None to declare.

References

J Antimicrob Chemother 2012
doi:10.1093/jac/dks290
Advance Access publication 24 July 2012


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Keywords: infectious diseases, ID, antibiotic therapy

Sir,

The new endocarditis treatment guidelines of the BSAC published in JAC recommend the fluoroquinolone and rifampicin combination as the treatment of choice for prosthetic valve bacterial endocarditis.1 We have some concerns about this recommendation.

Although the use of anticoagulants in the treatment of infective endocarditis is controversial due to an increased risk of intracranial haemorrhage, there are critical points about thromboembolic events in patients with prosthetic valve infective endocarditis. A meta-analysis of nine studies that evaluated cerebrovascular accidents, including both haemorrhagic and ischaemic events, associated with anticoagulant use in prosthetic valve infective endocarditis, showed not only no increased risk of haemorrhagic stroke in anticoagulated patients, but also a 4-fold decreased risk of ischaemic stroke.2 In the absence of a consensus statement concerning these two types of cerebrovascular accidents in patients with prosthetic valve infective endocarditis, many practitioners prefer to reconsider anticoagulants soon after the initiation of antibiotic therapy and valve replacement in these patients.

There are few reports of anticoagulant (warfarin) resistance following administration of penicillinase-resistant penicillins (PRPs), including nafcillin, dicloxacillin and flucloxacinill.3–6 The exact mechanism of this interaction has not been fully defined, but increased warfarin metabolism through non-specific enzyme induction with nafcillin has been described.4 In most of these reports, the effects of this interaction initiated within a few days and lasted for 10–15 days after PRP antibiotic cessation, and increased warfarin doses were unsuccessful in overcoming this resistance. Considering a 6 week duration of antibiotic therapy with oxacillins (recommended by the BSAC 2012 endocarditis guidelines1) and an additional 2 week period after the end of antimicrobial treatment, patients may remain unprotected against thromboembolic events associated with the prosthetic valves for an ~8 week period. In addition, due to an unpredictable pattern of warfarin response following oxacillin discontinuation, patients may be placed at increased risk of warfarin overdose after hospital discharge within 2 weeks.

There are few alternatives to warfarin in patients with prosthetic valves. Most of the alternatives are injectable (e.g. heparin and low-molecular-weight heparin) or high cost (e.g. dabigatran), while none of them is approved for this indication. Known antimicrobial alternatives for oxacillins in prosthetic valve bacterial endocarditis caused by Streptococcus spp. and methicillin-susceptible Staphylococcus aureus are first-generation cephalosporins. Interaction between cefazolin (an injectable first-generation cephalosporin) and warfarin is well defined and predictable. Cefazolin may increase the warfarin effect.7

In addition to these considerations, rifampicin itself is a potent inducer of warfarin metabolism and may increase the warfarin dosing requirement in >50% of situations, in order to achieve prothrombin time/international normalized ratio therapeutic goals. As with oxacillins, this effect may remain for >2 weeks after rifampicin discontinuation.8

In conclusion, many practitioners may encounter problems when managing the oxacillin/warfarin interaction and may prefer to not select oxacillins in the treatment of prosthetic valve bacterial endocarditis. It would possibly make it inconvenient to practice according to the BSAC 2012 endocarditis antimicrobial treatment guidelines in this specific category of patients, unless interactions between antibiotics and anticoagulant agents are fully considered.

Transparency declarations
None to declare.

References
1 Gould FK, Denning DW, Elliott TSJ et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the


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Keywords: anticoagulation, rifampicin, flucloxacillin

Sir, Najmeddin and Khalili1 raise an important point about drug interactions, which should always be considered as part of good medical practice. We acknowledge the interaction between rifampicin and warfarin, but note that satisfactory anticoagulation can usually be achieved in clinical practice with careful monitoring. Scottish Intercollegiate Network guidelines on anticoagulation recommend warfarin dosing adjustment when administered with rifampicin, rather than avoidance.2 Clearly, where appropriate anticoagulation cannot be achieved when rifampicin is administered with warfarin, omission of rifampicin, use of an alternative antimicrobial agent and temporary use of an alternative anticoagulant may all be required. In our experience problems with anticoagulation during therapy with a penicillinase-resistant penicillin are rare and would not currently warrant a wholesale change in therapeutic approach. If problems did arise and an alternative to a penicillinase-resistant penicillin was required, we would advise one of the antimicrobial regimens recommended for a penicillin-allergic patient.3 A prospective study of this interaction would seem sensible. Readers should note that the BSAC endocarditis guidelines3 cannot include all potential drug interactions and more detailed therapeutic information, including information in Drug Data Sheets or the British National Formulary,4 should always be sought where appropriate.