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Original Research Article

The factors associated with co-trimoxazole hypersensitivity in people living with HIV/AIDS: a retrospective study

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ABSTRACT

Background: Antibiotic adverse drug reactions (ADRs) can occurred during any treatment of infection, especially opportunistic infections in people living with HIV/AIDS (PLWHA). Co-trimoxazole is a sulfonamide fixed dose combination antibiotic, consisted of sulfamethoxazole and trimethoprim which is effective in treatment of several infections and for prophylaxis of pneumocystis jiroveci pneumonia. The universal use of co-trimoxazole for prophylaxis has been shown to decrease hospitalizations, morbidity and mortality among PLWHA, but potentially associated with ADRs include drug hypersensitivity reaction. The objective was to identify factors associated with co-trimoxazole hypersensitivity in PLWHA.
Methods: A retrospective study were enrolled 404 participants PLWHA who were received co-trimoxazole due to co-trimoxazole prophylaxis therapy (CPT), between January 2015–December 2018. The independence variables such as age, sex, history of allergy, hypersensitivity reactions, duration of therapy (days), CD4 (cells/µl) and opportunistic infection to co-trimoxazole hypersensitivity reaction were analyzed using spearman test.
Results: Mostly of the participants was male: 253 (62.60%). Eighteen (4.50%) with history of allergy, 64 (15.90%) were known co-trimoxazole hypersensitivity reaction. The most frequent clinical manifestation was maculopapular rash: 27 (42.3%), followed by urticaria alone: 17 (26.3%), fixed drug eruption: 12 (19.6%), and angioedema with or without urticaria: 8 (11.8%). The history of allergy, opportunistic infection and duration of treatment were associated factors to co-trimoxazole hypersensitivity reaction.
Conclusions: This study was identified, that history of allergy, duration of treatment and opportunistic infection were factors associated with co-trimoxazole hypersensitivity in PLWHA.

Keywords: People living with HIV/AIDS, Co-trimoxazole, Hypersensitivity, Associated factors

INTRODUCTION

Sulfonamide containing combination antibiotic that consists of sulfamethoxazole and trimethoprim in the weight ratio of 5:1 is co-trimoxazole.[1] Co-trimoxazole is a universal available, low-cost antibiotic, which has been wide used and this drug is effective for treatment of a variety of bacterial, fungal and protozoal infections. Co-trimoxazole is the pneumocystic jirovecii pneumonia drug of choice.[2-9] Co-trimoxazole prophylaxis has been suggested as a part of essential treatment and support package for symptomatic PLWHA.[10] Co-trimoxazole is associated with hypersensitivity in 1-3% of general population.[11] The frequency is higher (up to 34%) in PLWHA.[4,12]

Many contributing factors for an increased incidence of co-trimoxazole hypersensitivity reaction in PLWHA such

as multi-drug and long-term administration, low levels of intracellular glutathione. Co- trimoxazole are associated with various adverse drug effects, such as nausea, hematopoietic disorders, porphyria and hypersensitivity reactions.[13-16]

The most frequent clinical manifestation was maculopapular rash, followed by fixed drug eruption, urticaria alone, and angioedema with or without urticaria.[17] The history of allergy, opportunistic infection and duration of therapy were associated factors to co-trimoxazole hypersensitivity reaction. The wide use of co-trimoxazole for prophylaxis has been appeared to reduce morbidity, mortality and hospitalizations among PLWHA, but it has been associated with many ADRs includes drug hypersensitivity reaction.[18-22]

This study identified factors associated with co-trimoxazole hypersensitivity in PLWHA at Wangaya Hospital in Denpasar, Bali, Indonesia.

METHODS

PLWHA 18 years old and above who were reported to take Co-trimoxazole routinely at Wangaya hospital in Denpasar, Bali, Indonesia, between January 2015 and December 2018 enrolled in this study. The characteristics data: demographics and clinical manifestation were recorded. The common opportunistic infection in PLWHA such as oral candidiasis, that the diagnosis was based on the nature of clinical presenting features; the pseudo membranous candidiasis is commonly known as oral thrush.

Tuberculosis is diagnosed if there was a suspicion for TB (at least one of the positive symptom screening components), then a radiological and bacteriologic examination was done to identify the acid-fast bacilli (AFB). Diarrhoea is passing loose or watery solid discharges at least 3 times or more in a day (or more often than expected). Diagnosis of toxoplasma encephalitis (TE) was based on presumptive criteria include the clinical signs and symptoms, neuroimaging findings (CT scan of the head) which were compatible with TE and the response to therapy for toxoplasmosis. Serological study for toxoplasma IgG was not routinely performed to all patients because of facility constraints in our hospital and herpes zoster is characterized by a painful, unilateral vesicular eruption, which usually occurs in a restricted dermatomal distribution.

A maculopapular rash is a diffuse and symmetric eruption of erythematous macules or small papules. Urticaria are itchy, raised, reddish areas on the skin. Fixed drug eruption is round or oval patches of redness and swelling of the skin, sometimes surmounted by a blister. Angioedema is the swelling of the deeper layers of the skin, mucosa caused by a build-up of fluid.

Statistical analysis

The characteristics data, age, sex, history of allergy, hypersensitivity reactions, duration of treatment (days), CD4 cells count (cells/µl) and opportunistic infection were displayed by descriptive statistics, e.g. mean SD and percentages. Binary logistic correlation (Spearman test) was use for analysed. A p value<0.05 was considered to be statistically significant. All statistical data analyses were performed using SPSS for Windows version 15.0.

RESULTS

Among 404 PLWHA who were enrolled in this study, we found 64 (15.9%) patients with co-trimoxazole hypersensitivity reactions. Mostly the participants were male: 253 (62.60%), 49 (12.10%) with the opportunistic infection. The mean of age was 35.86±8.52 years old. We also found 18 (4.5%) with previous allergic history and 386 (95.5%) without previous allergic history. Duration of treatment (days): 21.8±16.3 and with CD4 counts: 157.7±109.9 cells/µl (Table 1).

Table 1: The participants characteristics data (n=404).

Characteristics	N (%) / Mean±SD
Age (years)	35.86±8.52
Sex	
Male	253 (62.60%)
Female	151 (37.40%)
CD4 (cells/µl)	157.7±109.9
Hypersensitivity reactions	
Yes	64 (15.90%)
No	340 (84.10%)
History of allergy	
Yes	18 (4.50%)
No	386 (95.50%)
Duration of Treatment (days)	21.8±16.349 (12.10%)
Opportunistic Infection	
Yes	49 (12.10%)
No	355 (87.90%)

CD4 = Cluster Differenciation-4

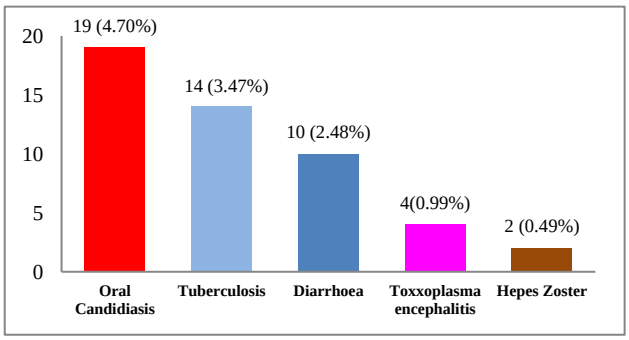

Figure 1: The opportunistic infection spectrum (n=404).

We found the opportunistic infection among 404 PLWHA in this study were about 49 (12.13%). The spectrum of opportunistic infection, the most frequent oral candidiasis 19 (4.70%), followed by tuberculosis 14 (3.47%), diarrhoea 10 (2.48%), toxoplasma encephalitis 4 (0.99%) and herpes zoster 2 (0.49%) (Figure 1).

Maculopapular rash was the most frequent clinical manifestation: 27 (6.68%), followed by urticaria alone: 17(4.21%), fixed drug eruption: 12 (2.97%), and angioedema with or without urticaria: 8 (1.98%) (Figure 2).

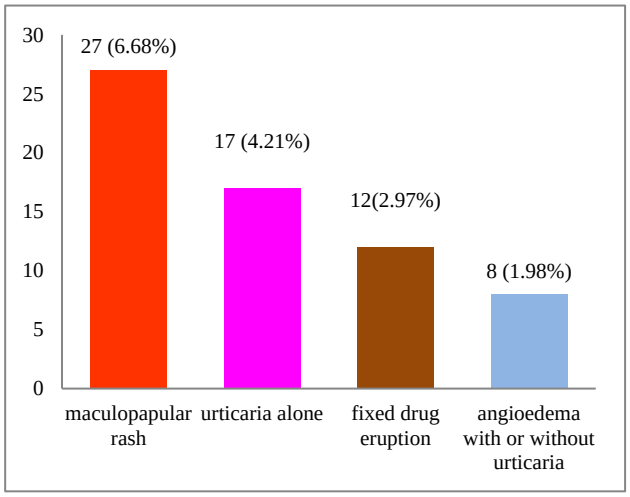

Figure 2: The clinical manifestation of co-trimoxazole hypersensitivity reaction (n=404).

DISCUSSION

Co-trimoxazole is a universal used, inexpensive and it is effective against an infections wide range. The drugs is well tolerated, but PLWHA have a potentially high rate of ADRs that significantly impact the management of opportunistic infections in PLWHA.[8,13] The hypersensitivity to co-trimoxazole has been shown to be almost exclusively because of the active metabolites of Sulfamethoxazole that is metabolized in the liver to Sulfamethoxazole-hydroxylamine, followed by non-enzymatic oxidation to produce nitroso-sulfamethoxazole (n-SMX).[23] This metabolite causing direct cellular toxicity by covalently binds to host proteins, This necrotic cell death may give a risk sign to sensitized T-cells leading to the cascade of immune response and cytokine release.[24]

A history of previous allergy has been proposed to be the risk factor for reactions to some drugs. We found that history of previous allergy has demonstrated a significantly contribution to co-trimoxazole hypersensitivity reaction (p=0.000) (Table 2). Some authors have reported that a history of previous allergy might increase the severity of cutaneous reactions.[25]

Duration of treatment has been proposed to be the risk factor for co-trimoxazole hypersensitivity reaction.[26] This study found that duration of treatment significantly contributed to co-trimoxazole hypersensitivity reaction (p=0.000) (Table 2). Macy and Poon reported that the antibiotics which had the highest incidence rate of hypersensitivity reactions in female was sulfonamide (3.4% compared with 1-1.5% of other classes of antibiotics). This might perhaps be due to its routinely take for urinary tract infection.[26,27]

Table 2: Bivariate analysis between co-trimoxazole hypersensitivity reactions and age, sex, CD4, history of allergy, duration of treatment, opportunistic infection (n=404).

Variable	P value
Age	0.576
Sex	0.272
CD4	0.603
History of allergy	0.000*
Duration of treatment	0.000*
Opportunistic Infection	0.000*

Binary logistic correlation (Spearman test) *Significant p<0.05, CD4= Cluster differentiation-4

The correlation between increasing risk of ADRs and progression of HIV infection is settled.[28] Low of CD4 levels have been proposed to be one of the risk factors for severe cutaneous drug eruptions.[14,29] This study showed that low CD4 levels was no significantly contribution to co-trimoxazole hypersensitivity reaction.

CONCLUSION

This study has identified history of allergy, duration of treatment and opportunistic infection were significant associated factors to Co-trimoxazole hypersensitivity reaction in PLWHA. The most frequent opportunistic infection was oral candidiasis followed by tuberculosis, diarrhoea, toxoplasma encephalitis, herpes zoster. Maculopapular rash was the most frequent clinical manifestations, followed by urticaria alone, fixed drug eruption and angioedema with or without urticaria.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Kongpan T, Mahasirimongkol S, Konyoung P, Kanjanawart S, Chumworathayi P, Wichukchinda N, et al. Candidate HLA genes for prediction of co-trimoxazole induced severe cutaneous reactions. Pharmacogenet Genom.2015;25:402-11.
2. Denue BA. Knowledge regarding co-trimoxazole preventive therapy among patients who are HIV positive in a tertiary health facility, northeastern Nigeria. Sub-Saharan Afr J Med. 2018;4:31-6.
3. Raizada N, Chauhan LS, Babu S, Thakur R, Khera A, Wares F, et al. Linking HIV-infected TB patients to cotrimoxazole prophylaxis and antiretroviral treatment in India. Plos One. 2009;4(6):1-7.
4. Chantachaeng W, Chularojanamontri L, Kulthanan K, Jongjareamprasert K, Dhana N. Cutaneous adverse reactions to sulfonamide antibiotics. Asian Pac J Allergy Immunol. 2011;29:284-9.
5. Daftarian MP, Filion LG, Cameron W, Conway B, Roy R, Tropper F, et al. Immune response to sulfamethoxazole in patients with AIDS. Clinic Diagn Laborat Immunol. 1995;2(3):199-204.
6. Suthar AB, Granich R, Mermin J, Riea AV. Effect of cotrimoxazole on mortality in HIV-infected adults on antiretroviral therapy: a systematic review and meta-analysis. Bull World Health Organ 2012;90:128–38C.
7. 7. Diriba L, Pharm B, Worku F, Girma T. Evaluation of prophylactic use of cotrimoxazole for people living with HIV/AIDS in Jimma university specialized hospital, Southwest Ethiophia. Ethiop J Health Sci. 2008;18(3):59-64.
8. Hasse B, Walker S, Fehr J, Furrer H, Hoffmann M, Battegay M, et al. Co-trimoxazole prophylaxis is associated with reduced risk of incident tuberculosis in participants in the Swiss HIV cohort study. Antimicrob Age Chemoth. 2014;58(4):2363-8.
9. Chintu C, Bhat GJ, Walker AS, Mulenga V, Sinyinza F, Lishimpi K. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. Lanc. 2004; 364:1865-71.
10. Denegetu AW, Dolamo BL. HIV screening among TB patients and co-trimoxazole preventive therapy for TB/HIV patients in Addis Ababa: facility based descriptive study. Plos One. 2014;9(2):1-7.
11. Watera C, Todd J, Muwonge R, Whitworth J, Miiro JN, Brink A, et al. Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1 infected adults attending an HIV/AIDS clinic in Uganda. J Acquir Immune Defic Syndr. 2006;42(3):373-8.
12. Davis CM, Shearer WT. Diagnosis and management of HIV drug hypersensitivity. J Allergy Clin Immunol. 2008;121(4):826-32.
13. Strom BL, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, et al. Absence of Cross-Reactivity between Sulfonamide Antibiotics and Sulfonamide Nonantibiotics. N Engl J Med. 2003;349:1628-35.
14. Schnyder B, Pichler WJ. Allergy to sulfonamides. J Allergy Clin Immunol. 2013;131(1):256-7.
15. Ku SW, Jiamsakul A, Joshi L, Pasayan MKU, Widhani A, Chaiwarith R, et al. Cotrimoxazole prophylaxis decreases tuberculosis risk among Asian patients with HIV. J Int AIDS Soc. 2019;22:e25264.
16. Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N. Trimethoprim-sulfamethoxazole revisited. Arch Intern Med. 2003;163:402-10.
17. Anglaret X, Chêne G, Attia A, Toure S, Lafont S, Combe P. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. Lanc. 1999;35:1463-8.
18. Kassie GM, Duga AL, Nebi PJ. Evaluation of co-trimoxazole as preventive therapy for people living with HIV/AIDS in Jimma health center, Southwest Ethiopia. Int Res J Pharm. 2014;5(5):403-6
19. Hamel MJ, Greene C, Chiller T, Ouma P, Polyak C, Otieno K. Does Cotrimoxazole Prophylaxis for the Prevention of HIV-Associated Opportunistic Infections Select for Resistant Pathogens in Kenyan Adults? Am. J. Trop. Med. Hyg. 2008;79(3):320-30.
20. Polyak CS, Yuhas K, Singa B, Khaemba M, Walson J, Richardson BA, et al. Cotrimoxazole prophylaxis discontinuation among antiretroviral treated HIV 1 infected adults in Kenya: a randomized non-inferiority trial. Plos Med. 2016;13(1):1-16.
21. Naisbitt DJ, Gordon SF, Pirmohamed M, Burkhart C, Cribb AE, Pichler WJ, et al. Antigenicity and immunogenicity of sulphamethoxazole: demonstration of metabolism-dependent haptenation and T-cell proliferation in vivo. Brit J Pharmacol. 2001;133:295-305.
22. Thong BY. Update on the management of antibiotic allergy. Allergy Ashtma Immunol Res. 2010;2(2):77-86.
23. Burkhart C, Greyerz SV, Depta JPH, Naisbitt DJ, Britschgi M, Park KB. Influence of reduced glutathione on the proliferative response of sulfamethoxazole-specific and sulfamethoxazole-metabolite-specific human CD4+ T-cells. Brit J Pharmacol. 2001;132:623-30.
24. Yunihastuti E, Widhani A, Karjadi TH. Drug hypersensitivity in human immunodeficiency virus-infected patient: challenging diagnosis and management. Asia Pac Allergy. 2014;4:54-67.
25. Lazarou J, Pomeranz BH, Corey PN. Incidence of Adverse Drug Reactions in Hospitalized Patients. A Meta-analysis of Prospective Studies. J Americ Medic Assoc. 1998;279(15):1200-5.
26. Macy E, Romano A, Khan D. Practical Management of Antibiotic Hypersensitivity in 2017. Clinic Managem Revi. 2017;577-86.
27. Pichler WJ, Srinoulprasert Y, Yun J, Hausmann O. Multiple Drug Hypersensitivity. Int Arch Allergy Immunol. 2017;129-38.

28. Legendre DP, Muzny CA, Marshall GD, Swiatlo E. Antibiotic Hypersensitivity Reactions and Approaches to Desensitization. Clinic Infect Diseas. 2014;58:1140-7.
29. Borges MS, Thong B, Blanca M, Ensina LFC, Diaz SG, Greenberger PA, et al. Hypersensitivity reactions to non beta-lactam antimicrobial agents, a statement of the WAO special committee on drug allergy. Worl Allerg Organizat J. 2013;6:1-23.

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