

# ***INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES***

**Pharmaceutical Sciences**

**Review Article.....!!!**

Received: 10-03-2020; Revised: 04-04-2020; Accepted: 06-04-2020

## **MULTIPLE DRUG THERAPY TREATMENT OF LEPROSY: A REVIEW ARTICLE**

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### **Keywords:**

Leprosy, Diagnosis,  
Treatment, Side effect

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### **ABSTRACT**

The WHO MDT leprosy treatment was officially introduced in Brazil in 1991 and comprises three drugs dapson, rifampicin and clofazimine. There are few good studies on the Frequency of Side effects attributable to MDT. Side effect of leprosy treatment with dapson are said to be uncommon with drug allergy occurring on only one of every several hundred patients treated with dapson.

## **INTRODUCTION**

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*, which can lead to cutaneous and neurological manifestation. Multidrug therapy (MDT) is used for the treatment of leprosy patients. According to the World Health Organization, dapsone is administered at a dose of 100 mg/day for 12 months in multibacillary and for 6 months in paucibacillary forms of leprosy.

Dapsone is considered to be one of the safest drugs for treating leprosy patients. The adverse drug reaction (ADR) resulting from intake of dapsone in MDT-treated patients. The most common reaction are allergies, such as itchy rash and blisters, exfoliative dermatitis, hemolytic anemia, jaundice, methemoglobinemia and dapsone syndrome. Among these, clinically severe (emerging) adverse reaction of dapsone in MDT are dapsone hypersensitivity syndrome (DHS), hemolytic anemia, methemoglobinemia and peripheral neuropathy with motor deficits.

Agranulocytosis is a rare ADR of dapsone it has been reported that agranulocytosis occurs in 0.23-0.42% of dermatitis herpetiformis patients treated with dapsone the other rare effects of dapsone are bone marrow suppression and peripheral pancytopenia.

It is evident from the literature that there are emerging side effects, such as agranulocytosis, bone marrow suppression, renal failure, etc, in leprosy patients due to the presence of dapsone in the MDT regimen. Therefore, we conducted this study to explore the side effect of dapsone in leprosy patients admitted to a rehabilitation centre of western Nepal. The objective is to find the side effects (common or rare) and occurrence of dapsone adverse reaction in leprosy patients. Thus, retrospectively, we planned to perfect the study on patients treated with MDT.

### **History**

The history of leprosy was traced by geneticists in 2005 through its origins and worldwide distribution comparative genomics. They determine that leprosy originated in East Africa or the near East and traveled with humans along their migration routes, including those of trade in goods and slaves. The four strains of *M. leprae* are based in specific geographic regions. Strain 1 occurs predominantly in East Africa, Asia and the Pacific region; strain 2 in Ethiopia, Malawi, Nepal/ North India; strain 3 in Europe, North Africa and Americas; and strain 4 in West Africa and the Caribbean.

In 1873 G. H. Armauer Hansen in Norway discover the causative agent of leprosy, *mycobacteriumleprae* .This was the first bacterium to be identified as causing disease in humans.Fromthe 19<sup>th</sup> century, European nations adopted some practices of India and China, administering naturally occurring oils. They given by injection and orally and were believed to cure some people, but results were often disputed. It was not until the 1940s that the first effective treatment, promine, become available. the search additional anti-leprosy drugs led to the use of clofazimine and rifampicin in 1960s and 1970s. Later, Indian scientist Shantaram yawalkar and his colleagues formulated a combined therapy using rifampicin and dapsone intended to mitigate bacterial resistance. Multidrug therapy (MDT) combining all three drugs was first recommended by the World Health Organization (WHO) of the United Nations in 1981. These three anti-leprosy drugs are still used in the standard MDT regimens.

India is considered the point of origin of leprosy with skeletal evidence of the disease dating to 2000 B.C. The disease is thought to have spread through trade and war to other parts of Asia, the Middle East, North Africa, and later Europe and the Americas. In ancient Indian society, individual suffering from leprosy were alienated because the disease was chronic contagious, resulted in disfigurement, had no cure at the time, and was associated with sin. In colonial India, the government enacted the leprosy the leprosy act of 1898, which institutionalized leprosy victims and separated them based on gender to prevent reproduction. These mainly affected the poor because those who were self-sufficient were not obligated to be isolated or seek medical treatment.

In 1991, India contained 75% of the world's leprosy cases. Leprosy treatment was handled by the National Leprosy Elimination Program, Which was completely separated from other healthcare services. In 2005, this was incorporated into the broader healthcare system, and shortly afterward, India announced that it had eliminated leprosy as a public health problem. However, this only means that there is less than 1 person in 10,000 infected with the disease. There is a lower percentage of affected individuals, but this number is still enormous in absolute terms, and India still makes up 58.8% Of the world's leprosy cases. Since this announcement, funding for leprosy prevention and education programs has been drastically reduced. The prevalence and rate of infection have remain steady from 2005 to 2015, and there are still significant delay in treatment, both from the patients and the healthcare system itself, due to a lack of knowledge about disease.

Current programs include house-to-house examination designed to identify hidden cases of leprosy.

### **3. Symptoms of leprosy**

The symptoms of leprosy can present differently in different people with the condition.

The main symptoms included:

- The appearance of skin lesions that are lighter than normal skin and remain for weeks or months
  - Patches of skin with decrease sensation, such as touch, pain, and heat
1. Muscle weakness
  2. Numbness in the hands, feet, legs, and arms, known as glove and stocking anesthesia
  3. Eye problem
  4. Enlarged nerves, especially in the elbows or knees
  5. Stuffy nose and nosebleeds
  6. Curling of the fingers and thumb, caused by paralysis of small muscles in the hand
  7. Ulcers on the soles of the feet.

Injuries, breaks, and burns can go unnoticed, due to the numbing of sensation caused by nerve damage, potentially becoming infected or more seriously injured. Over time, the extremities can be lost to repeated damage.

The wounds are also more likely to become infected, as immune defenses are weakened by leprosy. The reabsorption of cartilage by the body means that these secondary infections can result in tissue loss. This leads to the characteristic shortening of the toes and fingers seen in leprosy.

Damage to the mucous membrane that coats the inside of the nose can sometimes lead to internal damage and scarring. The nose might eventually collapse.

Leprosy can destroy the nerve responsible for blinking. This can lead to the eyes becoming dried out and prone to infections, potentially resulting in ulceration and blindness.

### **The stigma of leprosy**

Leprosy is not particularly contagious, and once treatment has been underway for 2 to 4 weeks, the individual is no longer contagious at all. Despite this fact, so-called “leper colonies” still operate in India, China, and some African countries.

There is no medical reason for leprosy patients to be removed from society.

In these countries, the significant social stigma around leprosy marks life with the condition isolated and difficult.

Although organization such as WHO are working tirelessly to reduce and eventually eradicate leprosy, the issue of stigma for sufferers of leprosy is proving harder to remove.

Individual bearing the scare of leprosy can earn significantly less money, chances of marriage can be significantly reduced, mothers with the disease may stop breastfeeding their babies, and affected children can be shunned from their homes and villages permanently.

The emotional stress and anxiety of leprosy can cause mental health problem, leading to further isolation and sometimes the cessation of treatment. Unemployment is common, and begging is often the only option left, adding to worthlessness.

Because of the fear of this stigma, people who have contracted leprosy sometimes hide their symptoms and do not seek help or treatment. This allows the condition to worsen and increases the risk of complications. It also increases the chances of transmission to others in the community.

#### **4. Classification of leprosy**

There are multiple forms of leprosy described in the literature. The forms of leprosy depends on the person's immune response to *M. leprae*. A good immune response can produce the so-called tuberculoid forms of the disease, with limited skin lesions and some asymmetric nerve involvement. A poor immune response result in the lepromatous form, characterized by extensive skin and asymmetric nerve involvement. Some patients may have aspects of both forms. Currently, a few two classification systems exist in the medical literature: the WHO system and the ridley-jopling system. The Ridley-Jopling system is composed of six forms or classification, listed below according to increasing severity of symptoms:

- Indeterminate leprosy: a few hypopigmented macules; can heal spontaneously, this form persists or advances to other forms
- Tuberculoid leprosy: a few hypopigmented macules, some are large and some become anesthetic (loss of pain IQ sensation); some neural involvement in which nerves become enlarged; spontaneous resolution in a few years; persist or advances to other forms; cell-mediated immune response appears in this classification but is almost absent in lepromatous leprosy



**Figure 1: Tuberculoid leprosy**

- Borderline tuberculoid leprosy: lesions like tuberculoid leprosy but smaller and more numerous with less nerve enlargement. This form may persist, revert to tuberculoid leprosy, or advance to other forms.



**Figure 2: Lepromatous leprosy**

- Mid-borderline leprosy: many reddish plaques that are asymmetrically distributed, moderately anesthetic, with regional adenopathy (swollen lymph nodes). The form may persist, regress to another form, or progress

- Borderline lepromatous leprosy: many skin lesions with macules (flat lesions) papules (raised bumps) , plaque, and nodules, sometimes with or without anesthesia; the form may persist, regress or progress to lepromatous leprosy
- Lepromatous leprosy: Early lesions are pale macules ( flat areas) that are diffuse and symmetric. Later medical professional can find many *M. leprae* organisms in the lesions. Alopecia (hair loss) occurs. Often patients have no eyebrows or eyelashes. As the disease progresses, nerve involvement leads to anesthetic areas to aseptic necrosis (tissue death from lack of blood to areas, including the face). The lepromatous form does not regress to the other less severe forms. Histoid leprosy is a clinical variant of lepromatous leprosy that presents with clusters of histiocytes (a type of cell involved in the inflammatory response) and a grenz zone (an area of collagen separating the lesion from normal tissue seen in microscopic tissue sections).

Globally, health care professionals use the Ridley Jopling classification in evaluating patients in clinical studies. However, the WHO classification system is more widely used. It has only two forms or classifications of leprosy. The 2009 WHO classifications depend on the number of skin lesions as follows:

- Paucibacillary leprosy: skin lesions with no bacilli (*M. leprae*) seen in a skin smear



**Figure 3: Paucibacillary leprosy**

- Multibacillary leprosy: skin lesions with bacilli (*M. leprae*) seen in a skin smear
- However, the WHO further modifies these two classifications with clinical criteria because “of the non-availability or non-dependability of the skin-smear services. The purpose of treatment includes the use of skin lesions and nerves involvement as the basis for grouping leprosy patients into multibacillary (MB) and paucibacillary

(PB) leprosy”. Investigators state that up to about four to five skin lesions constitutes paucibacillary leprosy, while about five or more constitutes multibacillary leprosy



**Figure 4:Multibacillary leprosy**

Multidrug therapy (MDT) with three antibiotics (dapson, rifampicin, and clofazimine) treat multibacillary leprosy, while a modified MDT with two antibiotics (dapson and rifampicin) is recommended for paucibacillary leprosy and composes most current treatments today (see treatment section below) Paucibacillary leprosy usually includes indeterminate, tuberculoid, and borderline tuberculoid leprosy from the Ridley-Jopling classification, while multibacillary leprosy usually includes the double (mid-) borderline, borderline lepromatous, and lepromatous leprosy

#### **How does disease spread?**

Untreated leprosy-affected person is the only known source for transmission of bacteria.

- Respiratory tract, especially nose, is the major route of exist of the organism from the body of infectious persons.
- Disease causing organisms enters the body commonly through respiratory system by droplets from the nose and mouth during close and frequent contact with untreated causes.
- After entering the body, the organism migrates towards the nerves and skin.
- If it is not diagnosed and treated in early stages, it may cause further damage to nerves leading to development of permanent disability.

#### **Modern treatment on leprosy (Multidrug therapy)**



Multidrug therapy (MDT) combining all three drugs was first recommended by a WHO Expert committee in 1981. These three anti-leprosy drugs are still used in the standard MDT regimens. None of them is used alone because of developing resistance.

As this treatment was quite expensive, it was not quickly adopted in most countries where the disease is endemic. In 1985, leprosy was still considered a public health problem in 122 countries. The 44<sup>th</sup> World Health Assembly (WHA), held in Geneva in 1991, passed a resolution to eliminate leprosy as a public-health problem by the year 2000- defined as reducing the global prevalence of the disease to less than 1 case per 10,000. At the assembly, the world Health Organization (WHO) was given the mandate to develop an elimination strategy by its member states. This was based on increasing the geographical coverage of MDT and patients accessibility to the treatment.

MDT is a combination of different drugs as leprosy should never be treated with any single anti leprosy drug.

- One should complete the full course of MDT as prescribed by a trained health workers according to the type of leprosy.
- MDT is available free of charge at most health facilities including in remote areas.

#### **Basic principles in using multidrug therapy**

In developing WHO MDT regimens, three main principles were adhered to: rifampicin 600 mg should be given at least once a month to all patients at least two anti-leprosy drugs should be used in the MB regimen and one anti-leprosy drug should be used in PB regimen, in addition to rifampicin, in order to prevent the occurrence of rifampicin resistance *M. leprae*.

#### **Combination of multidrug therapy in treatment of multibacillary (MB) and paucibacillary (PB) in leprosy**

The recommended standard regimen for multibacillary (MB) leprosy is: Rifampicin: 600 mg once a month Dapsone: 100 mg daily clofazimine: 300 mg once a month, and 50 mg daily Duration: 12 months. The recommended standard regimen for paucibacillary (PB) leprosy is: rifampicin: 600 mg once a month Dapsone: 100 mg daily Duration: 6 months. Children should receive appropriately reduced doses of the above drugs.

#### **Fixed duration treatment for MB and PB patients**

Fixed duration treatment for MB patients means that after taking 12 monthly doses of MDT this person is cured and should be removed from the register. Similarly, for

PB patients, after taking 6 monthly doses of MDT this person is cured and should be discharged.

### **Sever and common ADRs on MDT therapy**

The ADRs to dapsone were normally seen after intake of dapsone. The severe ADRs to dapson included DHS and hemolytic anemia. The other ADRs to dapsione were agranulocytosis and toxic epidermal necrolysis (TEN).

### **Side effects present after treatment with multidrug therapy**

- Jaundice (along with other symptoms)
- Exfoliative dermatitis (mainly in face and all over the body), along with other symptoms
- Hemolytic anemia (along with the above symptoms)
- Fever and headache
- Blisters over the body
- Skin rashes
- Agranulocytosis only (no other symptoms)
- Toxic epidermal necrolysis

### **Rare side effects**

For the patient who developed agranulocytosis after MDT, only dapsone was stopped. Both rifampicin and clofazimine were continued as usual. TEN was treated with azathioprine and with supportive care (such as administration of antibiotics) and intravenous fluids (such as normal saline).

### **Management for exfoliative dermatitis**

Cetirizine was given as an antiallergic drug. Cetirizine was generally given for 1-2 weeks. Coconut oil massage over the exfoliative region of the body was done. By observing the severity of the disease in some patients, hydrocortisone was given intravenously for about 4 days. Prednisolone was given in all cases because it has a role in the reduction of the symptoms of both leprae reaction and exfoliative dermatitis.

### **Management of jaundice**

Jaundice was treated symptomatically with vitamin B complex, lactulose, Hepa-Merz (detoxicant –hepatoprotector) and Liv-52 tablet for 4-10 weeks. Liv-52 is an ayurvedic medicine and a hepatoprotective herbal- mineral remedy to improve liver function. These drugs were given until the symptoms of jaundice subsided.

### **Management of anemia**

Iron tablets and multivitamins were given for 4-10 weeks to patients until the symptoms of anemia subsided. In severe anemic patients, based on the blood hemoglobin concentration, Whole blood transfusion was done. Two patients were transfused with two pints of whole blood due to low hemoglobin level (6.4%) in their blood. One of them expired due to severe anemia even after blood transfusion.

### **CONCLUSION:**

The common dapsone ADRs present in leprosy patient were jaundice, exfoliative dermatitis and hemolytic anemia in MDT-treated patients. Patients could be cured by managing the dapsone ADRs effectively on time. Some patients may die of dapsone ADRs if clinicians fail to manage the side effect on time.

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