

# Editorial

## Antibiotics for streptococcal endocarditis

Two groups of bactericidal antibiotics are used to treat streptococcal endocarditis, the penicillins and the aminoglycosides. Vancomycin has a role for highly resistant bacteria or the patient allergic to penicillin. Bacteriostatic agents such as tetracycline and chloramphenicol have no place—for example, even nine days' tetracycline treatment failed to prevent streptococcal endocarditis in a rabbit model,<sup>1</sup> and benzylpenicillin plus chloramphenicol failed in a patient who subsequently recovered on benzylpenicillin alone.<sup>2</sup>

Penicillins are the most used agents. Successful treatment requires enough penicillin at the target site within the bacterial cell wall, which implies absorption (if oral), enough free drug (as opposed to protein-bound) in the serum to allow diffusion into the valve, penetration into the bacterial cell wall, and finally selective action on whichever of the different penicillin-binding proteins is the critical target. Even then penicillins act only on bacteria about to multiply, and so do not kill all the organisms in a population at once. Bigger<sup>3</sup> found that at least three days' exposure to benzylpenicillin was needed to sterilise a culture of sensitive staphylococci, and called the survivors "persisters". As penicillins act on the bacterial cell wall, the bacteria are killed indirectly by osmotic lysis caused by the high pressure of bacterial cytoplasm (up to 20 atmospheres inside a streptococcus).

Commonly used agents are benzylpenicillin, phenoxymethylpenicillin, and amoxycillin (or ampicillin). Benzylpenicillin is given by parenteral injection; 50% is protein-bound, and although less bacteriostatic to enterococci than amoxycillin, it seems slightly more bactericidal.<sup>4</sup> Phenoxymethylpenicillin, amoxycillin, and ampicillin have been used for orally administered prophylaxis and therapy of *S. viridans* infections. Amoxycillin is well absorbed (absorption is independent of gastric content), giving twice the blood levels of an equivalent dose of ampicillin, and so a longer period of adequate levels before excretion. Moreover it is only 20% protein-bound, unlike phenoxymethylpenicillin which is 80% protein-bound. Thus amoxycillin may have

an increasing use in prophylaxis, especially against enterococci, and for oral treatment if this is attempted. Shanson *et al*<sup>5</sup> showed that a 2 g dose taken one hour before tooth extraction reduced the bacteraemia from 14/14 in control subjects to two out of 14 in those taking the antibiotic. Oakley<sup>6</sup> commends this as simple prophylaxis before dental manipulations.

The two aminoglycosides commonly used for endocarditis are streptomycin and gentamicin. There is long experience of the successful use of streptomycin. Gentamicin, although relatively new, has now been widely used in other infections for 10 years and enough experience has been gained to allow its safe and rational use with adequate dosage schedules and appropriate monitoring of cases in renal failure. As a result, the overcautious initially recommended standard dose has been increased from 40 to 120 mg three times daily. Furthermore gentamicin is virtually non-protein-bound, compared with 35% for streptomycin. Thus although higher blood levels are obtained with streptomycin, the actual effectiveness of gentamicin against enterococci will be double that of streptomycin.

Vancomycin is bactericidal to Gram-positive cocci and diphtheroids, and acquired resistance has never been reported. Like benzylpenicillin it works on the bacterial cell wall, but probably has another action, possibly on the membrane, as it does not induce L-forms. Only 10% is protein-bound. Vancomycin was eclipsed by the semi-synthetic penicillins but has remained available. Hook and Johnson<sup>7</sup> reported on its successful use and noted that phlebitis, fever, rashes, and rare instances of renal damage after therapy were probably caused by impurities present in early formulations, which have since been removed to leave a less toxic agent. Hearing loss occurs with sustained serum levels above 80–100 µg/ml, but by maintaining levels below 50 µg/ml no serious toxicity was found. *Vancomycin revisited*<sup>8</sup> recorded the successful therapy of five patients, three in combination with an aminoglycoside without obvious harm.

Erythromycin is relatively bacteriostatic and

resistant mutant bacteria are common, so it has a restricted role. It is usually used in combination therapy, but has been recommended for oral prophylaxis during dental manipulations in the benzylpenicillin allergic patient, for which many prefer it to vancomycin on grounds of ease of administration, cost, and lack of toxicity. Erythromycin is only 20% protein-bound and has been used with vancomycin to treat a variety of infections.

Hook and Guerrant<sup>9</sup> have summed up the requirements for successful endocarditis treatment: use bactericidal antibiotics whose efficacy on the infecting organism has been checked by *in vitro* bactericidal tests, give prolonged parenteral therapy, monitor serum bactericidal levels, and finally resist compromise. However three "traditional" controversies recur throughout endocarditis literature—single or combined therapy, continuous or bolus doses of antibiotic, and oral versus parenteral therapy. The duration of treatment is also worth exploring. Shorter courses of antibiotics would be cheaper and would perhaps have fewer side effects.

Most reported trials of treatment necessarily span a decade or more and include varying regimes. Pelletier and Petersdorf<sup>2</sup> note the need for a properly controlled prospective trial, and the National Institutes of Health have recently asked for applications for contracts to study the problem.<sup>10</sup> Meanwhile published reports are full of argument. *The Journal of the American Medical Association* of 27 April 1979 provides a good example. Articles by Karchmer *et al*<sup>11</sup> and Malacoff *et al*<sup>12</sup> conclude that single agent therapy is satisfactory for benzylpenicillin-sensitive *S. viridans* endocarditis. However, Resnick and Cohen's editorial<sup>10</sup> based on the mode of action of the antibiotics and experimental work in rabbits and other clinical studies refutes the papers, and reiterates Bryant and Kimbrough's recommendation<sup>13</sup> of 1.2 million units of penicillin given parenterally six-hourly for one month together with 0.5 g of streptomycin twice daily for two weeks. The recommendations are based on rabbit studies<sup>14</sup> and the clinical work of Wolfe and Johnson<sup>15</sup> and others. Oral phenoxymethylpenicillin has been used as an alternative with or without an aminoglycoside. Tan *et al*<sup>16</sup> concluded that two weeks of phenoxymethylpenicillin and streptomycin was adequate for the "mild" case while longer treatment was needed for the seriously ill or those slow to respond. Gray<sup>17</sup> reported good results in 65 patients after oral therapy originally with phenoxymethylpenicillin and later with amoxy-

cillin plus concomitant administration of probenecid. This therapy had to be reviewed on four occasions only.

Publications on continuous infusion versus bolus doses of benzylpenicillin are somewhat inconclusive. Penicillins are rapidly excreted by the normal kidney so that bolus doses result in alternating peaks and troughs of serum benzylpenicillin. Most authors—for example, Hook and Guerrant<sup>9</sup>—suggest continuous infusions as a matter of convenience where large doses are envisaged, but some prefer to avoid the hazards associated with an indwelling cannula. Oakley<sup>18</sup> regards the problem as solved in favour of the bolus dose, presumably on data that show better penetration into clots in a rabbit model, in which two hourly bolus doses were given. However Eagle<sup>19</sup> described the inhibitory effect of too high a benzylpenicillin concentration on the killing of certain strains of bacteria (notably enterococci), and Hamburger<sup>20</sup> found that the outcome of therapy for staphylococcal endocarditis in dogs related to the length of time bactericidal blood levels of 1:2 were sustained, rather than to the peak level attained after a dose.

The Papworth practice is to use combined therapy with benzylpenicillin and gentamicin for all streptococcal infections. We give the benzylpenicillin by the slow intravenous infusion of 20 million units per day, using a syringe pump so that the antibiotic is given in a small volume of saline, and does not have to be added to dextrose. The small amount of fluid involved is unlikely to embarrass a potentially failing heart. We prefer gentamicin to streptomycin because of its better activity. There is now considerable experience in the laboratory control of gentamicin therapy, built up through its use in other infections, including those complicated by renal failure. Levels are monitored to ensure peaks of 8–10 µg/ml and troughs of <3 µg/ml. The regime for "viridans" streptococci is used for two weeks. Then oral phenoxymethylpenicillin is substituted, and the dosage adjusted to give suitable bactericidal blood levels (usually about 8 g per day). This treatment has in the past been continued for another four weeks, but current feelings are that it may be reduced to two. We prefer phenoxymethylpenicillin to amoxycillin because the latter has a wider spectrum of action and selects out nosocomial organisms such as *klebsiella* which will colonise the patient's nose and throat, and could be a hazard if open-heart surgery is required. For therapy of enterococcal endocarditis, penicillin-resistant "viridans"

streptococci, culture-negative patients, and those referred after failure of therapy (usually because of inadequate penicillin dosage) our practice is to give the intravenous benzylpenicillin and intramuscular gentamicin for a month and then change to oral phenoxymethylpenicillin for two weeks. Vancomycin is used for the allergic patient. Despite the rabbit data, Hook and Guerrant<sup>9</sup> with 82% cures from benzylpenicillin and streptomycin (although two patients had shown no improvement on benzylpenicillin alone) do not wish to abandon this for something unproven and potentially more toxic. They note that streptomycin can be given four times daily to avoid too high peak serum levels, as ototoxicity appears to depend on the height of the peak.

Although ampicillin and amoxycillin have a better inhibitory effect against enterococci, there seems little difference in the bactericidal activity. Side effects with these agents are more common than with phenoxymethylpenicillin, and the effect on the normal bacterial flora is greater. Thus we prefer to avoid their use as final back-up therapy. However a case of successful therapy with oral amoxycillin and intramuscular streptomycin has been reported in a patient who could not tolerate an intravenous infusion.<sup>21</sup>

Once treatment has been started the avoidance of compromise becomes vital. Sometimes the patient's fever fails to settle, or settles and recurs. The diagnosis may be queried, and a different infection postulated. The answer is usually—NO. This situation is likely to be caused either by infarction from an embolus thrown off the valve (even if the embolus is sterile), or benzylpenicillin allergy, or immune complex disease. However a rare but sinister possibility is reinfection or septicaemia from an organism acquired via the intravenous drip.

The benzylpenicillin-allergic patient presents a problem. The history of allergy must be established. Many of those allergic to ampicillin are not benzylpenicillin-allergic. For the truly allergic patient Bryant and Kimbrough,<sup>13</sup> among others, suggest desensitisation or adding steroids. The only patient we treated with steroids threw off a large embolus into his brain. Since that incident we prefer to use vancomycin or possibly a cephalosporin.

The antibiotic treatment of streptococcal endocarditis is gradually approaching standardisation, but even when the optimal treatment is worked out, a considerable mortality will remain. However, the complementary role of early surgical excision of the infected valve is now being widely

explored, and should lead to a further improvement in the prognosis.

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