Concentrations of Trimethoprim-Sulfamethoxazole in Blood After a Single, Large Oral Dose

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Concentrations of trimethoprim (TMP) and sulfamethoxazole (SMZ) in blood were determined in seven healthy volunteers after ingestion of 720 mg of TMP and 3,600 mg of SMZ (nine tablets of TMP-SMZ, 1:5 ratio) as a single oral dose. The mean levels of drug in blood achieved during the first 8 h after drug administration ranged from 6.12 to 8.32 μg/ml for TMP and 98 to 120 μg/ml for SMZ. These concentrations easily exceeded the previously reported minimal inhibitory concentrations for clinical isolates of Neisseria gonorrhoeae. The combination of TMP-SMZ given as a single, large oral dose may be a useful therapeutic regimen for patients with uncomplicated gonorrhea and susceptible microorganisms.

Trimethoprim-sulfamethoxazole (TMP-SMZ) has been used to treat uncomplicated gonorrhea (1, 2, 4, 7-9, 11, 12). However, the cure rate has been somewhat variable, ranging from 62 to 98%. The treatment schedules instituted in these studies varied from a single-dose regimen for 1 to 5 days to multiple doses for several successive days. Although levels of TMP and SMZ were not determined, it would be anticipated that achievable concentrations of these drugs in blood would significantly differ depending on which treatment regimen was utilized. This, in part, may explain differences in therapeutic outcome.

To evaluate the potential usefulness of a single, large-dose regimen of TMP-SMZ for treatment of uncomplicated gonorrhea, preliminary studies were performed in healthy volunteers by administering 720 mg of TMP and 3,600 mg of SMZ. Serial blood concentrations of TMP and SMZ were determined at appropriate intervals. The data from this investigation are presented in this report.

EXPERIMENTAL

Seven healthy male and female volunteers between the ages of 24 and 34 years received a single oral dose of nine TMP-SMZ tablets (each tablet consisting of 80 mg of TMP and 400 mg of SMZ; courtesy of Hoffmann-La Roche, Inc., Nutley, N.J.). The medication was taken with 8 to 10 oz (ca. 0.24 to 0.3 liter) of water in the morning after an overnight fast. Food was not eaten until 5 h after ingestion of drugs. Thereafter, food and fluids were not restricted.

A total of 10 ml of oxalated blood was drawn at 0 (before drug administration), 2, 4, 6, 8, and 24 h. Serum samples were immediately frozen for subsequent analysis. The determination of TMP and SMZ concentrations in blood was performed through the courtesy of Robert Weinfield, Hoffmann-La Roche, Inc., Nutley, N.J., by previously described methods (5, 10).

RESULTS AND DISCUSSION

Levels of TMP and SMZ in blood from the seven volunteers are presented in Fig. 1 and 2, respectively. The mean blood concentrations of the drugs during the first 8 h after their administration ranged from 6.12 to 8.32 μg/ml (TMP) and 98 to 128 μg/ml (SMZ). At 24 h, the average levels of TMP and SMZ in blood were 2.16 and 31.7 μg/ml, respectively. The dose regimen was satisfactorily tolerated by most individuals, with two persons experiencing transient nausea.

Previous studies determining levels of TMP and SMZ in blood were performed in normal volunteers receiving relatively small, single oral doses of these drugs. One study administered 240 mg of TMP and 1,200 mg of SMZ and achieved average peak levels for TMP and SMZ of 3.0 and 65 μg/ml, respectively (3). Investigations by Kaplan et al. (6) in 24 healthy male volunteers after ingestion of a higher dose of the drugs, 400 mg of TMP and 2,000 mg of SMZ (five tablets of TMP-SMZ), revealed similar mean peak concentrations. However, in the present study after administration of nine tablets of trimethoprim-sulfamethoxazole, the mean peak concentrations achieved in the blood for TMP and SMZ were more than double...
there has been reported a clinical trial of nine tablets of TMP-SMZ as a single oral dose in males with gonococcal urethritis (W. C. Elliott, M. F. Rein, G. H. Reynolds, C. Thornsberry, H. W. Jaffe, and J. H. Armstrong, Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 15th; Washington, D.C., Abstr. 391, 1975). In this study, there was an inordinately high failure rate of 25% with this TMP-SMZ regimen. Additional clinical trials will obviously be necessary to confirm these results. Furthermore, studies in women with uncomplicated gonorrhoea using this TMP-SMZ dose schedule are lacking and need to be pursued.

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LITERATURE CITED