CASE REPORT

Problems in anticoagulation of a patient with antibiotic treatment for endocarditis: interaction of rifampicin and vitamin K antagonists

Lars Mizera,¹ Tobias Geisler,¹ Klaus Mörike,² Meinrad Gawaz,¹ Martin Steeg¹

¹Klinik für Kardiologie und Kreislaufkrankungen, Universitätsklinikum Tübingen, Tübingen, Germany

²Department für Experimentelle und Klinische Pharmakologie und Toxikologie, Eberhard Karls Universität Tübingen, Tübingen, Germany

Correspondence to

Professor Tobias Geisler, tobias.geisler@med.uni-tuebingen.de

Accepted 25 January 2018

SUMMARY

The cytochrome P450 is a superfamily of isoenzymes that are responsible for the metabolism of many drugs. Significant changes in pharmacokinetics and drug interactions may be due to induction of hepatic cytochrome P450 enzymes. Rifampicin is a common inducer of CYP3A4. We report a case of a 57-year-old woman who was suspected for endocarditis and therefore treated with rifampicin. Due to previous mechanical aortic valve replacement, she also received phenprocoumon for anticoagulation. Although continuing anticoagulant therapy, antibiotic coadministration led to normal international normalised ratio (INR) level. Fifteen days after the treatment with rifampicin ended, INR returned to therapeutic level.

BACKGROUND

Phenprocoumon is metabolised primarily by CYP2C9 and CYP3A4—two different isoenzymes of cytochrome P450.¹ Coumarin derivatives show a particularly narrow therapeutic range. Rifampicin remains one of the first-line antibiotics used in therapy of infective endocarditis. This drug also is a potent inducer of CYP450 enzymes. Coadministration of rifampicin and phenprocoumon may lead to adverse drug events like decreased plasma levels of oral anticoagulants. Here we present a case of an unfavourable drug interaction between phenprocoumon and rifampicin—requiring an alternative anticoagulant therapy.

CASE PRESENTATION

A 57-year-old woman presented to our emergency unit with a history of recurrent fever, diaphoresis, fatigue and loss of weight. As per her medical history, she underwent mechanical aortic valve replacement (19 mm On-XR prosthetic heart valve) due to severe aortic stenosis in April 2013. She also suffered from diffuse coronary artery disease without significant stenosis and mild hyperthyroidism. Her maintenance dose of phenprocoumon was 3 mg once a day. She was self-monitoring her coagulation status using the CoaguChekR system. Physical examination revealed a 3/6 mid systolic heart murmur, best heard in right parasternal region in the second intercostal space and slight peripheral oedema. Laboratory testing showed an elevated C reactive protein with 0.7 mg/dL (cut-off 0.5 mg/dL), anaemia, lymphocytosis, an insufficient

anticoagulation with phenprocoumon (international normalised ratio (INR)=1.6) and normal levels of electrolytes, creatinine and troponin.

In clinical suspicion of endocarditis, transoesophageal echocardiography was performed and showed a 2.5×5 mm vegetation within the left ventricular outflow tract without contact to the prosthetic aortic valve. Immediately after two blood cultures were taken, empiric antibiotic treatment with vancomycin, gentamicin and rifampicin was initiated according to European Society of Cardiology (ESC) guidelines of infective endocarditis for prosthetic valve endocarditis.²

A brain MRI revealed no evidence of cerebral ischaemia, haemorrhage or embolism. Abdominal sonography showed, apart from hepatic steatosis, no evidence of an intra-abdominal source of infection. No aerobic or anaerobic bacteria were found in blood cultures. According to the modified Duke criteria³ with transoesophageal echocardiogram (TOE) showing a vegetation (major criteria) and recent fever (minor criteria) infective endocarditis was possible.

When the patient presented to our emergency department and laboratory testing showed a subtherapeutic INR level of 1.6, additional partial thromboplastin time (PTT)-controlled intravenous unfractionated heparin administration was started immediately. INR and PTT monitorings were performed two times every day to ensure appropriate anticoagulation status. The patient took her usual dosage of phenprocoumon (3 mg) or twice the maintenance dose (6 mg) every day during her hospital stay (figure 1). Antibiotic treatment with rifampicin 600 mg intravenously two times a day resulted in the gradual reduction of the INR level to normal values, even though the therapy with phenprocoumon was continued. A detailed drug history did not reveal any evidence of common CYP450 inducers such as carbamazepine or St John's wort. After discontinuation of rifampicin treatment after 14 days, there was only a slow increase in the INR level over the next days. After a total of 15 days, INR level returned to therapeutic ranges implying that enzyme function returned to normal. Cumulative phenprocoumon intake over 29 days was 141 mg. Average daily intake of phenprocoumon was 4.86 mg.

Two weeks later, transoesophageal echocardiography was repeated and showed no further

To cite: Mizera L, Geisler T, Mörike K, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-215155

Figure 1 Interference of rifampicin with oral anticoagulants. Our patient was treated with 1200 mg rifampicin daily over 14 days. Despite continuing anticoagulant therapy, antibiotic coadministration led to decreased INR levels. Fifteen days after the treatment with rifampicin ended, INR returned to therapeutic ranges. Average daily intake of phenprocoumon was 4.86 mg. INR, international normalised ratio.

evidence of infective endocarditis. Floating structures could not be detected any more neither on the mechanical aortic valve nor within the left ventricular outflow tract. Here, we also found an elevated pressure gradient across the replaced aortic valve ($p_{\max}/p_{\text{mean}}$ 57/30 mm Hg). Later, cinefluoroscopy showed a proper motion of the two leaflets of the mechanical aortic valve.

DISCUSSION

We present a case of a patient, where the INR level decreased to normal ranges because of coadministration of rifampicin. This case also provides some information about how long it takes for the interaction to abate on cessation of the inducing agent. Our patient received phenprocoumon for anticoagulation and 1200 mg rifampicin daily over 14 days for antibiotic treatment. Fifteen days after rifampicin was discontinued, INR returned to therapeutic ranges, indicating that CYP2C9 and CYP3A4 activities returned to the baseline levels. Little information about this process of deinduction is available in the literature. These results are consistent with in vivo studies using cultured human hepatocytes, where a period of 14 days was found to be sufficient for enzyme function to return to baseline levels after rifampicin removal.⁴ On the other hand, Inui *et al* reported a period of 8 days for CYP3A activity to recover after rifampicin withdrawal in healthy subjects.⁵ The time span required for deinduction may be variable. A recent report about two warfarin-treated patients during and after receiving rifampicin cotreatment indicates a difference between CYP2C9 and CYP3A4.⁶ During the process of deinduction, gradually reducing the anticoagulant dose should be guided by close individual INR monitoring.

The molecular mechanism of rifampicin induction is not based on a direct allosteric activation of CYP enzymes, but on enhanced gene expression of CYP3A4 mRNA in hepatocytes. The initiation of gene transcription is mediated by the activation of nuclear pregnane X receptor (PXR) and retinoic acid receptor.⁷ For initiation of gene transcription, the heterodimer of both receptors binds to the promoter region of CYP3A4. The primary task of the nuclear receptor PXR is to detect toxic substances and to increase their clearance. This effect is observed not immediately and depends on pharmacological half-life of the inducing drug.⁸

After the prosthetic valve replacement, lifelong anticoagulation is required to prevent thrombotic events. The latest ECS guidelines from 2012 suggest vitamin K antagonists to achieve a target INR of 2.5 for prostheses with low thrombogenicity like ON-XR heart valves. If the patient has risk factors such as atrial fibrillation, venous thromboembolism or any hypercoagulable state, then with vitamin K antagonist administration an INR of 3.0–4.0 should be achieved.⁹ A PTT-controlled bridging therapy with intravenous unfractionated heparin in patients with mechanical heart valves is without any alternative, while INR is below the therapeutic target. Due to missing randomised controlled studies using low-molecular-weight heparin (LMWH) after mechanical valve replacement, LMWH cannot be recommended for bridging therapy. Direct thrombin inhibitors are also not recommended in patients with prosthetic heart valves. A study testing dabigatran versus warfarin in these patients was terminated prematurely because of major bleeding and thromboembolic events in patients using dabigatran.¹⁰

Apart from drug interactions, there are also different causes of inadequately responding to anticoagulant therapy with vitamin K antagonists than drug interaction. Antibiotics also can reduce vitamin K-producing bacteria in the gut and therefore additionally increase the INR level.¹¹ Sensitivity to vitamin K antagonists like warfarin is determined by the genotype of CYP2C9 and the single nucleotide polymorphisms (SNPs) of the vitamin K epoxide reductase gene *VKORC1*. The allelic variants CYP2C9*2 and CYP2C9*3 are associated with a reduced enzyme activity.

Learning points

- Close control of anticoagulation is necessary in patients with coadministration of CYP3A4 inducers like rifampicin to monitor enzyme function to prevent thromboembolic events.
- In patients who underwent mechanical heart valve replacement, bridging therapy with heparin is without any alternative, when INR is below the therapeutic level.
- Fifteen days after antibiotic treatment with rifampicin ended, enzyme activity returned to baseline level.

Carriers require lower doses of warfarin to maintain therapeutic levels.^{12 13} A C>T polymorphism at position 1173 in intron 1 of *VKORC1* is associated with a decreased metabolism of coumarin derivatives for carriers of the variant T allele. In contrast, carriers of the C allele tend to require more warfarin to achieve sufficient anticoagulation.^{14 15} Also, different heterozygous mutations in the *VKORC1* gene were found in individuals with warfarin resistance.¹⁶

Contributors LM and KM had the idea for the article. LM performed the literature search, wrote the article and is the guarantor. MS, MG and TG revised the publication.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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