High-dose oral amoxycillin in the treatment of infective endocarditis

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Summary

Oral antibiotic therapy for infective endocarditis is not yet widely accepted. A study was undertaken to assess the efficacy of oral amoxycillin in this condition. Fifteen patients were treated with high-dose oral amoxycillin for 6 weeks. Twelve responded to treatment and remain well at 3 years. There were 3 deaths — 1 at day 7 due to sudden aortic cusp rupture, and 2 late deaths due to pulmonary and cerebral embolism respectively. There was 1 relapse of streptococcal prosthetic valve endocarditis 8 weeks after oral treatment, but this responded to conventional intravenous therapy. Oral amoxycillin is effective in uncomplicated streptococcal endocarditis, and should not be used with prosthetic valve infections.

Intravenous administration of antibiotics has been the treatment of choice for bacterial infective endocarditis. With intravenous therapy adequate blood levels are achieved, compliance is not a problem and the cure rate has been high. The complications of thrombophlebitis and dislodgement of intravenous lines still remain. Frequent changing of drip sites may make therapy unpleasant and inconvenient for the patient.

Despite several reports in the literature, oral antibiotic therapy for infective endocarditis has not been widely accepted. Irregular gastro-intestinal absorption, gastric irritation, and poor bio-availability with older generation antibiotics, gave a low cure rate and thus were not acceptable. The newer antibiotics have better absorptive capacity, and higher blood levels have been achieved with oral therapy.

Amoxycillin is a semi-synthetic penicillin clinically related to ampicillin with a similar broad spectrum of antimicrobial activity. It has excellent intestinal absorption and less protein binding in the serum (17%), thus achieving high and predictable blood levels. Even higher blood levels have been achieved with the concomitant use of probenecid.

The use of high-dose oral amoxycillin in patients with infective endocarditis, with and without positive blood cultures, is reported.

Patients and methods

The diagnosis of infective endocarditis was made clinically and confirmed by blood culture. Where culture was negative, the presence of heart vegetations together with other supporting laboratory and clinical data was considered adequate for the diagnosis.

Fifteen patients with uncomplicated infective endocarditis were treated with oral amoxycillin. Patients were excluded if they were infected with a resistant organism, severely ill, allergic to penicillin, or haemodynamically unstable.

Using aerobic and anaerobic media, 6 - 12 blood cultures were done on each patient. In those patients with positive blood cultures antibiotic sensitivity testing was carried out. Bacteriological investigations such as haemoglobulin level, erythrocyte sedimentation rate (ESR), urea and electrolyte levels, microscopy of urine, and serum immune complexes were carried out before, during and after treatment.

The dose of amoxycillin was 4 - 9 g/24 h (mean 6.4 g) for a period of 6 weeks. Seven of the 15 patients also received probenecid 500 mg twice daily. Antibiotic therapy was monitored by measuring serum bactericidal activity as well as the minimum inhibitory concentration (MIC).

Therapeutic response was judged by clinical improvement in well-being and cardiac status, improvement in laboratory data and bacteriological sterility of the blood.

Results

One patient died suddenly on day 7 after the start of treatment and this was attributed to sudden aortic cusp rupture. The temperature responded to therapy by day 5 in 12 patients and by day 10 in the remaining 2. By the end of the second week all 14 patients had improved as judged by improved well-being and the absence of further peripheral signs. At the end of the third week all but 1 patient remained haemodynamically stable. This patient had worsening of aortic incompetence and required valve surgery. At operation there was no evidence of active infection and the excised aortic valve was sterile.

Laboratory data returned towards normality in 12 patients. One had a delayed response with leucocytosis and raised ESR persisting and this was attributed to sudden aortic cusp rupture. The temperature responded to therapy by day 5 in 12 patients and by day 10 in the remaining 2. By the end of the second week all 14 patients had improved as judged by improved well-being and the absence of further peripheral signs. At the end of the third week all but 1 patient remained haemodynamically stable. This patient had worsening of aortic incompetence and required valve surgery. At operation there was no evidence of active infection and the excised aortic valve was sterile.

Laboratory data returned towards normality in 12 patients. One had a delayed response with leucocytosis and raised ESR persisting into the 4th week. A second patient had persistent haematuria after successful oral therapy. Renal biopsy in this patient showed mesangiocapillary nephritis. In the 9 patients with positive blood culture, bacteriological sterility was evident by the end of the 1st week when repeat blood cultures were performed. To assess the bactericidal effect of oral amoxycillin on the infecting organism, the MIC was measured in 6 patients and found to be less than 0.03 µg/ml. To assess the greatest dilution of serum that inhibited the growth of the isolated organism, serum bactericidal titre (SBT) was measured in 4 patients showing a nadir of 1 in 256, and a peak of 1 in 512.

By the end of 8 weeks 1 patient presented with a relapse of streptococcal endocarditis on the prosthetic valve. Intravenous antibiotic therapy was started with good response but the patient died suddenly of massive pulmonary embolism while awaiting elective cardiac surgery.
Late results

Thirteen of the 15 patients were followed up for up to 3 years; there was no evidence of recurrence. During the follow-up period valve replacement was recommended in 8 patients. Two patients refused surgery and 1 died of a cerebral embolus while awaiting operation. Valve replacement was carried out in the remaining 5 and at operation there was no evidence of active infection on the valves.

Discussion

There has been a reluctance to use oral antibiotics for the treatment of infective endocarditis because until now adequate blood levels could not be achieved. Efficient gastro-intestinal absorption and protein-binding in the serum are important determinants in choosing an antibiotic for oral therapy. However, this study confirms the excellent absorption of amoxycillin from the gastro-intestinal tract; serum protein binding is less than 20% and hence adequate blood levels were assured. The SBT is obtained by titrating the patient's serum against the infective organism to assess the greatest dilution of serum that kills 99.9% of the organisms and should optimally be 1 in 8.2

The relapse rate in this series was 6% and is comparable with that of intravenous therapy (5 - 10%).3 Devastating complications such as major emboli and valve destruction are not necessarily avoided with intravenous therapy and may occur for up to 2 years after successful control of infection. Mortality in this series was 20%. This was not related to oral therapy in that 1 patient died of a massive pulmonary embolus and 1 patient died in cardiogenic shock because of valve disruption before surgery could be undertaken.

The largest series dealing with oral therapy in infective endocarditis is that reported by Gray.4 Ninety patients were treated over a period of 15 years with ampicillin or amoxycillin plus probenecid, showing an excellent response. Seventy-five per cent had positive blood cultures — mainly streptococci. Antibiotic failure occurred in 1 patient with Streptococcus faecalis infection (1,1%). Phillips and Watson5 treated 13 children orally with good response in 10. Three had a second attack — 2 with different organisms — one occurring 4 years later. Pinchas et al.6 followed up 11 orally treated patients for 2 - 4 years. During this period only 1 treatment failure occurred and there were no recurrences. Case reports in the literature confirm the efficacy of oral therapy. 7-10 Prosthetic valve endocarditis poses a special problem when infection occurs late after surgery. Two of the 3 patients in our series responded to oral therapy and remain well. None the less, because of the high relapse rate with prosthetic valve endocarditis, we recommend intravenous therapy as the treatment of choice.

The advantages of oral treatment in endocarditis are avoidance of pain and anxiety of intravenous therapy, reduced complications of indwelling cannulas — abscesses, phlebitis, sepsicaemia and secondary infection, avoidance of prolonged bed rest, and lack of drug inactivation by reaction with infusion fluids. Therapy could be continued at home after 2 weeks of inpatient treatment and is cost-effective. The cost of 6 weeks’ intravenous treatment with penicillin and gentamicin was estimated to be R2000 compared with R150 for a full course of high-dose oral amoxycillin.

Conclusion

The most common infecting organism in bacterial endocarditis is S. viridans,11 especially in Third-World countries where rheumatic heart disease is still rife and poor dental hygiene prevails.

Newer broad-spectrum antibiotics with better absorptive capacity permit more confidence in treating streptococcal endocarditis orally. Monitoring of bactericidal activity of the antibiotic is required.

This report shows that oral therapy of infective endocarditis with high-dose amoxycillin is effective. It should, however, be reserved for naturally occurring streptococcal infections, and not be used for prosthetic valve endocarditis.

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REFERENCES