

Antileprotic Drugs: An Overview

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ABSTRACT

Leprosy is a chronic disease caused by the bacteria *Mycobacterium leprae* that causes damage to the skin and the peripheral nervous system. The disease develops slowly (from six months to 40 years!) and results in skin lesions and deformities, most often affecting the cooler places on the body (for example, eyes, nose, earlobes, hands, feet, and testicles). Worldwide, two to three million people are estimated to be permanently disabled because of leprosy. India has the greatest number of cases, with Brazil second and Burma third. In 1999, the world incidence of Hansen's disease was estimated to be 640,000. In 2000, 738,284 cases were identified. In 2000, the World Health Organization (WHO) listed 91 countries in which Hansen's disease is endemic. India, Burma, and Nepal contained 70% of cases. India reports over 50% of the world's leprosy cases. In 2002, 763,917 new cases were detected worldwide, and in that year the WHO listed Brazil, Madagascar, Mozambique, Tanzania, and Nepal as having 90% of Hansen's disease cases. So there is need to treat this disease. Current recommendations for the treatment of leprosy suggest multidrug regimens rather than monotherapy because such a regimen has proven to be more effective, delays the emergence of resistance, prevents relapse, and shortens the duration of therapy. Established agents used in the treatment of leprosy are dapsone, clofazimine, and rifampin.

Keywords: Leprosy, *Mycobacterium leprae*, Antileprotic Drugs.

INTRODUCTION

Leprae, a rod-shaped bacillus that is an obligate intracellular (only grows inside of certain human and animal cells) bacterium. *M. leprae* is termed an "acid fast" bacterium because of its chemical characteristics. Leprosy, a chronic infectious disease caused by *Mycobacterium leprae*,¹ was identified by G. H. A. Hansen in 1873. The different clinical presentations of the disease are determined by the quality of the host immune response. When special stains are used for microscopic analysis, it stains red on a blue background due to mycolic acid content in its cell walls. The Ziel-Nielsen stain is an example of the special staining techniques used to view the acid-fast organisms under the microscope. Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. Host defenses are crucial in determining the patient's response to the disease, the clinical presentation, and the bacillary load. These factors also influence the length of therapy and the risk of adverse reactions to medication. *M. leprae* cannot

be grown on routine laboratory culture media, so drug sensitivity testing in vitro is not possible. Growth and drug susceptibility testing are done by injecting into animal models. One description of a clinical picture that results from tuberculoid leprosy is characterized by intact cell-mediated immunity, a positive lepromin skin reaction, granuloma formation, and a relative paucity of bacilli. At the other extreme, lepromatous leprosy is characterized by depressed cell-mediated immunity, numerous bacilli within the tissues, no granulomas, and a negative skin test for lepromin. Within these two extremes are the patients with an intermediate or borderline form of leprosy who show a variable lepromin reaction and few bacilli; they may progress to either tuberculoid or lepromatous leprosy.

Classification of leprosy

Multibacillary or paucibacillary leprosy

- Paucibacillary (PB) leprosy, negative smears at all sites, single or only

a few hypopigmented and hypoaesthetic skin lesions.

- Multibacillary (MB) leprosy - either positive smears at any site, or multiple (>5) hypopigmented, hypoaesthetic or erythematous skin lesions

Tuberculoid or lepromatous leprosy

After exposure to leprosy and the incubation period, leprosy may fluctuate between various stages depending on the individual's cell-mediated immune response or in response to therapy. Transition toward the tuberculoid leprosy (TT) end of the spectrum is referred to as upgrading (and may lead to a reversal or type I reaction) and transition toward the lepromatous leprosy (LL) pole as downgrading

1. Indeterminate stage - single skin lesion, frequently heals spontaneously
2. Tuberculoid leprosy (TT) - few skin lesion
3. Borderline tuberculoid leprosy (BT)
4. Borderline leprosy (BB)
5. Borderline lepromatous leprosy (BL)
6. Lepromatous leprosy (LL) - most severe stage, diffuse skin lesions and high bacterial load.

The good news is that leprosy is curable. In 1981, the WHO recommended the use of a combination of three antibiotics usually dapsone, rifampin, and clofazimine for treatment, which takes six months to a year or more. Certain cases may be treated with two antibiotics, but rifampin is a key component of either regimen. Since 1995, the WHO has provided these drugs free of charge to all leprosy patients worldwide. During the course of treatment, the body may react to the dead bacteria with pain and swelling in the skin and nerves. This is treated with pain medication, prednisone or thalidomide (under special conditions).^{2,3,4}

The majority of cases (mainly clinically diagnosed) are treated with antibiotics. The recommended antibiotics, their dosages and length of time of administration are based on the form or classification of the disease and whether or not the patient is supervised by a medical professional. In general, paucibacillary leprosy is treated with two

antibiotics, dapsone and rifampicin, while multibacillary leprosy is treated with the same two plus a third antibiotic, clofazimine. Usually, the antibiotics are given for at least six to 12 months or more. Each patient, depending on the above criteria, has a schedule for their individual treatment, so treatment schedules should be planned by a clinician knowledgeable about that patient's initial diagnostic classification. Antibiotics can treat paucibacillary leprosy with little or no residual effects on the patient. Multibacillary leprosy can be kept from advancing, and living *M. leprae* can be essentially eliminated from the person by antibiotics, but the damage done before antibiotics are administered is usually not reversible. Recently, the WHO suggested that single-dose treatment of patients with only one skin lesion with rifampicin, minocycline (Minocin), or ofloxacin (Floxin) is effective. Studies of other antibiotics are ongoing. The role for surgery in the treatment of leprosy occurs after medical treatment (antibiotics) has been completed with negative skin smears (no detectable acid-fast bacilli) and is often only needed in advanced cases. Surgery is individualized for each patient with the goal to attempt cosmetic improvements and, if possible, to restore limb function and some neural functions that were lost to the disease. Prevention of contact with droplets from nasal and other secretions from patients with untreated *M. leprae* infection currently is a way to avoid the disease. Treatment of patients with appropriate antibiotics stops the person from spreading the disease. People that live with individuals that have untreated leprosy are about eight times as likely to develop the disease, because investigators speculate that family members have close proximity to infectious droplets. Leprosy is not hereditary. While globally in 2008, 2.5 lakh new cases of leprosy were recorded, India accounted for 1.37 lakh of those cases followed by 38,914 cases in Brazil and 17,441 in Indonesia.⁵

Antileprotic drugs

A SULFONE is a chemical compound containing a sulfonyl functional group

attached to two carbon atoms. The central hexavalent sulfur atom is double bonded to each of two oxygen atoms and has a single bond to each of two carbon atoms, usually in two separate hydrocarbon substituents.

DAPSONE (diamino-diphenyl sulfone) is a medication most commonly used in combination with rifampicin and clofazimine as multidrug therapy (MDT) for the treatment of *Mycobacterium leprae* infections (leprosy). It is also second-line treatment for prophylaxis (prevention) against *Pneumocystis pneumonia* (PCP) caused by *Pneumocystis jirovecii* (formerly *P. carinii*) in HIV patients in whom CD4 counts are below 200/mm³.

Dapsone is an odorless white to creamy-white crystalline powder with a slightly bitter taste, used in combination with pyrimethamine in the treatment of malaria. Dapsone is commercially available as a gel 5% topical acne medication and is used as an acne treatment for mild to moderate acne in teens and adults. To treat acne, Dapsone is marketed as Aczone by Allergan. Oral Dapsone may also be prescribed for acne conglobata and acne fulminans, if conventional treatments for extremely severe acne, such as isotretinoin and prednisone, fail to work.

Mechanism

As an antibacterial, dapsone inhibits bacterial synthesis of dihydrofolic acid, via competition with para-aminobenzoate for the active site of dihydropteroate synthetase. Though structurally distinct from dapsone, the sulfonamide group of antibacterial drugs also work in this way.

When used for the treatment of skin conditions in which bacteria do not have a role, the mechanism or action of dapsone is not well understood.

Dapsone has anti-inflammatory and immunomodulatory effects. Dapsone blocks myeloperoxidase, which has been suggested to be its mechanism of action in treating dermatitis herpetiformis. Myeloperoxidase converts hydrogen peroxide (H₂O₂) into hypochlorous acid (HOCl) as part of the respiratory burst in neutrophils to kill bacteria. HOCl is the

most toxic and potent oxidant generated by neutrophils, which have potential to cause significant tissue damage in many inflammatory diseases. The respiratory burst uses large quantities of oxygen, and a single neutrophil may produce enough HOCl in one second to destroy 150 bacteria. In the absence of chloride ions or when there is excess hydrogen peroxide, the myeloperoxidase is converted to its inactive form. Dapsone reversibly inhibits myeloperoxidase activity by promoting the formation of an inactive intermediate of the enzyme, thus preventing the conversion of hydrogen peroxide to hypochlorous acid, an extremely potent neutrophil oxidant. Myeloperoxidase inhibition has also been suggested as a mechanism for a neuron-sparing effect in inflammatory neurodegenerative diseases such as Alzheimer disease and stroke. Although dapsone is not a steroid, and it is anti-inflammatory, it does not fit the usual definition of an NSAID, since it does not block cyclo-oxygenase as most NSAIDs do as their primary mechanism.

Administration

Dapsone is administered orally as a 100 mg tablet or alternatively as 25 mg tablets.

To deal with dapsone-resistant leprosy cases, multidrug therapy was introduced by WHO in 1981; dapsone is administered along with rifampin and clofazimine or other antileprotic drugs.

Dapsone is administered transdermally (via the skin) as a gel 5% topical acne medication and available in 3-, 30-, and 60-gram tubes. In normal use, 0.5 grams should be administered to the face per application twice a day.

Adverse effects

Effects on the blood

The most prominent side-effects of this drug are dose-related hemolysis (which may lead to hemolytic anemia) and methemoglobinemia. About 20% of patients treated with dapsone suffer hemolysis and the side-effect is more common and severe in those with glucose-6-phosphate dehydrogenase deficiency, leading to the dapsone-containing antimalarial combination

Lapdap being withdrawn from clinical use. Agranulocytosis occurs rarely when dapsone is used alone but more frequently in combination regimens for malaria prophylaxis. Abnormalities in white blood cell formation, including aplastic anemia, are rare but the cause of the majority of deaths due to dapsone therapy.

Effects on the liver

Toxic hepatitis and cholestatic jaundice have been reported by the manufacturer. Jaundice may also occur as part of the **dapsone reaction** or **dapsone syndrome** (see below). Dapsone is also known to inhibit the Cytochrome P450 system.

Other adverse effects

Other adverse effects include nausea, headache, and rash, which are common, and insomnia, psychosis, and peripheral neuropathy. Effects on the lung occur rarely and may be serious though are generally reversible.

Dapsone reaction

Hypersensitivity reactions occur in some patients. This reaction may be more frequent in patients receiving multiple-drug therapy.

The reaction always involves a rash and may also include fever, jaundice, and eosinophilia. In general, these symptoms will occur within the first six weeks of therapy or not at all, and may be ameliorated by corticosteroid therapy.

Specific considerations

Certain patients are at higher risks of adverse effects when using dapsone. Some specific issues that should be considered are:

- Related to the blood (a full blood count should be obtained prior to initiating therapy):
 - Porphyria
 - Anemia
 - Cardiac disease
 - Pulmonary disease
 - HIV infection
 - G6PD deficiency
- Related to the liver (obtain liver function tests before starting therapy):

- Liver impairment
- Related to allergy:
 - Sulfonamide allergy is associated with dapsone allergy.⁶

PHENAZINE (C₁₂H₈N₂ or C₆H₄N₂C₆H₄), also called **azophenylene**, **dibenzo-p-diazine**, **dibenzopyrazine**, and **acridizine**, is a dibenzo annulated pyrazine and the parent substance of many dyestuffs, such as the eurhodines, toluylene red, indulines and safranines.

CLOFAZIMINE is a fat-soluble riminophenazine dye used in combination with rifampicin and dapsone as multidrug therapy (MDT) for the treatment of leprosy. It has been used investigationally in combination with other antimycobacterial drugs to treat Mycobacterium avium infections in AIDS patients and Mycobacterium avium paratuberculosis infection in Crohn's disease patients. Clofazimine also has a marked anti-inflammatory effect and is given to control the leprosy reaction, erythema nodosum leprosum (ENL). Drug is given as an alternative to patients who can not tolerate the effects of dapsone for tuberculosis.

Mechanism

Clofazimine works by binding to the guanine bases of bacterial DNA, thereby blocking the template function of the DNA and inhibiting bacterial proliferation. It also increases activity of bacterial phospholipase A₂, leading to release and accumulation of lysophospholipids, which are toxic and inhibit bacterial proliferation

Supply

Clofazimine is marketed under the trade name Lamprene by Novartis. One of the only suppliers of clofazimine's active pharmaceutical ingredient in the world is Sangrose Laboratories, located at Mavelikara in the southern Indian state of Kerala.

Metabolism

Clofazimine has a very long half life of about 70 days. Autopsies performed on clofazimine patients have found crystallized clofazimine in the intestinal mucosa, liver, spleen, and lymph nodes.

Side effects

Eosinophilic enteritis, GI irritation, and discoloration of the skin upon exposure to the sun are the major reported side effects.

Clofazimine produces pink to brownish skin pigmentation in 75-100% of patients within a few weeks, as well as similar discoloration of most bodily fluids and secretions. These discolorations are reversible but may take months to years to disappear. The prescribing information indicates that several patients have developed depression as a result of this chronic skin discoloration, resulting in two suicides.

Cases of ichthyosis and skin dryness are also reported in response to this drug (8%-28%), as well as rash and pruritis (1-5%).

40-50% of patients develop gastrointestinal intolerance. Rarely, patients have died from bowel obstructions and intestinal bleeding, or required abdominal surgery to correct the same.

Immunosuppressive effects

The immunosuppressive effects of clofazimine were immediately noticed when applied in animal model. Macrophages were first reported to be inhibited due to the stabilization of lysosomal membrane by clofazimine. Clofazimine also showed a dosage-dependent inhibition of neutrophil motility, lymphocyte transformation, mitogen-induced PBMC proliferation and complement-mediated solubilization of pre-formed immune complexes in vitro. A mechanistic studying of clofazimine in human T cells revealed that this drug is a Kv1.3 (KCNA3) channel blocker. This indicates that clofazimine will be potentially used for treatment of multiple sclerosis, rheumatoid arthritis and type 1 diabetes. Because the Kv1.3-high effect or memory T cells (T_{EM}) are actively involved in the development of these diseases, and Kv1.3 activity is essential for stimulation and proliferation of T_{EM} by regulating calcium influx in the T cells.

Several clinical trials were also conducted looking for its immunosuppressive activity even before it was approved for leprosy by

FDA. It was first reported to be effective in treating chronic discoid lupus erythematosus with 17 out of 26 patients got remission. But later another group found it was ineffective in treating diffuse, photosensitive, systemic lupus erythematosus. Clofazimine also has been sporadically reported with some success in other autoimmune diseases such as psoriasis, Miescher's granulomatous cheilitis, Crohn's disease and ulcerative colitis. A recent clinical study of clofazimine was done in post-bone marrow transplantation patients with over 50% of them having skin involvement, flexion contractures or oral manifestations achieved complete or partial responses. 7 out of 22 patients were able to reduce other immunosuppressants such as cyclosporine A.⁷

RIFAMPICIN (INN) (or **rifampin** (USAN)) is a bactericidal antibiotic drug of the rifamycin group. It is a semisynthetic compound derived from *Amycolatopsis rifamycinica* (formerly known as *Amycolatopsis mediterranei* and *Streptomyces mediterranei*). Rifampicin may be abbreviated **R**, **RMP**, **RA**, **RF**, or **RIF** (US).

In 1957, a soil sample from a pine forest on the French Riviera was brought for analysis to the Lepetit Pharmaceuticals research lab in Milan, Italy. There, a research group headed by Prof. Piero Sensi (1920-) and Dr. Maria Teresa Timbal (1925 - 1969) discovered a new bacterium. This new species appeared immediately of great scientific interest since it was producing a new class of molecules with antibiotic activity. Because Sensi, Timbal and the researchers were particularly fond of the French crime story *Rififi* (about a jewel heist and rival gangs), they decided to call these compounds "rifamycins". After two years of attempts to obtain more stable semi-synthetic products, a new molecule with high efficacy and good tolerability was produced in 1959 and was named "rifampicin".

Rifampicin is also known as rifaldazine, R/AMP, rofact (in Canada), and rifampin in the United States. There are various types of rifamycins from which this is derived,

but the *rifampicin* form, with a 4-methyl-1-piperazinaminy group, is by far the most clinically effective.

Rifampicin is an intensely red solid, and the small fraction which reaches body fluids is known for imparting a harmless red-orange color to the urine (and to a lesser extent, also sweat and tears) of users, for a few hours after a dose. Maximal concentrations in the blood are decreased by about a third when the antibiotic is taken with food.

Rifampicin is used in the treatment of a number of bacteria, but best known for activity against *Mycobacterium* strains, such as cause tuberculosis and Hansen's Disease. Rifampicin can be used as monotherapy for a few days as prophylaxis against meningitis, but resistance develops quickly during long treatment of active infections, so the drug is always used against active infections in combination with other antibiotics.

Mechanism of action

Rifampicin inhibits DNA-dependent RNA polymerase in bacterial cells by binding its beta-subunit, thus preventing transcription to RNA and subsequent translation to proteins. Its lipophilic nature makes it a good candidate to treat the meningitis form of tuberculosis, which requires distribution to the central nervous system and penetration through the blood-brain barrier.

Rifampicin-resistant bacteria produce RNA Polymerases with subtly different β subunit structures which are not readily inhibited by the drug. In molecular biology research, plasmids containing rifampicin-resistant genes are often used for colony screening. Many plasmids containing these resistant genes are commercially available to researchers.

Adverse effects

The most serious adverse effect is related to rifampicin's hepatotoxicity, and patients receiving rifampicin often undergo baseline and frequent liver function tests to detect liver damage.

Upregulation of hepatic metabolism of hormones decreases their levels, and rifampicin can also in similar fashion reduce the efficacy of hormonal

contraception, to the extent the unintended pregnancies have been reported among users of oral contraceptives taking rifampicin in even short courses (for example, as prophylaxis against exposure to bacterial meningitis). The more common unwanted effects include fever, gastrointestinal disturbances, rashes, and immunological reactions.

Taking rifampicin can cause certain bodily fluids, such as urine and tears, to become orange-red in color, a benign side effect which can be frightening if it is not expected and prepared for. This effect may also be used to monitor effective absorption of the drug (if drug color is not seen in the urine, the patient may wish to move the drug dose farther in time from food or milk intake). The discolorization of sweat and tears is not directly noticeable, but sweat may stain light clothing orange, and tears may permanently stain soft contact lenses.

Since rifampicin may be excreted in breast milk, breast feeding should be avoided while it is being taken.

Adverse effects include:

- Hepatotoxic - Hepatitis, jaundice, liver failure in severe cases.
- Respiratory – breathlessness.
- Cutaneous - flushing, pruritus, rash, redness and watering of eyes
- Abdominal - nausea, vomiting, abdominal cramps with or without diarrhea
- Flu-like symptoms - with chills, fever, headache, arthralgia, and malaise. Rifampin has good penetration into the brain, and this may directly explain some malaise and dysphoria in a minority of users.

Pharmacokinetics

Orally-administered rifampicin results in peak plasma concentrations in about 2 to 4 hours. 4-Aminosalicylic acid (another antituberculosis drug) significantly reduces absorption of rifampicin, and peak concentrations may not be reached. If these two drugs must be used concurrently (which happens often in treatment of TB), they must be given separately with an interval of 8 to 12 hours between administrations.

Rifampicin is easily absorbed from the gastrointestinal tract; its ester functional group is quickly hydrolyzed in the bile; and it is catalyzed by a high pH and substrate-specific enzymes called esterases. After about 6 hours, almost all of the drug is deacetylated. Even in this deacetylated form, rifampin is still a potent antibiotic; however, it can no longer be reabsorbed by the intestines and it is subsequently eliminated from the body. Only about 7% of the administered drug will be excreted unchanged through the urine, though urinary elimination accounts for only about 30% of the dose of the drug that is excreted. About 60% to 65% is excreted through the feces.

The half-life of rifampicin ranges from 1.5 to 5 hours, though hepatic impairment will significantly increase it. Food consumption, on the other hand, inhibits absorption from the GI tract, and the drug is more quickly eliminated. When rifampicin is taken with a meal peak blood concentration fall by 36%. Antacids do not affect absorption, however. The decrease in rifampin absorption with food is sometimes enough to noticeably affect urine color, which can be used as a marker for whether or not a dose of the drug has been effectively absorbed.

Distribution of the drug is high throughout the body, and reaches effective concentrations in many organs and body fluids, including the CSF. Since the substance itself is red, this high distribution is the reason for the orange-red color of the saliva, tears, sweat, urine, and feces. About 60% to 90% of the drug is bound to plasma proteins.

rifampicin is considered as liver microsomal enzyme inducer lead to "high metabolic rate."

Interactions

Rifampicin is an inducer of many enzymes of the cytochrome P450 superfamily, including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP3A7. Thus it will speed up the metabolism of any drug that is metabolized by any of these enzymes in the body. A complete list of drugs metabolized by each of these enzymes can be found here.

Other possible interactions which may not be listed include antiretroviral agents, everolimus, atorvastatin, rosiglitazone/pioglitazone, celecoxib, clarithromycin, caspofungin, and lorazepam.⁸

ETHIONAMIDE

(2-ethylthioisonicotinamide, Trecator SC) is an antibiotic used in the treatment of tuberculosis.

It is a prodrug.

It has been proposed for use in combination with gatifloxacin.

The action may be through disruption of mycolic acid

MINOCYCLINE (INN) is a broad-spectrum tetracycline antibiotic, and has a broader spectrum than the other members of the group. It is a bacteriostatic antibiotic, classified as a long-acting type. As a result of its long half-life it generally has serum levels 2–4 times that of the simple water-soluble tetracyclines (150 mg giving 16 times the activity levels compared with 250 mg of tetracycline at 24–48 hours).

Minocycline is not a naturally-occurring antibiotic, but was synthesized semi-synthetically from natural tetracycline antibiotics by Lederle Laboratories in 1972, and marketed by them under the brand name *Minocin*.⁹

CLARITHROMYCIN is a macrolide antibiotic used to treat pharyngitis, tonsillitis, acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, pneumonia (especially atypical pneumonias associated with *Chlamydia pneumoniae* or TWAR), skin and skin structure infections. In addition, it is sometimes used to treat Legionellosis, *Helicobacter pylori*, and Lyme disease.

Mechanism of action

Clarithromycin prevents bacteria from growing by interfering with their protein synthesis. Clarithromycin binds to the subunit 50S of the bacterial ribosome and thus inhibits the translation of peptides. Clarithromycin has similar antimicrobial spectrum as erythromycin but is more effective against certain gram-negative bacteria, particularly *Legionella*

pneumophila. Besides this bacteriostatic effect, clarithromycin also has bactericidal effect on certain strains such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*.

Pharmacokinetics

Unlike erythromycin, clarithromycin is acid-stable and can therefore be taken orally without being protected from gastric acids. It is readily absorbed, and diffused into most tissues and phagocytes. Due to the high concentration in phagocytes, clarithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations of clarithromycin are released. The concentration of clarithromycin in the tissues can be over 10 times higher than in plasma. Highest concentrations were found in liver and lung tissue.

Metabolism

Clarithromycin has a fairly rapid first-pass hepatic metabolism. However, 14-hydroxy clarithromycin, clarithromycin's metabolite, is almost twice as active and has a half life of 7 hours compared to clarithromycin's 5. Clarithromycin and its metabolites main routes of elimination are urinary and biliary excretion. Of all the drugs in its class, clarithromycin has the best bioavailability at 50%, which makes it amenable to oral administration.

Side effects

Most common side-effects are gastrointestinal: Diarrhea, nausea, extreme irritability, abdominal pain and vomiting, facial swelling. Less common side-effects include headaches, hallucinations (auditory and visual), dizziness/motion sickness, rashes, alteration in senses of smell and taste, including a metallic taste that lasts the entire time one takes it. Dry mouth, panic and / or anxiety attacks and nightmares have also been reported albeit less frequently. In more serious cases it has been known to cause jaundice, cirrhosis, and kidney problems including renal failure. Uneven heartbeats, chest pain, and shortness of breath have also been reported while taking this drug.

Resistance

Many Gram positive microbes quickly develop resistance to clarithromycin after standard courses of treatment, most frequently via acquisition of the *erm(B)* gene, which confers high-level resistance to all macrolides.

Contraindications

Clarithromycin should be used with caution if the patient has liver or kidney disease, certain heart problems (e.g., QT prolongation or bradycardia), or an electrolyte imbalance (e.g., low potassium or magnesium levels). Many other drugs can interact with clarithromycin, which is why the doctor should be informed of any other drugs the patient is taking concomitantly. Clarithromycin is almost never used in HIV patients due to significant interaction with HIV drugs. Clarithromycin should not be used in pregnant patients.

Clarithromycin can also cause serotonin syndrome symptoms when taken in conjunction with buspirone (Buspar).

Drugs using clarithromycin

In the United States generic clarithromycin is available from Andrx, Genpharm, Ivax, Ranbaxy Laboratories, Roxane, Sandoz, Teva and Wockhardt. It is also used as part of a combination therapy to treat *Helicobacter pylori*. In the Middle East it is available as Claridar, produced by Dar Al Dawa. In India, Acnesol-CL gel, containing 1% w/w Clarithromycin, marketed by Systopic, is used to treat acne vulgaris.

Potential increased mortality using clarithromycin

In the CLARICOR Trial, the use of short-term clarithromycin treatment correlated with an increased incidence of deaths which were classified as sudden cardiac deaths.¹⁰

CONCLUSION

Leprosy or Hansen's disease (HD) is a chronic disease caused by the bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis*. Named after physician Gerhard Armauer Hansen, leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the

upper respiratory tract; skin lesions are the primary external sign. Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs and eyes. Contrary to folklore, leprosy does not cause body parts to fall off, although they can become numb or diseased as a result of secondary infections; these occur as a result of the body's defenses being compromised by the primary disease. Secondary infections, in turn, can result in tissue loss causing fingers and toes to become shortened and deformed, as cartilage is absorbed into the body. Although the mode of transmission of Hansen's disease remains uncertain, most investigators think that *M. leprae* is usually spread from person to person in respiratory droplets. Studies have shown that leprosy can be transmitted to humans by armadillos.

MDT for multibacillary leprosy consists of rifampicin, dapsone, and clofazimine taken over 12 months. Dosages adjusted appropriately for children and adults are available in all primary health centres in the form of blister packages. Single dose MDT for single lesion leprosy consists of rifampicin, ofloxacin, and minocycline.

The present overview summarizes the information about the leprosy & some antileprotic drugs used in the treatment of leprosy, which may helpful for researcher in future.

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