THE JOURNAL OF INFECTIOUS DISEASES • VOL. 145, NO. 6 • JUNE 1982
 0022-1899/82/4506-0006$00.75

Penetration of Amoxicillin, Cefaclor, Erythromycin-Sulfisoxazole, and Trimethoprim-Sulfamethoxazole into the Middle Ear Fluid of Patients with Chronic Serous Otitis Media

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Penetration into the middle ear of four antibiotics commonly used in treatment of otitis media was studied by administering a single oral dose of amoxicillin, cefaclor, erythromycin-sulfisoxazole, or trimethoprim-sulfamethoxazole to 83 children with chronic serous otitis media. The antibiotic was given 15–240 min before the removal of middle ear fluid (MEF) by ventilation tubes inserted through the tympanic membrane. At the time MEF was obtained, a sample of blood was drawn from the patient, and concentrations of antibiotic in both specimens were assayed either microbiologically by a disk diffusion method or by high-pressure liquid chromatography. Amoxicillin had the highest ratio of mean peak concentration in MEF to minimal inhibitory concentration (MIC) for the three most common pathogens of otitis media (*Streptococcus pneumoniae*, ampicillin-sensitive *Haemophilus influenzae*, and *Streptococcus pyogenes*), whereas trimethoprim-sulfamethoxazole had the highest ratio of mean peak concentration in MEF to MIC for ampicillin-resistant *Haemophilus influenzae*.

The treatment of infections of the middle ear by the oral route is complicated by the variable and often low level of penetration of the antibiotic into the middle ear fluid (MEF) [1–10]. One potential cause for persistent infection despite antibiotic therapy may be inadequate penetration of an antibiotic into MEF before the responsible pathogen has been eradicated. To decrease the possibility of a relapse of infection of the middle ear, an antibiotic should have good microbiologic activity against the most common pathogens that cause otitis media—*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes*—and a high degree of penetration into MEF. Although amoxicillin, cefaclor, erythromycin-sulfisoxazole, and trimethoprim-sulfamethoxazole meet the former criterion, no data comparing their relative penetration into MEF are available. In the present study we compared the concentrations of these antibiotics in MEF of children with chronic serous otitis media 15–240 min after the administration of the manufacturers' recommended single oral dose of each agent.

Received for publication August 7, 1981, and in revised form December 22, 1981.

Signed, informed consent was obtained from the parents of all of the patients, and the guidelines for human experimentation of Hartford Hospital were followed.

This study was supported in part by the Hartford Hospital Research Free Funds.

We thank Brian Remillard, Elaine Fleming, and Deborah Rose for technical and laboratory assistance and Diana Garry for assistance in manuscript preparation.

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Materials and Methods

Study population. Eighty-three children aged one to 12 years (mean, 4.6 years) who were scheduled for ventilation-tube placement for chronic serous otitis media were studied. A diagnosis of chronic serous otitis media was made if a patient had decreased mobility of the tympanic membrane, as shown by pneumatic otoscopy, and some degree of hearing loss, as determined by audiometry, for more than two months. These children had no clinical symptoms or signs suggesting purulent otitis media. An unsuccessful trial of decongestant therapy was instituted in all of the patients before myringotomy. Patients were excluded from this study if they had leukocytes (five or more white blood cells per high-power field) or bacteria on a Gram stain of MEF that was obtained during tube placement; a history of

penicillin, sulfonamide, or cephalosporin hypersensitivity; or had received any antimicrobial agent during the day before tube placement.

After an overnight fast, patients were randomly assigned to receive a single dose of amoxicillin (15 mg/kg of body weight; maximum, 500 mg), cefaclor (15 mg/kg; maximum, 1 g), erythromycin-sulfisoxazole (12.5 mg of erythromycin/kg; 37.5 mg of sulfisoxazole/ kg; maximum, 500 mg of erythromycin), or trimethoprim-sulfamethoxazole (4 mg of trimethoprim/kg; 20 mg of sulfamethoxazole/kg; maximum, 160 mg of trimethoprim) as a suspension administered orally 15 min to 4 hr before the removal of MEF. During the insertion of the tubes while the patient was under general anesthesia, MEF was aspirated by means of a plastic collection trap and placed on ice. About 3 ml of blood was obtained by venipuncture within 5 min of the collection of MEF.

Assay procedure. The MEF and blood samples were placed on ice and transported to the laboratory. The serum was separated, and both the serum and MEF were frozen at −80 C until assayed. A high-pressure liquid chromatograph (model no. 204; Waters Associates, Milford, Mass.) equipped with a UV monitor (model no. 440; Waters) and a reverse-phase, prepacked, 30-cm stainless steel micro-Bondpak C-18® column (Waters) was used to determine the concentrations of cefaclor, sulfisoxazole, trimethoprim, and sulfamethoxazole in the serum and MEF. The mobile phase consisted of 15% methanol, 84% water, and 1% acetic acid for cefaclor; 15% methanol in 0.05 M Sorenson's phosphate buffer (pH 5.9) for sulfisoxazole; and 20% methanol in 0.01 M Sorenson's phosphate buffer (pH 5.9) for trimethoprim and sulfamethoxazole. The spectrophotometric analysis of trimethoprim was performed at a wavelength of 280 nm, whereas a wavelength of 254 nm was used for all of the other antibiotics.

Serum standards for all of the antibiotics were prepared in freshly obtained, pooled human serum. Serum samples and standards for sulfamethoxazole, sulfisoxazole, and cefaclor were prepared by adding 200 μl of serum to 400 μl of a protein-precipitating reagent (methanol and acetonitrile mixtures containing an internal standard) in a polypropylene tube. The capped tube was vortexed and then centrifuged at 42,000 *g* for 20 min at 4 C. The supernatant was transferred to a small polypropylene tube, and 25 μl of this solution was injected directly onto the high-pressure liquid chromatograph column. Serum concentrations and standards of trimethoprim were assayed by the method of Mylotte et al. [11], and our results were consistent with their work. The analysis of cefaclor was also very reproducible, with a 0.9% ± 0.006% error. Serum concentrations and standards of amoxicillin and erythromycin were determined with microbiologic assays using a disk diffusion method [12, 13]. *Sarcina lutea* (ATCC 9341; American Type Culture Collection, Rockville, Md.) was used as the test organism for measuring the concentration of erythromycin in serum and MEF and the concentration of amoxicillin in MEF, whereas *Bacillus subtilis* (ATCC 6633) was used as the test organism for measuring the concentration of amoxicillin in serum.

The MEF was weighed, mixed with an equal volume of buffer, homogenized, and mixed with two volumes of acetonitrile. The mixture was homogenized a second time and then centrifuged at 42,000 *g* for 20 min at 4 C. All of the MEF standards were prepared in buffer. For sulfamethoxazole, sulfisoxazole, and cefaclor, the supernatant was directly injected onto the high-pressure liquid chromatograph column. Trimethoprim was extracted from the supernatant in the manner described by Mylotte et al. [11]. For amoxicillin and erythromycin, 20 μl of the supernatant was spotted directly onto paper disks and placed on media using the test organisms given above. All of the microbiologic assays were performed in triplicate. All of the high-pressure liquid chromatograph samples were injected at least twice. In all of the assays, the concentrations of antibiotics in the serum and MEF samples were determined using a linear regression analysis of the data derived from the standard curve of each antibiotic. The sensitivity limits of our assays were: amoxicillin, 0.1 μg/ml; cefaclor, 0.5 μg/ml; trimethoprim, 0.2 μg/ml; sulfamethoxazole, 0.2 μg/ml; erythromycin, 0.2 μg/ml; and sulfisoxazole, 0.2 μg/ml.

Results

Nineteen children received amoxicillin, 26 received cefaclor, 15 received erythromycin-sulfisoxazole, and 23 received trimethoprim-sulfamethoxazole.

Table 1. Concentrations of antibiotics in the serum and middle ear fluid (MEF) of 83 children with chronic serous otitis media after the oral administration of amoxicillin (Amox), cefaclor (Cfc), erythromycin-sulfisoxazole (Er-SSX), or trimethoprim-sulfamethoxazole (TMP-SMX).

Sample, time after antibiotic was given (min)	Amox	Cfc	SSX	Er	TMP	SMX
MEF						
0–30	0.17	3.8 ± 2.8	0.22	ND	0.6	1.8 ± 2.0
30–60	2.2	2.8 ± 2.1	0.75	ND	0.9 ± 0.5	3.2 ± 1.3
60–90	2.0 ± 1.6	2.3 ± 1.3	0.6 ± 0.3	ND	1.0 ± 0.5	6.0 ± 2.9
90–120	2.3 ± 1.5	1.3 ± 0.3	3.7 ± 0.7	ND	1.9 ± 1.4	17.0 ± 6.7
120–180	5.6 ± 4.6	. . .	6.4 ± 5.0	ND	2.0	14.0
180–240	2.7 ± 0.7	. . .	20.9	ND	1.4 ± 1.5	18.7 ± 11.3
Serum						
0–30	6.8 ± 3.0	12.8 ± 6.7	45.7 ± 25.4	0.57 ± 0.31	0.5 ± 0.3	47.3 ± 41.4
30–60	6.5 ± 2.5	16.8 ± 6.5	16.6	0.93	1.2 ± 0.6	47.3 ± 35.2
60–90	13.6 ± 7.3	11.2 ± 3.6	48.5	1.06	1.8 ± 1.2	38.2 ± 17.2
90–120	9.4 ± 1.3	6.9 ± 2.6	87.4 ± 35.2	0.40 ± 0.20	1.6 ± 1.1	62.4 ± 15.5
120–180	5.8 ± 0.3	. . .	105.6 ± 23.4	0.36 ± 0.28	2.9 ± 0.6	70.3 ± 6.5
180–240	3.1 ± 2.2	. . .	65.7	0.20	3.1 ± 0.9	53.8 ± 16.5

NOTE. Data are expressed as the mean ± SD in μg/ml. ND = nondetectable.

A serum sample was obtained from every child, whereas 113 MEF samples (right and/or left ear) were obtained from 59 children in sufficient quantities such that the contentration of antibiotic in MEF could be determined. For all of the children who were given erythromycin-sulfisoxazole or trimethoprim-sulfamethoxazole and four of the children who were given amoxicillin, MEF samples from both ears were combined to yield an amount sufficient for the determination of antibiotic concentration. For all of the children who received cefaclor and five of the children who received amoxicillin, the antibiotic concentration in MEF was analyzed separately for each ear. There was no significant difference in antibiotic concentration in MEF between the right and left ears of five children who were given amoxicillin (right ear, 2.5 μg/ml; left ear, 1.9 μg/ml; $P = 0.5$) or 12 children who were given cefaclor (right ear, 2.5 μg/ml; left ear, 3.5 μg/ml; $P = 0.2$). The MEF was characterized as thick, viscid, and mucoid in 69 samples and serous in 12 samples. There was no significant difference in antibiotic concentration between mucoid and serous MEF.

The antibiotic concentrations in serum and MEF samples that were obtained from several patients within 0.5-hr intervals of the time of antibiotic administration were averaged so that the change in antibiotic concentration over time could be analyzed (table 1). The mean number of concentrations averaged per data point was five, although there was only one concentration for a few data points. Mean peak concentrations of antibiotic in MEF samples occurred from a few minutes to 2 hr after the peak in serum and, except for trimethoprim were less than half the concentrations in serum samples (figure 1). The mean peak concentrations of antibiotic in MEF samples, expressed in μg/ml and as a percentage of peak concentrations of antibiotic in serum samples, were: trimethoprim, 2.0 μg/ml (65%); amoxicillin, 5.6 μg/ml (41%); sulfamethoxazole, 18.7 μg/ml (27%); cefaclor, 3.8 μg/ml (23%); and sulfisoxazole, 20.9 μg/ml (20%). None of the 15 patients who were given erythromycin-sulfisoxazole had detectable concentrations (≥0.20 μg/ml) of erythromycin in the MEF samples.

The mean peak concentrations of amoxicillin, cefaclor, and trimethoprim-sulfamethoxazole in MEF were compared with the 90% MIC values, obtained from the literature [14–23], for *S. pneumoniae*, *H. influenzae*, and *S. pyogenes* (table 2). Amoxicillin had the highest ratio of MEF concentration to MIC for all of the pathogens except ampicillin-resistant *H. influenzae*. Trimethoprim-sulfamethoxazole had the highest ratio of MEF concentration to MIC for ampicillin-resistant *H. influenzae* and was second after amoxicillin for

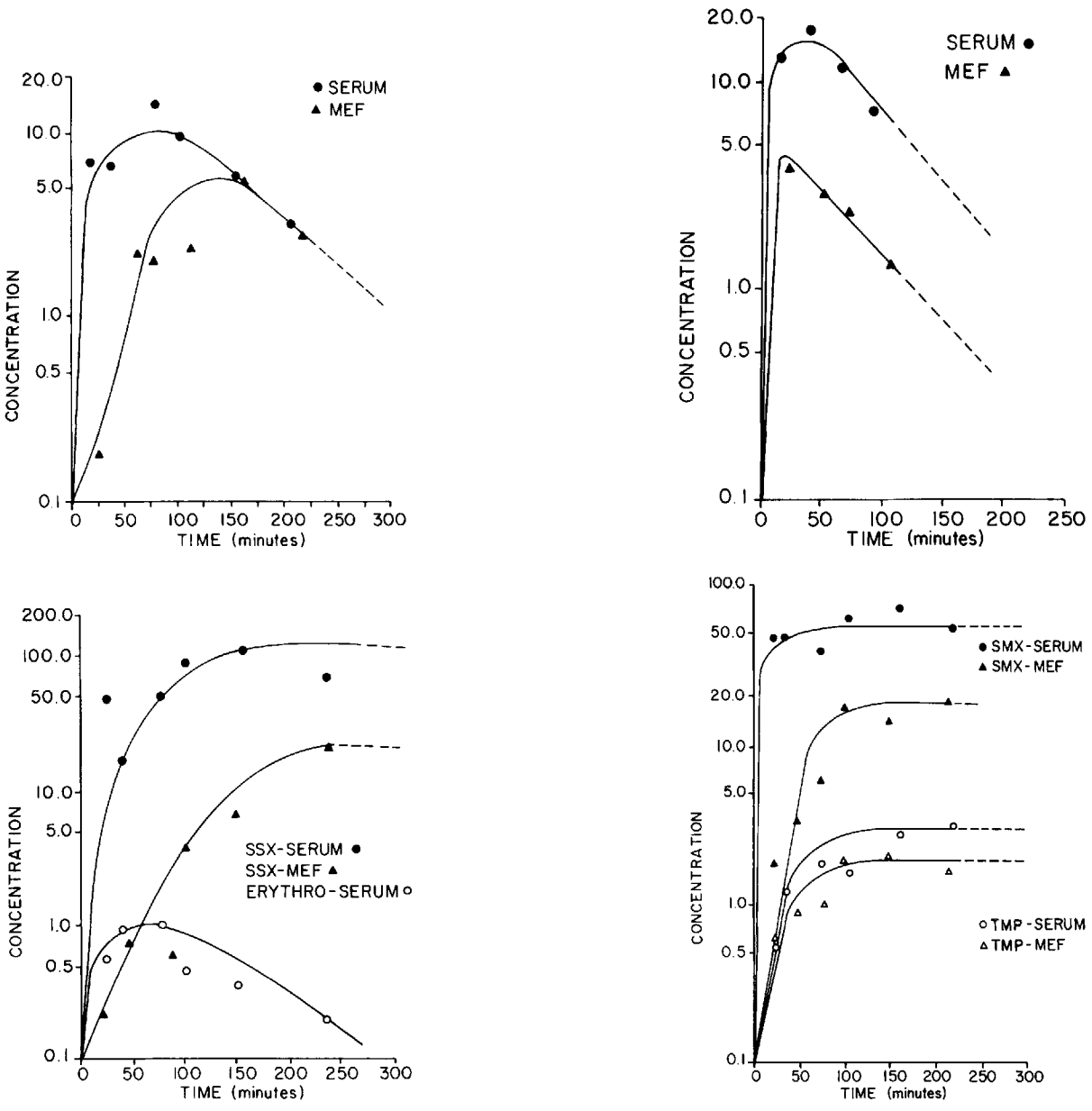

Figure 1. The change in concentration (μg/ml) of antibiotics in the serum and middle ear fluid (MEF) of 83 children with chronic serous otitis media 15–240 min after oral administration of (*upper left*) amoxicillin, (*upper right*) cefaclor, (*lower left*) sulfisoxazole (SSX) and erythromycin (ERYTHRO), or (*lower right*) trimethoprim (TMP) and sulfamethoxazole (SMX). The mean number of concentrations averaged per data point was five, although there was only one concentration for a few data points.

the other pathogens. The peak concentration of cefaclor in MEF was several times its MIC for *S. pneumoniae* and *S. pyogenes*.

Discussion

The evaluation of antibiotic therapy for otitis media is difficult because of the high rate of spontaneous recovery. Heller [24] evaluated 588 cases of otitis media and noted a spontaneous resolution in 50% of the cases, resolution after spontaneous rupture of the tympanic membrane in 16% of the cases, and resolution with myringotomy in 34% of the cases, results which suggest that almost any type of antibiotic therapy might be associated with a cure rate of >90%. In a more recent study with a

Table 2. The ratio of the mean peak concentration of amoxicillin, cefaclor, and trimethoprim-sulfamethoxazole (TMP-SMX) in the middle ear fluid (MEF) of children with chronic serous otitis media to the standard MIC of the antibiotics for three bacterial pathogens of otitis media.

	Streptococcus pneumoniae		*Haemophilus influenzae*				*Streptococcus pyogenes*	
			Ampicillin-sensitive		Ampicillin-resistant			
Antibiotic	MIC	MEF:MIC ratio	MIC	MEF:MIC ratio	MIC	MEF:MIC ratio	MIC	MEF:MIC ratio
Amoxicillin	0.05	112	0.2	28	. . .	. . .	0.025	224
Cefaclor	0.25	15	6.0	0.6	8.0	0.5	0.13	29
Combination								
TMP	0.1	20	0.03	67	0.06	33	0.05	40
SMX	2.0	9	0.59	32	1.2	16	1.0	19

NOTE. Data are expressed as the mean peak concentration of antibiotic in MEF (μg/ml) to the standard MIC (≥90% of strains inhibited at the given concentration [14–23]). For a description of the procedure in which the concentrations of antibiotic in the MEF were measured, see Materials and Methods.

smaller number of patients, spontaneous resolution of otitis media was noted in 30% of the 280 cases studied [25]. It is clear that very large numbers of patients are needed to evaluate properly the comparative clinical efficacy of different antibiotics in the treatment of otitis media, but large-scale comparative trials are not yet available for the antibiotics we studied. Pharmacologic data in patients with chronic serous otitis media are helpful in choosing the appropriate antibiotic for treatment of recurrent otitis media, and such data could be useful in choosing an antibiotic for prophylaxis of acute otitis media. The concentrations of several antibiotics in MEF have been shown to be greater in patients with acute otitis media than in patients with chronic serous otitis media [1, 4, 10]. The resolution of acute otitis media, however, may be as dependent on high concentrations of antibiotic in MEF during the latter part of therapy —when inflammation has subsided—as during the acute phase of the illness.

The antibiotic concentrations in the MEF and serum samples that were noted in this study are similar to those obtained in other studies [6–9, 26–32]. Lildholdt et al. [33] noted lower mean peak concentrations of cefaclor in serum (8.49 ± 7.89 μg/ml) and MEF (0.47 ± 0.78 μg/ml) in patients with chronic serous otitis media than those in our study. However, they used a bioassay in which cefaclor is subject to a greater amount of degradation than with the high-pressure liquid chromatographic assay. Bass et al. [5] noted higher concentrations of erythromycin in MEF (average, 0.84 μg/ml) from children with acute otitis media who received multiple doses of erythromycin ethyl succinate than those in MEF from our patients (<0.20 μg/ml) who had serous otitis media and received a single dose of erythromycin-sulfisoxazole.

Our data provide support for the current recommendation of amoxicillin as the initial preferred drug in the treatment of acute otitis media in children [34]. Although the peak concentration of amoxicillin in MEF was less than that of the sulfonamides and cefaclor, it had the best ratio of peak MEF concentration to antimicrobial activity against *S. pneumoniae*, ampicillin-sensitive *H. influenzae*, and *S. pyogenes* because of its much lower MIC for these organisms. Cefaclor, trimethoprim-sulfamethoxazole, and erythromycin-sulfisoxazole are often suggested as possible alternative drugs in patients with a history of penicillin hypersensitivity or treatment failure with amoxicillin due to ampicillin-resistant strains of *H. influenzae*. Because of the poor penetration of the erythromycin component of erthromycin-sulfisoxazole in MEF noted in this study, it would appear that either trimethoprim-sulfamethoxazole or cefaclor might be a better alternative choice. Yet, in clinical studies erythromycin-sulfonamide combinations have been shown to be as effective as these other antibiotics in the treatment of otitis media [9, 35]. Two possible explanations for this result are that (*1*) the lower limit of our erythromycin assay (0.20 μg/ml) was greater than the 90% MIC of erythromycin for *S. pneumoniae* (0.12 μg/ml) and *S. pyogenes* (0.1 μg/ml) or (*2*)

erythromycin requires significantly lower MICs to inhibit bacteria that are associated with otitis media in the presence of sulfisoxazole [36].

Large comparative studies are necessary to determine which of the four antibiotics we studied is the preferred agent in the treatment of acute otitis media, but the pharmacokinetic data in this study support the use of amoxicillin in most cases and of trimethoprim-sulfamethoxazole in those children with a history of penicillin hypersensitivity or a poor clinical response to amoxicillin.

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