Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 2, 2015

Case Study

DAPSONE INDUCED HYPERSENSITIVITY SYNDROME–A CASE REPORT

R LAKSHMI, SUNNY LINIYA, S VIJAYALAKSHMI

Department of pharmacy practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham University, AIMS Health Sciences Campus, Ponekkara P. O, Kochi, Kerala, India 682041
Email: lakshmir87@gmail.com

Received: 08 Nov 2014 Revised and Accepted: 03 Dec 2014

ABSTRACT

4,4'-Diaminodiphenylsulphone (Dapsone) is widely used for a variety of infectious, immune and hypersensitivity disorders, with indications ranging from Hansen's disease, inflammatory disease and insect bites. However, the use of dapsone may be associated with a plethora of adverse effects, some of which may involve the pulmonary parenchyma, methemoglobinemia with resultant cyanosis, bone marrow aplasia and/or hemolytic anemia, peripheral neuropathy and the potentially fatal dapsone hypersensitivity syndrome (DHS). DHS typically presents with a triad of fever, skin eruption and an internal organ (lung, liver, brain and other systems) involvement, occurring several weeks to as late as 6 months after the initial administration of the drug. In this sense, it may resemble a DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms). DHS must be promptly identified as untreated and the disorder could be fatal. Moreover, the pulmonary/systemic manifestations may be mistaken for other disorders. Eosinophilic infiltrates, pneumonitis, pleural effusions and interstitial lung disease may be seen. This syndrome is best approached with the immediate discontinuation of the offending drug and prompt administration of oral or intravenous glucocorticoids. An immunological-inflammatory basis of the syndrome can be envisaged based on the pathological picture and excellent response to anti-inflammatory therapy. Since dapsone is used for various indications, physicians from all specialties may encounter DHS and need to familiarize themselves with the salient features of the syndrome and its management.

Keywords: Dapsone, Hypersensitivity syndrome, Dermatological manifestations, Glucocorticoids.

INTRODUCTION

Dapsone has been used for many indications because of its antibiotic and anti-inflammatory effects. Since the advent of the era of Acquired Immunodeficiency Syndrome (AIDS), dapsone has been increasingly utilized in the chemoprophylaxis of *Pneumocystis carinii* infection in combination with Trimethoprim/Sulfamethoxazole. This has led to an increasing incidence of dapsone-related complications. Table1 enlists the multiple adverse effects of Dapsone, including the dapsone hypersensitivity syndrome (DHS) and DRESS syndrome. Hemolysis (more likely to occur with deficiency of glucose 6-phosphate dehydrogenase /G6PD), bone marrow aplasia, renal disease, peripheral neuropathy, methemoglobinemia, nausea, dizziness, fatigue and other systemic manifestations may occur singly or in combination in patients on dapsone therapy. DHS is characterized by the onset of fever, skin eruption and internal organ involvement several weeks to as late as 6 months after administration of this drug. If untreated the syndrome can lead to severe organ dysfunction and even death. The definite mechanism of DHS is unclear, but it is hypothesized that it is mediated by immune activation and elaboration of inflammatory cytokines [1]. This case report emphasizes the dermatological effects associated with DHS. The following sections provide an overview of the presentations, pathogenesis, diagnosis and management of DHS.

Table 1: Adverse reactions of dapsone

Systems involved	Adverse reactions
Cardiovascular	Tachycardia
Central nervous system	Fever,headache,insomnia,vertigo,psychosis
Dermatologic	Bullous and exfoliative dermatitis, phototoxicity, necrolysis, urticartia, Steven Johnson Syndrome
Endocrine and metabolic	Hypoalbuminemia, male infertility
Gastrointestinal	Nausea, vomiting, abdominal pain
Hepatic	Hepatitis, cholestatic jaundice
Renal	Albuminuria, nephrotic syndrome, renal papillary necrosis.
Hematologic	Hemolysis, methemoglobinemia,agranulocytosis,anemia

Case report

A forty two-year old housewife, with significant past medical history of hypothyroidism and pure red cell aplasia, presented with fever, weakness, vomiting, itching, allergy to penicillins, ANA-positive and ESR highly elevated. She was evaluated and based on the presumed diagnosis that this represented as bullous systemic lupus erythematosus and she was treated with dapsone (100 mg once daily for 7 days) as an anti-inflammatory agent. This was based on some data supporting the use of this drug for systemic lupus erythematosus, although this now appears to be a controversial approach. After seven days of therapy the patient developed progression of her symptoms, developing fever with chills, myalgia and nausea associated with diffuse abdominal pain, exfoliative dermatitis, oral erosions, dark-colored urine, swelling of the mouth, lips, face, tongue, yellowing of skin /eyes and jaundice[2]. She also noticed a new onset non-pruritic, ascending, maculo-papular skin eruption, with progressive shortness of breath. She had cough, haemoptysis, or chest pain at this time. On admission, the patient had jaundice, with a respiratory rate of 24 sbreath/minute, heart rate of 102 beats/minute, blood pressure of 140/90 mm of Hg, and a temperature of 99°F.

The patient's oxygen saturation was 86 % on room air and subsequently she was given higher amount of oxygen to the point that she was requiring 100 % non-rebreather mask in order to maintain her oxygen saturation above 92 %. Oral mucosa was abnormal with visible lesions. Neck examination was shows with no palpable lymphadenopathy or evidence of thyroid enlargement. Lung examination revealed bilateral diffuse crackles, decreased breath sounds in both bases and dullness to percussion. Cardiac examination showed tachycardia without audible murmur while the abdominal examination revealed hypoactive bowel sounds with diffuse mild tenderness on deep palpation without palpable organomegaly or evidence of rebound tenderness. The patient demonstrated a diffuse maculopapular eruption with sparing of the hands, feet, and mucosa. The laboratory data on admission is shown in table 2. Liver function abnormalities consistent with transaminase elevation were seen. The peripheral smear showed normocytic, normochromic anemia with toxic granulations and also demonstrated mild anisocytosis, poikilocytosis and reticulocytosis.

The blood and stool cultures were negative. The patient showed positive for coomb's test and negative included ELISA for HIV 1–2 and testing for Legionella, Influenza A and B, Leptospirosis, Ebstein-Barr virus (EBV), Cytomegalovirus (CMV) and Parvovirus.

Table 2: The haematological laboratory data

Parameters	21/10/2013	22/10/13	25/10/2013	26/10/2013	Normal value
HB	9.5	9.56	7.8	7.8	M: 14-17,F: 12.3-15.3(g/dl)
RBC	5.7	2.61	2.29	2.29	M: 4.5-5.9,F: 4.5-5.1(M/ul)
Platelets	162	152	192.3	205	150-450(K/ul)
Neutrophil	72.4	55	63	65	37-80(%)
Lymphocytes	15.1	30.8	42.4	32.2	10-50(%)
Monocytes	-	13.3	13.9	18	0-12(%)
CRP	67.7	-	-	35	<1(mg/dl)

Table 3: The liver function laboratory data

Parameters	21/10/2013	22/10/13	24/10/2013	25/10/2013	26/10/2013	Normal Value
Total serum protein	6.29 ↓	-	-	-	-	6.6-8.7(g/dl)
Albumin	3.51	-	-	-	-	3.5-5.0(g/dl)
Globulin	2.8	-	-	-	-	2.5-4.0(g/dl)
T. Bilirubin	3.39 ↑	-	-	-	-	0.2-1.0(mg/dl)
ALP	343.9↑	-	-	-	-	39-117(IU/L)
ALT	1750 ↑	3093↑	1572↑	1013↑	682↑	M: 5-41,F: 5-31(IU/L)
AST	1948 ↑	3280↑	373 ↑	142 ↑	65 ↑	M: 5-38,F: 5-32(IU/L)

Based on the clinical picture of multisystem involvement, lack of a definite microbiological cause and the progression of disease a diagnosis of DHS with dermatological manifestations was made. The patient was immediately initiated on intravenous hydrocortisone 100mg every 8 hours and intravenous N- Acetylcysteine 600mg in 100 ml normal saline over 1 hour every 8 hours then to oral prednisolone 60mg once daily for one week with dramatic improvement in her symptoms and clinical disease. This improvement is shown in table 3 including improvement in transaminase and inflammatory parameters. This was also supported by stabilization of hypoxemia with less need for oxygen administration.

DISCUSSION

DHS is characterized as a hypersensitivity response to the drug, dapsone which is a sulfone. Dapsone (4,4'-Diaminodiphenyl sulphone) is used mainly as an anti-inflammatory and anti-bacterial agent for the treatment of skin diseases caused by bacteria and fungi. The anti-inflammatory effects of dapsone are mainly related to its interference with neutrophil chemotactic migration and adherence [3]. This describes the suppression of neutrophil recruitment, inhibition of local production of toxic respiratory and secretory products as well as the formation of oxidants. These mechanisms not only kill bacteria but also damage bystander tissues. In addition to this, dapsone can inhibit the release of prostaglandins and leukotrienes by blocking their inflammatory effects. Overall the side effects of dapsone are very low if plasma concentration of the drug is below 5 mg/L.

The classic triad of DHS consists of fever, eruption and internal organ involvement. Fever, hepatitis, exfoliative dermatitis, adenopathy and hemolytic anemia might be seen in varying combinations and sequence. While traditionally hepatitis or transaminitis is seen and cholangitis has also been described as a component of the DHS. Studies have shown that this syndrome may begin as early as 7–10 days after administration of the drug or as late as 6 months into therapy with dapsone. Cutaneous lesions can range from erythematous papules as in this patient, to plaques, pustules, and eczematous lesions. The severity of the cutaneous changes does not correlate with the severity or extent of internal organ involvement which may remain asymptomatic of even life-threatening [4]. Cutaneous lesions usually begin to resolve within 2 weeks after the discontinuation of therapy. Some patients may also develop severe dermatitis and complications such as the Steven Johnson syndrome or toxic epidermal necrolysis (Table1). These patients may experience prolonged morbidity and even mortality with the complications. Especially in severe cases malnutrition, protein loss and secondary infections may complicate the illness and such patients need to be monitored for complications more aggressively. In traditional DHS antibiotics have little or no role unless there is an obvious infection, cellulitis or sepsis. The dermatological manifestations of DHS are;

- Exfoliative dermatitis
- Eczematous/maculopapular eruption
- Oral erosions
- Vesicles and bullae
- Photosensitivity

The patient presented here suffered from DHS with dermatological manifestations. The clinical presentation of the patient along with the dramatic clinical response to glucocorticoids, strongly suggests a drug-induced hypersensitivity with Exfoliative dermatitis. The rapid clinical deterioration seen with DHS can lead to renal failure as seen in this patient and sometimes death if untreated or unrecognized [5].

Treatment options for DHS are listed inTable 4. The main treatment for DHS is immediate discontinuation of the drug with initiation of oral or parenteral glucocorticoids, depending on severity. Glucocorticoids (such as prednisone, prednisolone or methylprednisolone) have profound anti-inflammatory actions, as explained earlier. The usual starting doses are mentioned in Table 4 but are approximations only. Glucocorticoids should be tapered gradually over a period of more than one month because dapsone is found to persist in the body for up to 35 days. It should be remembered that glucocorticoids are medications with multiple side effects including hyperglycemia, hypokalemia, osteoporosis, glaucoma and cataracts. Patients with risk factors for any of these complications need close monitoring. Measurements of blood sugar, bone mineral density, frequent measurements of electrolytes and thorough ophthalmologic evaluations are essential [6].

According to *Reeve et al* patients can be desensitized to dapsone following DHS by a very gradual re-introduction of the drug at low doses, but this hypothesis was not supported by *Pavithran K. et al*. who did not advise re-challenge with dapsone. According to the literature, patients with viral hepatitis (B, E) are at increased risk for

the development of DHS, suggesting the need to perform a screening test for hepatitis B before starting dapsone [7]. Another important issue to remember in the management of patients with DHS is that those patients might be at higher risk for the development of hypothyroidism after three months, suggesting the need to repeat thyroid function tests at three-month intervals and considering thyroid replacement therapy if the patient develops clinical hypothyroidism as a delayed complication. The etiology attributed to the development of hypothyroidism is linked to the presence of autoantibodies, including antimicrosomal antibodies. In fact, patients who are unable to detoxify reactive metabolites produced by thyroid peroxidase will be more in favour of developing a hypersensitivity reaction leading to hypothyroidism [8].

It is important to consider supportive therapies in patients with more severe and protracted illness as listed in table 4. Nutritional support (total parenteral nutrition, nutrition supplementation or enteral feeding), meticulous fluid and electrolyte balance, control and prevention of infectious complications (cellulitis, sepsis) and skin care if necrotizing disease (TENS or Steven Johnson Syndrome were to ensue). For patients with dapsone-induced hemolysis, Vitamin E supplementation might be beneficial while in patients with methemoglobinemia co administration of cimetidine can have an ameliorative effect.

Table 4: Ttreatment approaches to DHS

Interventions	Comments
1. Withdrawal of offending medication (dapsone)	Drug discontinuation
2. Supportive therapy	
• Volume replacement	• Intravenous fluid replacement
• Nutritional support	• Enteral/parenteral nutrition
• Antibiotics	• Early antibiotics in case of concomintant sepsis.
• Skin care	• Preventing skin superinfections
3. Specific therapy	
• Glucocorticosteroids	• Recommended dose 1mg/kg/day

In selected cases where glucocorticoids cannot be used or are associated with severe complications (glaucoma, severe osteoporosis, hyper glycemia or severe psychosis), alternative drug therapies might be required. Unfortunately this being a rare disorder, other therapeutic options such as methotrexate, azathioprine, cyclosporine or hydroxyl chloroquin, have not been vigorously studied. These drugs may provide benefit in the same patient [9].

Severe internal organ involvement such as pericarditis, hepatitis, pneumonitis and colitis can cause death. These can occur at any time and hence vigilance is required in these sick patients. It is to be remembered that in some patients, in spite of drug withdrawal and steroid therapy, a relapsing and chronic course might ensue.

Since genetic factors are involved in the pathogenesis of DHS relatives should be instructed about DHS and their enhanced risk of developing similar adverse reactions.

CONCLUSION

A high index of suspicion is needed for early diagnosis of DHS. Patients initiated on dapsone for various indications need to be observed carefully for the development of the DHS. If and when this occurs DHS can be mistaken for progression of the primary disease. If the drug is not withdrawn it could have deleterious and potentially fatal effects due to major organ dysfunction.

In this patient the association of hypoxemic dermatological disease, hypothyroidism and pure red cell aplasia led to serious problems. The prompt withdrawal of the offending drug, administration of glucocorticoids and supportive management led to rapid recovery in this patient.

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. J Am Acad Dermatol. J Am Acad Dermatol 2001;45:420-34.
2. Leslie KS, Gaffney K, Ross CN, Ridley S, Barker TH, Garioch JJ. A near fatal case of the dapsone hypersensitivity syndrome in a patient with urticarial vasculitis. Clin Exp Dermatol 2003;28:496–8.
3. Itha S, Kumar A, Dhingra S, Choudhuri G. Dapsone induced cholangitis as a part of dapsone syndrome: a case report. BMC Gastroenterol 2003;3:21.
4. Camus P, Bonniaud P, Fanton A, Camus C, Baudaun N, Foucher P. Drug-induced and iatrogenic infiltrative lung disease. Clin Chest Med 2004;25:479–519.
5. Knowles SR, Shapiro LE, Shear NH. Reactive metabolites and adverse drug reactions: clinical considerations. Clin Rev Allergy Immunol 2003;24:229–38.
6. Prussick R, Shear NH. Dapsone hypersensitivity syndrome. J Am Acad Dermatol 1996;35:346–9.
7. Chogle A, Nagral A, Soni A, Agale S, Jamadar Z. Dapsone hypersensitivity syndrome with coexisting acute hepatitis E. Indian J Gastroenterol 2000;19:85–6.
8. Gupta A, Eggo MC, Uetrecht JP, Cribb AE, Daneman D, Rieder MJ, *et al*. Drug-induced hypothyroidism: the thyroid as a target organ in hypersensitivity reactions to anticonvulsants and sulfonamides. Clin Pharmacol Ther 1992;51:56–67.
9. McKenna JK, Leiferman KM. Dermatologic drug reactions. Immunol Allergy Clin North Am 2004;24:399–423.