

Case reports

Lessons from practice

Impact of drug interactions when medications are stopped: the often forgotten risks

Erica Y Tong

BPharm(Hons),
MClinPharm,
Senior Clinical Pharmacist¹

Melanie Kowalski

BPharm,
Clinical Pharmacist¹

Gary S Yip

MB BS, FRACP,
General Physician¹

Michael J Dooley

BPharm,
GradDipHospPharm, PhD,
Professor of Clinical
Pharmacy²

¹General Medical Unit,
Alfred Health,
Melbourne, VIC.

²Monash University,
Melbourne, VIC.

e.tong@alfred.org.au

doi: 10.5694/mja13.11361

Clinical record

An 82-year-old man sustained an unwitnessed mechanical fall within his residential care facility, after which he developed lower back pain and intermittent dizziness. On review by his general practitioner 3 days later, he was found to have extensive bruising of his back, buttocks and thighs. Pathology tests 6 days after the fall showed a haemoglobin level of 69 g/L (reference interval [RI], 122–170 g/L). On arrival at the Alfred Hospital emergency department, he had mild abdominal pain, appeared lethargic and displayed clinical signs of anaemia.

Initial investigations revealed a haemoglobin level of 57 g/L, an international normalised ratio (INR) of > 20 (RI, 0.9–1.3), a prothrombin time of > 200 s (RI, 10.6–15.3 s), and an activated partial thromboplastin time of 95.4 s (RI, 26.0–38.0 s). He also had acute kidney injury, with an estimated glomerular filtration rate of 28 mL/min/1.73 m² (RI, > 90 mL/min/1.73 m²; baseline, 40 mL/min/1.73 m²).

His medical history included chronic kidney disease, type 2 diabetes mellitus, atrial fibrillation, pulmonary embolism with associated cardiac arrest, colon cancer and tuberculosis. Tuberculosis was diagnosed 11 months before the current admission on bronchoscopically collected sputum specimens. The treatment regimen was rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, and rifampicin and isoniazid for a further 7 months. He was on chronic warfarin prophylaxis (target INR, 2–3) in the setting of atrial fibrillation. The warfarin therapy was managed by his GP, and all his medications were managed using a dose administration aid. While taking rifampicin, INR monitoring occurred on a 2–4-weekly basis via his usual private pathology service.

He was admitted to hospital and given intravenous phytomenadione 5 mg and Prothrombinex-VF (CSL Biotherapies) 2500 IU, with rapid effect. Subsequently, he was transfused with 5 units of packed red blood cells, with restoration of haemoglobin to 98 g/L 2 days later. Computed tomography imaging showed an intramuscular haematoma in the right gluteal region. There was no clinical evidence of blood loss in any other body compartment, and computed tomography imaging of the brain was unremarkable.

The treating team of doctors and pharmacists reviewed the possible contributing factors to the extreme supratherapeutic anticoagulation, and determined that a drug interaction between rifampicin and warfarin was most plausible. There were no other changes to the patient's medications, health status (such as cardiac or liver failure) or diet, and no concerns about medication preparation or adherence.

Throughout the 9 months of antimycobacterial therapy, his anticoagulation was largely stable on a warfarin dose of 12 mg daily. Before commencing antimycobacterial therapy, his usual warfarin dose was 4 mg daily. His antimycobacterial regimen was ceased by the treating specialist 7 weeks before the current admission.

Five days after admission, warfarin was safely recommenced at 4 mg daily. As a consequence of this case, an education process was instigated by the Pharmacy Department at Alfred Health, to heighten knowledge among clinicians about the clinical implications of the rifampicin–warfarin interaction, especially around the time of rifampicin withdrawal. ♦

The use of rifampicin to treat tuberculosis and methicillin-resistant *Staphylococcus aureus* infections is increasing in Australia, yet it remains a specialised medication that is mostly prescribed by infectious diseases physicians. In contrast, warfarin is widely used — monitored by general practitioners, haematologists, cardiologists or pathology providers — but there are not necessarily mechanisms to reliably notify clinicians of medication changes.¹

Rifampicin is a potent inducer of the hepatic and intestinal cytochrome P450 (CYP) enzyme system and the P-glycoprotein transport system, resulting in the potential for a broad range of clinically significant drug interactions.² The effect of rifampicin on the pharmacokinetics of warfarin has been established since the 1970s,³ but may not be well known to all clinicians engaged in the management of warfarin. The proposed mechanism for the rifampicin–warfarin interaction involves the induction of CYP2C9, CYP3A4, CYP1A2 and CYP2C19.⁴

Following the commencement of rifampicin, our patient's warfarin dose changed from 4 mg daily to 12 mg daily. This demonstrates that the magnitude of the effect of rifampicin on warfarin requirements can be profound — well beyond the effect of the myriad other medications that interact with warfarin. In most cases, the introduction of rifampicin heralds the need to progressively escalate the warfarin dose. As rifampicin therapy is usually continued over several months, patients often become stabilised on a new warfarin dose, and the presence of the rifampicin–warfarin interaction recedes in prominence. Therefore, when the end of the rifampicin treatment course is reached, clinicians often overlook the likely need for reducing the warfarin dose and monitoring the international normalised ratio (INR) more frequently.

After rifampicin is discontinued, the induced CYP enzymes decline in activity over a period of time. This means that the intensive INR monitoring needs to be maintained until it is certain that the drug interaction is no

Lessons from practice

- Important drug interactions must be considered when commencing a new medication and when discontinuing a medication.
- Different prescribers contributing to a patient's care must ensure reliable communication when high-risk medications are used.
- The primary care practitioner, with the aid of prescribing software, remains the central figure in maintaining quality use of medicines.
- Keeping consumers informed and educated about their medications may be a safeguard against adverse outcomes.

longer relevant. Our patient was hospitalised 7 weeks after rifampicin was withdrawn. Previous case reports have shown that the interaction may persist for over 4 weeks after rifampicin cessation.^{5,6}

This case illustrates the importance of promoting awareness of the rifampicin–warfarin interaction. In addition, improved strategies must be developed to ensure that communication is accurate and timely between physicians who are managing antimicrobial therapy and those managing anticoagulant therapy. The challenges posed to the management of warfarinisation by the fragmented nature of medical care have previously been described.¹ In relation to warfarin dosing, this is compounded by the use of subcontracted pathology services, which lack dynamic access to patients' complete health information.

Automated alerts in GP prescribing software and pharmacy dispensing systems are designed to moderate the potential adverse outcomes from drug interactions at the time of medication initiation. However, these aids do not safeguard against adverse outcomes from drug interactions occurring at the time of medication cessation. Educating patients at the point of initiation about interacting drugs and the extra vigilance required when the drug is

later ceased may be a useful strategy in appropriate circumstances.

The novel anticoagulants, such as dabigatran, may also interact with rifampicin; however, there are no laboratory testing methods available to monitor such an interaction.⁷

Serious adverse events may occur if monitoring of warfarin is inadequate on discontinuation of rifampicin therapy. The key elements to avoiding these outcomes include increasing the level of understanding about this interaction among clinicians, improving interclinician communication, creating alert systems at the point of care for doctors and pharmacists, and ensuring that patients are informed about the safe use of medicines.

Competing interests: No relevant disclosures.

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