Comparison of the effect of benzathine penicillin G, clarithromycin, cefprozil and amoxicillin/clavulanate on the bacteriological response and throat flora in group A beta hemolytic streptococcal tonsillopharyngitis

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SUMMARY: Yıldırım İ, Ceyhan M, Gür D, Kaymakoğlu İ. Comparison of the effect of benzathine penicillin G, clarithromycin, cefprozil and amoxicillin/clavulanate on the bacteriological response and throat flora in group A beta hemolytic streptococcal tonsillopharyngitis. Turk J Pediatr 2008; 50: 120-125.

Bacteriological failure with penicillin that has been used widely for years in group A beta hemolytic streptococcal (GABHS) tonsillopharyngitis is being reported as high as 30%. Because of this unresponsiveness, many different agents are being used as alternative options. We evaluated the effect of clarithromycin, amoxicillin/clavulanate (CAM), cefprozil and benzathine penicillin G (Pen G) on the bacteriological cure, beta-lactamase production, pharyngeal microflora and alpha hemolytic streptococci (AHS) when used in the treatment of pediatric GABHS tonsillopharyngitis. Intramuscular Pen G and oral clarithromycin, CAM and cefprozil were administered to 70 patients who were between 2-16 years of age. Three throat swabs were obtained from each patient (before treatment, and 3 days and one month after treatment). The cultures were evaluated for aerobic and anaerobic bacteria, beta lactamase production, AHS and fungi isolation. Bacteriological cure rates were similar in the four treatment groups ($p>0.05$). Isolation rates of AHS were 97.1% and 77.9% in clarithromycin group, 100% and 83.8% in CAM group, 97.2% and 98.6% in cefprozil group and 100% and 83.8% in the Pen G group before and after treatment, respectively. The most prominent inhibitory effect on AHS was observed with CAM, while cefprozil had the least effect ($p<0.001$). No significant difference was noted among groups regarding beta-lactamase production, anaerobic bacteria, Gram negative bacteria and fungi isolations. Overall, cefprozil seems to be advantageous in GABHS eradication by having less inhibitory effect on AHS.

Key words: GABHS, treatment, bacteriological failure, antibiotics, tonsillopharyngitis, alpha hemolytic streptococci.

Oral penicillin has been the drug of choice for the therapy of group A beta hemolytic streptococcal (GABHS) tonsillitis for the past several decades. After the reports indicating nearly 30% treatment failure, cephalosporins and macrolides were used as alternative antibiotics[1]. Isolation of beta-lactamase-producing bacteria (BLPB) and ideas about the role of BL in these clinical failures have lead to use of beta-lactam/beta-lactamase inhibitor combinations such as amoxicillin/clavulanate (CAM) in some centers.

The cause of treatment failure with penicillin has been studied by many authors. With the results of these studies, it has been postulated that normal throat flora, especially alpha hemolytic streptococci (AHS), have the capacity to inhibit the growth of GABHS[2]. The existence of BLPB in the throat flora has also been mentioned as a reason for treatment failure in GABHS tonsillitis treated with penicillin[3,4].

Oral penicillin, macrolides, cephalosporins and beta-lactam/beta-lactamase inhibitor combinations have been compared for their

effectiveness in streptococcal pharyngitis in several studies[5-8]. Most of the trials compared oral penicillins as the standard therapeutic drug with an alternative antibiotic. Treatment failures were evaluated by investigating the effect on AHS, anaerobic flora and BL induction in some recent studies, and superiority of cephalosporins against oral penicillin was shown in most of them[8].

Although 10-day therapy with oral penicillin is the first-line treatment of pediatric GABHS tonsillitis in developed countries, giving oral drugs 3 to 4 times a day for 10 days is difficult in developing countries because of low educational and social levels. In those countries, one dose intramuscular benzathine penicillin G (Pen G) is the drug of choice in GABHS tonsillitis. However, the effect of Pen G on clinical cure and throat flora has not yet been compared with alternative drugs such as cephalosporins, macrolides and beta-lactam/beta-lactamase inhibitor combinations.

Therefore, the present study aimed to compare the effects of Pen G, a cephalosporin (cefprozil), a macrolide (clarithromycin) and a beta-lactam/beta-lactamase inhibitor combination (CAM) on throat flora (AHS) after the treatment of GABHS tonsillitis and clinical correlation of this effect. The negative effect on normal flora was also evaluated by identifying the situation of anaerobic bacteria, BLPB and staphylococcal and fungal colonization.

Material and Methods

Patients

A total number of 70 patients admitted to Hacettepe University İhsan Doğramacı Children's Hospital outpatient clinics over six months were enrolled in the study. The study was explained to the parents and written informed consents were obtained. A history and physical examination were completed and a throat culture was obtained. Eligibility criteria were as follows: age between 2 and 16 years and signs and symptoms of acute tonsillopharyngitis such as sore throat, fever and GABHS isolation in throat culture. Subjects who had received antimicrobials during the previous month and those with a history of hypersensitivity to the study drugs were excluded.

Therapy

One of the following antibiotics was given to the patients randomly when the throat culture was positive for GABHS: 1) Clarithromycin 20 mg/kg per day divided into two doses, given orally for 10 days; 2) CAM 80 mg/kg per day divided into two doses, given for 10 days; 3) Pen G 600,000 IU for patients aged 6 years or younger and 1.2 million IU for children over 6 years of age given as a single injection; and 4) Cefprozil 30 mg/kg per day divided into two doses, given for 10 days.

Microbiological Evaluation

The first throat swabs were taken before the treatment and the second one three days after the treatment. In the Pen G group the second swab was taken 21 days after the completion of treatment. In all groups, a third throat culture was obtained one month after the treatment. The specimens were obtained by rotating a tonsillar calcium alginate swab over the surface and down into the crypts of the tonsils. Swabs were immediately placed in appropriate transport media and promptly sent to the hospital microbiology laboratory where they were processed by laboratory personnel unaware of the treatment group assignment. The tonsillar swabs were inoculated on sheep blood agar and chocolate agar and incubated at 35°C in 5% carbon dioxide for up to 48 hours. A reduced, enriched thioglycolate broth with vitamin K and hemin was used and the culture plates were incubated at 35°C under anaerobic conditions with the use of a gaspack pouch (Becton Dickinson Microbiology Systems, Cockeysville, USA) for anaerobic bacteria. All cultures were evaluated for aerobic and anaerobic bacterial and fungal growth. AHS growth was also evaluated. Aerobic and anaerobic bacteria were determined by using conventional methods[4]. BL activity was tested by a chromogenic assay using nitrocephin (Glaxo, Middlesex, England) as substrate. Rate of AHS isolation was determined by dividing agar surface into four quadrants. Quantitative estimation of these bacteria was made on a scale of 1+ to 4+ according to their presence in the four quadrants (Fig. 1).

Statistical Methods

Analysis was performed by using SPSS (Release 12.0; SPSS Inc., Chicago, USA) statistical software. Treatment differences were assessed with the use of ANOVA and $\chi 2$. In all tests, a 0.05 significance level (p) was used.

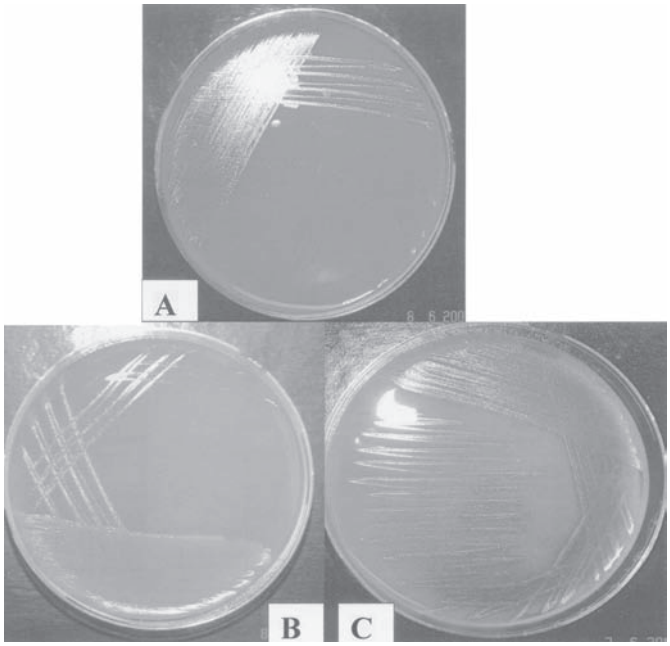

Fig. 1. Evaluation of alpha-hemolytic streptococcal growth: A: Growth in two quadrants (2 points), B: Growth in three quadrants (3 points), C: Growth in four quadrants (4 points).

Results

Of the 70 patients, two cases in the CAM group were excluded because of noncompliance. Of the 68 patients who could be evaluated, 32 (47%) were girls and 36 (53%) boys. The mean age was 6.67 (2-13) years. Seventeen patients were treated with clarithromycin, 17 with Pen G, 16 with CAM and 18 with cefprozil. The distribution of the patients and their ages was similar ($p>0.05$). On cultures obtained three days after completion of the treatment, GABHS were isolated from 1 of 17 (5.9 %) patients treated with clarithromycin, 1 of 17 (5.9 %) patients treated with Pen G, 1 of 16 (6.2 %) patients treated with CAM and from none of the 18 patients treated with cefprozil (Fig. 2). There

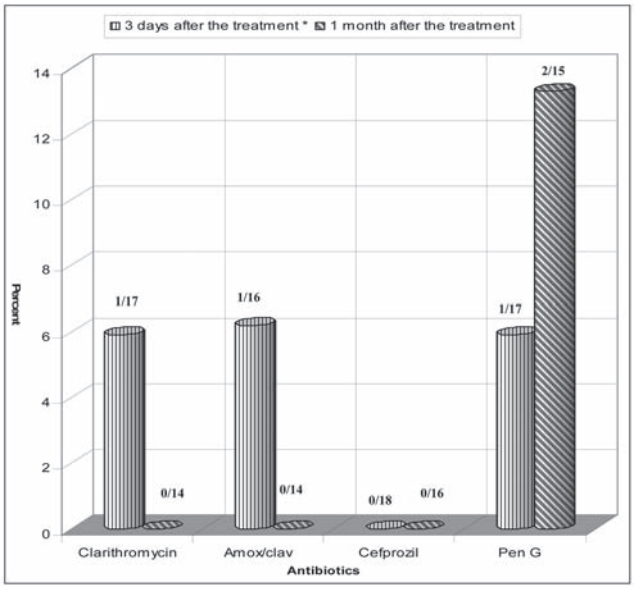

Fig. 2. Comparison of the effects of antibacterial drugs on the throat cultures after treatment (* The second culture was obtained 21 days after treatment in the Pen G group; p (3 days after treatment) =0.566; p (one month after treatment) =0.712).

was no statistical difference among the groups in the comparison of the responses after the treatment ($p>0.05$). On the cultures obtained one month after the treatment, 2 of the 15 patients receiving Pen G had GABHS growth while the patients receiving clarithromycin, cefprozil and CAM had negative cultures (Fig. 2).

Patients treated with cefprozil had a significantly higher rate of AHS isolation compared with those treated with other study drugs ($p<0.01$). The lowest AHS isolation was obtained in the CAM group ($p<0.001$) (Fig. 3).

Beta-lactamase-producing bacteria were isolated from 1 of 17 (5.9%) patients treated with clarithromycin, 1 of 16 (6.2%) patients treated with CAM, 3 of 17 (17.6%) patients treated with Pen G and 2 of 18 (11.1%) patients treated with cefprozil (Fig. 4). The predominant BLPB were *Staphylococcus aureus* (4 before treatment and 5 after treatment) and *Moraxella catarrhalis* (1 before treatment and 2 after treatment) (Fig. 4). The difference was insignificant among the groups ($p>0.05$).

Isolation of anaerobic bacteria, Gram negative bacteria, *S. aureus* and fungi were also evaluated, but there was no statistically significant difference among the four treatment groups (Fig. 5).

Discussion

Because eradication of GABHS is necessary to prevent nonsuppurative and suppurative sequelae, the primary outcome and antibiotic treatment goal of interest should be eradication

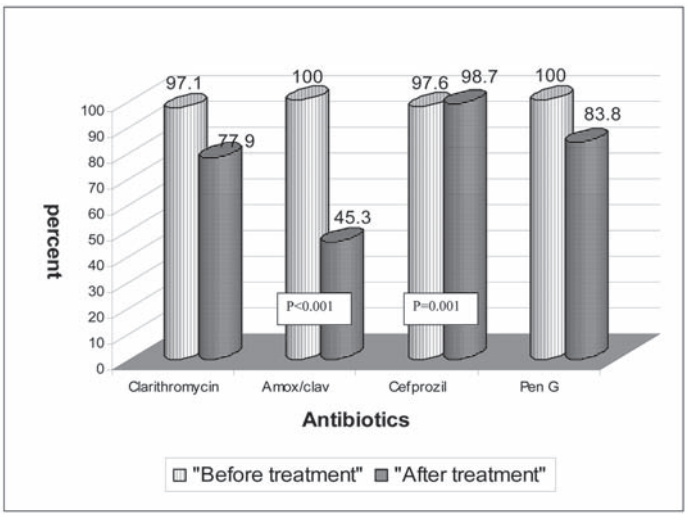

Fig. 3. Alpha-hemolytic streptococcal growth rate before and after treatment in the clarithromycin, amoxicillin/clavulanate, cefprozil and Pen G groups.

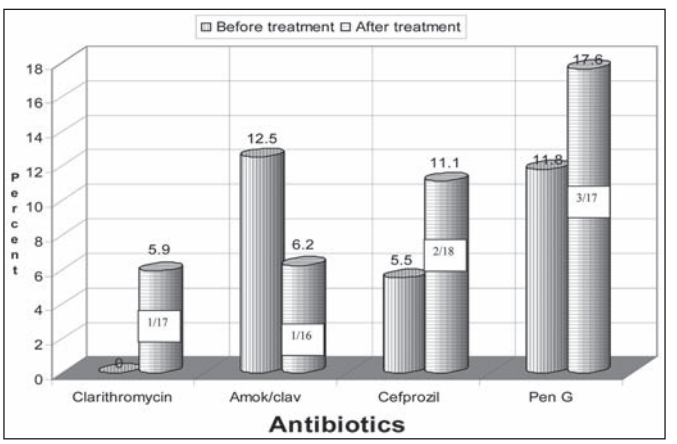

Fig. 4. Comparison of beta-lactamase induction in each antibiotic group ($p=0.648$).

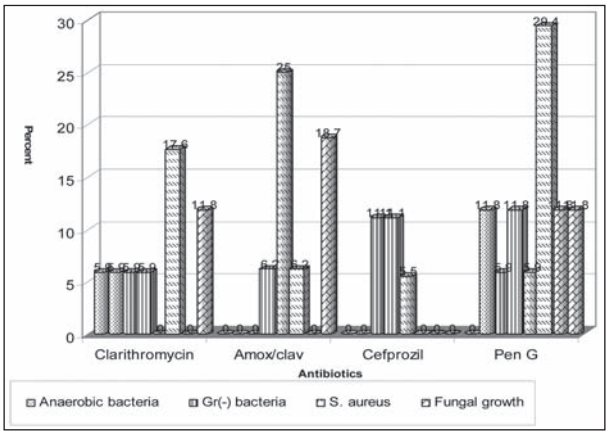

Fig. 5. Effects of study drugs on anaerobic bacteria, Gram (-) bacteria, *S. aureus* and fungal growth (The first bars represent the isolation rates before the treatment, and the second bars the isolation rates after the treatment).

of the bacteria[5,6]. Among the antibiotics that have been used in the treatment of GABHS tonsillitis, oral penicillin has been the first-line drug, and oral cephalosporins, macrolides and beta-lactam/beta-lactamase inhibitor combinations were the alternatives. Although some reports suggested that oral cephalosporins had produced superior bacteriologic cures when compared with oral penicillin for treatment of GABHS tonsillitis, three important problems have not been resolved yet:[1] Some authors believed that the difference in the cure rates might have resulted from the presence of carriers in the study groups in whom penicillin is not very effective in eradicating the streptococci from the pharynx;[2] While oral penicillin is the drug of choice in developed countries, one dose intramuscular Pen G is the drug used most often in developing countries, the effect of which on eradication of GABHS and throat flora is not fully known; and[3] Although penicillin and an alternative drug have been compared for efficacy, all of the antibiotics used for GABHS tonsillitis have rarely been evaluated in the same study.

Despite not achieving statistical significance, there was no GABHS in the cultures taken after the therapy in the cefprozil group, whereas one positive result was observed in each of the clarithromycin, CAM and Pen G groups. Cultures obtained one month after cessation of the therapy revealed 13.3% (2/15) GABHS in Pen G group with no growth in the other treatment groups. Cephalosporins were found to be more bactericidal than oral penicillin[1,7,8]. We observed positive results only in the Pen G group (13.3%) one month later with no statistical importance. Although some authors believe that the difference between cephalosporins and penicillins in some studies results from inclusion of the carriers[9], only symptomatic cases were eligible for this study.

Since several investigations have shown that AHS constituting the normal flora have inhibitory effects on the growth of pathogens, disturbed AHS flora has been postulated as one of the most important reasons for failures and recurrences in GABHS tonsillitis[10-12]. Several investigators showed the role of the AHS located in the throat in resistance to infection with group A streptococcus[13,14]. Those findings encouraged the investigators to use AHS as a spray to prevent recurrence of GABHS tonsillitis[11]. The present study shows that a cephalosporin, cefprozil, has no harmful effect on AHS; however, clarithromycin and Pen G have medium level and CAM has a high level of inhibition on these bacteria. Therefore, we suggest that not only oral penicillin, which has been shown as a disturbing agent on alpha-hemolytic bacteria, but Pen G, macrolides and especially beta-lactam/beta–lactamase inhibitor combinations have harmful effect on throat flora, and patients using these antibiotics are prone to have resistant and recurrent GABHS tonsillitis.

The existence of BLPB in the throat has been mentioned as one of the reasons for treatment failure in GABHS tonsillitis treated with penicillin. Some authors demonstrated a higher treatment failure if *S. aureus* was present in throat cultures[15,16]. The presence of

BLPB (5 *S. aureus* and 2 *M. catarrhalis*) was not different among the antibiotic groups in our study. Despite the low subject number in our study, it can be postulated that BL production is not as important as AHS in the resistance of GABHS to antibacterial therapy with oral penicillin or Pen G.

We also studied the effect of four study drugs on anaerobic and Gram negative bacteria and fungi to determine the negative effects of these antibiotics on normal throat flora and detected no difference in this comparison. It can be suggested that none of the compared drugs has an advantage in this manner.

In conclusion, this study showed the superiority of cefprozil in the treatment of GABHS tonsillitis by having no inhibitory effect on AHS in the throat flora when compared to Pen G, clarithromycin and CAM; CAM has the most disturbing effect on normal throat flora.

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