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A case of *Streptococcus mitis* endocarditis successfully treated by linezolid

以利奈唑烷治癒緩症鏈球菌引致的心內膜炎

We report the successful treatment of infective endocarditis caused by *Streptococcus mitis* with linezolid in a patient with pre-existing valvular heart disease. The patient had multiple allergies to conventional antibiotics. Linezolid may provide an oral alternative in the treatment of infective endocarditis in patients with adverse drug reactions to traditional antibiotic regimens.

本文報告以利奈唑烷治癒緩症鏈球菌引致的感染性心內膜炎，病者一向患有瓣膜性心臟病，對常用的抗生素有過敏反應。有感染性心內膜炎的病人接受慣常的抗生素治療時，如對藥物有不良反應，可以口服利奈唑烷來代替。

Case report

A 37-year-old man was admitted to hospital on 27 February 2004 with a 6-week history of intermittent fever. He had a medical history of chronic rheumatic heart disease and one episode of infective endocarditis complicated by a cerebrovascular accident that left him with a mild residual right hemiparesis. He had not attended any regular medical follow-up. Medical records for the infective endocarditis that was treated 15 years ago at another hospital could not be retrieved. At that time he had also been diagnosed with beta-lactam allergy due to a generalised skin rash that developed within 1 day of a penicillin injection. During this admission, he reported no recent events, such as dental or endoscopic procedures, that would predispose him to infective endocarditis. He denied any history of intravenous drug use.

On admission, he was febrile with a temperature of 38.5°C. Physical examination revealed no peripheral stigmata of infective endocarditis. Cardiovascular examination revealed merely clinical findings of mitral regurgitation, including soft second heart sound and grade 3/6 pansystolic murmur best heard at the apex with radiation to the axilla. Other systems were unremarkable except for facial asymmetry and mildly reduced power over the right side, possibly due to the previous cerebrovascular accident. Urinalysis revealed no microscopic haematuria or other abnormalities.

Blood tests showed an elevated white cell count of 16.1 x 10^9 /L with neutrophilia. Inflammatory markers, including erythrocyte sedimentation rate and C-reaction protein, were also markedly elevated. Two sets of blood culture, collected at different times, grew *Streptococcus mitis*. The isolates were fully susceptible to penicillin with a penicillin minimum inhibitory concentration of 0.06 μg/mL. Blood culture isolates were also susceptible to linezolid based on the disc diffusion test according to Clinical and Laboratory Standards Institute.[1] Urgent transthoracic echocardiogram

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revealed one vegetation over the mitral valve that was not measured. The patient was diagnosed with infective endocarditis according to Duke Criteria (one major and three minor criteria). In view of the history of beta-lactam allergy, combination therapy with vancomycin and gentamicin was prescribed. Fever subsequently began to subside with improvement in his general status. Nonetheless, a generalised itchy maculopapular rash developed after 4 days and became progressively worse despite the administration of intravenous chlorpheniramine and a reduction in the vancomycin infusion rate to 750 mg over 2 hours.

Vancomycin and gentamicin were stopped and intravenous linezolid at a dose of 600 mg twice daily was commenced. It was well tolerated with complete resolution of the skin rash. A recurrence of fever (up to 38°C) was presumed due to intravenous catheter-related thrombophlebitis. Fever subsided following catheter removal and blood cultures taken on day 4 and day 10 of linezolid therapy were sterile. Another transthoracic echocardiogram performed on day 15 demonstrated complete regression of the vegetation. Intravenous linezolid was switched to oral for another 4 weeks with the same dosing regimen. The patient was discharged on day 16 of linezolid therapy. He remained afebrile and asymptomatic after discharge. In view of the good clinical response to linezolid, with prompt clearance of bacteraemia, the serum bactericidal titre was not measured. On day 32 of linezolid therapy and 1 month after completion of therapy, the patient remained clinically well with normal blood results and no evidence of myelosuppression.

Discussion

Infective endocarditis is a life-threatening condition that requires prolonged, high-dose intravenous antibiotic therapy. Adverse drug reactions are common. Major problems include allergic reactions and drug-induced marrow suppression as well as problems inherent in maintaining long-term vascular access.

This patient presented a difficult problem in selection of appropriate antibiotic therapy because of his allergic reaction to vancomycin and gentamicin, and his previous history of beta-lactam allergy. One option would have been to withhold the antibiotics until the allergic reaction subsided. As the patient remained febrile with active infection, we elected to try a new class of antibiotics, oxazolidinones.

The oxazolidinones act by binding to the 50S subunit of ribosomal RNA to prevent the formation of a 70S initiation complex involved in protein synthesis. Originally developed as a monoamine oxidase inhibitor for the treatment of depression,[2] it was later found to have antimicrobial activity. In the 1970s, it was used to control bacterial and fungal diseases in various plants. After some chemical modifications, antimicrobial agents with good antibacterial activity and reduced toxicity were discovered. Linezolid, the first oxazolidinone, has some potential advantages over conventional antibiotics such as the beta-lactams and glycopeptides. First, linezolid demonstrates excellent in-vitro activity against almost all pathogenic gram-positive organisms, including *Staphylococcus*, *Streptococcus*, and *Enterococcus* species. Resistant organisms, including vancomycin-resistant enterococcus, methicillin-resistant *Staphylococcus aureus*, and intermediate vancomycin-resistant *S aureus*, are also susceptible to linezolid.[3] Second, the drug has an excellent oral bioavailability. It is almost completely absorbed to achieve a serum level comparable with intravenous administration. Third, linezolid is well tolerated by most patients with relatively few adverse drug reactions. One of the major side-effects is bone marrow suppression, although it generally occurs with prolonged treatment longer than 28 days.

Case reports have shown both success[4-7] and failure[8,9] in the treatment of infective endocarditis with linezolid. The patient in this report appears to be the first case of *S mitis* infective endocarditis successfully treated with linezolid and no significant adverse effects.

Most cases of infective endocarditis are caused by gram-positive organisms; *S aureus*, *Streptococcus viridans*, and *Enterococcus* in native valve infection, and coagulase-negative *Staphylococcus* in prosthetic valve infection. Oxazolidinone has excellent antibacterial activity against these common pathogens, including those resistant to conventional antibiotics like beta-lactam and vancomycin. The good oral bioavailability makes early oral switching and outpatient therapy possible. It also prevents the problem of difficult intravenous access and catheter-related infection, unlike other conventional antibiotic regimens. Nonetheless several points need to be considered before using linezolid to treat infective endocarditis. The first-line treatment of a severe life-threatening infection such as infective endocarditis should be a bactericidal agent. Linezolid is considered a bacteriostatic agent as it acts by inhibiting the protein synthesis. It is not known how this will affect the response or relapse rate of patients with infective endocarditis. In addition, there is little

current information about the efficacy of linezolid in treating infective endocarditis. The United States Food and Drug Administration have approved linezolid for the treatment of pneumonia and skin and soft-tissue infection only, not infective endocarditis. The high cost of linezolid may also prohibit its prescription.

In summary, linezolid may provide an alternative for the future treatment of infective endocarditis caused by gram-positive organisms in patients who cannot tolerate more conventional antibiotics. Further systematic studies are warranted to evaluate the efficacy of this new class of antibiotic in treating infective endocarditis.

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