

Dapsone hypersensitivity syndrome: A rare life threatening complication of dapsone therapy

Kolar Vishwanath Vinod, Karyampudi Arun, Tarun Kumar Dutta

Department of General Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Dhanvantrinagar, Puducherry, India

ABSTRACT

Dapsone can cause several adverse effects, the most serious being dapsone hypersensitivity syndrome (DHS), which is potentially fatal. Here we report a case of severe, life threatening dapsone systemic hypersensitivity syndrome in a 17-year-old male who presented with high grade fever, eosinophilia, lymphadenopathy, skin rash, hepatitis and encephalopathy, which was managed successfully with oral steroids. The case is being reported to emphasize the need for timely diagnosis and prompt treatment of this rare complication for successful outcomes. DHS is also reviewed in brief.

Key words: Drug rash, eosinophilia, hepatitis, hypersensitivity

INTRODUCTION

Dapsone (4,4'-diaminodiphenylsulfone) is useful for treating a variety of infectious, immunological and hypersensitivity disorders.^[1] Commonly encountered adverse effects of this drug include dose unrelated (idiosyncratic) skin hypersensitivity reactions and dose-related hemolytic anemia and methemoglobinemia. Other notable adverse effects include insomnia and psychosis. A rare, potentially fatal idiosyncratic systemic hypersensitivity syndrome- namely dapsone hypersensitivity syndrome (DHS), characterized by fever, skin rash, eosinophilia, lymphadenopathy, hepatic, pulmonary and other systemic manifestations can complicate dapsone therapy.^[1-5] DHS can cause irreversible organ damage or even death if not recognized early and managed properly.^[2,5]

Here we report a case of severe, life threatening DHS with multi-organ dysfunction in a 17-year-old male, which was managed successfully with oral steroids. A brief review of DHS is also presented.

CASE REPORT

A 17-year-old male student was brought with complaints of high grade fever associated with chills and rigors, jaundice and itchy skin rash for 10 days. One month prior to current admission, he was started on dapsone 100 mg/day by a dermatologist for suspected lichen planus. He had discontinued the medication 10 days earlier when he developed the above complaints. On admission, he had high grade fever (103-104°F), deep icterus, palpable lymph nodes in the cervical and axillary regions but without palpable liver or spleen. He had a toxic look, was agitated and confused, with generalized skin erythema and extensive scaling - suggesting exfoliative dermatitis [Figures 1 and 2]. There was angular cheilitis with a crusted lesion over the lip, subconjunctival hemorrhage but oral mucosa and penile mucosa were normal [Figure 2]. Patient later developed shock (blood pressure: 70/40 mm Hg) and right internal

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.110917

Address for correspondence:

K. V. Vinod, Department of General Medicine, JIPMER, Dhanvantrinagar, Puducherry - 605 006, India.

E-mail: drkvv@rediffmail.com



Figure 1: Skin erythema with extensive scaling on face and neck

jugular central venous catheter was placed. Noradrenaline was started as the hypotension did not respond to fluid challenge. Empirical broad spectrum antibiotic cover (meropenem and vancomycin) was given keeping the possibility of severe sepsis with septic shock, in view of breach in integrity of the skin.

Laboratory evaluation revealed neutrophilic leucocytosis with eosinophilia (Hb: 12.3 g/dl, leucocytes: 12,700/ μ l, platelets: 2,10,000/ μ l, differential count: Neutrophils-78%, Lymphocytes-12%, Eosinophils-10%), hepatitis [bilirubin: 13.5 mg/dl (direct fraction: 10.2 mg/dl), AST: 239 IU/l, ALT: 430 IU/l, alkaline phosphatase: 538 IU/l], hypoalbuminemia (2.8 g/dl), coagulopathy (prothrombin time: 26 s (control: 14 s), aPTT: 48 s (control: 28-34 s)), normal urine examination and renal function. Tests for malaria, leptospirosis, typhus fever, cytomegalovirus (CMV), Epstein Barr virus (EBV), ELISA for HIV-1 and 2, hepatitis A, B, E and C were negative. Antinuclear antibodies were negative. Repeated blood and skin swab cultures were sterile. Chest radiography and abdominal sonography were unremarkable.

Patient's blood pressure improved and noradrenaline was stopped after 4 days of admission. He continued to have high grade fever despite being on antibiotics for 5 days. A diagnosis of dapsone systemic hypersensitivity syndrome was made based on history of dapsone intake, followed by fever, skin rash, eosinophilia, lymphadenopathy and hepatitis. He was started on oral prednisolone 50 mg/day (1 mg/kg) from day 6. He improved over next 10 days with gradual subsidence of fever, rash and hepatitis. Antibiotics were discontinued after 10 days and he was discharged on day 18 of admission. Prednisolone 1 mg/kg/day was continued for 1 month and then tapered off over next 6 weeks, with complete normalization of liver function and resolution of lymphadenopathy.



Figure 2: Deep icterus, subconjunctival haemorrhages, angular cheilitis, crusted lesion over the lip with normal oral mucosa and resolving scaly lesions over face, neck and upper trunk (after 4 days of starting steroid therapy)

DISCUSSION

Dapsone is used for treatment or prophylaxis of several infections (leprosy, *Pneumocystis jirovecii* infection, toxoplasmosis, malaria, cutaneous mycetoma), in several dermatological conditions (bullous dermatoses, acne, cutaneous vasculitis and dermatitis herpetiformis) and in immune thrombocytopenic purpura. Dapsone is one of the commonly implicated drugs in drug induced systemic hypersensitivity syndrome, apart from anticonvulsants, sulfonamides, allopurinol, non-steroidal anti-inflammatory drugs and minocycline.^[1,6] DHS is a rare dose independent adverse effect reported with dapsone use in leprosy, malaria prophylaxis, dermatitis herpetiformis, lichen planus and various other conditions. DHS can develop several weeks to as long as six months after treatment initiation and the reported incidence ranges from 0.5% to 3%.^[1]

Manifestations of DHS include high grade fever, skin rash, lymphadenopathy, eosinophilia, hepatitis, acute pneumonitis, neurological and other systemic features of multi-organ dysfunction. The drug hypersensitivity syndrome associated with **Drug Rash, Eosinophilia and Systemic Symptoms**, as noted in the present case, is called **DRESS** syndrome.^[1] Our patient had severe systemic manifestations-namely hepatitis with mixed hepatocellular and cholestatic features, coagulopathy, encephalopathy, shock and exfoliative dermatitis-a serious form of skin hypersensitivity, as reported earlier.^[1-5] Various cutaneous manifestations like erythroderma/exfoliative dermatitis, papular erythematous/pustular eruptions, erythema multi-forme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been described in DHS.^[7] Although acute pneumonitis (eosinophilic pneumonia) with hypoxia and pleural effusion has been reported in DHS,^[1] no overt pulmonary manifestation was seen in this patient.

The diagnosis of DHS is based on clinical findings of fever, skin rash, lymphadenopathy, hepatitis and other systemic features,^[8] along with history of antecedent dapsone exposure. Skin biopsy findings are non-specific. In the present case, the diagnosis was based on typical clinical manifestations following 3 weeks of dapsone intake, after excluding other drug exposures and close differential diagnoses-namely viral hepatitis, rickettsial infections, CMV, EBV infections, complicated malaria, leptospirosis and was further supported by prompt response to systemic steroids. Rechallenge with dapsone is not recommended, as it can be hazardous.

Pathogenesis of DHS is unclear but proposed mechanisms implicate metabolites of dapsone, which form haptens with the production of anti-dapsone antibodies.^[9] Differences in dapsone metabolism, which affect the production and detoxification of its reactive metabolites might be responsible for differential susceptibility of people to the adverse effects of dapsone.^[10] The inter-individual variability in the metabolism of dapsone by N-hydroxylation to hydroxylamines by the hepatic microsomal cytochrome P-450 system has been implicated in the haematological toxicity^[10] (methemoglobinemia, hemolytic anaemia and agranulocytosis) but its role in determining the risk of DHS is unclear.^[1]

The management involves prompt discontinuation of dapsone, systemic steroids (oral prednisolone 1 mg/kg/day or intravenous methylprednisolone in equivalent doses) with supportive care.^[6] Gradual tapering of prednisolone (over more than a month) is recommended considering the persistence of dapsone in the body up to 35 days.^[6] Mortality as high as 12-23% has been reported in severe DHS.^[5] Thus, a high index of suspicion for early diagnosis, along with prompt treatment

are essential to prevent fatalities and late complication of interstitial pulmonary fibrosis.

Physicians, dermatologists, rheumatologists and leprologists prescribing dapsone for various clinical conditions should be aware of potentially fatal DHS, which can present with fever, rash and multi-organ involvement to ensure timely diagnosis and appropriate management.

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How to cite this article: Vinod KV, Arun K, Dutta TK. Dapsone hypersensitivity syndrome: A rare life threatening complication of dapsone therapy. *J Pharmacol Pharmacother* 2013;4:158-60.

Source of Support: Nil, **Conflict of Interest:** None declared.