Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 79 (2016) 314–319

www.jcma-online.com

Original Article

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

Hui-Min Chang [a], Hung-Chin Tsai [b,c,e,*], Susan Shin-Jung Lee [b,c], Calvin Kunin [d], Pei-Chin Lin [a], Shue-Ren Wann [b,c], Yao-Shen Chen [b,c]

[a] *Department of Pharmacy, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC*
[b] *Section of Infectious Diseases, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC*
[c] *College of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[d] *Department of Medicine, Ohio State University, Columbus, OH, USA*
[e] *Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, ROC*

Received March 1, 2015; accepted December 10, 2015

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.

* Corresponding author. Dr. Hung-Chin Tsai, Section of Infectious Diseases, Department of Medicine, Kaohsiung Veterans General Hospital, 386, Ta-Chung First Road, Kaohsiung 813, Taiwan, ROC.
E-mail address: hctsai1011@yahoo.com.tw (H.-C. Tsai).

http://dx.doi.org/10.1016/j.jcma.2016.01.007

(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]

2.6. Statistical analysis

Statistical analysis was performed using the SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA).All continuous variables were expressed as medians and differences between groups were analyzed using the Mann–Whitney *U* test. The categorical variables were expressed as percentages and numbers. Pearson's Chi-square test or Fisher's exact test was used to analyze correlations between variables. Kaplan–Meier curves were estimated to determine the association between adverse drug and dosage of TMP/SMX. A Cox proportional analysis was used to calculate hazards ratios for ADRs. All explanatory variables with a p value < 0.5 in the univariate analyses were eligible to enter the multivariate Cox proportional hazards model with the backward elimination method and considered to be significant when $p < 0.05$.

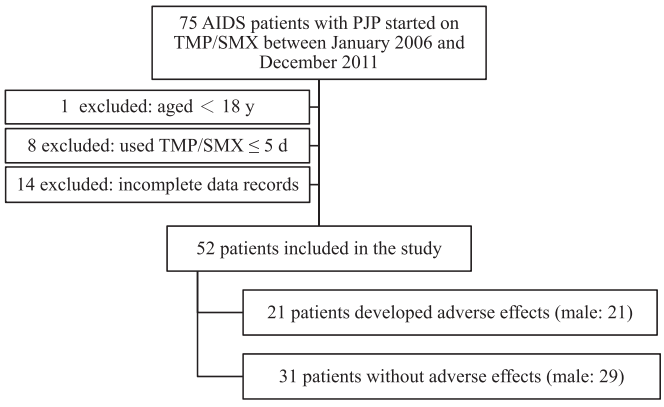
3. Results

Seventy-five patients were treated with TMP/SMX for presumed PJP and AIDS from January 2006 to December 2011. Twenty-three were excluded for the reasons shown in Fig. 1, and the remaining 52 patients were eligible for detailed analysis. Twenty-one of the 52 patients (40.3%) developed one or more ADRs attributable to TMP/SMX. The baseline characteristics of the patient population according to whether they had a TMP/SMX-related ADR are shown in Table 1.There were no significant differences between the groups in survival, risk behaviors, HIV-1 markers, serum creatinine, or dose of corticosteroids. The only significant difference between the groups was the median daily dose of TMP/SMX; 16.5 mg/kg body weight for patients with an ADR versus 14.7 mg/kg body weight for those without an ADR, $p < 0.036$.

The frequency, median time, and range of onset for each ADR, following the initial dose of TMP/SMX, are shown in Table 2. 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%), as noted in Table 2. The combination antiretroviral therapy (cART) regimens included PI/r in 16 (30.7%) of the 52 patients; NNRTI in 27 (51.9%) of the patients, which consisted of nevirapine (37%), efavirenz (63%), whereas nine (17.3%) of the patients were not prescribed cART. Only five of the 52 patients (9.6%) concomitantly used cART and TMP/SMX. The likelihood that the adverse event was associated with the antiretroviral agent was excluded by the physician in all of the five patients. Most of the ADRS occurred within the 1st 2 weeks of TMP/SMX therapy. The median time of onset for any ADR was 12 days (range, 1–25 days). The median time to onset of gastrointestinal symptoms was significantly shorter (median 5 days) than other adverse effects (median 12 days), $p = 0.02$. Assessment by the Naranjo score revealed that 81.6% of the ADRs could be categorized as "probable" (scores ranged from 5 to 8), while 18.4% of the ADRs were categorized as "possible" (score ranged from 1 one 4). Assessment of the preventability of an ADR, based on the modified Schumock and Thornton[10] scale revealed that most of the ADRs were "not preventable". Nausea, vomiting, and gastrointestinal symptoms were considered to be "definitely preventable". Seventeen of the 21 patients (80.9%) fully recovered after adjustment of the dose or a change to another form of therapy. These included switching TMP/SMX to primaquine plus clindamycin in eight patients (38.1%), reducing the dose in nine patients (42.9%), discontinuing TMP/SMX in two patients (9.5%), and continuing the same dose of TMP/SMX together with a medication that relieved the ADR in two patients (9.5%).

Univariate analysis revealed no significant differences between patients who did or did not develop an ADR in relation to body mass index, hematological findings, intravenous and oral forms of TMP/SMX, and CD4 cell count. A Cox proportional analysis revealed that a greater daily dose of TMP/SMX and age were independent factors for ADRs (Table 3).

To further explore the relationship between the dosage of TMP/SMX and the occurrence of ADRs over time, we divided the patient population into those who received a daily dose of $\geq$ 16 mg/kg and $\geq$ 15mg/kg. The Kaplan–Meier curve is shown in Fig. 2.



PJP = *Pneumocystis jirovecii* pneumonia; TMP/SMX = trimethoprim/sulfamethoxazole.

Fig. 1. Flow chart of the study population according to entry criteria.

4. Discussion

TMP/SMX remains the drug of choice for the treatment and prophylaxis of PJP in patients with AIDS, but its use is limited by the high incidence of hypersensitivity reactions and other ADRs.*3–5* The frequency is estimated to be 29–65%.[7] In the current retrospective study, we found that 40.3% of our patients developed an adverse reaction to TMP/SMX. Most occurred within 2 weeks following the initial dose. We suspected that higher daily doses might be responsible when we noted that physicians at our hospital often estimated body weight based on visual inspection rather than by actual weight. After adjustment for demographic, clinical, and laboratory risk

Table 1
Baseline characteristics of AIDS patients with and without ADRs to TMP/SMX.

Variable	Patients with ADRs ($n = 21$)	Patients without ADRs ($n = 31$)	p
Age (y)	34 (22–66)	35 (20–59)	0.993
Survival	17 (81)	24 (77.4)	0.762
Male	21 (100)	29 (93.5)	0.24
Exposure			0.251
Homosexual		15 (48.4)	
Heterosexual		6 (19.4)	
Bisexual		1 (3.2)	
Unknown		9 (29)	
BMI (kg/m^2)	19.83 (15.24–26.45)	20.95 (15.43–27.4)	0.198
Newly HIV diagnosed	19 (90.5)	19 (61.3)	0.489
≥12 tablets daily of TMP/SMX	15 (28.8)	23 (44.2)	0.535
Daily dose of TMP (mg/kg)	16.5 (11.21–21.33)	14.7 (7.38–19.2)	0.036
≥15 mg/kg of TMP	14 (28)	13 (26)	0.13
IV form	7 (33.3)	11 (35.5)	0.874
WBC (1000/cumm)	6.83 (4.63–10.9)	5.6 (2.97–13.59)	0.189
Hgb (%)	12.2 (10.2–16)	11.6 (6.4–14.8)	0.271
Lym (%)	13 (5–31)	18 (0–40)	0.327
LDH (U/L)	354 (132–964)	432 (167–665)	0.947
Serum creatinine (mg/dL)	0.98 ± 0.2	0.93 ± 0.22	0.4
Latest plasma HIV RNA load, patients with data	21 (100)	27 (87)	
≥5 log copies/mL	17 (81)	24 (89)	0.77
CD4+ count (cells/mL)	18 (2–90)	21 (0–151)	0.765
Standard steroid dose (equivalent to prednisone)	11 (21.1)	21 (40.3)	0.24
ART-regimen			
PI + NRTI	4 (7.5)	5 (9.5)	
Kaletra + kivexa	2 (3.7)	5 (9.5)	
NRTI + NNRTI	1 (1.7)	2 (3.7)	
NVP + kivexa	3 (5.7)	6 (11.5)	
EFV + kivexa	4 (7.5)	4 (7.5)	
EFV + combivir	4 (7.5)	3 (7.5)	
No ART prescribed	3 (5.7)	6 (11.5)	

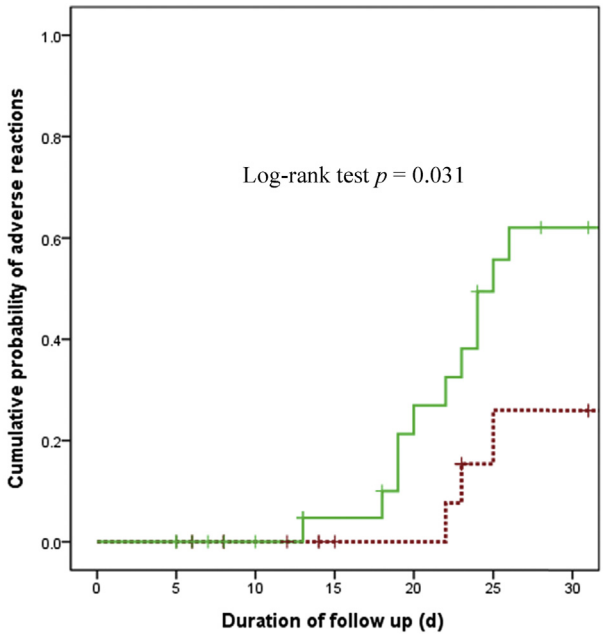
Data are presented as n (%),median (range), or mean ± standard deviation.
ADR = adverse drug reaction; ART = antiretroviral therapy; BMI = body mass index; EFV = efavirenz; HIV = human immunodeficiency virus; Hgb = hemoglobin; LDH = lactate dehydrogenase; Lym = lymphocytes; NNRTI = nonnucleoside reverse-transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; TMP/SMX = trimethoprim/sulfamethoxazole; WBC = white blood cells.

factors, the only significant independent association was with higher daily doses of TMP/SMX based on body weight.

Several explanations have been offered for the association between TMP/SMX and ADRs among patients with PNP and AIDS. In a review of the literature, Carr et al[7] noted that suggested causes included the degree of immunodeficiency, longer duration, and higher dose of TMP/SMX therapy, coexisting cytomegalovirus, or Epstein–Barr virus infection, slow acetylator phenotype, rate of HIV replication, atopic diathesis, and glutathione deficiency. In a retrospective study, they found that hypersensitivity reactions, defined as a cutaneous morbilliform eruption, occurred in 39 (27%) of 143 patients. On regression analysis they found that a CD4:CD8 ratio of > 0.10 and treatment for < 14 days were independently predictive of hypersensitivity. Use of corticosteroids tended to reduce the frequency of reactions. They postulated that T lymphocytes may be important in the pathogenesis of these reactions. They did not consider whether there was a relationship between the dose of TMP/SMX and onset of rash.[7] Lee et al[12] found that a higher daily dose of TMP/SMX and use of adjunctive steroids were associated with acute psychosis. The incidence increased from none in 16 patients who received a daily TMP dose of < 12 mg/kg to 23.5% (4/17) in those who received a daily dose of > 18 mg/kg. They did not note the occurrence of other TMP/SMX-associated ADRs. Hughes et al[13] reported that the incidence of anemia, neutropenia, and azotemia increased with increasing trimethoprim plasma concentration, while other adverse events

Table 2
Frequency of each adverse drug reaction (ADR) to trimethoprim/sulfamethoxazole among 21 AIDS patients with *Pneumocystis jirovecii* pneumonia.

	Frequency n (%)	Onset of ADR (d) Median (range)
Cutaneous	10 (47.6)	12 (2–20)
Gastrointestinal	3 (14.3)	5 (1–12)
Liver dysfunction	9 (42.9)	12 (10–25)
Renal dysfunction	8 (38.1)	13 (5–22)
Fever	4 (19)	12 (12–13)
Pancytopenia	1 (4.8)	21
Lactate acidosis	1 (4.8)	8
Acute psychosis	1 (4.8)	10



No. at risk

15 mg/kg	23	17	13	8
16 mg/kg	27	21	13	8

Fig. 2. Kaplan–Meier curve estimating the probability of an adverse drug reaction to trimethoprim/sulfamethoxazole according to a daily dose of 16 mg/kg is shown by the solid line and 15mg/kg is shown by the dotted line.

Table 3
Hazard ratio for adverse reactions to trimethoprim/sulfamethoxazole in patients with pneumocystis pneumonia and AIDS.

Risk factor	Unadjusted		Adjusted	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age (y)				
34	0.00		0.00	
35	3.83 (1.25–11.77)	0.019	4.30 (1.52–12.14)	0.006
Exposure				
MSM	0.00		0.00	
Heterosexual/ other/unknown	0.9 (0.27–2.98)	0.9	0.9 (0.27–2.98)	0.86
WBC (1000/cumm)	0.97 (0.71–1.33)	0.842	0.97 (0.71–1.33)	0.86
CD4+ count (cells/mL)				
49	0.00		0.00	
50	0.65 (0.14–3.00)	0.58	0.67 (0.19–2.38)	0.53
Steroid				
No	0.00		0.00	
Yes	1.27 (0.29–5.45)	0.75	1.35 (0.52–3.48)	0.54
Daily dose of TMP (mg/kg)				
15	0.00		0.00	
16	4.11 (1.26–13.42)	0.019	3.80 (1.40–10.35)	0.009

CI = confidence interval; MSM = men who have sex with men; TMP = trimethoprim; WBC = white blood cells.

(gastrointestinal disorders, rash, fever, and liver function abnormalities) were independent of plasma concentration.

Serum creatinine has been shown to rise in a dose-related manner in patients treated with trimethoprim. It is caused by a decrease in tubular secretion of creatinine associated with a slight increase in creatinine clearance. It is not considered to be due to renal impairment.[14] We included elevated creatinine as an ADR because the attending physicians were unaware of this effect and altered the dose accordingly.

In the current study, we found that a higher daily dose of > 16 mg/kg/d TMP/SMX was an independent factor for cutaneous and other ADRs. Steroid use was not associated with the occurrence of ADRs in our series.

The reason why higher daily doses of TMP/SMX are associated with an increase in ADRs in patients with PJP and AIDS remains unclear. High doses of TMP/SMX are known to produce ADRs even in healthy individuals.[14–16] SMX are well-known to produce skin eruptions. Some have postulated that TMP toxicity is associated with glutathione deficiency,[4,17–20] altered levels of thiols, disulfides, and plasma cysteine.[21]

We observed ADRs associated with increasing age and greater TMP/SMX exposure. Previous studies have shown that there are age-related changes of pharmacokinetics and pharmacodynamics.[22–24] Age had a pharmacokinetic influence including absorption, distribution, metabolism, and elimination influence, such as reduced renal and hepatic clearance.[25–29] Because TMP/SMX is eliminated via the renal system, it may be anticipated that renal dysfunction would influence the pharmacokinetics and pharmacodynamics of TMP/SMX with ageing.

The current study has several limitations. Firstly, it was a retrospective study. The diagnosis of a TMP/SMX-related ADR was determined by the attending physician rather than an independent observer. Serum concentrations of TMP/SMX were not measured. All the patients received a standard dose of corticosteroids, which might have masked some of the ADRs. It is difficult to compare our findings with those of others because we included all potential ADRs while others focused on skin eruptions or acute psychosis, and an elevated serum creatinine does not necessarily reflect a decrease in renal function. All of the adverse effects occurred before Day 25 after TMP/SMX use for PJP and we did not use prophylactic dose of TMP/SMX in our patients. Indeed, the possibilities of antiretroviral therapy-related ADRs were possible and difficult to differentiate with TMP/SMX related ADRs in our study, even only a small proportion of patients developed ADRs after 3 weeks of treatment. In addition, we could not compare the different kinds of ADRS to the relevance of high dose due to a relatively small sample size. The strengths of this study include the relatively large number of patients studied in a single institution over a 5-year period, the use of actual body weight to assess the daily dose of TMP/SMX, and inclusion of the virological and immunological markers of HIV infection. Prospective, protocol guided studies, with independent observers are needed to clarify these issues.

In conclusion, 40.3% of AIDS patients developed ADRs while receiving TMP/SMX for PJP. Our findings indicate that a daily dose of > 16 mg/kg of TMP/SMX with patients ≥ 34 years of age increases the risk of ADRs. A large, well-designed, prospective study is needed to confirm our findings.

Acknowledgments

This study was funded by Veterans General Hospitals and University System of Taiwan Joint Research Program grant (VGHUST103-G3-2-1).

References

1. Huang L, Morris A, Limper AH, Beck JM. An official ATS workshop summary: Recent advances and future directions in pneumocystis pneumonia (PCP). *Proc Am Thorac Soc* 2006;**3**:655−64.
2. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009; **58**:1−207.
3. Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984;**100**:495−9.
4. Van der Ven AJ, Koopmans PP, Vree TB, van der Meer JW. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991;**338**:431−3.
5. Carr A, Cooper DA. Pathogenesis and management of HIV-associated drug hypersensitivity. *AIDS Clin Rev* 1995:65−97.
6. Salter AJ. Trimethoprim-sulfamethoxazole: an assessment of more than 12 years of use. *Rev Infect Dis* 1982;**4**:196−236.
7. Carr A, Swanson C, Penny R, Cooper DA. Clinical and laboratory markers of hypersensitivity to trimethoprim-sulfamethoxazole in patients with *Pneumocystis carinii* pneumonia and AIDS. *J Infect Dis* 1993;**167**:180−5.
8. Veenstra J, Veugelers PJ, Keet IP, van der Ven AJ, Miedema F, Lange JM, et al. Rapid disease progression in human immunodeficiency virus type 1-infected individuals with adverse reactions to trimethoprim-sulfamethoxazole prophylaxis. *Clin Infect Dis* 1997;**24**:936−41.
9. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239−45.
10. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm* 1992;**27**:538.
11. American Psychiatric Association. *Task Force on D-I. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*. Washington, DC: American Psychiatric Association; 2000.
12. Lee KY, Huang CH, Tang HJ, Yang CJ, Ko WC, Chen YH, et al. Acute psychosis related to use of trimethoprim/sulfamethoxazole in the treatment of HIV-infected patients with *Pneumocystis jirovecii* pneumonia: a multicentre, retrospective study. *J Antimicrob Chemother* 2012;**67**:2749−54.
13. Hughes WT, LaFon SW, Scott JD, Masur H. Adverse events associated with trimethoprim-sulfamethoxazole and atovaquone during the treatment of AIDS-related *Pneumocystis carinii* pneumonia. *J Infect Dis* 1995;**171**: 1295−301.
14. Naderer O, Nafziger AN, Bertino Jr JS. Effects of moderate-dose versus high-dose trimethoprim on serum creatinine and creatinine clearance and adverse reactions. *Antimicrob Agents Chemother* 1997;**41**: 2466−70.
15. Sattler FR, Cowan R, Nielsen DM, Ruskin J. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A prospective, noncrossover study. *Ann Intern Med* 1988;**109**:280−7.
16. Stevens RC, Laizure SC, Williams CL, Stein DS. Pharmacokinetics and adverse effects of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole in healthy adult subjects. *Antimicrob Agents Chemother* 1991;**35**:1884−90.
17. Carr A, Cooper DA, Penny R. Allergic manifestations of human immunodeficiency virus (HIV) infection. *J Clin Immunol* 1991;**11**:55−64.
18. Battegay M, Opravil M, Wuthrich B, Luthy R. Rash with amoxycillin-clavulanate therapy in HIV-infected patients. *Lancet* 1989;**2**:1100.
19. Pullen H, Wright N, Murdoch JM. Hypersensitivity reactions to antibacterial drugs in infectious mononucleosis. *Lancet* 1967;**2**:1176−8.
20. Klemola E. Hypersensitivity reactions to ampicillin in cytomegalovirus mononucleosis. *Scand J Infect Dis* 1970;**2**:29−31.
21. Slatore CG, Tilles SA. Sulfonamide hypersensitivity. *Immunol Allergy Clin North Am* 2004;**24**:477−90.
22. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, Quesenberry Jr CP. Older age and the response to and tolerability of antiretroviral therapy. *Arch Intern Med* 2007;**167**:684−91.
23. Sabin CA, Smith CJ, Delpech V, Anderson J, Bansi L, Gilson R, et al. The associations between age and the development of laboratory abnormalities and treatment discontinuation for reasons other than virological failure in the first year of highly active antiretroviral therapy. *HIV Med* 2009;**10**:35−43.
24. Kang SC, Hwang SJ, Wong WW. Characteristics of human immunodeficiency virus infections among the elderly in Taiwan: a nationwide study. *J Chin Med Assoc* 2011;**74**:215−9.
25. Evans MA, Triggs EJ, Cheung M, Broe GA, Creasey H. Gastric emptying rate in the elderly: implications for drug therapy. *J Am Geriatr Soc* 1981; **29**:201−5.
26. Lee HC, Huang KTL, Shen WK. Use of antiarrhythmic drugs in elderly patients. *J Geriatr Cardiol* 2011;**8**:184−94.
27. Aymanns C, Keller F, Maus S, Hartmann B, Czock D. Review on pharmacokinetics and pharmacodynamics and the aging kidney. *Clin J Am Soc Nephrol* 2010;**5**:314−27.
28. Castleden CM, George CF. The effect of ageing on the hepatic clearance of propranolol. *Br J Clin Pharmacol* 1979;**7**:49−54.
29. Lamy PP. Comparative pharmacokinetic changes and drug therapy in an older population. *J Am Geriatr Soc* 1982;**30**:S11−9.