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Effect of penicillin or cefprozil therapy on tonsillar flora

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The effect on the tonsillar bacterial flora of antimicrobial therapy with penicillin or a second-generation cephalosporin (cefprozil) was studied. Sixty children scheduled for elective tonsillectomy because of recurrent group A β-haemolytic streptococcal tonsillitis participated in a prospective randomized study that divided them into three groups. One group received no therapy, and the others were given either penicillin or cefprozil for 10 days prior to surgery. The core of the patients' tonsils was cultured for aerobic bacteria. Group A β-haemolytic streptococci (GABHS) were isolated from 15/20 (75%) of untreated, 11/20 (55%) of penicillin, and 2/20 (10%) of the cefprozil group ($P < 0.001$). Thirty-two β-lactamase-producing bacteria were recovered from 19/20 (95%) of untreated, 33 from 17/20 (85%) treated with penicillin and six from 4/20 (20%) treated with cefprozil ($P < 0.01$). α-Haemolytic streptococci (AHS) inhibiting GABHS were less often isolated from patients treated with penicillin. These data illustrate the ability of a second-generation cephalosporin to eradicate GABHs, as well as β-lactamase-producing bacteria, while preserving AHS.

Introduction

The failure of penicillin to eradicate tonsillitis caused by group A β-haemolytic streptococci (GABHS) is of great concern.[1] Various theories have been suggested to explain this phenomenon. One theory is that β-lactamase-producing bacteria (BLPB) protect GABHS by inactivating penicillin.[2] In previous studies, BLPB were recovered from over three-quarters of the cores of tonsils of patients who had had tonsillectomy because of recurrent infection.[2] Another explanation is that preservation of the α-haemolytic streptococci (AHS) as part of the normal oral flora is an important contributor to the eradication of GABHS.[3] Some of these bacteria have been shown *in vitro* to compete and, thus, interfere with GABHS growth.[3]

Administration of antimicrobial agents can influence the composition of tonsillar flora.[4] Agents that are active against streptococci and BLPB have been found to be effective in eradicating streptococci and BLPB from recurrently inflamed tonsils in young children.[2] Cephalosporins have also been found to be more effective than penicillin in the eradication of GABHS tonsillar infection.[5] However, the mechanism of their efficacy has not been studied. A possible explanation for the improved efficacy of cephalosoporins compared with penicillin is their activity against BLPB, and their relative inactivity against AHS.

This prospective, randomized study investigated the effect of penicillin and cefprozil therapy on the core tonsillar aerobic microflora of paediatric patients with recurrent tonsillitis.

Patients and methods

Patients

Sixty patients (48 males), consecutively scheduled for elective tonsillectomy because of recurrent GABHS tonsillitis, participated in this study. Their mean age was 7 years, 8 months (range 4–15 years). Criteria for inclusion were a history of recurrent GABHS pharyngotonsillitis (at least six episodes during the preceding 2 years, at least four due to GABHS), and age at least 4 years. Informed consent was obtained. Subjects who had received antimicrobials or had had any infection during the previous month, or those allergic to penicillin or cefprozil, were excluded. All had general physical and otolaryngological examinations, a complete blood cell count, and urinalysis.

Microbiology

The tonsils were processed and cultured as previously described.[4] The inhibitory activity of the AHS strains

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recovered from each patient was tested against a single recent clinical isolate of the patient's GABHS, as previously described.[6] β-Lactamase activity was determined on five colonies of each morphological feature of all isolates by using the cefinaz disc (BBL, Cockeysville, MD, USA).

Study design

The patients were randomized into three treatment groups of 20 patients each. Group 1 received therapy with oral penicillin V, 17 mg/kg or 250 mg (>15 kg) every 8 h. Group 2 received cefprozil 7.5 mg/kg or 250 mg (>33 kg) every 12 h. Group 3, the control group, received no medication. The distribution of the patients' age, sex and previous antimicrobial therapy was similar in the three groups. The patients were scheduled for tonsillectomy 3–6 weeks later. They were instructed to start taking the medication 12 days before surgery and to discontinue therapy 48 h before the procedure. Patient compliance was checked by inspection for unused medication. Statistical significance was calculated by Student's *t*-test.

Results

Patients treated with antimicrobials had fewer isolates recovered than those who received no therapy (Table). Differences were noted in the type of bacteria isolated in each group. GABHS were isolated from 15/20 (75%) of the untreated patients, 11/20 (55%) of those treated with penicillin, and 2/20 (10%) of the patients treated with cefprozil ($P < 0.01$) (Table).

Thirty-two BLPB were isolated from 19/20 (95%) of the untreated patients, 33 from 17/20 (85%) treated with penicillin, and six from 4/20 (20%) treated with cefprozil ($P < 0.001$ compared with both other groups). The predominant BLPB were *Staphylococcus aureus*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Patients treated with penicillin had a significantly lower number of AHS (including

Table. Aerobic organisms isolated from the core of excised tonsils from 60 children

Organism	No. of isolates from each group of 2 children: group 1 (penicillin)		group 2 (cefprozil)		group 3 (no therapy)	
Gram-positive cocci						
Streptococcus pneumoniae	2		0		4	
α-haemolytic streptococci[a]	6	(1)[c]	16	(9)	18	(8)
γ-haemolytic streptococci	8		12		15	
β-haemolytic streptococci						
group A	11		2[c]		15	
group B	0		0		1	
group C	1		1		1	
group F	1		0		2	
S. aureus[b]	13	(13)	2	(2)[c]	12	(12)
Staphylococcus epidermidis[b]	3	(1)	1	(0)	2	(1)
Gram-negative cocci						
M. catarrhalis[b]	8	(7)	2	(2)	10	(9)
Gram-positive bacilli						
Lactobacillus species	0		0		2	
diphtheroid species	1		0		3	
Gram-negative bacilli						
H. influenzae						
type b[b]	4	(2)	1	(0)	3	(1)
non-type b[b]	11	(7)	3	(1)[c]	11	(6)
Haemophilus parainfluenzae[b]	2	(2)	0		2	(2)
Eikenella corrodens	2		1		1	
Pseudomonas aeruginosa	1	(1)	1	(1)		
Escherichia coli					1	(1)
Total	74	(33)	42	(6)[c]	103	(32)

[a] Number of strains inhibiting GABHS is given in parenthesis.
[b] Number of BLPB is given in parenthesis.
[c] $P < 0.01$ *versus* other group.

those with inhibiting capability) and γ-haemolytic streptococci compared with those treated with cefprozil, or compared with untreated patients.

Discussion

This study compared two modes of therapy of recurrent tonsillitis due to GABHS, one using penicillin, and the other a second-generation cephalosporin (cefprozil). Of the two, cefprozil was more effective in eradicating GABHS, reducing the number of BLPB and preserving AHS which can inhibit GABHS. However, since no core cultures were done prior to antimicrobial therapy, the comparison was made between patient groups and not between individual patients.

The superiority of cefprozil may be due to its activity against the aerobic BLPB recovered from the patients (i.e., *S. aureus*, *H. influenzae* and *M. catarrhalis*) and its relative lack of activity against AHS (some of which can interfere with GABHS).

One explanation for the failure of penicillin to eradicate GABHS tonsillitis is that repeated administration of penicillin may result in selection of BLPB that can protect not only themselves but also penicillin-susceptible pathogens.[2] The recovery of aerobic and anaerobic BLPB in more than three-quarters of the patients with recurrent GABHS tonsillitis,[2–4] the ability to measure β-lactamase activity in the core of the tonsils,[7] and their response to antimicrobial agents effective against BLPB[2,5] lend support to this explanation.

An additional effect of penicillin therapy is the potential eradication, in the absence of BLPB, of AHS that can inhibit GABHS.[3,8] These AHS may have a beneficial role by competing with GABHS, preventing colonization and subsequent infection with GABHS. However, because these organisms are usually as susceptible to penicillin as is GABHS, they can also be eradicated by penicillin therapy.[9] In contrast, AHS are usually more resistant to cephalosporins.[9,10] This difference in susceptibility and the resistance of cephalosoporins to β-lactamase produced by *S. aureus* and other aerobic bacteria may explain the improved activity of these agents compared with penicillin in the treatment of acute GABHS tonsillitis.[5] The presence of AHS that inhibit the growth of GABHS has been described by Crowe *et al*.,[9] who observed increased bacteriocin production by AHS after GABHS colonization. This led to the hypothesis that bacteriocin production may result from selective pressure exerted by GABHS, and also that these substances might inhibit colonization of the upper respiratory tract and aid in eradication of GABHS. Others[3,6] have also shown that production of β-lactamase by the normal oropharyngeal flora and the lack of colonization of the pharynx and inhibiting AHS were associated with the failure of penicillin to cure GABHS tonsillitis.

The occurrence of these phenomena was recently shown *in vivo* using a subcutaneous abscess model in mice.[10] In mice infected with GABHS and an interfering AHS (*Streptococcus salivarius*), penicillin eliminated both organisms. Penicillin did not, however, reduce the number of GABHS or the AHS in the presence of a BLPB (*S. aureus*). In contrast, cefprozil eliminated GABHS and *S. aureus*, but not the cephalosporin-resistant AHS. β-Lactamase-producing *S. aureus* protected GABHS from penicillin but not from the cephalosporin. Furthermore, cephalosporin therapy eradicated GABHS while preserving the AHS.

This study offers an explanation for the observed superiority of cephalosporins over penicillin in the eradication of GABHS tonsillitis.[5] Further studies are warranted to evaluate the efficacy of these agents on BLPB and AHS in the treatment of acute and recurrent tonsillitis.

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