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Serum Peak Sulfamethoxazole Concentrations Demonstrate Difficulty in Achieving a Target Range: A Retrospective Cohort Study

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ABSTRACT

Objectives: Trimethoprim (TMP)/sulfamethoxazole (SMX) has consistently demonstrated great interindividual variability. Therapeutic drug monitoring may be used to optimize dosing. Optimal peak SMX concentration has been proposed as 100 to 150 μg/mL. The objective of our work was to determine the success rate of a TMP/SMX dosing guideline in achieving a targeted serum peak SMX concentration range.
Methods: Our retrospective cohort study enrolled 305 adult hospitalized patients who received treatment with TMP/SMX and underwent serum peak SMX concentration monitoring from January 2003 to November 2011. Patients receiving low-dose TMP/SMX therapy (TMP < 15 mg/kg/d) were compared with those receiving high-dose therapy (TMP > 15 mg/kg/d).
Results: Patients were classified into peak and modified peak SMX concentration cohorts based on time between TMP/SMX dose and SMX quantification. The association between dosing group and the outcome of the SMX level within the goal range was measured using logistic regression models. The primary outcome measured was serum peak SMX concentration 100 to 150 μg/mL. Serum peak SMX concentrations were attained within range for the peak and modified peak cohort 29% and 26% of the time, respectively. The median peak SMX concentration was 144 μg/mL (range 25–471 μg/mL). The low daily dose cohort demonstrated a trend toward improvement in the odds of target peak concentration range attainment. The results were similar regardless of the method used to adjust for baseline characteristics. The pure peak and modified peak cohorts had 44% and 46% of patients with above-target SMX peak concentrations, respectively.
Conclusions: Attainment of the intended target concentration range was low with no difference in attainment between the low-dose and high-dose cohorts. Higher proportions of patients had an above-target SMX peak, which may indicate that the dosing algorithm is overly aggressive in obtaining the therapeutic goal.

Introduction

Trimethoprim (TMP)/sulfamethoxazole (SMX) is a broad-spectrum antimicrobial combination effective in treating a variety of microorganisms and has been used in clinical practice for more than 50 years.[1] High response rates demonstrated in clinical studies support TMP/SMX as the drug of choice for serious infections such as *Stenotrophomonas maltophilia*, *Pneumocystis jiroveci*, and *Nocardia* spp.[2–4,5]

Since its discovery, pharmacokinetic studies of TMP/SMX serum concentrations have consistently demonstrated great interindividual variability[6,7] and the use of therapeutic drug monitoring was attempted to optimize clinical efficacy while minimizing adverse effects.[7–9] Hughes et al[10] determined low peak SMX concentration was associated with treatment failure in a study of 55 randomized pediatric patients with *Pneumocystis carinii* pneumonia (PCP pneumonia) and proposed 100 to 150 μg/mL as the optimal therapeutic range based on concentrations assayed from the 26 patients assigned to the TMP/SMX arm combined with any levels drawn from patients who crossed between treatments. This therapeutic range was further investigated for clinical efficacy in a study of treatment for AIDS-associated PCP pneumonia in HIV-positive adult patients, of whom 21 were assigned to receive

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TMP/SMX. Mortality in TMP/SMX-treated patients was similar to previous studies with a high rate of TMP/SMX-related adverse events.[7] Additionally, peak SMX concentrations >200 μg/mL demonstrated an association with severe adverse effects.[9,11,12] Despite extensive clinical experience, difficulties remain in achieving the proposed therapeutic SMX peak serum concentration of 100 to 150 μg/mL.[8] The limited data surrounding a relationship between peak SMX serum concentrations and clinically meaningful outcomes call into question the use of routine therapeutic drug monitoring during high-dose TMP/SMX therapy.

The use of TMP/SMX therapy at our institution is frequently coupled with therapeutic drug monitoring in an effort to attain a targeted SMX peak serum concentration. Our institutional dosing algorithm has not been verified for its accuracy of attainment of the prespecified peak serum SMX concentration goal of 100 to 150 μg/mL. The purpose of our study is to compare the performance of a TMP/SMX dosing algorithm in achieving targeted serum peak SMX concentrations in hospitalized patients who received therapeutic doses of TMP/SMX.

Materials and Methods

Eligible patients

This single-center, retrospective cohort study was approved by the Mayo Clinic Institutional Review Board and conducted at Mayo Clinic in Rochester, Minnesota. Consecutive adult patients who received therapeutic doses of TMP/SMX between January 2003 and November 2011 were evaluated. Patients were included if they were aged 18 years or older and underwent serum peak SMX monitoring during TMP/SMX therapy. Intravenous or oral administration was allowed due to the nearly complete bioavailability of the oral formulations.[13] Patients were excluded if they received TMP/SMX for infection prophylaxis, underwent TMP/SMX desensitization, or had the serum SMX plasma concentration monitored outside of their hospitalization. Data collection was limited to the earliest chronologic occurrence of therapeutic TMP/SMX administration with concurrent therapeutic drug monitoring for the purposes of maintaining independent data. Only the first peak serum SMX concentration was considered during this evaluation.

Laboratory assessment

SMX serum concentration levels were determined by HPLC by our institution's Clinic Toxicology and Drug Monitoring Laboratory.[14]

Definitions

The goal peak SMX concentration range of 100 to 150 μg/mL was defined per our institution's antimicrobial therapy guide.[15] Serum SMX concentrations were considered peak concentrations if they were measured between 1 and 2 hours after intravenous administration or between 2 and 3 hours after administration of an oral dose at the onset of steady-state conditions.[15] Serum SMX concentrations were considered modified peak if they were measured within 4 hours after intravenous administration and within 5 hours of oral administration. The peak values in the modified peak group served as surrogate peak levels in the absence of multilevel sampling and pharmacokinetic estimation. The peak and modified peak cohorts were categorized into 2 dosing groups—high dose or low dose—according to our institution's dosing algorithm for the prespecified subgroup analysis (**Table I**). The high-dose group received a total daily dose ≥15 mg/kg actual body weight of the TMP component. The low-dose group received a total daily dose <15 mg/kg actual body weight of the TMP component. The dosing intervals ranged from every 6 hours to every 24 hours, depending on the patient's creatinine clearance (**Table I**).[16,17] Patients were assessed for dosage adjustments based on estimated creatinine clearance using the Cockcroft-Gault formula.[18]

Table I
Trimethoprim/sulfamethoxazole dosing algorithm.*

Creatinine clearance	High dose	Low dose
≥30 mL/min	15–20 mg/kg/d in 3–4 divided doses	<15 mg/kg/d in 2–4 divided doses
<30 mL/min†	7–10 mg/kg/24 h in 2 divided doses	<7 mg/kg/24 h divided q12h–q24h

* Dose based on trimethoprim component.
† Patients receiving dialysis were recommended to receive the dose indicated for patients with CrCl < 30 ml/min with the dose scheduled after dialysis on dialysis days.

Data collection

Clinical and demographic data were retrospectively abstracted from medical records and divided into 3 categories: demographic data, infectious disease data, and TMP/SMX data. Demographic data included age, sex, body weight, serum creatinine, estimated creatinine clearance calculated by the Cockcroft-Gault formula, and absence/presence of preexisting chronic kidney disease or immunocompromised status as documented in electronic medical records before the date of admission. Additionally, chronic kidney disease was verified through a search for ICD-9-CM and ICD-10-CM diagnosis codes for chronic kidney disease (585 and N18, respectively). Infectious disease data included site of infection and infectious organism. Lastly, TMP/SMX data included TMP/SMX start date and time; TMP/SMX dose (milligrams per kilogram TMP component); and interval, date, time, and value of peak serum peak SMX concentration. The primary outcome measured was the frequency of serum peak SMX concentration within the defined goal of 100 to 150 μg/mL.

Statistical analysis

Variables were summarized as median (range or interquartile range) or frequency (%), as appropriate. Baseline comparisons between high- and low-dose groups were done using the Wilcoxon rank-sum test for continuous variables or Pearson χ^2 test for discrete variables. To adjust for possible covariate imbalance between the high- and low-dose groups, propensity scores of the probability of receiving a high dose were computed for each patient using a multivariable logistic regression model that included variables for chronic kidney disease, dialysis, immunocompromised status, intensive care unit admission, pulmonary diagnosis, identified infectious organism (eg, *Stenotrophomonas maltophilia, Pneumocystis jiroveci, Nocardia* spp, *Staphylococcus* spp, or polymicrobial), body mass index (BMI), and creatinine clearance.[19] The association between dosing group and the outcome of the SMX level being within the therapeutic range was measured using 4 different logistic regression models: including only the dose group as a predictor (unadjusted model), including the dose group and all the variables that went into the propensity score computation (standard covariate adjustment model), including the dose group and the propensity score as a covariate (propensity score covariate adjustment model), and model stratified by propensity score quintile groups with a predictor of dose group (propensity score stratified model). Models 2 through 4 adjust for the covariates, but in different ways. Model 1 is provided for