monitored more closely. Ideally this would have been evaluated within 72 hours of commencing antibiotic therapy and should be monitored frequently.

Greater utilisation of the wider multidisciplinary team should have been used, to guide the dosing. For example, the possibility to reduce warfarin dosage may have enabled safer administration of antibiosis by the prescriber through mitigation of hemorrhagic risk.

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