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Original Article

High daily doses of trimethoprim/sulfamethoxazole are an independent risk factor for adverse reactions in patients with pneumocystis pneumonia and AIDS

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Abstract

Background: Trimethoprim/sulfamethoxazole (TMP/SMX) is currently the most effective therapeutic agent for *Pneumocystis jirovecii* pneumonia (PJP) in patients with AIDS. The major drawback is the frequent occurrence of adverse reactions (ADRs).The current study was designed to determine the frequency and risk factors for TMP/SMX-related ADRs among patients with PJP and AIDS.
Methods: A retrospective study was conducted in adult patients with PJP and AIDS who were admitted to the Veterans General Hospital in, Kaohsiung, Taiwan between January 2006 and December 2011. Charts were reviewed to determine the effect of age, risk behaviors, severity of illness, viral load, CD4 cell counts, use of corticosteroids, and dosage and duration of TMP/SMX on ADRs during hospitalization. Patients who received TMP/SMX for $\leq$ 5 days or with an incomplete medical record were excluded. Multivariate logistic regression was used to calculate the hazard ratio (HR) for ADRs.
Results: Fifty two of 75 patients with PJP and AIDS met the study criteria. Of these patients, 21/52 (40.3%) developed an ADR. Among the 21 patients who suffered an ADR, skin rash was noted in 10 (47.6%), liver function impairment in nine (42.9%), elevated creatinine in eight (38.1%), fever in four (19%), and gastrointestinal symptoms in three (14.3%). Most of the ADRs occurred within the 1st 2 weeks of TMP/SMX therapy. Cox proportional hazards analysis revealed that a daily dose of TMP/SMX of $\geq$ 16 mg/kg (HR, 3.8; 95% confidence interval, 1.40–10.35; $p = 0.009$) and age 34 years (HR, 4.30; 95% confidence interval, 1.52–12.14; $p = 0.006$) were independently associated with ADRs.
Conclusion: We found a high incidence of ADRs among patients with PJP and AIDS treated with TMP/SMX, and most involved the skin and liver. A daily dose of $\geq$ 16 mg/kg of TMP/SMX and age 34 years were independent risk factors for ADRs.

Keywords: adverse drug reaction; HIV; *Pneumocystis jirovecii*; pneumonia; trimethoprim/sulfamethoxazole

1. Introduction

Pneumocystis jiroveci pneumonia (PJP) is a major cause of morbidity and mortality among immunocompromised patients. It continues to be a common early manifestation of AIDS.[1] The recommended treatment for PJP has been unchanged for many years.[2] Trimethoprim/sulfamethoxazole

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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(TMP/SMX) remains the drug of choice for the treatment and prophylaxis of PJP in patients with AIDS. TMP/SMX has the advantages of good tissue penetration and the bioavailability of the oral form is comparable to parenteral administration. It provides the most rapid clinical response among the current antipneumocystis agents. Although highly effective, the use of TMP/SMX for patients with AIDS is limited by the high frequency of adverse reactions (ADRs) ranging from 29% to 65%.[3–5] By contrast, ADRs are reported to occur in less than 10% of the general population and in immunocompetent patients treated with TMP/SMX.[6]

The risk factor for ADRs to TMP/SMX remains poorly understood. Carr et al[7] reported hypersensitivity to TMP/SMX in 39/143 (27%) of AIDS patients with PJP. They found that a CD4:CD8 ratio of > 0.1 and treatment for < 14 days were independent predictive factors for hypersensitivity. Veenstra et al[8] found that a low CD4 cell count at baseline and the use of antiretroviral therapy, before starting TMP/SMX prophylaxis for human immunodeficiency virus (HIV) infected patients, were predictors of ADRs to TMP/SMX. The current study was designed to determine whether the daily dose of TMP/SMX based on body weight might be an independent risk factor for ADRs in AIDS patients treated for PJP. It was based on our clinical observation that TMP/SMX-related ADRs appeared to occur more often among lower-weight patients receiving a standard dose of TMP/SMX.

2. Methods

2.1. Ethical statements

This study was approved by the Institutional Review Board of the Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan. The study complied with all ethical considerations involving human participants. All of the data was decoded and the patient's informed consent was not mandatory.

2.2. Study populations

We conducted a retrospective chart review of all adult patients treated for PJP at the Kaohsiung Veterans General Hospital between January 2006 and December 2011. Patients were included in the analysis if they were treated with TMP/SMX for a first episode of PJP, had not received TMP/SMX previously for PJP prophylaxis, and had no prior history of ADRs to TMP/SMX. Patients were excluded if they were younger than 18 years, had received TMP/SMX for ≤ 5 days, or the records were incomplete. The diagnosis of PJP was based on cytology, histopathology, or polymerase chain reaction assay of respiratory specimens or typical radiological findings of interstitial pneumonitis in patients with AIDS.[2]

2.3. Data collection

A standardized case record form was used to collect the demographic and comorbid characteristics of the population, laboratory findings (hemogram, electrolytes, serum creatinine, and hepatic profile), mode of diagnosis of PJP, radiologic findings, body weight, height and body mass index, dosage of TMP/SMX, use of adjunctive steroids, and in-hospital mortality. The HIV-related variables included sexual behavior, CD4 cell count, plasma HIV RNA load, and current antiretroviral therapy. An ADR record form was used to identify ADRs according to the involved organ systems. The Naranjo score which was used to estimate the probability of a temporal relationship between the drug and an ADR. A score of > 8 was considered to be definite, 5–8 probable, 1–4 possible, and < 1 doubtful.[9] The preventability of an ADR was evaluated using the criteria developed by Schumock and Thornton.[10]

The initial daily dose of TMP/SMX was based on a visual estimate of body weight by the attending physician and administered by the oral or intravenous route every 6–8 hours. We recalculated the dosage based on the body weight on admission.

2.4. Criteria for TMP/SMX-related ADRs

A potential adverse reaction was suspected when treatment with TMP/SMX was discontinued or the dose was changed prior to the completion of therapy. The physicians' notes were reviewed to determine the reason for the change as drug failure, a potential ADR, or other reasons. We excluded laboratory or clinical abnormalities that could have been caused by an underlying disease, or another drug (such as aminoglycoside nephrotoxicity). The total daily dose of TMP/SMX was recorded by body weight and the number of days treated before being stopped. Cutaneous reactions were defined as the development of a rash with or without fever or pruritus. Gastrointestinal symptoms were defined as the occurrence of nausea, vomiting, dyspepsia, or diarrhea. Hepatitis was defined as alanine transaminase or alkaline phosphatase two or more times normal or with two-fold or more increase. Elevated creatinine was defined as ≥ 1.5 mg/dL, or a ≥ 30% increase. Pancytopenia was defined as anemia with hemoglobin < 12 g/dL combined with leukopenia (leukocyte count < 4000/μL or with a ≥ 1000/μL decrease) and thrombocytopenia (platelet count < 150×10^3/μL or with ≥ 30×10^3/μL decrease). Lactic acidosis was defined as serum lactate level > 2.1 mmol/L. Hyperkalemia was defined as serum potassium level > 5 mmol/L. The diagnosis of acute psychosis was based on the diagnostic criteria for substance-induced psychotic disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR).[11]

2.5. Treatment

The standard initial recommended treatment for PJP at our hospital is TMP/SMX at a dose of 15–20 mg/kg/d for 21 days to all patients except those with a history of sulfonamide hypersensitivity. The actual dosage was at the discretion of the treating physicians. This led to instances of under- or overdosing TMP/SMX because most physicians based the dose on estimated body weight. Prednisolone was administered at a dose of 40 mg twice daily for 5 days, 40 mg daily for 5 days, and 20 mg daily for 11 days for patients with severe hypoxemia.[2]