
Case reports

Hypersensitivity syndrome associated with dapsone/pyrimethamine (Maloprim) antimalaria chemoprophylaxis

Bernard Yu-Hor Thong, MBBS, MRCP (UK); Khai-Pang Leong, MBBS, MRCP (UK); and Hiok-Hee Chng, MBBS, m med (Int Med), FRCP (Glasg)

Background: Dapsone 100 mg/pyrimethamine 12.5 mg (Maloprim; Beacons Chemicals Pte Ltd, Singapore) is routinely prescribed for antimalarial chemoprophylaxis in military servicemen in Singapore who are not glucose-6-phosphate dehydrogenase-deficient.

Methods: We report a series of three male National Servicemen with hypersensitivity syndrome from Maloprim.

Results: The three patients were diagnosed with hypersensitivity syndrome based on the presence of features of a drug hypersensitivity syndrome including fever, lymphadenopathy, maculopapular exanthema, hepatitis, and definite exposure to weekly Maloprim alone. A mild Coombs positive hemolytic anemia was also observed in one patient. All the clinical, hematologic, and biochemical derangements normalized within 3 months of tapering regimens of moderate-dose prednisolone.

Conclusions: Drug hypersensitivity syndromes can occur even on low-dose, weekly drug regimens. Hypersensitivity syndrome from weekly Maloprim is potentially reversible when recognized and treated early.

Ann Allergy Asthma Immunol 2002;88:527–529.

INTRODUCTION

Dapsone 100 mg/pyrimethamine 12.5 mg (Maloprim; Beacons Chemicals Pte Ltd, Singapore) is routinely prescribed for antimalarial chemoprophylaxis in military servicemen in Singapore who are not glucose-6-phosphate dehydrogenase (G6PD)-deficient. It is an effective chemoprophylaxis in places with chloroquine-resistant malaria. We report a series of three male Chinese National Servicemen (NSF) with hypersensitivity syndrome from Maloprim.

CASE HISTORIES

Patient 1

A 22-year-old NSF had commenced weekly Maloprim 2 weeks before an

overseas training exercise. The day after the third dose of Maloprim, he developed fever, a generalized pruritic, erythematous, exfoliative, maculopapular rash, non-tender left cervical and right inguinal lymphadenopathy and hepatosplenomegaly. Maloprim was discontinued after the onset of symptoms and he was hospitalized.

Investigations revealed hemoglobin (Hb) 16.0 g/dL, white cell count $8.7 \times 10^9/L$, polymorphs 71%, lymphocytes 15%, monocytes 12%, eosinophils 1%, platelet count $185 \times 10^9/L$. Renal function was normal. Serum bilirubin was 6 $\mu\text{mol/L}$ (normal range 3 to 24), alkaline phosphatase (ALP) 69 U/mL (normal range 32 to 103), alanine aminotransferase (ALT) 84 U/mL (normal range 7 to 36), aspartate aminotransferase (AST) 30 U/mL (normal range 15 to 33). Two days later, Hb dropped to 13.0 g/dL with 4% reticulocytosis. Direct Coombs test was weakly positive

with anti-C3d and anti-C3b antibodies. Antinuclear antibody (ANA) was negative. Serum haptoglobin, complements and G6PD levels were normal. No malaria parasite was seen in the peripheral blood films. Epstein-Barr virus and parvovirus serologies were negative. He was treated with oral prednisolone 30 mg per day, tapered over 2 months with resolution of the rash, systemic symptoms and signs.

Patient 2

A 21-year-old NSF developed a pruritic, erythematous maculopapular rash over the backs of both hands and neck the day after the ninth dose of weekly Maloprim. He continued Maloprim until the 12th dose, by which time the rash had become generalized, associated with fever, chills, multiple palpable cervical lymph nodes, and oral ulcers. He stopped Maloprim after this.

Upon investigation, Hb was 12.5 g/dL, white cell count $6.8 \times 10^9/L$ with normal differential counts, and platelet count $376 \times 10^9/L$. Renal function was normal. Serum bilirubin was 30 $\mu\text{mol/L}$, ALP 109 U/mL, ALT 532 U/mL, and AST 366 U/mL. Hepatitis B surface antigen was positive; 'e' antigen (HBeAg), IgM antibodies to hepatitis B core antigen (anti-HBc IgM), and antibodies to hepatitis B 'e' antigen (anti-HBe) were negative. Serum hepatitis B viral deoxyribonucleic acid (HBV-DNA) was undetectable. G6PD levels were normal. Direct Coombs test and antinuclear antibody were negative. Blood film for malarial parasite was negative. He was given prednisolone 30 mg daily, which was

Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore. Received for publication June 20, 2001.

Accepted for publication in revised form October 11, 2001.

tapered gradually over a longer duration of 3 months to prevent reactivation of hepatitis B.

Patient 3

A 19-year-old NSF developed fever and a generalized, pruritic, erythematous maculopapular rash after the sixth dose of weekly Maloprim. This was associated with buccal and glans mucosal erosions but no lymphadenopathy or hepatosplenomegaly. He had a history of atopic eczema and childhood asthma.

Evaluation showed Hb was 11.8 g/dL, white cell count $9.0 \times 10^9/L$, polymorphs 68%, lymphocytes 15%, monocytes 4%, eosinophils 0%, atypical monocytes 13%, and platelets $300 \times 10^9/L$. Renal function was normal. Serum bilirubin was 58 $\mu\text{mol/L}$, ALP 207 U/mL, ALT 336 U/mL, and AST 157 U/mL. Hepatitis B and C serologies were negative, as was blood film for malarial parasite. G6PD levels were normal. He was started on prednisolone 30 mg daily which was subsequently tapered.

DISCUSSION

Severe cutaneous reactions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with the use of weekly pyrimethamine-sulfadoxine (Fansidar, Roche Pharmaceuticals, Nutley, NJ) for antimalarial chemoprophylaxis in non-human immunodeficiency virus (HIV)-infected^{1,2} individuals and biweekly prophylaxis against *Pneumocystis carinii* pneumonia in HIV-infected individuals.³⁻⁵ Most of the reactions were neither attributed directly to the sulfadoxine nor pyrimethamine components. In the case of HIV-infected individuals, this was more often attributed to sulfadoxine rather than pyrimethamine in view of the predisposition to sulfonamide allergy in HIV infection. A positive lymphocyte transformation test to sulfadoxine and negative test to pyrimethamine were demonstrated in one patient with hypersensitivity pneumonitis from pyrimethamine-sulfadoxine antimalarial chemoprophylaxis.⁶

Hypersensitivity syndrome from weekly Maloprim antimalarial chemoprophylaxis, however, is uncommon. There has only been one previous report, which was attributed to dapson rather than pyrimethamine, as the patient had previously taken pyrimethamine-sulfadoxine without any adverse reaction.⁷

Dapsone syndrome (DDS) is a drug hypersensitivity syndrome which usually occurs during the first 3 to 8 weeks of daily dapsone therapy for a variety of conditions including leprosy and autoimmune skin disorders. In our three patients, DDS occurred after the third to ninth dose of weekly Maloprim.

The diagnosis is based on clinical features including fever, malaise, exfoliative dermatitis (papular, bullous, plaques, or eczematoid), hemolytic anemia, lymphadenopathy, leukopenia, or leukocytosis with mononucleosis. Reversible cholestatic hepatitis and fulminant hepatitis have both been described.⁸ Eosinophilia, hepatosplenomegaly,⁹ tonsillar membrane¹⁰ and hypothyroidism¹¹ occurring 3 months or more after DDS have been described. There have, however, been no reports of a Coombs' positive hemolytic anemia.

The pathogenesis of DDS is still not well understood. Slow acetylators and those with decreased levels of glutathione in plasma/lymphocytes eg, acquired immunodeficiency syndrome, resulting in accumulation of reactive dapsone metabolites, may be at risk for DDS.¹² The findings of Saito et al¹³ of positive lymphocyte stimulation test and predominantly activated cytotoxic T cells in the dermis of DDS-affected skin suggests an allergic rather than idiosyncratic reaction. It is possible that genetic factors may also play a part in DDS.¹⁴

Early recognition of DDS and prompt withdrawal of the drug is essential. Although the evidence for the efficacy of the use of oral glucocorticoids is anecdotal, their use is recommended for patients with visceral manifestations.¹⁵ Tapering regimens over 1 month are advised because dapsone persists for up to 35 days in organs via protein binding and enterohepatic cir-

culation. The course of the adverse reaction is variable, but may last 4 weeks or more. Morbidity and mortality depend on the severity of the reaction and extent of organ involvement, both increasing in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or fulminant hepatitis.¹⁶

Although the majority of drug hypersensitivity reactions from pyrimethamine-containing drugs have been reported with pyrimethamine-sulfadoxine and pyrimethamine-sulfadiazine,¹⁷ there have been a few reports of drug eruptions attributed to pyrimethamine alone.^{18,19} Lymphocyte transformation tests to each component would be useful in elucidating the cause in combination drugs, especially if either drug needs to be used again and the risks of a drug challenge far outweigh the benefits, particularly in severe hypersensitivity reactions. We did not carry out lymphocyte transformation tests to dapsone or pyrimethamine in our patients as there was no immediate need to use either of these drugs.

CONCLUSION

We report three case histories of military serviceman with hypersensitivity syndrome from weekly Maloprim. This was diagnosed clinically with the aid of simple laboratory tests of hematologic, renal, and liver function. It is potentially reversible and must be recognized early, especially where Maloprim is widely used for antimalarial chemoprophylaxis. It is of particular importance in our country where military service is compulsory for all male citizens.

REFERENCES

1. Miller KD, Lobel HO, Satriale RF, et al. Severe cutaneous reactions among American travelers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986;35:451-458.
2. Curley RK, Macfarlane AW. Fatal multisystemic toxicity associated with prophylaxis with pyrimethamine and sulfadoxine. *Br Med J (Clin Res Ed)* 1985;290:471-472.
3. Fansidar-associated fatal reaction in an

- HIV-infected man. *MMWR Morb Mortal Wkly Rep* 1988;37:571–572, 577.
4. Kimura S, Oka S, Mohri H, et al. Three cases of acquired immunodeficiency syndrome complicated with toxic epidermal necrolysis. *Jpn J Med* 1991;30: 553–558.
5. Raviglione MC, Dinan WA, Pablos-Mendez A, et al. Fatal toxic epidermal necrolysis during prophylaxis with pyrimethamine and sulfadoxine in a human immunodeficiency virus-infected person. *Arch Intern Med* 1988;148: 2683–2685.
6. Daniel PT, Holzschuh J, Berg PA. Sulfadoxine specific lymphocyte transformation in a patient with eosinophilic pneumonia induced by sulfadoxine-pyrimethamine (Fansidar). *Thorax* 1989;44:307–309.
7. Grayson ML, Yung AP, Doherty RR. Severe dapsone syndrome due to weekly maloprim. *Lancet* 1988;1:531.
8. Johnson DA, Cattau EL Jr, Kuritsky JN, Zimmerman HJ. Liver involvement in the sulfone syndrome. *Arch Intern Med* 1986;146:875–877.
9. Kumar RH, Kumar MV, Thappa DM. Dapsone syndrome—a five year retrospective analysis. *Indian J Lepr* 1998; 70:271–276.
10. Chan HL, Lee KO. Tonsillar membrane in the DDS (dapsone) syndrome. *Int J Dermatol* 1991;30:216–217.
11. Gupta A, Eggo MC, Uetrecht JP, et al. Dapsone-induced hypothyroidism: the thyroid as a target organ in hypersensitivity reactions to anticonvulsants and sulfonamides. *Clin Pharmacol Ther* 1992;51:56–67.
12. Guo R, Thormann W, Lauterberg B. Relationship between high incidence of adverse dapsone reactions and slow acetylate phenotype or low plasma/lymphocyte glutathione level. *Chin Med J* 1996;109:933–936.
13. Saito S, Ikezawa Z, Miyamoto H, Kim S. A case of the “dapsone syndrome.” *Clin Exp Dermatol* 1994;19:152–156.
14. Jamrozik K. Dapsone syndrome occurring in two brothers. *Lepr Rev* 1996; 57:57–62.
15. Roujeau JC. Treatment of severe drug eruptions. *J Dermatol* 1999;26: 718–722.
16. Chalasani P, Baffoe-Bonnie H, Jurado RL. Dapsone therapy causing sulfone syndrome and lethal hepatic failure in an HIV-infected patient. *South Med J* 1994;87:1145–1146.
17. Caumes E, Bocquet H, Guernonprez G, et al. Adverse cutaneous reactions to pyrimethamine/sulfadiazine and pyrimethamine/clindamycin in patients with AIDS and toxoplasmic encephalitis. *Clin Infect Dis* 1995;21: 656–658.
18. Piketty C, Weiss L, Picard-Dahan C, et al. Toxic dermatitis caused by pyrimethamine in patients with acquired immunodeficiency virus infection [in French]. *Presse Med* 1995;24:1710.
19. Costello JM, Becroft DM. Drug reaction simulating malignant lymphoma: a case due to pyrimethamine. *N Z Med J* 1977;86:430–432.

Reprints for requests should be addressed to:
Dr Bernard Yu-Hor Thong
Department of Rheumatology, Allergy and Immunology
Tan Tock Seng Hospital
11 Jalan Tan Tock Seng
Singapore 308433
E-mail: bernard_thong@ttsh.com.sg

Answers to CME examination—Annals of Allergy, Asthma, and Immunology, May 2002 Custovic A, Murray CS, Gore RB, Woodcock A: Controlling indoor allergens. *Ann Allergy Asthma Immunol* 2002;88:432-442.

1. d
2. c
3. e
4. d
5. b