Cutaneous adverse reactions to sulfonamide antibiotics

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Summary

Background: **Sulfonamides are divided into two main groups which are sulfonamide antibiotics and sulfonamide non-antibiotics. The wide use of sulfonamide antibiotics leads to increasing incidence of sulfonamide cutaneous reactions.**

Objective: **The purpose of this study is to explore the cutaneous manifestations induced by sulfonamide antibiotics in a large number of Thai patients, including human immunodeficiency virus (HIV) and non-HIV infected individuals. The second purpose is to determine the risk factors for development of sulfonamide cutaneous reactions.**

Methods: **We retrospectively studied 191 patients with sulfonamide antibiotics cutaneous reactions attending the adverse drug reaction center, Siriraj Hospital, Bangkok between 2006 and 2010.**

Results: **Majority of the patients was female (59.7%).Maculopapular rash was the most common cutaneous manifestation (37.7%), followed by fixed drug eruption (22%), angioedema with or without urticaria (12.6%) and urticaria alone (12%). Among those with known HIV serology, maculopapular eruption occurred more frequently in the HIV positive group while fixed drug eruption occurred more frequently in HIV-negative group.**

Conclusion: **From our study, there were no significant determination factors to develop serious drug reactions. However, the HIV-positive status and lower level of CD4 count had a tendency to increase risk of developing serious cutaneous reactions.** ***(Asian Pac J Allergy Immunol 2011;29:284-9)***

Key words: *cutaneous reactions, sulfonamide antibiotic drugs, co-trimoxazole*

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Introduction

Sulfonamides are a group of drugs containing sulfur dioxide (SO_2) and nitrogen (N) moiety directly linked to a benzene ring as a basic structure. They are divided into two main groups according to chemical structure and therapeutic action; sulfonamide antibiotics such as sulfamethoxazole, sulfaisodimidine, sulfadiazine, sulfadimethoxine and sulfamethoxypyridazine and sulfonamide non-antibiotics such as furosemide, hydrochlorothiazide and glipizide.[1] The major structural difference between these two groups is the arylamine group at the N4 position, which is exclusively found in the sulfonamide antibiotics group.[2] This arylamine group is thought to be the key to formation of the reactive hydroxylamine intermediate and subsequently to haptenation, which is required for drug eruptions.[3] Reported cutaneous drug eruptions due to sulfonamide antibiotics reported range from minor types, for examples; maculopapular eruption, fixed drug eruption to major life-threatening types, for example Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and anaphylactic reaction.[4]

Although there are many formulations of oral sulfonamide antibiotics, co-trimoxazole (sulfamethoxazole/trimethoprim) is the one which is widely used in Thailand. Co-trimoxazole is associated with hypersensitivity in 1-3% of general population.[5] The frequency is higher (up to 34%) in patients infected with HIV.[6] Many contributing factors for an increased incidence of cutaneous drug eruptions in HIV patients are proposed, such as multi-drug administration and low levels of intracellular glutathione.[7] In Thailand, the data about co-trimoxazole reactions is still limited. The largest study of cutaneous drug eruptions in five major hospitals in Bangkok was done by Puavilai et al.[8] in 2001. Among 19 cases of co-trimoxazole-induced cutaneous drug eruptions, the most frequent manifestation was maculopapular rash (11 cases), followed by fixed drug eruption (3 cases), SJS (3 cases), TEN (1 case) and urticaria (1 case).

Our purpose was to study the characteristics of cutaneous allergic reactions to sulfonamide

antibiotics in a large number of Thai patients, including human immunodeficiency virus (HIV) infected and non-HIV infected individuals. The second purpose is to determine the risk factors for developing sulfonamide antibiotics cutaneous reactions.

Methods

This study was approved by Siriraj Institutional Review Board, Mahidol University, Bangkok, Thailand. Patients who were diagnosed with drug-induced cutaneous reactions were reported to the Adverse Drug Reaction (ADR) Center by attending physicians. Well-trained pharmacists of the ADR Center and/or dermatologists reviewed the event and assessed the causative agents based on history, clinical manifestations and laboratory data. We included patients 18 years of age and above who were reported to ADR center between May 2006 and May 2010, if an assessment revealed a sulfonamide antibiotic as one of the causative agents. Cutaneous reactions were classified into two groups; serious drug reactions and non-serious drug reactions. Anaphylaxis, drug hypersensitivity syndrome, SJS, TEN and angioedema with or without urticaria were considered to be serious drug reactions whereas maculopapular rash, urticaria without systemic symptoms, erythema multiforme and fixed drug eruption were considered to be non-serious drug reactions.[4] Demographic data, suspected drugs and clinical features were studied. We also recorded personal histories of atopic diseases (allergic rhinitis, asthma, atopic dermatitis and allergic conjunctivitis) and previous histories of drug allergy of any type. Food intolerance was defined as cutaneous eruptions of any types occurring within 2-24 hours of ingestion of a suspected food, most commonly presenting as urticaria or an exacerbation of preexisting atopic dermatitis.[9-10] In HIV-infected patients, additionally the CD4 status was recorded if available. The causality assessment of ADR was classified into six levels according to World Health Organization (WHO) causality assessment of ADR.[11] They are:

1. **Certain,** which means that the adverse reaction has occurred during the time period corresponding with the drug usage. In addition, the reaction could not be explained by pre-existing disease, other concomitantly used drug(s) or other chemical substance. Furthermore, the adverse reaction obviously improved or disappeared after the patient stopped using the drug, but recured after they started using it again. Thus, the pharmacological mechanism of the adverse event is clearly evident as an explanation.
2. **Probable,** which means that the adverse reaction has occurred during the time period corresponding with the drug usage and is probably not associated with pre-existing disease, concomitantly used drug(s) or other chemical substances. When the patient stopped using the drug, the adverse reaction improved or disappeared. However, information about repeat drug use may not be available.
3. **Possible,** which means that the adverse reaction has occurred during the time period corresponding with the drug use, but maybe explained by pre-existing disease, concomitantly used drug(s) or other chemical substances. Information about the patient stopping use of the drug is not complete or is not available.
4. **Unlikely**. which means that the adverse reaction has occurred during a time period which does not correspond with the drug use and cannot be explained by pre-existing disease, concomitantly used drug(s) or other chemical substance.
5. **Unclassified,** which means that more data is essential for a proper assessment or that the additional data are under examination.
6. **Unclassifiable**, which means that the information available is insufficient or contradictory and does not allow a judgment to be made about the relationship between the health product and the adverse event. Data cannot be supplemented or verified.

Statistical analysis

Demographic data, personal history of atopy, underlying disease, previous drug allergy, the suspected drug, clinical characteristics, management and outcomes were displayed by descriptive statistics, e.g. mean, median, minimum, maximum and percentages. The chi-squared test and Fisher's exact test were used for the categorical data. The Mann-Whitney U test was used in a comparison between median CD4 levels of HIV-positive group and HIV-negative group. A p-value < 0.05 was considered to be statistically significant. All statistical data analyses were performed using SPSS for Windows version 17.0

Table 1. Demographic data of patients with cutaneous reactions to co-trimoxazole (n=191)

Characteristics	Number (%)
Gender	
Male	77 (40.3)
Female	114 (59.7)
History of atopy*	**40 (20.9)**
History of food intolerance	**31 (16.2)**
Underlying diseases	**60 (31.4)**
Cardiovascular related diseases	28 (14.7)
Autoimmune diseases	8 (4.2)
Other diseases	24 (12.5)
History of previous drug reactions of any types	**51 (26.7)**
Penicillin	18
Nonsteroidal anti-inflammatory drugs	13
Tetracycline	10
Others	19
Sulfonamide non-antibiotics	0

*, A history of atopy included atopic dermatitis, allergic rhinitis, asthma and allergic conjunctivitis

Results

One hundred and ninety one patients were enrolled. In Siriraj hospital, there are two oral sulfonamide antibiotics available which are co-trimoxazole (sulfamethoxazole/trimethoprim) and sulfadiazine. All reported patients had reactions to co-trimoxazole. Female patients (59.7%) were predominant, with a female to male ratio of 1.5:1. The ages of the patients ranged from 18 to 96 years with the mean (SD) age of 47.2 (16.8) years. Table 1 demonstrates the demographic data of the patients with cutaneous reactions to co-trimoxazole. The most common reported food causing reactions was seafood. Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) were autoimmune diseases detected in our study. Concerning patients with history of previous drug allergy, the most common previous cutaneous reaction was a maculopapular rash (21 of 51 patients). Eight patients were allergic to two distinct medications. Penicillin was the most common culprit drug, followed by tetracycline and nonsteroidal anti-inflammatory drugs (NSAIDs). Others were dapsone, erythromycin, ketoconazole, fluconazole, paracetamol, spiramycin, streptomycin, terramycin, and tramadol. There were no patients with a history of sulfonamide non-antibiotic allergy in this study.

According to the WHO causality assessment of ADR, 177 patients (92.7%) were diagnosed as possible reactions and 14 patients (7.3%) with probable cutaneous reactions to co-trimoxazole. No patients were diagnosed as 'certain reactions', due to the absence of data concerning re-challenge with co-trimoxazole. Table 2 shows the cutaneous manifestations of co-trimoxazole hypersensitivity in our patients.

Table 2. Cutaneous manifestations of co-trimoxazole hypersensitivity in 191 patients

Cutaneous manifestations	Number (%)
Maculopapular rash	70 (36.6)
Fixed drug eruption	42 (22.0)
Angioedema with or without urticaria	24 (12.6)
Urticaria alone	23 (12.0)
Stevens-Johnson syndrome	16 (8.4)
Drug hypersensitivity syndrome	6 (3.1)
Erythema multiforme	4 (2.1)
Anaphylaxis	2 (1.0)
Others*	4 (2.1)

*, Others include pruritus(3) and photosensitivity(1)

Maculopapular rash was the most common cutaneous manifestation followed by fixed drug eruption, angioedema with or without urticaria and urticaria alone, respectively. Extracutaneous involvement was detected in a minority of our patients. Twenty-two patients (11.5%) described respiratory symptoms such as breathlessness or nasal congestion. Nine patients (4.7%) had gastrointestinal symptoms.

Concerning HIV status, 42 patients (22%) were HIV positive whereas 27 patients (14.1%) were HIV negative and 122 patients (63.9%) had an unknown HIV status. Among the HIV-negative group, the most common manifestation was fixed drug eruption (33.3%), followed by maculopapular eruption (29.6%) and angioedema with or without urticaria (18.5%). In the HIV-positive group, maculopapular rash was the most common cutaneous eruption (54.8%), followed by SJS (21.4%), drug hypersensitivity syndrome (7.1%) and fixed drug eruption (7.1%). There were no statistically significant difference in the frequency of development of serious reactions among different HIV status patients (p =0.319), but a statistically significant difference was found between HIV status and the development of following reactions; Stevens-Johnson syndrome, maculopapular rash, urticaria and fixed-drug eruption (Table 3.). Among those reactions, further comparison between different subgroups of HIV status was carried out. Between the HIV-positive and the HIV-negative patients, the HIV-positive group developed maculopapular eruption more frequently (p =0.04) whereas the HIV-negative group developed fixed drug eruption more often (p =0.01). Between the HIV-positive and the HIV-unknown group, SJS occurred in the HIV-positive group more frequently (p <0.001), whereas the other three non-serious reactions occurred in HIV-unknown group more frequently with statistical significance.

Table 3. Cutaneous manifestations of co-trimoxazole reactions in HIV negative group and HIV positive group

Drug reactions	HIV negative (n=27)	HIV positive (n=42)	HIV unknown** (n=122)	P value
	No. (%)	No. (%)	No. (%)	
Types				
Serious	7 (25.9)	15 (35.7)	25 (20.5)	0.319
Non-serious	20 (74.1)	27 (64.3)	93 (76.2)	
Serious				
Angioedema with/without urticaria	5 (18.5)	2 (4.8)	17 (13.9)	0.18
Drug hypersensitivity syndrome	1 (3.7)	3 (7.1)	2 (1.6)	0.14
Stevens-Johnson syndrome	1 (3.7)	9 (21.4)	6 (4.9)	0.005*
Anaphylaxis	0	1 (2.4)	0	0.361
Non-serious				
Maculopapular eruption	8 (29.6)	23 (54.8)	40 (32.8)	0.03*
Urticaria	3 (1.1)	0	20 (16.4)	0.02*
Erythema multiforme	0	1 (2.4)	3 (2.5)	1
Fixed drug eruption	9 (33.3)	3 (7.1)	30 (24.6)	0.02*

*, *p* value <0.05., statistical significant

**, Other reactions included; pruritus (3) and photosensitivity(1)

Table 4. Comparison of cutaneous manifestations of co-trimoxazole reactions between different subgroups

	P value		
	HIV positive Vs HIV negative	HIV Positive Vs HIV unknown	HIV negative Vs HIV unknown
Serious			
Stevens-Johnson syndrome	0.08	<0.001*	1
Non serious			
Maculopapular eruption	0.04*	0.01***	0.75
Urticaria	0.056	0.005***	0.77
Fixed drug eruption	0.01**	0.01***	0.35

*, the reaction(s) occurred more frequently in HIV-positive group

**, the reaction(s) occurred more frequently in HIV-negative group

***, the reaction(s) occurred more frequently in HIV-unknown group

Among 42 patients who were HIV positive, the CD4 level of 30 patients was recorded during the onset of the co-trimoxazole reaction or within 3 months. The median CD4 levels of cases with serious drug reactions and those with non-serious reactions were 132.5 cells per micro liter and 163 cells per micro liter, respectively. However, there was no statistical association between the median CD4 counts of these two groups. (Mann-Whitney test, p =0.71) (Table 5.).

Other possible risk factors for developing serious drug reactions are shown in Table 5. A history of atopy, food intolerance, autoimmune diseases, previous drug allergy and HIV status did not have significant associations with the development of serious co-trimoxazole reactions.

The symptoms of most patients improved within 3-7 days. Most patients received oral antihistamines and topical corticosteroids. Systemic corticosteroids were used in eight patients and exclusively in non-HIV patients (3 patients with SJS, 2 patients with drug hypersensitivity syndrome and 2 patients with maculopapular rash). The dosages of systemic corticosteroids ranged from 0.5-1 mg/kg/day.

Discussion

Co-trimoxazole (sulfamethoxazole/trimethoprim) is well known to be an effective antibiotic and is widely used in Thailand. According to the recommendation of the Center of Disease Control and Prevention, co-trimoxazole is suggested as a primary prophylaxis antibiotic for HIV patients with a CD4 count of less than 200 cells per micro liter or with a history of oropharyngeal candidiasis.[12] The study of self-reported antibiotic allergy by Macy and Poon reported that the antibiotics that had the highest incidence rate of hypersensitivity reactions in females was sulfonamides (3.4% compared with 1-1.5% of other classes of antibiotics). This might perhaps be due to its routine use for urinary tract infection.[13] Patients in our study were also predominantly female.

Proposed immunologic mechanisms for these reactions include the N1 heterocyclic ring and the N4 arylamine group as immunogens. Non-type I immunologic mechanisms also take part of the process, involving a reactive nitroso-metabolite, metabolite haptenation, directed cytotoxicity and stimulation of the T cell immune response.[14,15] A history of atopy has been proposed to be the risk factor for reactions to some drugs, such as penicillin.[16] Some authors have stated that atopy might increase the severity of cutaneous reactions.[14] Also, one study revealed a slightly higher rate of sulfonamide allergy in asthmatic children and adolescents.[17] However, our results show that atopy was not significantly related to serious cutaneous co-trimoxazole allergy. SLE has been proposed to be a risk factor for sulfonamide antibiotic allergy, as reactions occur less commonly in the normal

Table 5. Determination factors of patients at risk to develop serious drug reactions

Determination factors	Non-Serious drug eruptions (n=142) Number (%)	Serious drug eruptions (n=49) Number (%)	p-value (Chi-square test)
History of atopy			0.18
No	109 (72.2)	42 (27.8)	
Yes	33 (82.5)	7 (17.5)	
History of food intolerance			0.38
No	117 (73.1)	43 (26.9)	
Yes	25 (80.6)	6 (19.4)	
Underlying autoimmune diseases			1
No	136 (74.3)	47 (25.7)	
Yes	6 (75)	2 (25)	
History of previous drug allergy			0.73
No	105 (75)	35 (25)	
Yes	37 (72.5)	14 (27.5)	
HIV status			0.55
Negative	20 (74.1)	7 (25.9)	
Positive	27 (64.3)	15 (35.7)	
CD 4 count; median±SD	66±91.2 (n=13)	85.5±115.8 (n=10)	

population or in patients with other rheumatologic diseases, such as RA.[18,19] Jeffries et al. reported in a cohort study of 417 lupus patients that 27.3% developed allergy to sulfonamide medications.[20] Our study included 8 patients with autoimmune diseases (6 cases of SLE, 2 cases of RA). Regarding a hyperactive immune system, we found no increased risk of serious drug eruption in our admittedly small number of autoimmune patients.

Strom et al. conducted a retrospective cohort study of 969 patients with allergic reactions to sulfonamide antibiotics, who had received sulfonamide non-antibiotics, and a control group of 19,257 patients who had no allergic reaction after sulfonamide antibiotics. They found that an association between allergic reactions to sulfonamide antibiotics and hypersensitivity to sulfonamide non-antibiotics probably was due to a predisposition to allergic reactions, rather than to cross-reactivity with the other sulfonamide-based drug.[14] None of our patients reported cross-reactivity to sulfonamide non-antibiotics.

From the comparison of cutaneous reactions among subgroups with different HIV status, we found a significant correlation between HIV-positive patients and maculopapular eruption and HIV-negative patients and fixed drug eruption. There were no statistical significant differences between the HIV-negative and HIV-unknown groups but, with many additional factors influencing types of reactions we could not draw any conclusions as laboratory testing for HIV status had not been done.

The increased level of interferon-gamma and drug-specific CD4+ T lymphocytes in HIV infected patients interact with and specifically kill keratinocytes, which are the target of drug eruption. CD8+ T cells also play role in more severe cutaneous drug eruptions, especially bullous eruptions. Lower CD4 levels have been proposed to be one of the risk factors for severe cutaneous drug eruptions, since CD8 will subsequently be more dominant.[21] These reasons might explain the increased number of SJS and serious drug reactions in the HIV-infected group when compared with the HIV negative group in our study. We also investigated CD4 level of the HIV positive patients; the CD4 level in the serious drug reaction group tended to be lower than the non-serious drug reaction group. To date, in vitro testing had been studied in order to predict sulfamethoxazole allergy in HIV-infected patients but at the present time there is no valid marker available.[22]

Our study was limited by its inability to exclude patients with isolated trimethoprim allergy. However, the reports of trimethoprim allergy are not frequent and most of manifestations are enanthema or oral mucosal fixed drug eruptions which were not detected in our patients.[23]

In conclusion, our study has demonstrated the characteristics of cutaneous manifestation of sulfonamide antibiotics (co-trimoxazole) reactions in Thai patients. Regardless of HIV status, the most common skin manifestation was maculopapular eruption, followed by fixed drug eruption and angioedema with or without urticaria, respectively. Among those with known HIV serology, maculopapular eruptions occurred more frequently in the HIV positive group, while fixed drug eruptions occurred more frequently in HIV-negative group. A history of atopy, food allergy, autoimmune diseases, previous drug allergy and HIV status were not significantly associated with an increased risk of developing serious reactions. However, HIV-positive status and lower CD4 count were associated with a tendency to an increased risk of developing serious cutaneous reactions, especially SJS.

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