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# *Brief clinical and laboratory observations*

## *Penetration characteristics of trimethoprim-sulfamethoxazole in middle ear fluid of patients with chronic serous otitis media*

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TREATMENT of middle ear infection by the oral route has traditionally been difficult owing to the variable and often low penetration of antibiotics into the middle ear fluid. It can be speculated that the relatively high incidence of recurrent otitis media following an acute attack may be caused by the incomplete eradication of the pathogen, possibly from inadequate passage of the antimicrobial agent into MEF as the degree of inflammation decreases. In the treatment of middle ear infections, antibiotics with a high degree of microbiologic activity against the usual pathogens of this type of infection (*Haemophilus influenzae* and *Streptococcus pneumoniae*) and with a high degree of penetration characteristics into MEF should be a logical choice. Although amoxicillin meets these criteria,[1] it cannot be administered to patients with a history of penicillin allergy and may be ineffective

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**See related article, p. 1081.**

Abbreviations used
MEF: middle ear fluid
TMP: trimethoprim
SMX: sulfamethoxazole

0022-3476/80/061087+03$00.30/0 

**Table.** Concentrations of sulfamethoxazole (SMX) and trimethoprim (TMP) in the middle ear fluid of pediatric patients with chronic serous otitis media

| *Patient* | *Time (min)* | *Middle ear fluid concentration (μg/ml)* | | | | *Middle ear fluid/serum concentration ratio** | |
|---|---|---|---|---|---|---|---|
| | | *Ear* | *SMX* | *TMP* | *SMX/TMP ratio* | *SMX* | *TMP* |
| 1 | 170 | Right | † | † | – | – | – |
| | | Left | † | † | – | – | – |
| 2 | 75 | Right | 2.81 | 0.20 | 13.9 | 0.083 | 0.187 |
| | | Left | † | † | – | – | – |
| 3 | 80 | Right | 5.48 | 1.43 | 3.83 | 0.160 | 0.490 |
| | | Left | 12.6 | 1.58 | 7.94 | 0.366 | 0.541 |
| 4 | 70 | Right | 4.87 | 1.08 | 4.51 | 0.151 | 1.17 |
| | | Left | 5.21 | 0.66 | 7.87 | 0.162 | 0.717 |
| 5 | 90 | Right | 17.8 | 2.70 | 6.59 | 0.262 | 0.941 |
| | | Left | 25.7 | 2.68 | 9.57 | 0.379 | 0.934 |
| 6 | 60 | Right | 4.05 | 1.13 | 3.58 | 0.174 | 0.974 |
| | | Left | 3.23 | 1.53 | 2.11 | 0.139 | 1.32 |
| 7 | 65 | Right | 6.46 | ‡ | – | 0.281 | – |
| | | Left | 4.39 | ‡ | – | 0.190 | – |
| 8 | 80 | Right | † | † | – | – | – |
| | | Left | 5.94 | 0.91 | 6.56 | 0.088 | 0.278 |
| | Mean | Right | 6.91 | 1.31 | 6.48 | 0.185 | 0.752 |
| | (SD) | | (5.5) | (0.90) | (4.3) | (0.07) | (0.40) |
| | | Left | 9.50 | 1.47 | 6.81 | 0.221 | 0.758 |
| | | | (8.6) | (0.78) | (2.8) | (0.12) | (0.40) |
| | | Overall | 8.21 | 1.39 | 6.65 | 0.203 | 0.755 |
| | | | (7.0) | (0.80) | (3.5) | (0.10) | (0.38) |

*Uncorrected for specific gravity of serum (1.03).
†Sample not collected.
‡Insufficient sample size for accurate determination.

in the eradication of amoxicillin-resistant *H. influenzae,* which are being recognized with greater frequency as a cause of otitis media.[2]

Although trimethoprim-sulfamethoxazole has excellent microbiologic activity against *H. influenzae* (both amoxicillin or ampicillin sensitive and resistant types)[3, 4] and *Streptococcus pneumoniae,* and although it can be given with safety in patients with a history of penicillin hypersensitivity, there are no data regarding its penetration characteristics into MEF. We studied the ability of this drug to pass into the MEF of children with chronic serous otitis media.

Eight children between the ages of 2 and 6 years with persistent middle ear effusions (chronic serous otitis media) received a single oral dose of trimethoprim 4 mg/kg and sulfamethoxazole 20 mg/kg one to three hours before the insertion of ventilation tubes into the tympanic membrane. At the time of the insertion of the tube, we obtained simultaneous samples of middle ear fluid and blood, and measured the concentrations of total SMX (SMX and its $N^4$ acetylated metabolite) and TMP in these specimens using high pressure liquid chromatography. The mean levels in μg/ml were as follows: serum SMX 44.6 ± 22, serum TMP 2.03 ± 1.2, MEF SMX 8.2 ± 7.0, and MEF TMP 1.39 ± 0.80 (Table). The serum levels of SMX and the $N^4$-acetyl SMX were similar in each patient. Since these concentrations of TMP and SMX are above the usual concentrations required to inhibit the common pathogens of otitis media, this antibiotic combination should be effective in the treatment of most middle ear infections, which has already been shown in a number of clinical studies.[5, 6]

Because most drugs pass more easily through inflamed biologic membranes, it can be predicted that the levels of TMP-SMX achieved in patients with acute otitis media should be even higher than those observed in this study. Whether the excellent penetration of TMP-SMX into the MEF even in the absence of an acute infection will decrease the likelihood of relapse remains to be determined in large clinical studies.

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# *Kanamycin in children: Pharmacology and lack of toxicity of an increased dosage regimen*

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A RECENT REAPPRAISAL of the pharmacology of kanamycin in the neonate by Howard and McCracken[1] demonstrated that an increase in dosage from the standard 7.5 mg to 10 mg/kg/dose was necessary to achieve optimal peak serum levels of 15 to 25 μg/ml. A review of the literature for the proper dosage of kanamycin beyond the neonatal period[2-4] suggested that the dose of kanamycin (15 mg/kg/24 hours) recommended for infants and children might fail to achieve optimal peak serum levels and could result in clinical failures as well as promote emergence of resistant strains by exposure of bacteria to sublethal concentrations of kanamycin. We previously reported that single doses of 10 mg/kg im produced mean peak serum levels of 17.6 μg/ml.[5] We now report the results of using the increased dosage regimen (30 mg/kg/24 hours) for entire courses of therapy in infants and children.

## METHODS AND MATERIALS

The study population consisted of patients over 30 days of age being treated at Parkland Memorial Hospital and Children's Medical Center, Dallas. All patients had normal renal function. After signed, informed parental consent was obtained, therapy was begun with kanamycin in a dosage of 10 mg/kg every eight hours given intramuscularly or as a 20-minute intravenous infusion. Serum specimens were collected by heel- or fingerstick or by a heparin lock daily for determination of peak 30 minutes iv; and trough (8 hours) kanamycin concentrations, which were assayed by the micromethod of Simon and Yin[6] using *Bacillus subtilis* as the test organism. Serum was stored at −20°C and assayed within three days of collection. Penicillin was eliminated from samples by preincubation with β-lactamase. Microtiter serum inhibition tests were performed against strains of Enterobacteriacae recovered from patient's clinical specimens. The bacterial inoculum was $10^5$ organisms delivered into each microtiter well with serial twofold dilutions of the serum in brain heart infusion broth (Difco).

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| Abbreviations used | |
|---|---|
| im: | intramuscular |
| iv: | intravenous |
| MIC: | minimal inhibitory concentration |

Laboratory monitoring of hematologic (complete blood count, differential, and estimation of platelets) and renal (urinalysis, blood urea nitrogen, creatinine) toxicity was performed at the initiation, day 7 and/or at the last day of therapy. Hearing sensitivity was assessed using pure tone audiometry at 2,000, 4,000, and 8,000 Hz by an audiologist within 48 hours of the initiation of therapy, at the end of therapy and, whenever possible, several weeks after discharge from the hospital.

## RESULTS

Sixteen patients received an average of 16.7 doses of 10 mg/kg of kanamycin. The study population of six girls

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