

Comparative Tolerability of Ampicillin, Amoxicillin, and Trimethoprim-Sulfamethoxazole Suspensions in Children with Otitis Media

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The tolerabilities of ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole (TMP-SMX) suspensions were evaluated in 263 children with otitis media. Because of watery stools, therapy was discontinued in 6 of 83 patients treated with ampicillin, in none of 89 patients treated with amoxicillin ($P < 0.01$), and in 1 of 91 patients treated with TMP-SMX ($P < 0.03$). Of the patients who completed the treatment courses, 13 recipients of ampicillin suffered loose or watery stools for 4 or more days, compared with 6 of the amoxicillin recipients ($P < 0.04$) and 5 of the TMP-SMX recipients ($P < 0.02$). Thus, ampicillin was clearly less well tolerated than either amoxicillin or TMP-SMX.

The results of previous studies suggest that ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole (TMP-SMX) are equally effective in the treatment of acute otitis media in children (1, 2, 4-6). These studies, which were primarily concerned with efficacy, gave little attention to the relative tolerabilities of these drugs. The issue of tolerability was the primary concern of the study described here.

(The results were presented in part at the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., 22-24 September 1980.)

MATERIALS AND METHODS

A total of 282 children who were 2 months to 7 years old, had acute otitis media, and were seen in the private practices of four physician groups were enrolled in the study. Each of these children had at least one acute symptom of otitis media (ear pain, fever, upper respiratory infection, or irritability) plus a bulging tympanic membrane with decreased mobility (4). None of the children was allergic to any of the drugs tested, had received an antibiotic during the previous month, or displayed a stooling change before starting therapy.

The children were randomly divided into three treatment groups. Each group received 10 days of therapy. One group received ampicillin in a daily dose of 70 mg/kg administered in four equal fractions, which were delivered 0.5 h before each of the three meals and at bedtime. A second group received amoxicillin in a daily dose of 30 mg/kg administered in three equal fractions 0.5 h before each meal. The third group received TMP-SMX in a daily dose of 7.5-37.5 mg/kg administered in two equal fractions 0.5 h before the morning and evening meals. Neither the physicians nor the parents knew which drug was administered. After the diagnosis of otitis media was made by the physician, a nurse explained the study, obtained in-

formed consent, and distributed the drug and a dosage spoon. Parents were asked to keep a diary of the bowel movements of the children, recording the daily number of stools and whether they were formed, loose, or watery. The parents also kept a record of other side effects, such as nausea, vomiting, abdominal pain, and rash, and of other drugs taken, such as antihistamines and decongestants. The patients returned at 14 days to have their ears examined and to return their diaries, and their bottles of antibiotic with or without remaining drug. Statistics were done by using chi-square analysis. When the data were recorded from the diaries, the investigator was blinded.

RESULTS

Altogether, 263 patients provided data, which were analyzed (83 recipients in the ampicillin group, 89 recipients in the amoxicillin group, and 91 recipients in the TMP-SMX group). These treatment groups were well matched with respect to age, sex, and severity of otitis media. Of the original 282 children enrolled in the study, 8 withdrew, and 11 were lost to follow-up.

As Table 1 shows, therapy was interrupted in 6 of the 83 children on ampicillin because they had five or more watery stools per day for 1 to 3 days. The decision to stop the ampicillin treatment was made by the parents of the children. An additional 13 children on ampicillin suffered loose or watery stools for 4 or more days but completed the treatment course. Another five recipients of ampicillin had one to three episodes of loose or watery stools, and two others developed a generalized rash, which resolved after treatment.

All 89 children in the amoxicillin group completed the full course of therapy. Six suffered loose or watery stools for 4 or more days, and

TABLE 1. Side effects of ampicillin, amoxicillin, and TMP-SMX in children with otitis media

| Treatment | No. of patients | No. in which therapy was discontinued (≥ 5 watery stools per day) | Continued therapy | | | | |
|-------------|-----------------|---|---|--|-------------------------|---------------|-----------------------------|
| | | | No. with loose or watery stools for ≥ 4 days | No. with 1 to 3 episodes of loose or watery stools | No. with abdominal pain | No. with rash | No. with decreased stooling |
| Ampicillin | 83 | 6 | 13 | 5 | 2 | 2 | 0 |
| Amoxicillin | 89 | 0 ^a | 6 ^a | 7 | 2 | 2 | 2 |
| TMP-SMX | 91 | 1 ^a | 5 ^a | 2 | 2 | 5 | 12 |

^a $P < 0.05$ compared with ampicillin by chi-square analysis.

another seven had one to four episodes of loose stools. Two amoxicillin-treated patients exhibited a generalized rash that resolved after the conclusion of the treatment.

Therapy was stopped in only 1 of the 91 children on TMP-SMX; this patient had more than five watery stools on each of 2 days. Five other recipients of TMP-SMX suffered loose or watery stools for 4 or more days without interruption of treatment. Two TMP-SMX recipients had two episodes of loose stools. Five patients developed generalized skin rashes. In three children the rash resolved during therapy, and in two the rash resolved after therapy. An additional 12 patients in the TMP-SMX group had decreases in bowel movements.

Two children in each group had abdominal pain that was not severe enough to interrupt therapy. Thrush occurred in one patient on amoxicillin. Nausea and vomiting were not reported.

The remaining drug returned by the patients at 14 days was measured by using a graduated cylinder; 81% of the patients took at least 80% of the ampicillin, 83% of the patients took at least 80% of the amoxicillin, and 94% of the patients took at least 80% of the TMP-SMX. The three drug suspensions, which were all fruit flavored, were well accepted by the patients.

Resolution of the initial otitis media symptoms took a mean of slightly less than 2 days for each of the three treatment groups. At the 14-day visit eardrum mobility was improved or normal in 58% of the ampicillin-treated patients, 63% of the amoxicillin-treated patients, and 70% of the TMP-SMX-treated patients. However, it should be noted that tympanocentesis and tympanograms were not used to confirm the presence of middle ear fluid.

DISCUSSION

The results of previous studies (1, 2, 4-6) of the comparative tolerabilities of ampicillin, amoxicillin, and TMP-SMX are equivocal. Aronovitz (1) reported no diarrhea in 19 ampicillin-treated patients and 48 amoxicillin-treated patients, whereas Jones (5) reported diarrhea in 1 of 25 ampicillin-treated patients and 3 of 50

amoxicillin-treated patients. Howie et al. (4) reported diarrhea in 15 of 52 ampicillin-treated patients and 5 of 87 amoxicillin-treated patients. More recently, Cooper et al. (2) reported that 2 of 31 amoxicillin-treated patients developed diarrhea, compared with 1 of 29 TMP-SMX-treated patients. Shurin et al. (6) reported diarrhea severe enough to interrupt therapy in 2 of 55 ampicillin-treated patients and in none of 77 TMP-SMX-treated patients.

In this study, therapy was discontinued in significantly more ampicillin-treated patients than amoxicillin-treated patients ($P < 0.01$) or TMP-SMX-treated patients ($P < 0.03$). Also, among the patients who completed therapy, significantly more ampicillin-treated patients developed loose stools than amoxicillin-treated patients ($P < 0.04$) or TMP-SMX-treated patients ($P < 0.02$).

ACKNOWLEDGMENTS

I thank the following physicians who participated in the study: Peter Hine, Ronald Cohen, David Brown, Robert Harris, Lee Hoffman, Daniel Spada, Donald Timmerman, and Mark Tuttle. I also thank Alex Cardoni for helping initiate this study, James Lipsky, Lynn Cates, and Paul Lietman for their critical review, and Theresa Feder and Diane Delap for editorial assistance.

This investigation was supported in part by a grant from Burroughs Wellcome Co.

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