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Once weekly azithromycin in secondary prevention of rheumatic fever

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KEYWORDS

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ABSTRACT

Rheumatic fever and rheumatic heart disease (RHD) are still important problems in developing countries. Secondary prophylaxis which is the most cost-effective method in preventing recurrences of rheumatic fever is fraught with problems of drug compliance. The utility of 500 mg once weekly azithromycin (AZT), an orally effective long-acting antibiotic was evaluated against oral penicillin (phenoxy methyl penicillin 250 mg twice daily) in this study. Forty-eight consecutive patients (44% males, mean age 29.4 years) with established RHD were randomised into two groups—26 patients received AZT and 22 received oral penicillin. Patients were evaluated at randomisation, at 1 month, 3 months, and 6 months, clinically, serologically and by throat swab culture. End points were absence of streptococcal colonisation, infection or fever at the end of 6 months. During the study, 4 patients (15.4%) in the AZT group developed sore throat and fever, had positive throat culture and positive serology indicating streptococcal infection. None satisfied the criteria for rheumatic fever reactivation. None in the oral penicillin group developed streptococcal infection. In conclusion, weekly 500 mg of AZT is not effective in the prevention of streptococcal throat infection compared to oral penicillin therapy in adult patients with established RHD.

Introduction

Rheumatic fever and rheumatic heart disease (RHD) are still important problems in developing countries like India.[1–4] Recurrent subclinical or manifest streptococcal infection and rheumatic carditis will lead to the development or progression of rheumatic valvular lesions.[3]

Secondary prophylaxis is the most cost-effective method in preventing recurrences of rheumatic fever.[5–7] Of the available options, injectable benzathine penicillin is better than oral penicillin or sulfadiazine.[8] The main problem with the different regimens of secondary prophylaxis is compliance.[9,10] So, we are on the look-out for safer alternatives with improved patient compliance.

Azithromycin (AZT) is an orally effective antibiotic and there are reports highlighting its utility in the prevention of streptococcal infection.[11–13] It has a long half-life and hence can be given once a week. The effectiveness of once weekly oral AZT in preventing group A beta haemolytic streptococcal throat colonisation, infection, and acute rheumatic fever was evaluated against oral penicillin in this study.

Methods

Consecutive patients attending the RHD clinic of SCTIMST, who were initiated on oral rheumatic prophylaxis for the first time, and willing to be followed up as per protocol, not allergic to pencillin and AZT were randomised to receive either weekly 500 mg AZT orally or phenoxy methyl penicillin 250 mg twice daily were included in this open label study. Patients who were changed over from injectable benzathine penicillin to oral penicillin for many reasons (e.g. non-availability) were also included. All patients gave a formal informed consent. The study was approved by the departmental ethics committee.

The following definitions were made.

1. Streptococcal colonisation: those with positive throat culture alone.
2. Streptococcal throat infection: those associated with positive throat swab culture and two-fold rise in anti-streptolysin-O (ASO) titre.

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3. Rheumatic fever: diagnosis based on modified Jones criteria (World Health Organization [WHO] 2003 modification).[4]
4. Cure of group A beta haemolytic streptococcus (GABHS) infection was defined as negative throat culture at the end of 10 days of antibiotic treatment. Further evaluation for rheumatic fever recurrence was done at 3 weeks.

Every attempt was made to prevent rheumatic reactivation following a throat infection during the study period. All patients were instructed to report immediately if they developed sore throat for evaluation and 'sledgehammer treatment' as per WHO recommendation[4] was initiated at the earliest, to eradicate the nidus of infection.

It was planned to cross over the groups if recurrence of throat infection occurred. A third recurrence was taken as an indication to change over to benzathine penicillin. Patients were evaluated at randomisation, at 1 month, 3 months and 6 months, clinically and by ASO and throat swab culture. End points were absence of streptococcal colonisation, infection or fever at the end of 6 months.

Laboratory studies

Lab personnel were blinded with regard to the treatment arms. Throat culture, antibiotic sensitivity and serology were done by standard methods. Throat swab was obtained and immediate plating was done in blood agar. Gram-stain was done after 48 hours of culture and sub-culture was done whenever necessary. Anti-streptolysin-O titre was estimated using latex agglutination in serial dilutions.

Results

There were 48 patients in the study who were randomised into two groups—26 patients receiving AZT and 22 receiving oral penicillin. Twenty-one patients (44%) were males and the mean age was 29 years, and the median age was 30 years for the whole group. Nineteen patients (%) were from poor socio-economic class. Base line characters were comparable in both groups (Table 1).

Twenty-five patients (42%) gave a prior history of rheumatic fever (Table 2). The median age of first attack of rheumatic fever obtained from history was 11.5 years. All patients who had rheumatic fever reported antecedent sore throat at the time of their first ever attack. Mitral valve disease was the most common RHD of which mitral stenosis was the predominant lesion.

Most patients were in New York Heart Association (NYHA) functional class II symptom status (56.3%). Rest of the patients were in class I, 94% of the patients were in normal sinus rhythm, while the rest had atrial fibrillation.

One patient among the 48 had an episode of rheumatic fever 2 months prior to the enrolment, for which he received treatment with aspirin for 6 weeks. None of the other patients had recent history of rheumatic fever. None of the patients at entry to the study had isolation of GABHS from throat culture or history of rheumatic fever.

Table 1
Baseline characteristics.

	Azithromycin*	Penicillin*
n	26	22
Mean age (yr)	29.2	30
Sex (male)	11	10
Low socio-economic class (%)	54.6	45.4
History of rheumatic fever (%)	54	50
RHD		
MS	13	12
MR	4	5
AR	4	3
Sinus rhythm	24	21
Symptom class		
NYHA class I (%)	45	55
NYHA class II (%)	51	43

*P=not significant. AR: aortic regurgitation, MR: mitral regurgitation, MS: mitral stenosis, NYHA: New York Heart Association, RHD: rheumatic heart disease.

Table 2
Data on first attack of rheumatic fever (n=25).

Mean age (yr)	11.8
Fever (%)	50
Sore throat (%)	50
Arthritis (%)	41
Chorea	Nil

Table 3
Features of patient who had sore throat while on azithromycin prophylaxis.

Age	Sex	SES	Valve lesions	Clinical features	Time of recurrence (mo)
24	M	L	Mild MR	Sore throat, cervical adenopathy	3
31	M	L	Post BMV	Sore throat	3
42	F	H	Mild MR	Sore throat, cervical adenopathy	1
37	F	H	Mild MS, MR	Sore throat	2

BMV: balloon mitral valvotomy, MR: mitral regurgitation, MS: mitral stenosis, SES: socio-economic status.

Median duration since the last episode of rheumatic fever in the study population was 10 years. Two patients in the AZT group and 3 patients in the penicillin group gave history of throat pain lasting 3–4 days within the last 1 year prior to entry into the study. One patient had received antibiotics from the local doctor. None of the remaining patients had consulted a doctor for the sore throat.

During the study, 4 patients (15.4%) in the AZT group developed sore throat and fever. Cervical lymphadenopathy was seen in 2 of them. All 4 patients who had throat infection had positive throat culture for group A streptococcal (GAS) and elevated ASO indicating GAS infection of throat. None satisfied the criteria for rheumatic fever reactivation.

The clinical details of patients who suffered of GABHS infection while on prophylaxis are outlined in Table 3. All patients who had sore throat reported within 3 days of onset of

symptoms since they were instructed to do so. 'Sledgehammer' therapy was initiated as per the WHO recommendation.[4] On follow-up for 4 weeks, no evidence of rheumatic reactivation was confirmed in any of them. Acute phase reactants (C-reactive protein) erythrocyte sedimentation rate (ESR), and PR interval in electrocardiogram remained normal.

As per the protocol, these patients were put on oral penicillin prophylaxis. No further recurrence of infection occurred in any of the patients. Three patients (11.5%) in the AZT group complained of symptoms of gastric irritation, but they could tolerate the drug, so the treatment was continued. None of the patients in the penicillin group reported of any gastrointestinal problem.

The mean follow-up period was 12.2 ± 2.3 months. Patients who had failure of AZT therapy was initiated on oral penicillin prophylaxis and after a mean follow-up of 7.2 months none of the 4 patients had any recurrence of sore throat or rheumatic fever.

The status of valvular lesions and cardiac function remained the same throughout the study period in all patients. None required hospitalisation for any purpose.

Since the AZT group had significant failure, all patients were started on rheumatic prophylaxis with oral penicillin at the end of the study, except for 1 patient who was allergic to penicillin was started on erythromycin 250 mg twice daily.

Cost-effectiveness—Treatment cost of weekly oral 500 mg AZT and twice daily 250 mg oral penicillin is the same.

Discussion

Rheumatic fever and its sequelae, RHD is still an important public health problem in developing countries.[1–4] The compliance to different prophylactic regimens is relatively poor.[9,10]

Azithromycin, with a long half-life, which can be administered once weekly was thought to improve the compliance.[14] So we decided to study the effectiveness of AZT in the secondary prophylaxis of rheumatic fever.

Females predominated (58%) in our study population in contrast to the male predominance in a usual cohort of RHD patients.[14] This was because there is a referral bias for patients with mitral valve disease who were referred to our hospital for percutaneous and surgical interventions.

We could enrol only patients with established RHD, since ours is a tertiary care centre. No patient at entry into the study had isolation of GABHS in throat culture or had features of acute rheumatic fever.

Median age of the study population was 30 years. This is because of the referral bias of our centre, which primarily caters to those patients requiring valvular interventions. We included older patients who changed over from benzathine penicillin to oral penicillin in the study population.

Past history of rheumatic fever was present in 50% of our patients. This is in concordance with the studies reporting prevalence of this history in patients with established RHD.[15,16] Incidence of arthritis in our population was 41%, though in the literature it is 75%. It is reported that arthralgia predominates in the Indian population rather than arthritis.[17]

None of the patients in the penicillin group had treatment failure, i.e. either GAS throat infection or colonisation. But the reported streptococcal throat infection rate in patients under 'good' oral penicillin prophylaxis is 7.3–16.2 per 100 patient years.[18,19]

A significant number of patients (15.4%) in AZT group in our study had GABHS throat infection as evidenced by clinical pharyngitis, positive throat culture, and elevated ASO titre. However, none had recurrence of rheumatic fever as per the modified Jones criteria. After curative treatment, when the treatment was changed over to penicillin, no recurrence was noted.

There are no data in the literature on the use of AZT in the secondary prophylaxis of rheumatic fever. But there are reports of the successful use of once weekly AZT in preventing colonisation and recurrences of streptococcal throat infections.[11,12]

Gray et al.[12] reported superiority of weekly oral AZT in the prevention of upper respiratory infection over penicillin when used as prophylaxis in 1016 US marine trainees at high-risk of respiratory disease. Azithromycin group reported less side-effects, respiratory symptoms and serological evidence for sterptococcal, mycoplasmal, and chamydial infections.

However, there is a report by Ghirga[20] on the occurrence of rheumatic fever after a successful treatment of GAS throat infection by AZT.

Our study showed a recurrence of infection as high as 15.4%. This is definitely high for this small cohort of patients. It is possible that these patients with established RHD constitute a high-risk group.

Why AZT failed to prevent GAS infection in 15.4% of patients is not very clear. One possibility is that drug dosage was too widely spaced. Though AZT has a long half-life, drug concentration might not have been adequate in this high-risk population at the end of the dosage interval.

Treatment with a 3-day, once daily 10 mg/kg AZT for GABHS pharyngitis is associated with similar high levels of clinical efficacy, but lower levels of bacteriologic eradication, than with 10-day 100,000 IU/kg/day penicillin V.[21]

Casey et al.[22] in a meta-analysis has reported that in children, AZT administered at 60 mg/kg per course was superior to the 10-day course of penicillin, with treatment failure occurring 5 times more often in patients receiving penicillin. Azithromycin administered at 30 mg/kg per course was inferior to the 10-day courses of penicillin, with bacterial failure occurring 3 times more frequently in patients receiving AZT. Three-day AZT regimens were inferior to 5-day regimens. So, AZT treatment may be required in higher doses and for a more prolonged duration to be effective in preventing recurrences of GABHS throat infection. Azithromycin treatment was cost-effective in the regimen which we used in this study. If we increase the dosage or the frequency, it may not be cost-effective.

Other possibilities of failure of AZT might include poor patient compliance, failure of the drug to reach adequate concentration in the mucosa, microbial tolerance to AZT, recurrent exposure of patients to virulent strains of GAS, suppression of natural immunity and disturbance of normal

flora of throat. Azithromycin inhibits growth of alpha streptococci that are normal defenders of pharyngeal mucosa against pathogens at lower MIC.[23]

Intracellular accumulation of macrolides have been shown in leucocytes but not in epithelial cells, which are probably the principal cells targeted by GABHS. In leucocytes AZT accumulates predominantly in lysosomes, whereas intracellular GABHS is found in phagosomes and cytosol.[24]

Recently single 2.0-g dose of AZT microspheres has become available and found to be as effective and well tolerated as a 7-day course of extended-release clarithromycin in the treatment of adults with mild-to-moderate community acquired pneumonia.[25] A further advantage of single-dose therapy is the potential for use as directly-observed therapy, which may be useful in prophylaxis of rheumatic fever.[26]

In conclusion, weekly 500 mg of AZT is not effective in prevention of streptococcal throat infection compared to oral penicillin therapy in adult patients with established RHD.

It is worthwhile evaluating newer long-acting preparations of AZT as the compliance rate of the available regimens are very poor.

Limitations

1. Age of the study population, well above the usual age of rheumatic fever, 5–15 years.
2. Small number of patients.
3. All patients were having established RHD.
4. Microbiological studies to assess the rheumatogenicity of streptococcal strains were not undertaken.

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