Effects of Moderate-Dose versus High-Dose Trimethoprim on Serum Creatinine and Creatinine Clearance and Adverse Reactions

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Trimethoprim (TMP) is known to cause reversible increases in serum creatinine, reportedly by inhibiting its renal tubular secretion (2–4, 9–11, 14–16, 18) without causing a change in the glomerular filtration rate. The increase in serum creatinine causes an apparent decrease in the calculated creatinine clearance. To date, studies examining the effect of TMP on serum creatinine concentration have primarily investigated dosages ranging from 200 to 400 mg per day, which are typically used in the treatment of urinary tract infections. However, the effect of high-dose TMP therapy (i.e., 15 to 20 mg/kg of body weight/day [the dose used in the treatment of Pneumocystis carinii pneumonia]) on serum creatinine has not been evaluated (7, 8, 12, 13). It is important to assess the magnitude of serum creatinine elevation in patients on high-dose TMP therapy because this rise in serum creatinine may be misinterpreted as a deterioration of renal function. If a downward dosage adjustment of other drugs is made in response to a perceived impairment of renal function, administration of subtherapeutic dosages with the potential for treatment failure may occur. The aims of this study were to evaluate the effects of high-dose TMP (20 mg/kg/day) versus that of moderate-dose TMP (10 mg/kg/day) on serum creatinine, creatinine clearance, urinary creatinine, and serum folate.

(Trial was presented in part at the 98th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, San Diego, Calif., 5 to 8 March 1997.)

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Bassett Healthcare. Written informed consent was obtained from each subject. Normal healthy volunteers, both males and premenopausal females, were recruited for the trial. Twenty subjects (10 male and 10 female) were enrolled. Subjects could not be enrolled if they were positive for human immunodeficiency virus (HIV). Male subjects were included if they were 18 to 65 years of age. Premenopausal female subjects were enrolled if they were aged 18 to 50 years. Female subjects were required to use a barrier form of birth control or be surgically sterile. Subjects were excluded if they had an allergy to TMP, were pregnant or lactating, had renal disease (defined as a serum creatinine level of greater than 1.5 mg/dl), or had hepatic disease (defined as an aspartate aminotransferase [AST] or alanine aminotransferase [ALT] level greater than 1.5 times the upper limit of the normal range). In addition, patients were excluded if they had been exposed to TMP or sulphonamide-containing medications within the 2 weeks before the study began, had been exposed to nephrotoxins (defined as amphotericin B, aminoglycosides, or contrast media) within 30 days of the study, if they were on concomitant phenytoin or cimetidine, or if they were malnourished or overweight. Nutritional status was assessed by diet history and weight. A subject was not enrolled if his or her actual body weight was ±50% of the ideal body weight. Ideal body weight was calculated by the method of Devine (6).

The subjects were randomized for an initial study period of either high-dose TMP (20 mg/kg/day, dosed as 5 mg/kg every 6 h) or moderate-dose TMP (10 mg/kg/day, dosed as 5 mg/kg every 12 h) by using a random number table. TMP was kindly supplied as 100-mg tablets (Trimoxep, lot no. 0437; Roche Laboratories, Nutley, N.J.) and was taken by mouth. Each subject’s dosage was based on his or her actual body weight. Dosages were rounded to the nearest 100 mg. The study was divided into two periods, period I and period II. The duration of therapy for each period was 10 days, and there was a 21-day washout phase between periods. Subjects were then crossed over to the alternate treatment study group in period II. Compliance was monitored by the use of tablet counts. If a subject took ≥90% of the tablets, he or she was deemed compliant. During each investigational period, baseline serum creatinine, folate, AST, ALT, urine pregnancy test (for females), and 24-h urinary creatinine (for creatinine clearance) data were obtained. During the remainder of the investigational periods, serum samples were obtained from patients on days 2, 4, 6, 8, and 10 during TMP therapy and on days 2, 5, 7, and 10 of the washout phase for determination of serum creatinine concentrations. Twenty-four-hour urine specimens for determination of creatinine clearance were obtained on days 3, 7, and 10 of TMP therapy and on days 2, 5, 7, and 10 of the washout phase for determination of serum creatinine concentrations. Twenty-four-hour urine specimens for determination of creatinine clearance were obtained on days 3, 7, and 10 of TMP therapy and on days 2 and 10 during the washout phase. Specimens for the determination of serum folate were obtained on day 10 of both phases of the TMP therapy. Adverse drug reactions (ADRs) for each period were assessed and recorded by the physician investigator.

Creatinine values for serum and urine were analyzed at Bassett Healthcare Clinical Laboratories by using the enzymatic Kodak Ektachem CREA clinical chemistry slide. The coefficient of variation of the assay for serum creatinine was 2% at 0.9 mg/dl and 2.7% at 1.1 mg/dl. The coefficient of variation for the urine creatinine assay was 3% at 25 to 300 mg/dl.

Statistical analyses were performed with SAS version 6.08 (17) and EPI Info.
The completion of the second phase, three subjects completed moderate-dose TMP therapy and four completed high-dose TMP therapy. In period II, two subjects on high-dose TMP discontinued the study medication. Thus, a total of 10 subjects completed the moderate-dose phase and 7 subjects completed the high-dose phase. One subject discontinued because of the appearance of a rash, and one dropped out because of severe headaches. In both periods, all subjects complied with the medication regimen.

Serum creatinine levels in both the high- and moderate-dose groups consistently increased over the first 5 days of therapy and then plateaued. During TMP dosing, the mean ± SD increases in serum creatinine levels between days 0 and 10 were 0.20 ± 0.13 mg/dl (average, 22.2%; \( P < 0.005 \)) and 0.28 ± 0.18 mg/dl (average, 31.3%; \( P < 0.0005 \)) with respect to the baseline for the moderate- and high-dose groups, respectively (Fig. 1 and 2). Measured creatinine clearance values declined 20.3 ± 22.2 ml/min/1.73 m² (average, 21.3%; \( P = 0.01 \)) and 16.1 ± 27.8 ml/min/1.73 m² (average, 16%; \( P = 0.08 \)) with respect to the baseline in the moderate- and high-dose phases, respectively (Fig. 3). Urine creatinine levels decreased 0.12 ± 0.25 g (\( P = 0.1 \)) and increased 0.23 ± 0.33 g (\( P < 0.05 \)) with respect to the baseline in the moderate- and high-dose phases, respectively (Fig. 4). Using Student’s \( t \) test for paired comparisons, changes in serum creatinine, measured creatinine clearance, and urine creatinine did not differ statistically between the high- and low-dose groups. With a multivariate linear regression model (using dose, duration of TMP therapy, and dose times duration), there remained no predictors of changes

### RESULTS

In period I, 20 subjects were enrolled (10 in the high-dose group and 10 in the moderate-dose group). The baseline demographics of the subjects are shown in Table 1. All variables were similar with the exception of the initial TMP dose. Three subjects (two in the high-dose group and one in the moderate-dose group) dropped out within the first 2 days and were not used in the final statistical analyses of effects on serum and urine creatinine levels since few data on them were available. Data from these subjects were used in the toxicity analysis. The reasons for dropping out included a sudden onset of nausea and vomiting and a rash in one subject, severe headache in another, and nervousness and shakiness in the third. Of the 17 remaining subjects (9 in the moderate-dose group and 8 in the high-dose group), 7 in the moderate-dose group and 3 in the high-dose group completed drug treatment. ADRs leading to dropping out of the moderate-dose group included a rash in one person, and one person withdrew from the study. In the high-dose group, treatment of four subjects was discontinued due to the appearance of a rash and one dropped out due to severe nausea, vomiting, and headache. Prior to the start of period II, one subject who would have been assigned to the high-dose group was lost to follow-up. The remaining nine subjects were started in the crossover phase (period II), three in the moderate-dose group and six in the high-dose group. At

![Graph](http://example.com/graph.png)

**FIG. 1.** Changes in serum creatinine levels in the moderate-dose TMP group. TMP (10 mg/kg) was given from days 1 to 10, with serum creatinine levels being followed for an additional 10 days.

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**TABLE 1.** Subject demographics and laboratory dataa

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**version 5 (5).** Analyses included Student’s \( t \) test for paired comparisons and multiple linear regression. ADRs were analyzed by Fisher’s exact test. Statistical significance was defined as a \( P \) value of ≤0.05. All data are presented as means ± standard deviations (SD).
in serum creatinine, measured creatinine clearance, or urine creatinine.

After TMP dosing ended, serum creatinine returned to baseline over 5 days. The mean decreases in serum creatinine were 0.19 ± 0.12 mg/dl (P < 0.001) and 0.31 ± 0.16 mg/dl (P < 0.0001) versus the levels on the last day of TMP treatment in the moderate- and high-dose phases, respectively (Fig. 1 and 2). Measured creatinine clearance increased by 11.3 ± 33.7 ml/min/1.73 m² (nonsignificant P value) and 17.6 ± 28.8 ml/min/1.73 m² (P = 0.08) versus the levels on the last day of TMP treatment in the moderate- and high-dose phases, respectively (Fig. 3). Urine creatinine increased 0.08 ± 0.40 g (P = 0.1) and 0.04 ± 0.23 g (nonsignificant P value) compared to the values on the last day of TMP treatment in the moderate- and high-dose phases, respectively (Fig. 4). Using a multivariate linear regression model, changes in serum creatinine, measured creatinine clearance, and urine creatinine did not differ significantly for the moderate- and high-dose TMP phases between the end of TMP therapy and day 20.

No significant reduction from baseline occurred in serum folate concentrations during moderate-dose TMP therapy. Serum folate concentrations decreased from 8.25 ± 5.7 mg/dl to 5.5 ± 4.3 mg/dl after 10 days of high-dose TMP (P < 0.01).

ADRs seen in our volunteers included rashes, gastrointestinal symptoms (i.e., nausea and vomiting), and central nervous system effects (i.e., nervousness, headache, and alterations in smell and taste). The total ADRs for the two treatment groups in period I were found to differ significantly (11% for the low-dose group versus 75% for the high-dose group; P < 0.02). In period II, the total ADRs for the two dosage groups did not differ significantly. This is most likely due to the small number of subjects left to enter period II. Rashes were seen in 10% of the subjects receiving moderate-dose TMP and in 60% of the subjects receiving high-dose TMP.

**DISCUSSION**

Previous studies examining the effect of TMP on serum creatinine in healthy individuals have shown an average increase of between 15 and 35% (2–4, 9–11, 14–16, 18). This effect is most likely due to a reduction in tubular secretion of creatinine. Studies of the effect of TMP on serum creatinine have typically shown that there are statistically significant differences between the creatinine values obtained at the beginning of therapy and those measured at end of therapy. European studies examining this phenomenon have consistently shown that during therapy the serum creatinine values, although initially elevated, tend to move back toward normal before the dose is discontinued. These differences, although not statistically significant, are similar to the trends that we observed in the high- and moderate-dosage groups. A study examining TMP and its effect on patients with normal renal function and those with chronic renal failure (14) showed that the serum creatinine levels of patients with normal renal function did not differ statistically from baseline levels while those of patients with chronic renal failure did show significant changes from the baseline.

The results obtained in our study correspond well with the data from these previous studies. In our study population, patients had normal renal function at baseline and had only modest increases in serum creatinine concentrations at either dosage level. While the changes are statistically significant, these increases can be considered clinically unimportant. Be-
cause these patients were healthy and were not taking other nephrotoxic drugs, they had no reason to exhibit changes in their glomerular filtration rates. As would be expected, changes in serum creatinine levels were accompanied by the opposite changes in measured creatinine clearance and urine creatinine excretion. These changes are consistent with the known effect of TMP on tubular secretion of creatinine. Although statistically significant, the clinical relevance of the changes in serum creatinine levels with respect to dosage appears to be negligible. Greater differences might have been achieved if the subjects had compromised renal function, since in patients with renal dysfunction there is a greater reliance on tubular secretion of creatinine for excretion. Thus, a greater effect of TMP on serum creatinine, measured creatinine clearance, and urine creatinine may be observed in those with certain types of renal dysfunction.

Of particular interest in the current study is the incidence of ADRs in the high- and moderate-dose groups. ADRs occurred at a very high rate in the high-dose group (seven times that of the moderate-dose group). This phenomenon has been previously described in patients with HIV, for whom the incidence of ADRs ranges upward of 90% (7, 8). This increasing incidence of ADRs does not appear to occur only in patients with HIV infection. In our trial, the subjects enrolled were healthy volunteers. None was being treated for an opportunistic infection, and none had been diagnosed with HIV or AIDS. In previous trials, patients with ADRs who had TMP dosage reductions often had resolution of their symptoms. Stevens et al. noted a dose-response effect for TMP-sulfamethoxazole (SMZ) adverse reactions in normal volunteers (19, 20). This dose-response effect for ADRs is supported by our findings of increased TMP toxicity at higher dosages. During period I, subjects who were randomized to the high-dose group were seven times more likely to develop an ADR. In period II, subjects who had completed the moderate-dose phase in period I without developing an ADR had an ADR incidence of 50% on high-dose TMP therapy. However, due to the large number of dropouts, the ADR incidence did not differ statistically in the crossover phase. This is most likely due to the small number of subjects remaining in each group during period II. When each type of ADR was examined individually in each phase, no type of ADR was found to be significantly different.

Substantial clinical relevance can be placed on the ADR data obtained. Significant dose-related toxicity with TMP was observed in a healthy, immunocompetent group of volunteers. To date, many of the ADRs associated with TMP-SMX have been attributed to the sulfonamide portion of the drug or to an increased incidence of ADR in patients with HIV. Our data demonstrate that normal healthy volunteers experience significant rates of adverse experiences, particularly rashes, with moderate- and high-dose TMP therapy. Therefore, the high rate of ADRs reported in patients taking TMP-SMX and in HIV patients may not be unique to either group of patients.

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REFERENCES


