International Journal of Pharmaceutical research and Applications
Volume 8, Issue 4, Jul.-Aug. 2023, pp: 530-532 www.ijprajournal.com ISSN: 2456-4494

Case Report: Dapsone Induced Liver Injury in Multibacillary Hansen's Disease

Hasila MM[1*], Muhammed Alfas M[1], Ananthu R Krishnan[1], Dr. R.L.N. Murthy[2]
[1]*Pharm D Interns, TVM College of Pharmacy, Ballari, Karnataka*
[2]*HOD, Department of Pharmacy Practice, TVM College of Pharmacy, Ballari, Karnataka*

Date of Submission: 04-07-2023 Date of Acceptance: 16-07-2023

ABSTRACT
Leprosy, also known as Hansen's disease, is a slowly progressive, chronic, granulomatous infectious disease found mainly in humans caused by *Mycobacterium leprae*. Here, we present a case of a 30 years old male patient complaining of giddiness and easy fatiguability since 3 days, nasal obstruction and tinnitus since 2 weeks had been admitted in hospital with a past history of known case of Hansen's Disease (Multibacillary) and was started multibacillary multi-drug therapy (MB-MDT) since 37 days which consisted of a monthly dose of 600 mg rifampicin and 300 mg clofazimine, a daily dose of 100 mg dapsone and 50 mg clofazimine. The patient developed liver injury due to dapsone therapy. Dechallenge of dapsone resulted in an appreciable recovery from liver injury within 2 weeks.

KEYWORDS
Hansen's disease, Dapsone, MB-MDT, Liver Injury, Dechallenge, Hepato-protectant

I. INTRODUCTION

Leprosy, also known as Hansen's disease, is a slowly progressive, chronic, granulomatous infectious disease found mainly in humans. It is primarily caused by an aerobic, slowgrowing, rod-shaped mycobacterial species, *Mycobacterium leprae* or *Hansen's bacillus*. The main causative agent of leprosy was first identified by a Norwegian physician, G.H.A. Hansen, in 1873; hence the terms Hansen's disease and Hansen's bacillus[1].

The Ridley–Jopling classification of leprosy classifies leprosy into five groups, namely; Tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL) and lepromatous (LL)[2]. Tuberculoid leprosy is a localised, minimally contagious, paucibacillary form of Hansen's disease with a less severe disease course. In tuberculoid leprosy, patients exhibit strong cell-mediated and low humoral immune responses. At the opposite end of the disease spectrum, there is lepromatous leprosy that is a systemic, highly contagious, multibacillary form of Hansen's disease with a more severe disease course. Lepromatous leprosy is characterised by a strong humoral and a low to nonexistent cell-mediated immune response. Between these two immunologically stable polar types, there are the unstable borderline forms of Hansen's disease: borderline tuberculoid, borderline borderline and borderline lepromatous.

Hansen's disease primarily affects the cooler, superficial areas of the human body, such as the skin, the peripheral nerves within or close to the skin, and the mucosa of the upper airways. Other parts of the human body like bones may also be involved in leprosy[1].

A number of adverse reactions to sulfonamides has been reported during the thirty years that have elapsed since the introduction of these drugs. Dapsone is a sulfonamide related drug used for the therapy of leprosy. Dapsone (dap' sone) is 4,4' diaminodiphenylsulfone and is bacteriostatic for *Mycobacterium leprae*. Like other sulfonamides, dapsone is believed to act by inhibition of folate synthesis. Bacteria including M. leprae are acutely sensitive to this inhibition as folate is necessary for protein, DNA and RNA synthesis. Dapsone is usually started at a low dose in the range of 50 mg daily and titrated upward to a total daily dose of 100 to 300 mg. In the therapy of leprosy, the combination of dapsone with clofazimine and rifampin is recommended for 6 or 12 months followed by monotherapy with dapsone until all clinical signs are controlled and biopsies are negative for at least a year. Common side effects of oral dapsone include hemolysis and anemia, nausea, abdominal pain, tinnitus, vertigo, blurred vision, headache, insomnia, and rash. Dapsone is also associated with more severe side effects including peripheral neuropathy, acute

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psychosis, nephrotic syndrome, acute liver injury, hemolysis, agranulocytosis, aplastic anemia, hypersensitivity reactions and a lupus-like syndrome.

Dapsone, like other sulfonamides, causes a characteristic idiosyncratic liver injury that has features of drug allergy or hypersensitivity. The pattern of injury is typically cholestatic or mixed and can be complicated and prolonged. In rare instances, dapsone induced liver injury has resulted in acute liver failure. However, most cases resolve rapidly, usually within 2 to 4 weeks of stopping dapsone, unless cholestasis is severe[3].

The multidrug therapy combination of clofazimine, rifampin and dapsone, however, is associated with instances of jaundice and hepatitis, which are most likely attributable to dapsone ("dapsone syndrome") and marked by fever, rash, eosinophilia and hepatic involvement (DRESS syndrome) typically arising within 8 weeks of starting the drug regimen. Dapsone induced liver injury can be severe and the mortality rate in cases with jaundice is as high as 25% to 33%. The liver injury usually resolves with stopping therapy and most patients have later tolerated restarting of clofazimine and rifampin[4].

II. CASE REPORT

A 30 years old male patient complaining of giddiness and easy fatiguability since 3 days, nasal obstruction and tinnitus since 2 weeks had been admitted in hospital with a past history of known case of Hansen's Disease (Multibacillary) since 37 days and was started multibacillary multi-drug therapy (MB-MDT) which consist of a monthly dose of 600 mg rifampicin and 300 mg clofazimine, a daily dose of 100 mg dapsone and 50 mg clofazimine. Routine investigations were done at the time of admission and repeated after 2 weeks (Table 1).

PARAMETERS	DAY 1	DAY 14
AST	50 U/L	48 U/L
ALT	64 U/L	45 U/L
ALP	287 U/L	129 U/L
Total Bilirubin	4.7 mg/dl	2.1 mg/dl
Direct Bilirubin	2.6 mg/dl	0.7 mg/dl
Indirect Bilirubin	2.1 mg/dl	1.4 mg/dl

Table 1: Monitoring of leprosy patient at the time of admission and after 2 weeks

The patient was an ex-alcoholic who stopped drinking 2 years back. The patient haven't took any OTC medications since 2 months. The ALP was 287 U/L and total bilirubin level was 4.7 mg/dl at the time of admission. On examination the patient was having mild icterus condition. USG Abdomen reported by radiologist was acute hepatitis.

Advised the patient to hold on dapsone intake until a further suggestion. Symptomatic treatment was given for the patient for the present complaints and also for the liver injury. The treatment provided for the patient during hospital admission were Tab.Ursodeoxycholic acid, Tab.Acetylcysteine, Tab.Betahistine, Tab.B Complex and Tab.Vitamin C.

The patient got discharged after 3 days and was advised to review with the LFT reports after 10 days. On 14th day, ALP was 129 U/L and total bilirubin was 2.1 mg/dl.

III. DISCUSSION

Leprosy is a bacterial infection causing disfigurement of the affected individual. Leprosy is endemically ubiquitous in tropical countries, particularly in underdeveloped and developing countries across the globe. Around 80% of the reported global new cases come from India, Brazil, and Indonesia[3].

Dapsone is used as a primary drug for leprosy. Dapsone is usually started at a low dose in the range of 50 mg daily and titrated upward to a total daily dose of 100 to 300 mg[3]. Here the patient was receiving 100 mg of dapsone daily as a part of MB-MDT since 37 days. The patient haven't exposed to any other hepatotoxic drugs like painkillers since 2 months.

Dapsone induced liver injury can result in acute liver failure within 8 weeks of its therapy but most cases resolve rapidly with discontinuation of drug and full recovery is expected within 2 to 8 weeks. The liver injury usually resolves with stopping therapy and most patients have later tolerated restarting of clofazimine and

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rifampin[4].Here the LFT of 37th day of MB-MDT was elevated (Table 1). As the result, dechallenge of dapsone was recommended and patient was provided with symptomatic treatment including hepatoprotectant. Patient was also advised to perform LFT after 2 weeks to analyse the progress of the dechallenge and patient showed remarkable improvement.

Apart from dechallenge, prednisone can also be used to treat dapsone related liver injury with variable success, but may be particularly helpful in patients with prominent allergic features with systemic features and fever, rash and eosinophilia[3]

IV. CONCLUSION

Leprosy is a slowly progressive, chronic, granulomatous infectious disease and dapsone is a drug of paramount importance in the treatment regimen of Leprosy. Liver injury is one of the major adverse effect of dapsone which usually occurs within 8 weeks of initiation of the therapy. Dechallenge of dapsone is one of the important step that can be taken to overcome the hepatic adverse effect of dapsone where the studies have shown restoration of liver function within 2 to 8 weeks. Apart from this, hepato-protectant like ursodeoxycholic acid was also recommended for the patient. In this present case study we could able to detect and diagnose liver injury at earlier stages. So, we implemented dechallenge and prescribed hepato-protectant for the patient. Hence the patient showed partially improved LFT values within 2 weeks of dechallenge.

So, we would like to emphasize that the patients should be regularly monitored for manifestation of clinical signs and symptoms of liver damage and if necessary, LFT should be performed especially, within 8 weeks of initiation of dapsone therapy.

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