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Adverse effects of trimethoprim-sulfamethoxazole for the prophylaxis of Pneumocystis pneumonia in dermatology

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Abstract:	Objectives: Trimethoprim-sulfamethoxazole (TMP/SMX) combination is used for the prophylaxis of Pneumocystis pneumonia (PCP). Although TMP/SMX is frequently used in dermatology for cases treated with corticosteroids and/or immunosuppressants, it is often difficult to continue the administration of TMP/SMX due to adverse events. There are only a few reported studies on the prophylaxis of PCP in dermatology. This is the first review focused on adverse events of TMP/SMX among patients with dermatological diseases compared to previous reports. Methods: In this study, we retrospectively investigated 132 cases treated with TMP/SMX and examined the adverse events. Results: Adverse events occurred in 32 cases (24.2%), and the incidence in this study was higher than in previous reports. Thrombocytopenia occurred in 17 cases (12.5%), which was the most frequent adverse event. The possible causes of adverse events were the standard dose of TMP/SMX might be excess for most Japanese, in addition to the long administration period, and the concomitant use of corticosteroids and/or immunosuppressants in almost all cases. Conclusion: We must consider the risks of PCP and adverse events of TMP/SMX in each case. It is desirable to examine possible administration methods that can be continued by adjusting the dose and interval of TMP/SMX.

Adverse effects of trimethoprim-sulfamethoxazole for the prophylaxis of *Pneumocystis* pneumonia in dermatology

Running title: Adverse effects of TMP/SMX

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Abstract

***Objectives**:* Trimethoprim-sulfamethoxazole (TMP/SMX) combination is used for the prophylaxis of *Pneumocystis* pneumonia (PCP). Although TMP/SMX is frequently used in dermatology for cases treated with corticosteroids and/or immunosuppressants, it is often difficult to continue the administration of TMP/SMX due to adverse events. There are only a few reported studies on the prophylaxis of PCP in dermatology. This is the first review focused on adverse events of TMP/SMX among patients with dermatological diseases compared to previous reports.

***Methods**:* In this study, we retrospectively investigated 132 cases treated with TMP/SMX and examined the adverse events.

***Results**:* Adverse events occurred in 32 cases (24.2%), and the incidence in this study was higher than in previous reports. Thrombocytopenia occurred in 17 cases (12.5%), which was the most frequent adverse event. The possible causes of adverse events were the standard dose of TMP/SMX might be excess for most Japanese, in addition to the long administration period, and the concomitant use of corticosteroids and/or immunosuppressants in almost all cases.

***Conclusion**:* We must consider the risks of PCP and adverse events of TMP/SMX in each case. It is desirable to examine possible administration methods that can be continued by adjusting the dose and interval of TMP/SMX.

Key words: Adverse effects, Antibiotic Premedication, Asians, Dermatology, Trimethoprim-Sulfamethoxazole

Introduction

Pneumocystis pneumonia (PCP) is a serious disease caused by *Pneumocystis jirovecii*, and the survival rate is 52.9% for dermatology patients.[1] It develops in the background of underlying diseases, such as AIDS, malignant tumors, and collagen diseases treated with high-dose corticosteroids and/or immunosuppressants.

Trimethoprim-sulfamethoxazole (TMP/SMX) combination has been reported to have a preventive effect against PCP.[2] Dermatologists frequently administer TMP/SMX to patients with pemphigus, pemphigoid, dermatomyositis, and systemic lupus erythematosus. Because we treat

these patients with corticosteroids and/or immunosuppressants for a long period of time, adverse events often occur, so we often reduce the dose of TMP/SMX due to adverse events.[3] We have managed to use TMP/SMX without causing adverse events.[4] A non-blind randomized controlled trial is now in progress.[5] However, there are only a few reported studies on the prophylaxis of PCP in dermatology.[6] In this study, we investigated the frequency of adverse events in patients with dermatological diseases who received TMP/SMX for the prophylaxis of PCP.

Methods

Patients: We enrolled patients with dermatological diseases who were hospitalized at the Department of Dermatology of Shiga University of Medical Science and who received TMP/SMX for prophylaxis of PCP from July 2010 to October 2017. We administered TMP/SMX to patients who were treated with high-dose corticosteroids (>20 mg/day for ≥1 month, until reduced approximately <10 mg/day).

Study design: A retrospective review of 132 patients who were administered TMP/SMX was conducted. Each tablet of TMP/SMX

included 80 mg TMP and 400 mg SMX. We administered TMP/SMX at the dosage of 1 tablet daily, 0.5 tablet daily, 1 tablet every other day, 2 tablets twice weekly, or 2 tablets daily depending on the case without specific rules. Data included age, sex, primary diseases, dosage of TMP/SMX, presence or absence of adverse events, and their contents. Follow-up period was from July 2010 to October 2017. We regarded adverse events in cases for whom other causes for the events were excluded, TMP/SMX was needed to be reduced or discontinued, and then confirmed an improvement of adverse events. Instead of rechallenge, we administered atovaquone or pentamidine isethionate by inhalation. This study was approved by the Research Ethics Committee of Shiga University of Medical Science (reference number R2017-221).

Statistical analysis*:* We collected the case data and compared the incidence of adverse events for each primary disease, dosage of TMP/SMX, presence or absence of concomitant drugs, and patients' ages. Statistical analysis was performed using χ^2 test or Student's t-test.

Results

***Patient characteristics**:* A total of 132 patients were enrolled (60 males and 72 females aged 17 to 49 years; Table 1). The primary diseases were bullous pemphigoid (28 patients), dermatomyositis (22 patients), pemphigus vulgaris (9 patients), pyoderma gangrenosum (7 patients), adult Still's disease (6 patients), malignant lymphoma (5 patients), systemic lupus erythematosus (5 patients), pemphigus foliaceus (5 patients), and others (45 patients). Adverse events occurred below 13 years old (0 case), at 13 to 65 years old (20 of 72 cases; 27.8%), and above 65 years old (12 of 60 cases; 20.0%). There was no statistical significance in the incidence of adverse events between their age, sex, and primary diseases.

***Incidence of adverse events**:* Although no patients developed PCP, adverse events occurred in 32 cases (24.2%). Adverse events included erythrocytopenia (2.2%), leukocytopenia (2.2%), thrombocytopenia (12.5%), elevated liver enzyme (5.9%), renal dysfunction (1.5%), and drug eruption (4.5%). Out of 6 drug eruptions, 5 cases were maculopapular eruption (day10, 11, 12, 21, 30), and 1 case was toxic epidermal necrolysis (day 11). Adverse events occurred at the dosage of 1 tablet daily (29 of 115 cases), 0.5 tablet daily (1 of 7 cases), 2 tablets daily (1 of 2 cases), 2 tablets

twice weekly (0 of 6 cases), and 1 tablet every other day (1 of 2 cases). We summarized the incidence of adverse events in this study and from previous reports (Table 2).[7-10] The incidence of hematologic problem and elevated liver enzyme in this study (daily administration; n = 124) was significantly higher than that of El-Sadr, et al. (daily administration; n = 1312). There are no relationship and significant difference between the accumulated doses of TMX/SMX and onset of adverse events.

Time of onset of adverse events: The time of onset of adverse events was within 1 week (18.8%), from 1 week to 1 month (26.3%), and more than 1 month (25.0%). We created a box-and-whisker plot that shows the day of onset of each adverse event (Figure 1). The onset of adverse events was on days 2 to 66; renal dysfunction most often occurred at about 1 week, elevated liver enzyme and drug eruption at about 2 weeks, and cytopenia at about 2 to 3 weeks. There were no significant differences in the day of onset of each adverse event.

Discussion

In our study, there were significant differences in the incidence of hematologic problem and elevated liver enzyme.[7-10] Of course, we could not simply compare these results due to the difference of primary diseases, observation period, and definition of adverse events. We discuss three perspectives for these results. (1) Prophylaxis of TMX/SMX needs longer-term than administration as a treatment of an infection, which may increase the chances of adverse events. Although cytopenia was relatively rare in a treatment of infection, it was frequently seen in our study: erythrocytopenia (2.6%), leukocytopenia (2.2%), and thrombocytopenia (12.5%). It was considered that TMP/SMX caused cytopenia by impairing folic acid metabolism and that long-term administration might cause metabolic abnormalities and folate deficiency depending on the period, resulting in increased incidence of cytopenia.[11] However, there were no significant difference between the accumulated doses of TMX/SMX and onset of adverse events. It is not clear whether an administration period is related to the incidence of the adverse events.

(2) We treated our patients with combined medication of corticosteroids and/or immunosuppressants for primary diseases in almost all cases.

Immunocompromised patients sometimes needed other various drugs, for example, ganciclovir for cytomegalovirus infection, which might have interacted with TMP/SMX. (3) In Table 2, the results of El-Sadr WM et al. showed that the dosage of TMP/SMX apparently involved the incidence of adverse events. One study proved that there was a significant dose-dependent increasing trend in adverse events of TMP/SMX.[12] For Japanese, it might be better to reduce the dose or frequency of TMP/SMX, although we could not prove that the incidence of adverse events was related the race or BMI of patients. There are no reports that discussed whether or not we can reduce the dosage of TMP/SMX in safety.

It was reported that the incidence of adverse events with thrice-weekly administration of TMP/SMX was significantly lower than that with daily administration, and there was no significant difference in the PCP incidence rate between daily and thrice-weekly administration.[9] The results of our study were similar to that of previous reports, although the number of cases was limited.

Although we should be cautious of adverse events, some reports showed that the odds ratio of PCP development due to discontinuation of

TMP/SMX is 4.77 times in HIV-infected patients.[9] Guidelines in the United States suggested that we better eventually restart TMP/SMX for cases in which it was discontinued due to a mild adverse event. Approximately 70% of patients were able to continue TMP/SMX by reducing the dose/interval or desensitization therapy.[13]

Although the mechanism of adverse effects of TMP/SMX and the risk factors have been almost clear,[11] we need to be cautious of the occurrence of adverse events of TMP/SMX for each case. One study reported that routine prophylaxis is unnecessary for patients with autoimmune blistering diseases, who do not usually need strong immunosuppression.[14] We should consider the risks of PCP and adverse events of TMP/SMX in each case, as necessary, and examine possible administration methods that can be continued by adjusting the dose and interval of TMP/SMX for patients with dermatological diseases.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest declared.

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FIGURE LEGEND

Figure 1. Box-and-whisker plot shows the day of onset of each adverse event

TABLES

Table 1. Patient characteristics

Table 2. The incidence of adverse events comparison with previous reports

* Daily administered cases of this study versus daily administered cases of El-Sadr WM, et al.

HIV: human immunodeficiency virus; LT: liver transplantation; ND: Not described; RD: Rheumatic diseases

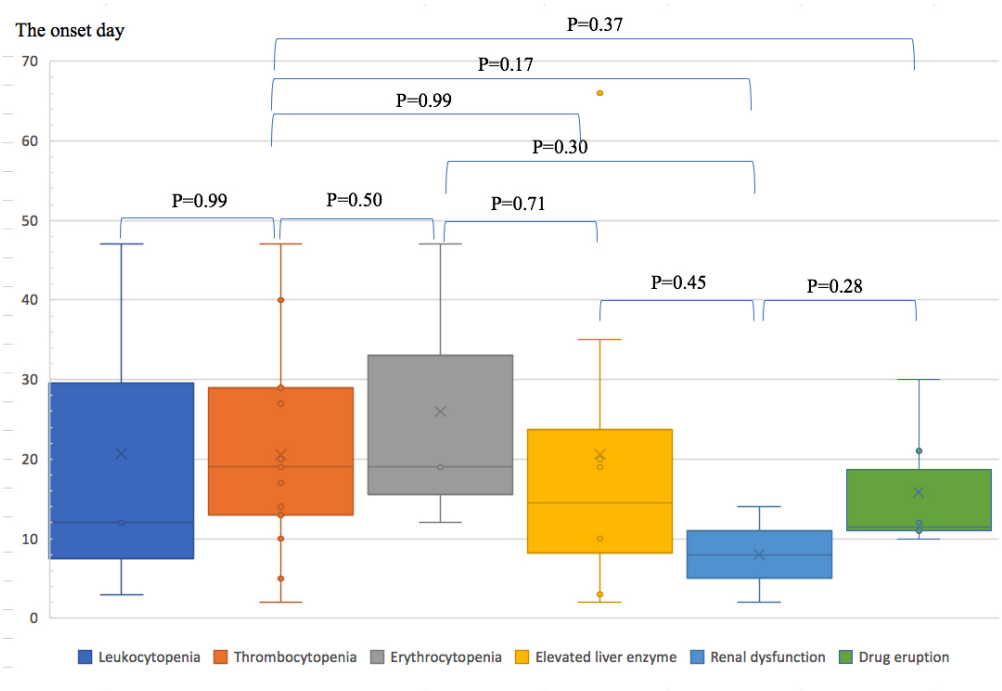

Figure 1. Box-and-whisker plot shows the day of onset of each adverse event

380x260mm (72 x 72 DPI)

Table 1 Patient characteristics

	Our cases (n= 132)	Adverse events (n= 32)	P value
Age (average± standard deviation)	60.6± 17.8	59.0± 18.0	0.54
Sex (man/woman)	60/72	10/22	1
Primary disease			
Bullous pemphigoid (%)	28	7 (25%)	0.97
Dermatomyositis (%)	22	6 (27.7%)	0.9
Pemphigus vulgaris (%)	9	3 (33.3%)	0.83
Pyoderma gangrenosum (%)	7	1 (14.3%)	0.82
Adult still's disease (%)	6	2 (33.3%)	0.86
Malignant lymphoma (%)	5	1 (20%)	0.94
Systemic lupus erythematosus (%)	5	2 (40%)	0.78
Pemphigus foliaceus (%)	5	1 (20%)	0.94
Others (%)	45	9 (20%)	0.78

Table 2 The incidence of adverse events comparison with previous reports

	This study						#7	#8	#9		#10	
Disease	Dermatological diseases						RD	After LT	Patients infected with HIV			
Daily dose of Trimetho-prim (mg)		80	40	160	320	80	ND	80	160	320		
Daily dose of Sulfametho-xazole (mg)		400	200	800	1600	400	ND	400	800	1600		
Dosing interval	Total	Daily			Twice weekly	Every other day	Daily or thrice-weekly	Daily		Twice weekly	Thrice weekly	*P* value*
Number of cases	132	115	7	2	6	2	262	60	1312	1313	104	
Adverse events (%)	32 (24.2)	29 (25.2)	1 (14.3)	1 (50)	0	1 (50)	34 (13.0)	11 (18.3)	255 (19.4)	126 (9.6)	ND	0.15
Hematologic (%)	20 (15.2)	18 (15.7)	1 (14.3)	0	0	1 (50)	6 (2.3)	6 (10.0)	72 (5.5)	17 (1.3)	ND	<0.0001
Erythrocyto-penia (%)	3 (2.6)	3 (2.6)	0	0	0	0	2 (0.8)	ND	ND	ND	21 (20.2)	ND
Leukocyto-penia (%)	3 (2.2)	3 (2.6)	0	0	0	0	1 (0.4)	3 (5.0)	ND	ND	39 (37.5)	ND
Thrombocy-topenia (%)	17 (12.5)	15 (13.0)	1 (14.3)	0	0	1 (50)	3 (1.2)	3 (5.0)	ND	ND	11 (10.6)	ND
Elevated liver enzyme (%)	8 (5.9)	8 (7.0)	0	0	0	0	6 (2.3)	3 (5.0)	11 (0.8)	2 (0.2)	18 (17.3)	<0.00001
Renal dys-function (%)	2 (1.5)	2 (1.7)	0	0	0	0	5 (1.9)	ND	7 (0.5)	3 (0.2)	ND	0.16
Drug eruption (%)	6 (4.5)	5 (4.3)	0	1 (50)	0	0	7 (2.7)	ND	ND	ND	9 (8.7)	ND
Intestinal problem (%)	0	0	0	0	0	0	2 (0.8)	2 (3.3)	24 (1.8)	10 (0.8)	17 (16.3)	0.16
Hypersen-sitivity (%)	ND	ND	ND	ND	ND	ND	ND	ND	130 (9.9)	86 (6.5)	ND	ND
Others (%)	0	0	0	0	0	0	9 (3.4%)	ND	6 (0.5)	4 (0.3)	14 (13.5)	0.48

*Daily administered cases of this study versus daily administered cases of El-Sadr WM, et al.

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