Successful Therapy of Endocarditis Due to Gentamicin-Resistant Enterococci with Ofloxacin and Ampicillin: A Case Report.

Amorn Leelarasamee M.D.
Suwanna Trakulsomboon M.Sc.

Endocarditis caused by enterococci accounts for 10-30% of the cases in whom bacteria can be isolated from blood. Conventionally, benzylpenicillin 15-24 million units per day or ampicillin 8-12 gm per day plus gentamicin 240 mg per day or streptomycin 1-2 gm per day are drugs of first choice for therapy of the patients and yields approximately 70% cure rate. Although enterococci are usually sensitive to penicillin and ampicillin, the MICs are higher than for the other streptococci. In addition, the enterococci have characteristically been either tolerant or resistant to the bactericidal activity of penicillin. The problem of drug resistance is further complicated by the finding of Murray BE et al who were able to isolate a strain of enterococci that was highly resistant to several aminoglycosides and produced penicillinase bound to the cell wall. At Siriraj Hospital high level resistance to streptomycin and gentamicin is not uncommon and poses real problem for current treatment of enterococcal endocarditis. Vancomycin acts only bacteriostatically and does not qualify as a substitute for gentamicin. Since gentamicin-resistant enterococci are sensitive to newer fluoroquinolones, we reported herein the first case of enterococcal endocarditis successfully treated with ampicillin and ofloxacin at Siriraj Hospital.

CASE REPORT

A 41-year-old doctor was admitted to Siriraj Hospital in July 1987, suffering from a feeling of periodic chill and progressive malaise of three
months' duration. Oral temperature was never above 37.0°C on several records at the time he felt this discomfort. One month before hospitalization, cardiac examination by himself revealed a soft diastolic blowing murmur audible at left sternal border and aortic regurgitation was suspected. Drop beats were also experienced on several occasions. He had no history of parenteral drug abuse and polyarthralgias. Serological test for syphilis was negative. Pertinent physical findings on admission included oral temperature of 36.5°C, blood pressure of 130/60 mm Hg, heart rate of 84 beats per minute with occasional premature ventricular contractions, a grade 2/6 systolic murmur, a grade 2/6 diastolic blowing murmur. Pertinent laboratory findings included mild anemia but normal leucocyte count and differential count, and no microhematuria on urinalysis. A two-D-echocardiogram revealed aortic and mitral regurgitation but no demonstrable vegetation. Fever had never been recorded during the first ten days of hospitalization. Bacterial endocarditis came to suspect when two hemorrhagic spots were simultaneously noticed, one on the retina upon fundoscopy and the other at the soft palate in the oral cavity. Benzyl penicillin was initiated at the dose of 12,000,000 units per days for 10 days. Body temperature began to rise and ranged between 37.0-38.2°C. After 12 days of incubation, enterococci was isolated from three blood cultures and was sensitive to penicillin, ampicillin, ofloxacin but was resistant to streptomycin, gentamicin and amikacin. The minimal inhibitory and bactericidal concentration of various antimicrobials were later studied and the result was shown in Table 1.

The following antimicrobial combination were subsequently used to demonstrate synergistic effect by disc method; penicillin-ofloxacin, ampicillin-ofloxacin, ampicillin-ofloxacin, imipenem-ofloxacin, penicillin-ofloxacin and imipenem-ofloxacin. Synergy was demonstrable only with the combination of ampicillin-ofloxacin, imipenem-ofloxacin and ampicillin-ofloxacin. The time-kill curve (tube method) revealed that 100 or 200 mg/l of ofloxacin reduced the inoculum size (10⁵ CFU/ml) by three logs after 24 hour incubation.

Table 1 Activity of various antimicrobials against enterococci isolated from this patient.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC (mg/l)</th>
<th>MBC (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>0.2</td>
<td>25</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.8</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.6</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Imipenem</td>
<td>0.4</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1.6</td>
<td>100</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt; 2000</td>
<td>25</td>
</tr>
</tbody>
</table>

After the disc susceptibility test was reported, intravenous ampicillin (2 gm every 6 hours) was chosen to substitute for benzyl penicillin since ampicillin was more active against enterococci than penicillin G. However ampicillin exhibits only bacteriostatic activity for this micro-organism and this phenomenon was substantiated later by the study of minimal inhibitory and bactericidal concentrations (MIC and MBC) of ampicillin against the isolated enterococci (Table 1). Since antibiotic combinations are routinely used to exert bactericidal effect in the therapy of enterococcal endocarditis and the isolated enterococci showed resistance to streptomycin and gentamicin, ofloxacin was added on the following day to see if it was able to raise serum bactericidal level. In this case, the addition of oral ofloxacin 900 mg per day to ampicillin increased the trough and peak serum bactericidal levels from < 1:2 to 1:2 and 1:16 to 1:64 respectively. When the result of the MIC and MBC study was known and showed that benzyl penicillin has a lower MIC and MBC than ampicillin, ampicillin was still selected to use since its combination with ofloxacin yielded satisfactory serum bactericidal level.

After a few days of therapy with the two drugs, the patient regained appetite and experienced no more chilly feeling. He was able to tolerate well and was cured after 4 weeks of ampicillin and ofloxacin therapy. Six months later his cardiac function gradually deteriorated due to frequent premature ventricular contractions in spite of intensive antiarrhythmic drugs therapy. Consequently he underwent an aortic valve replacement. At operation a small vegetation was present on the aortic valve, but Gram's stain and cultures of the vegetation were negative. Blood cultures were also negative. No active inflammation was demonstrable in the vegetation upon histological examination. He made a full recovery and did well while on therapy with anti-arrhythmic drugs.

DISCUSSION

Enterococci continues to be important human pathogens in spite of the recent availability of various new broad-spectrum antimicrobials. This is in part due to increasing incidence of high level streptomycin-gentamicin resistant enterococci throughout the world. At our Microbiological Laboratory in Siriraj Hospital, 37% of enterococci clinically isolated, were resistant to 2,000 mg per litre of gentamicin. This finding is of great concern since many strains tested were the causative agent of endocarditis as happened in this reported case. Since bactericidal regimen is needed for therapeutic success in enterococcal endocarditis and the micro-organism is highly resistant to gentamicin, another anti-microbial is needed in addition to ampicillin. To use only ampicillin in this case
may put him at risk of intolerable treatment failure or relapse.

Vancomycin is not suitable for substitution of gentamicin since it is conventionally recommended to substitute for penicillin in penicillin-allergic patient and is used together with gentamicin. Moreover we can not obtain adequate information on the therapeutic effect of the combination of penicillin and vancomycin in enterococcal endocarditis. Its high cost and possible side-effect which are hypotension and tachycardia prohibited us from its use in this case who already experienced cardiac arrhymia and hypotension. Augmentin and imipenem are beta-lactam antibiotics which act principally on the same target as does penicillin. Fluoroquinolone compounds were recently introduced into Thai market and ofloxacin was the only oral antimicrobial agent available at that moment and was active against enterococci.

Although ofloxacin in combination with ampicillin has never been used at this hospital for therapy of enterococcal endocarditis and we were unable to find supportive clinical evidence from world’s English literatures after an extensive search in the library, we felt compelling to select a fluoroquinolone to be added to ampicillin. Hence ofloxacin was chosen to substitute for aminoglycosides because of its convenient administration, i.e., oral route with more than 90% absorption and prolonged half-life with easily attainable therapeutic serum level for this bacteria. In addition, it is very stable since less than 2% of the ingested compound are biotransformed and excreted as metabolites. Most at all, ofloxacin is well tolerated and least expensive among newer fluoroquinolones when cost per day is used for comparison. Unlike gentamicin, renal toxicity is rarely found with prolonged use of ofloxacin.

We don’t know whether the addition of ofloxacin or other newer fluoroquinolones to the combined regimen which consists of penicillin or aminopenicillin and streptomycin or gentamicin for the treatment of enterococcal endocarditis will benefit such patients in term of higher successful therapeutic rate with fewer relapse and shorter duration of therapy if the enterococci are fully sensitive to the three drugs. Our case with endocarditis due to gentamicin-resistant enterococci showed good clinical response to the combination of ampicillin and ofloxacin. A brief duration of therapy with 12,000,000 units of penicillin G can not be accounted for the therapeutic success. Neither ampicillin nor ofloxacin exhibited bactericidal activity against the enterococci isolated when each drug was assayed in vitro test. When various concentrations of ampicillin and ofloxacin were combined in an attempt to show synergy by the time-kill curve technique, synergistic effect was unable to demonstrate even in the test tube containing 400 mg of ampicillin and 200 mg of ofloxacin. Hence the therapeutic success in this case can not be explained on the basis of synergy or bactericidal effect usually exhibited by the combination of the two antimicrobials. In vitro susceptibility test revealed that ciprofloxacin and ofloxacin exhibited good activity against enterococci but their clinical use for treatment of enterococcal infection was never mentioned. We feel that much data with regards to the therapeutic effect of combining newer fluoroquinolone with penicillin or aminopenicillin for enterococcal endocarditis are needed, although newer fluoroquinolones and, in this case, ofloxacin may be goood alternative for aminoglycoside in this condition especially in endemic area of infection due to gentamicin-resistant enterococci.

In search of a new antimicrobial which is able to cope with the increasing problem of resistance among streptococci; teicoplanin, a new glycopeptide antibiotic that is related to vancomycin, exhibits potent in vitro activity against virtually all gram-positive bacteria, including Enterococcus fecalis. Clinical evaluation of teicoplanin for therapy of 7 cases of endocarditis revealed therapeutic success in only two cases. Successful therapy for enterococcal infection with teicoplanin was achieved in only two of four cases. The authors concluded that teicoplanin may not be a potentially effective antimicrobial agent for therapy of bacteremic infections caused by gram-positive bacteria. Hence, there will not be a new and effective antimicrobial to fight against serious infections due to enterococci in the near future. This problem is further complicated by the lack of clinical information available on the therapeutic effect with the combination of amoxycillin and clavulanic acid. Imipenem may provide an alternative but at a very high cost. In view of increasingly resistant enterococci encountered clinically, newer fluoroquinolones, ofloxacin in particular, may prove to offer a new hope to combat the difficult-to-treat infections due to this micro-organism in the near future. Future development of some newer quinolones should be also directed to improve the antibacterial activity against enterococci.

In conclusion, this is a case of endocarditis due to gentamicin-resistant enterococci who responded quite satisfactory to the combination of ampicillin and ofloxacin. Peak and trough serum bactericidal level was 1:64 and 1:2 respectively with the combined regimen. A newer fluoroquinolone may be an appropriate substitute for gentamicin to which the enterococci showed high level of resistance.

REFERENCES


