Sulphamethoxazole prophylaxis in the otitis-prone child

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SUMMARY A bedtime dose of sulphamethoxazole was effective in preventing ear infections in otitis-prone young children. Thirty-three such children were studied by means of a random, double-blind, placebo-controlled, cross-over protocol. Nine (27%) of 33 children treated with sulphamethoxazole experienced 10 episodes of acute suppurative otitis media or otitis media with effusion while 19 (58%) of 33 children given a placebo experienced 27 episodes of acute otitis media or otitis media with effusion. No new episode of otitis media was observed in 11 children in whom serial urine samples uniformly had a positive response to *Micrococcus lutea* bioinhibition test, the method we chose to monitor compliance. Otitis media with effusion (secretory otitis media) was detected less often in the children who were given sulphamethoxazole; this fact suggests that prophylaxis with sulphamethoxazole may prevent persistent middle ear effusion in otitis-prone young children.

A young child who has had at least three episodes of otitis media within the previous 12 months has been called 'otitis-prone'.¹ Data derived from a longitudinal study conducted in a private practice in Huntsville, Alabama¹ and a collaborative study from Boston, Massachusetts² show that otitis-prone children constitute 20% of the paediatric population below age 2 years. Continuous or intermittent chemoprophylaxis for the otitis-prone child may help to reduce the number of episodes of illness.³⁻⁵ Encouraged by the salutary experience of Perrin *et al.*,⁶ we initiated a double-blind placebo-controlled, cross-over study to evaluate the effectiveness of a single bedtime dose of sulphamethoxazole (SMZ) for preventing ear infections in this population.

Patients, methods, and materials

In December 1979 and January 1980, after obtaining signed informed parental consent, 43 white children from middle-class families were enrolled in the study. Thirty-three of them completed the study.

These children were drawn from two suburban private paediatric practices. A letter explaining the purpose of the study was sent to parents of any child who had had multiple episodes of acute otitis media. All patients had experienced at least three episodes of acute otitis media in the preceding 12-month period, and with few exceptions, had had recent attacks. Twenty-nine children had experienced a total of 62 episodes of acute otitis media in the

preceding 3-month period, while 4 children had had the third episode longer than 3 months before the study. The patients were assigned at random to a set of coded bottles by a project nurse who did not know the child's history or the condition of the middle ear on entry into the study.

The 19 boys and 14 girls ranged in age between 4 and 72 (mean 31) months. Only one child was over 5 years old. For the two groups, otitis media was defined by three criteria: (1) bulging of the opacified eardrum, (2) impaired eardrum mobility as shown by the response to pneumo-massage, and (3) yellow, or fiery-red colour of the tympanic membrane.

A flat tympanogram was obtained for 5 (29%) of 17 children who began the study on SMZ and for 9 (56%) of 16 children who began with the placebo, done by chance and not by design. A single bedtime dose of SMZ 25 mg/kg, or a placebo identical in appearance with SMZ, was given to each child. Both medications were prepared at the pharmaceutical company and could be identified only by one of 6 coded symbols. Only 2 nurses knew the code. After 2 months the alternate suspension, either the drug or the placebo, was given to each child. Pneumo-otoscopic and tympanometric examinations were performed on each child at the time of admission to the study, at 2 and 4 weeks after admission, and then monthly for the remaining 3 months of the study. Parents were instructed to bring in any child who developed signs of an upper

respiratory tract infection even if otalgia was not present. If any patient developed acute otitis media during the study, the experimental medication was stopped and he underwent a 10-day course of amoxycillin treatment. On the 11th day, the test drug or placebo to which the patient had been assigned was reinstated and continued as previously described. Tympanocentesis was not performed on any child.

Tympanometric recordings were obtained from each child at each visit using a Teledyne (model TA 1-D) acoustic impedance meter. Only a type B pattern (flat tympanogram) was considered to support the diagnosis of otitis media with effusion. Children with acute otitis media or otitis media with effusion (secretory otitis media) had a flat tympanogram.

Compliance with the study regimen was encouraged by asking the parents to affix a printed reminder of the protocol to the refrigerator door. In addition, mothers were asked to collect a urine specimen in a numbered vial on the day of each follow-up visit and to place the vial immediately in the freezer compartment of the home refrigerator. Urine specimens were tested for antibacterial activity using a *Micrococcus lutea* bioinhibition assay using the method of Charney *et al.*¹⁰

Results

After random assignment and during the initial period of the study, 10 children dropped out, 6 taking SMZ and 4 the placebo. Six of these 10 patients failed to return for follow-up visits during the first month and were excluded from the study. Three children refused to take the bitter tasting SMZ and were also excluded.

A total of 9 (27%) of the 33 SMZ-treated children experienced 10 episodes of acute otitis media or otitis media with effusion in contrast to 19 (57.5%) of the 33 children in the placebo group who experienced 27 episodes of acute otitis media or otitis media with effusion. The difference between the number of children with acute otitis and otitis media with effusion in each treatment group is significant ($x^* = 2.25$ $P < 0.02$). Four placebo-treated children had two episodes of acute otitis media or acute otitis media with effusion and 2 placebo-treated patients had three episodes. One SMZ-treated child had two episodes of acute otitis media or acute otitis media with effusion and none had three episodes.

During the initial 2 months of the study, four episodes of acute suppurative otitis media or acute otitis media with effusion were noted in 17 children who received SMZ prophylactically. In contrast,

12 episodes of acute otitis media or acute otitis media with effusion were detected in 16 children who received the placebo ($x^* = 2.87$ $P < 0.01$). After cross-over, 2 months later, five episodes of otitis media were noted in the 17 children who received the placebo (Table 1).

No significant difference was noted between the two treatment groups during the second 2-month interval in this study. However, there is a significant decrease from twelve episodes of otitis media in the 16 children who received the placebo during phase one, to five episodes after cross-over to SMZ ($x^* = 2.5$ $P < 0.02$). By comparison, those who received SMZ in phase one suffered only four episodes of otitis media. After cross-over to placebo, they had seven episodes of otitis media. This difference is not significant. However, during the entire 4-month period, the number of episodes of otitis media in patients who started the study on placebo (twelve episodes in 16 patients) does differ significantly from the number of episodes of otitis media observed in the group who started the study on SMZ prophylaxis (7 episodes in 17 patients) $x^* = 1.98$ $P < 0.05$.

Regardless of the type of treatment, 11 (33%) of 33 children in the study had no episode of otitis media during the 4-month study period; however, 3 of these 11 otitis-free children developed otitis media during an 8-week observation period immediately after the study ended.

Table 2 shows the frequency and clinical course of persistent otitis media with effusion,* documented by tympanogram, and the episodes of otitis media which developed subsequently. During the first 2 weeks of the study, none of 5 SMZ-treated children who entered the study with a flat tympanogram developed symptoms of pain or a bulging eardrum. Moreover, 4 children who were given SMZ had a flat tympanogram *de novo*, while 13 of the 33 in the placebo group had such a tympanogram ($P < 0.05$).

*Previously known as middle ear effusion or secretory effusion.

Table 1 Children with at least one episode of otitis media during treatment with sulphamethoxazole compared with placebo

Period	Sulphamethoxazole		Placebo	
	No of children	No of episodes	No of children	No of episodes
December-February	17	4 ^a	16	12 ^{a, c, d}
February-April	16	5 ^{b, c}	17	7 ^{b, d}
Total	33	9 Δ †	33	19 Δ Δ †

Δ 10 episodes, Δ 27 episodes.

† $x^* = 2.55$ $P = < 0.02$, ^a $x^* = 2.87$ $P = < 0.01$, ^b NS, ^c $x^* = 2.5$ $P = < 0.02$, ^d $x^* = 1.98$ $P = < 0.05$.

Table 2 Otitis media with effusion

Tympanometry	Treatment at time of diagnosis	
	Sulphamethoxazole*	Placebo*
Flat tympanogram at the beginning of the study (OME=14)	5 (0)	9 (4)
Flat tympanogram detected <i>de novo</i> during the course of the study (OME=17)	4 (1)	13 (9)

Patients who subsequently developed otitis media shown in brackets.
*Flat tympanogram and physical examination compatible with otitis media with effusion.

OME=otitis media with effusion.

By means of comparison, 9 of the placebo group had a flat tympanogram on entry and in 4 cases the child soon began to complain of earache and the tympanogram was bulging.

We studied the relationship between the presence of bioinhibitory activity in urine and episodes of otitis media. No episode of otitis media was observed in 11 children in whom the urine sample uniformly had antimicrobial activity, and two episodes of otitis media were noted in 9 children in whom the urine specimens indicated an acceptable degree of compliance with the study regimen. Of the 13 patients who submitted at least 2 urine specimens lacking in bioinhibitory activity (fair compliance), or who did not submit any urine specimens, eight episodes of otitis media were detected (Table 3). A comparison of children with excellent pharmacological compliance with those in whom we did not have objective documentation of such compliance (0/11 compared with 10/22) achieves statistical significance ($P = <0.0001 [\chi^2]$).

The only adverse reaction to the study drug was a morbilliform rash, which was probably caused by SMZ. During an 8-week observation period after the study had ended, during which no chemoprophylaxis was administered, there were 12 episodes of acute otitis media in 10 children. Analysis of these episodes of otitis media cases was done. Six children with eight episodes had just finished the placebo, while the other four episodes were noted in 4 children who had just finished SMZ. Of this group,

3 children had no episode of acute otitis media while receiving SMZ or placebo.

Discussion

In studies lacking statistically acceptable controls, Ensign *et al.*³ and Maynard *et al.*⁴ demonstrated a 50% reduction in episodes of acute otorrhoea in Alaskan eskimo children given either continuous daily sulphonamides or ampicillin. In contrast, Reed and Dunn,⁵ using a monthly benzathine penicillin injection, found no such reduction. Investigators from St Jude's Hospital, in a 2-year, random, double-blind, placebo-controlled study, evaluated the efficacy of trimethoprim-sulphamethoxazole (TMP-SMZ) for the prevention of *Pneumocystis carinii* pneumonia in 160 children with cancer. In addition to preventing infection of the lung with the opportunistic protozoan *P. carinii*, an unexpected but beneficial result of the study was that otitis media was detected 50 times in the placebo group and only 6 times in the TMP-SMZ treated children.⁷ The results of this study are encouraging; however, according to the instructions on the package, TMP-SMZ should not be used for prophylaxis of otitis media.

More recently Biedel,^{8,9} a practising paediatrician, studied 129 children who had just recovered from 233 episodes of acute otitis media. Episodic doses of prophylactic sulphonamide were used. He instructed the parents of each child to notify his office each time the child had symptoms typical of a common cold, at which time a prescription was telephoned to a pharmacy. Either a proprietary decongestant (control group), or a sulphonamide drug (30 mg/kg per dose) without a decongestant (treatment group), was given 4 times a day for at least 6 days, or for as long as the infection of the upper respiratory tract persisted. There were 4 (6%) cases of recurrent otitis for the entire treatment group and 15 (20%) cases in the control group, a highly significant difference ($P < 0.001$). Only one adverse reaction to the sulphonamide, a mild rash, was reported.

In 1974, Perrin *et al.*⁶ reported a randomly assigned, double-blind, placebo-controlled, cross-over study of otitis-prone children. Each child, serving as his own control, received 3 months of sulphafurazole twice daily and 3 months of placebo during a single winter season in Rochester, New York. They noted a 72% reduction in episodes of acute otitis media. There were 4 cases of otitis in 4 children who had received the sulphonamide, compared with 28 episodes in 21 children who had received the placebo.

Our study modelled closely to that of Perrin and associates, leads us to conclude, as they did,

Table 3 Compliance during study

Compliance	No of patients	Episodes of otitis media
Complete	11	0+
Acceptable	9	2}
Fair	9	5}+
Specimens not returned	4	3}

Acceptable compliance=two of three urine specimens positive for antibiotic, fair compliance=one urine specimen positive.

+ $P = <0.0001 [\chi^2]$.

that sulphonamide chemoprophylaxis is effective in reducing episodes of acute otitis media in otitis-prone young children; however, some differences are apparent in the designs of these two studies.

Because Perrin *et al.* found no benefits to chemoprophylaxis in 18 children older than 5 years of age, we limited our study to children of 72 months or younger. Instead of using a twice daily dose of sulphafurazole, we chose a single bedtime dose. Moreover, in our study, compliance was monitored by testing serial urine specimens for bioinhibitory activity, while Perrin *et al.* ascertained the volume of sulphonamide suspension periodically. In Perrin's study, neither tympanometry nor pneumo-otoscopy was used to diagnose otitis media with effusion. Since publication of the earlier study, the importance of otitis media with effusion and its diagnosis by pneumo-otoscopy or tympanometry has been appreciated.

We found that signs and symptoms of otitis media were more likely to occur in children with otitis media with effusion who changed to the placebo during the second 2-month period. It is tempting to speculate that the more rapid resolution of otitis media with effusion in children receiving the study drug made them less likely to have acute otitis media. Perhaps sulphonamide reduces the frequency and duration of otitis media with effusion as well as preventing episodes of acute otitis media.

We think that chemoprophylaxis for recurrent otitis media may act in a similar manner to low-dose sulphonamides in preventing recurrent urinary tract infection. Sulphonamides are generally active against two common bacteria causing otitis media and are attractive chemoprophylactic agents because they have a low incidence of side effects.

The cost of 4 months of SMZ, estimated at \$20, would be more than offset by the monetary saving if a single episode of acute otitis media were prevented. By reducing the frequency of otitis media with effusion, some children might also avoid the insidious, fluctuating, conductive hearing loss

caused by middle ear effusion. There are also incidental savings in time, transport, and parental concern, factors which, although difficult to estimate, are none the less important.

During the winter, when most episodes of otitis media occur,¹¹ we suggest that low dose sulphafurazole or sulphamethoxazole be given once or twice daily in any young child who has had at least three episodes of acute otitis media within the last 6 months and has another infection.

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