International Core Journal of Engineering Volume 7 Issue 1, 2021
ISSN: 2414-1895 DOI: 10.6919/ICJE.202101_7(1).0035

Research on Medicines to Cure Leprosy

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Abstract

As mentioned in British writer Victoria Hislop's novel island, government declared that all the leprosy patients should be isolated from the secular world and hidden in Spinalonga and people had to leave their home to go to that island once they are diagnosed leprosy. That is how they treat leprosy patients. In fact, in Ancient Egypt about 1000 years ago, leprosy had spread around the world and patients were usually treated cruelly. Even in the current period, leprosy is always discriminated. There are many kinds of diseases and different origins to cause this disease. More importantly, each kind of disease has its symptoms and the base and methods for ordinary people to confirm reasons of disease. It is well-known that antibiotic is a kind of normal drug to cure infectious diseases and it is used for clinical application since 1941. It can be said that antibiotics is the greatest medical finding in the twentieth century and it prolongs the lifespan of human beings for at least 10 years. It is incurred by one microorganism and it has the function of restraining or killing under the circumstance of low concentration. Chaulmosulfone and Rifampicin Capsules are two medicines to effectively cure leprosy and this paper will discuss these two medicines in depth.

Keywords

Rifampicin; Chaulmosulfone; Dapsone; Leprosy; Mycobacterium; Sulfanilamide.

1. Overview of Diseases

1.1 Symptoms

Leprosy is also called Hansen's Disease, a kind of chronic infectious disease.[1] Mycobacterium leprae is similar to mycobacterium tuberculosis in terms of shape and staining. It is slim, a little bit bent and arranged in the form of sarciniform. Gram and acid fast stain are both positive.After treatment, it shapes as quarter butt, particle or beads. It is possible the L variation. If it is not cured completely, the disease may relapse.The staining of leprosy bacillus antiacid is red and staining of gram is positive.If it is put in a dry environment for 7 days, it can still reproduce.And within low temperature environment, it can live a little longer. Under the temperature from -60℃ to -13℃, it can live for several months and under the temperature of 0℃, it can live for 3 weeks.

After it leaves the human body and is exposed in sun for 2-3 hours, the reproduction ability will disappear. And if it is treated for 1 hour or shone by ultraviolet ray for two hours, it will die. Mycobacterium leprae is a typical intracellular bacteria and it can be seen that many Mycobacterium leprae exists within cells by observing effusion specimen smear. And the cytoplasm of this cell is in bubble shape. Leper is the natural host of Mycobacterium leprae and is usually seen within the cells of skin, mucosa, surrounding nerves, lymph gland and so on.

When an individual is infected by Mycobacterium leprae, he/she will get the disease leprosy.The bacteria that can trigger leprosy should reproduce themselves for a long time. That is why the related symptom appear slowly. After one person is infected by this disease, symptoms usually show out five to seven years later. The normal symptoms include erythrosis and dry spots. The initial symptoms are

ISSN: 2414-1895 DOI: 10.6919/ICJE.202101_7(1).0035

that patients have red or black spots, which are completely not sensitive to touch or heat. The infected skin gradually triggers the swelling or lumps. If swelling or lumps occur on the face, they will cause disfigurement. Other problems include tingling arms and legs or numbness, blindness or even losing fingers or toes. In the addition, leprae can also cause feeble muscle or even deformation of skeletons.

Leprosy is usually categorized into three kinds, the single damage caused by a little leprosy bacillus, a small amount of leprosy bacillus and much leprosy bacillus. In clinical, skin smear is used to distinguish how much leprosy bacillus is. In fact, to some extent, the effect of skin smear is not ideal and the statistical result is not accurate enough.

1.2 Impact and Number of Mortalities

Skin, mucosa and surrounding nervous tissue are the main targets of entrenchment.

If the illness is serious, the deep tissues and organs are also affected by leprosy.

1.2.1. Primary abnormalities

The skin and nerve damage can cause direct hurt to the leprosy patients and the affected skin will have the symptoms of blocks, node and anabrosis or even deformation of hand, wrist and feet. The damage of skin develops slowly because of the difference of immunity, the symptoms of skin is also different. Some patients have tubercuioid leprosy and others show the borderline leprosy or even cause difficulty for skin feeling.

1.2.2. Immune reaction damage

The damage to immune reaction is triggered by leprosy bacillus antigen.

The leprosy bacillus will release material of antigen and it can cause the immune reaction of body or cause damage to the tissues, like erythema nodosum leprosum, neuritis and all of these will happen before the symptoms of skin and nerves.

1.2.3. Nerve injury

The surrounding nerve cover is damaged seriously so that the muscle tissues controlled by nerve is weak and fragile and feeling of skin meets obstacle.

Leprosy mainly prevails around Asia, Africa and South America. According to the formal report of world health organization, at the end of 2015, the registered prevalence rate of global leprosy is 0.18 per 10000 people. The mortality number of leprosy in China from January to June 2018 is 333 and this number is 301 in 2017. According to related statistics, there are about 3million or 4 million people disabled for leprosy and about 120000 people deformed because of leprosy and about 40000 people lose the ability of labor force.

Figure 1 **Distribution of new cases reported in 115 countries, by WHO Region, 2012**
Figure 1 **Répartition des nouveaux cas notifiés dans 115 pays, par Région OMS, 2012**

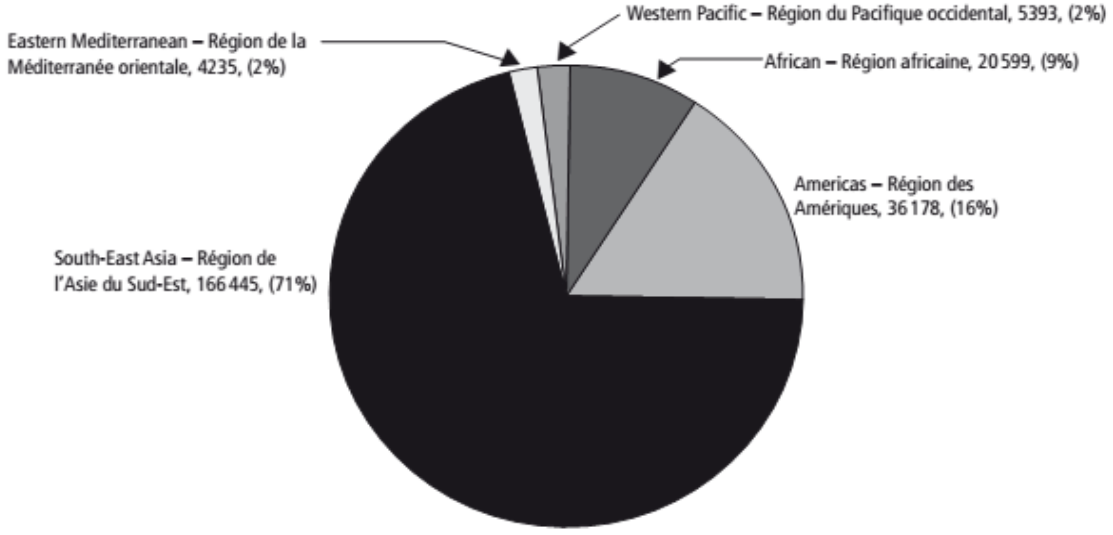

Figure 1 Shows the overall situation of leprosy cases by 2012

ISSN: 2414-1895 DOI: 10.6919/ICJE.202101_7(1).0035

1.3 Significance in China and Other Countries in the World

In 2012, the total registered number of cases of leprosy worldwide was 189018(3.3/100000) and number of the infected reached 232857 cases (4.00/100000).

Figure1 shows the regional distribution of new cases of 115 countries in 2012.

From 1981-1992, there were 73 cases of leprosy registered in Germany and seven cases were Germans. During period of 15 years, 5 cases of leprosy were found. From 1979-2002, 184 cases of leprosy were found in Toronto, Canada and there were about 7.7 cases found annually. The delayed diagnosed period are 4.8 years and most of them have no family medical history. Up until 2005, there had been 50 cases found in UK. 64% patients were from Indian subcontinent, 62% patients contact source of infection before getting the diseases, 10% patients have reaction at the very beginning of diagnosis and 50% patients have nerve damage.

1.4 Drugs Used to Treat the Disease and Their Origins

DDS can restrain leprosy bacillus greatly and it has following features, including restraining sulfanilamide, the part of skin diseases thicker than normal part, removing or restraining the growth of bacteria, long course of treatment and combining medicines. Its mechanism of resisting bacteria is similar to sulfonated brain, but it has no antibacterial activity to gram-positive bacteria and gram-negative bacteria and has stronger restraining function to leprosy bacillus.[2] After patients eat it for 3 to 6 months, the symptom can be improved, blennasis turns better, bacteria disappears gradually and the damaged skin or never can recover. However, the tumor patients need more time to make bacteria disappear and the leprosy bacillus can have have drug resistance toward DDS, so to adopt combination treatment method can prolong or sustain the happening of medicine. For the plan recommended by WHO, the DDS is drunk 100gm/day and rifampicin is drunk about 600 and 300mg each month and the treatment duration is lasted for two years.

Then, the treatment will continue to be used and observed accordingly. The adverse effect is acute hemolytic anemia, especially for the people lack of G-6-PDH. Sometimes, symptoms of gastrointestinal irritation, headache, sleepless or anaphylaxis happens. If patients have too much medicine, it can also trigger liver damage or pityriasis rubra. At the earlier period of treatment, patients may have the reaction of symptoms aggregating and it is normally thought that acute reaction is triggered to biomass pyrolysis. The other treatment includes reducing the amount of medicine or using another kind of medicine. The clinical research finds that DDS has strong function of anti-inflammatory and it has nothing to do with antibiosis. Some researches show that DDS may affect the multiple functions of neutrophile granulocyte. Some other scholars still thin that though medicines can restrain functions of these neutrophile granulocyte, the nflammatory cells and lessen its infiltration in the skin lesions.

Rifampicin is used to cure leprosy as well and the this medicine is combined other antitubercular agent to cure the disease, including treatment of tubercular meningitis. And when this medicine is combined with other medicine, it is also used to cure leprosy. And when rifampicin is combined with erythrocin, it can also be used to the serious infection of legionella. This medicine has obvious bactericidal effect on mycobacterium tuberculosis or non-mycobacterium tuberculosis inside or outside of host cell. It combines with RNA polymerase β sigmasubunit of RNA in order to restrain the compound of bacteria RNA and prevent the joint between this enzyme and DNA.

2. Description of Chemical Structure of Drugs

2.1 Nomenclature

English Name: Rifampicin

Formula:C43H58N4O12

Molecular Weight:822.94000

Accurate Quality:822.40500

ISSN: 2414-1895 DOI: 10.6919/ICJE.202101_7(1).0035

PSA:220.15000
LogP:4.34920

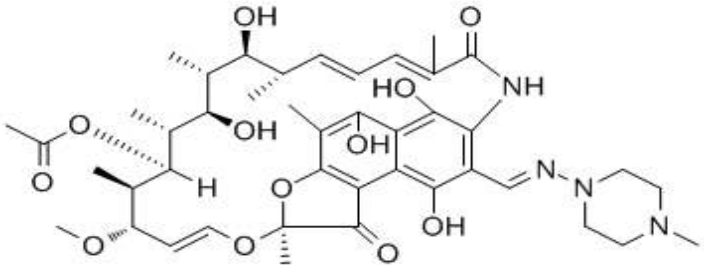

Figure 2 shows the chemical structure of Rifampicine[4]

English Name:dapsone
Other Name: 4,4'-Diaminodiphenylsulfone; Benzenamine, 4,4‘-sulfonylbis-; 4-(4-aminophenyl) sulfonylaniline;
CAS No.:80-08-0
Formula:C12H12N2O2S
Molecular Weight:248.30100
Accurate Quality:248.06200
PSA:94.56000
LogP:3.92700

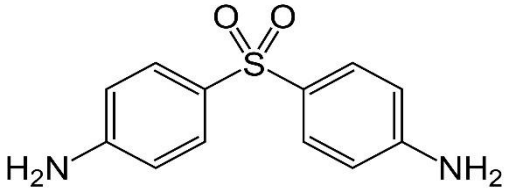

Figure 3 shows the chemical structure of dapsone[5]

2.2 Chemical Properties

Rifampicin is a kind of semisynthetic derivative of rifamycin SV. Rifamycin SV is oxidized as rifamycin S and then undertake formylation reaction with formaldehyde and tert-butylamine to generate 3-Rifamycin formyltert-butylamine and then use Vitamin C to restore, then condensate with 1-methyl-4-Piperazinamine.

Add DDS, acetone powder, cuprous chloride and ammonium hydroxide into autoclave and heat under mixing. Under the pressure of 170-202℃,chemical reaction is on-going for 14h and then temperature cools to 60℃, then through filtering, water washing and drying to get the coarse product.

3. Discussion of Drug Pharmacology

3.1 Description of Drug Targets and How Their Function is Affected by the Drugs

The key part joining drug and biomacromolecule is the drug target and it is concerned with receptor, enzyme, ion channel, transporter, immune system and gene. Additionally, some drugs play the function through other physical or chemical function or complementing the scarce material.Within current drugs, above 50% medicine uses receptor as the target and it becomes the main and most important target, especially enzyme and inhibitor. It takes an important position in the clinical application because 6% medicine uses ion channel as the target, 3% medicine uses nucleic acid as

ISSN: 2414-1895 DOI: 10.6919/ICJE.202101_7(1).0035

target and 20% medicines' target still needs further research. The drug target of rifampicin is to restrain RNA polymerase which is used to restrain mycobacteria to depend on DNA.

The target is RNA polymerase's βsubunit. The antibacterial action of Rifampicin is that specificity restrains the DNA of sensitive creature and dependence RNA polymerase and prevents the compound of mRNA.

3.2 Mode of Delivery

DDS can be absorbed quickly and completely after oral medication.The combination rate of protein is 50%-90%. And after absorption, it spread around the tissues and body fluid and the concentation of liver and kidney is the highest. This medicine is etabolized through N-acetyltransferase. And patients can be categorized into slow acetylation type and quick acetylaion type. And the former is eaten, the concentration of flood will become high and negative reaction will be triggered. When patients use the later one, they should pay attention to the quantity. This medicine circulates within liver and gall. After the medicine is stopped, it can still maintains within blood for several weeks. About 70%-85% medicine quantity is released out of the body with the form of metabolite.

The digestion of rifampicin is good and the blood concentration of medicine can reach the peak value. The peak concentration of blood medicine is 11mg/L and children from 6 months to 5 years old can drink 10mg/kg. This medicine spreads well in most tissues, including cerebrospinal fluid. The combination rate of protein is 80-90% and the absorption of medicine declines by 30%.

3.3 Pharmacokinetics

Oral medication for rifampicin can reach the maximum effect and the blood drug can reach the peak after 1.5-4 hours.[3] For adults, they can take the drug 600mg and then the Cmax is 7-9mg/L. For children 6 months to 5 years old, they should take the drug 10mg/kg and the Cmax is 11mg/L. This drug can distribute well within most tissues or body liquid, including cerebrospinal fluid. When there is meningitis, the concentration of cerebrospninal fluid can increase and it can also reach the concentration of curing within spit and this drug can go through placenta. The Vd is 1.6L/kg, the combination rate of protein is 80%-91%. After taking food, the drug absorption will reduce 30% and the blood removing period is 3-5 hours. Within the liver, this medicine can quickly do deacetylation due to the function of auto-induction microsomal oxygenase to become deacetylation rifampicin with antimicrobial activity and then it is released with the form of inactive metabolin.

4. Discussion of Drug Production

Polypeptide synthases can be used in the process of drug production.Typical I type PKS is a large scale enzyme compound and many modes is arranged according to the linear assembly line. The loading mode is responsible for the loading and activation of initial substrate and then each extension plate catalyzes the extension reaction of chains.And each extension modes at least includes 3 catalyzed zones.

This method adopts 1, 3-Oxyazacyclopentanes within the aprotogenic solvent polarity organic solvent, which reacts with organic acid to generate intermediate products in blue color an then 1-amidogen-4-methyl piperazine to get rifampicin. The reaction liquid mixes with water in the acid condition and then extract with suitable quantity of organic solvent to remove it and then make isolation. The isolated rifampicin uses the ordinary method to crystallize.

Add DDS,acetone powder,cuprous chloride and ammonium hydroxide into autoclave and heat under mixing. Under the pressure of 170-202℃, chemical reaction is on-going for 14h and then temperature cools to 60℃, then through filtering, water washing and drying to get the coarse product. According to function of product, refine the coarse product, such as dissolving the coarse product within the 10% muriatic acid, add muriatic acid to fade, filter and cool below 10℃.And then use sodium carbonate to adjust the value to 2-2.5. By filtering, water washing until the neutral and the completed product

ISSN: 2414-1895 DOI: 10.6919/ICJE.202101_7(1).0035

is gotten after being dried. The rate of success is above 78%. Nitrochlorobenzene is used as the raw material.

Rifamycin SV can automatically be oxidized as Rifamycin S and then under the function of transketolase Rif15, transfer the 2-ketose's C2 perssad to the Rifamycin S and then rearrange to generate Rifamycin L including C-O ester bond structure. Then, P450 monooxygenase Rif16 selects atom on Rifamycin L C-39 hydrogen to formulate oxygen free radical to attack the adjacent C-4 bit to formulate five-membered ring structure and then through the selection of electronic rearrangement and the second selection of C-1 hydrogen atom selection on phenolic hydroxyl group to generate unstable intermediate compound Rifamycin O. Under the condition of NADPH, this compound is quickly hydrolyzed as stable end product.

Rifamycin B.

On a commercial scale, the production process of Rifamycin, the raw materials are bought and then checked to be sent to the workshop. Then, adding some supplementary materials or flow aid to press it to slice or make it as capsule. And then they are packed and sold.

5. Discussion of Drug Economics

5.1 Cost

Assume that those two drugs are strong medicines to sterilize and these two medicines can be well accepted by patients. Within the regions that the prevalence rate of leprosy ‰10 and to use these two drugs in combination to calculate the cost. The cost of drugs in India region.

Table 1 The Cost of Taking Drugs for Every Patient (India Rupee)

Age Group	Federal Germany	The Republic of Malta	WHO Plan- Rifampicin	India Plan
Adult(2 years)	720	2628	718	825
Children(2 years)	360	1314	359	413
Adult(6 months)	180	657	28	28
Children(6 months)	90	329	14	14

The price of Rifampicin (150 mg) is 0.8 rupee per capsule and the price of DDS (100 mg) is 0.05 rupee every capsule.

Table 2 The Ages and Cases of Leprosy and Types Distribution

Age Group	Total Cases	Polybacteriosis Cases	Paucibacillary Cases	Familial Amyloidotic Polyneuropathy of Paucibacillary
Adult	2948(70%)	371(13%)	2577(87%)	2061(80%)
Children	1321(30%)	19(2%)	1302(88%)	260(20%)
Total	4269	390	3879	2321

Table 3 The Expense of Drugs in Different Cure (Indian Rupee)

	Federal German Plan	The Republic of Malta Plan	WHO Plan	India Plan
Multibacillary	65.52	239.148	65.338	75.075
Paucibacillaryleprosy	109.62	100.113	17.052	17.052
Total	203.76	743.871	88.68	98.721

The table 3 shows that within the different methods of having drugs, the multibacillary leprosy patients have been treated completely and the curing is finished within 2 years and paucibacillary's curing is finished within 6 months. Similar with that recommended by the WHO, the cost of operation is not included. The analysis of medicine shows that patients are cured with at least 6 months. Within

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the IAL, the fees of strengthening curing with Rifampicin increases and the advantage of this treatment method is still not clear. In terms of Malta plan, within 10 years, except that 10 cases are checked and Bacillus solidus is found. There is no patients to get the disease again. When Isoprodian combines with rifampicin, the effect is much better. When they are used to cure leprosy, the cost is lower and effect is better. And leprosy is always epidemic around this area. To have the drug riafampicin was once promoted to prevent the generation of bacterial strain. Within the plan of Malta, there is no case to resist the drug. Up until now, Borstel report shows the same result. In contrast, to have the drug brokenly is more possibly suitable for the generation of drug resistance.

5.2 Number of Prescription and Sales

Currently, the sales of these two drugs are not optimistic. In the middle of 19th century, numerous doctors argued about the rooted reasons of leprosy.Up until 1940, one doctor in America coincidentally finds that sulfones drugs can cure leprosy. One year later, America started to use this drug to cure this disease. In the 1950s, sulfones are used to cure leprosy and after 1960s, doctors consistently found that the combined drugs rifampicin and dapsone can be used to cure leprosy.

Currently, a kind of new drug DADDS is used to cure active leprosy cases and prevent the infection to this diseases and it is tried successfully since 1972.

6. Conclusion

Rifampicin is used to cure leprosy as well and the this medicine is combined other antitubercular agent to cure the disease, including treatment of tubercular meningitis. And when this medaicine is combined with other medicine, it is also used to cure leprosy. And when rifampicin is combined with erythrocin, it can also be used to the serious infection of legionella. This medicine has obvious bactericidal effect on mycobacterium tuberculosis or non-mycobacterium tuberculosis inside or outside of host cell. It combines with RNA polymerase β sigmasubunit of RNA in order to restrain the compound of bacteria RNA and prevent the joint between this enzyme and DNA. DDS can restrain leprosy bacillus greatly and it has following features, including restraining sulfanilamide, the part of skin diseases thicker than normal part, removing or restraining the growth of bacteria, long course of treatment and combining medicines. Its mechanism of resisting bacteria is similar to sulfonated brain, but it has no antibacterial activity to gram-positive bacteria and gram-negative bacteria and has stronger restraining function to leprosy bacillus.[2] Up until now, leprosy has been controlled, but it is still not completely removed. The most important points is to give accurate curing to the patients. And it also needs normalized leprosy treatment. Thirdly, it needs to strengthen precaution work and recovery work. In combination with the clinical need, the researchers need to launch work. People should accurately need to understand the implication of basic elimination and fulfill the target. This disease is not horrific and it can be prevented. In the clinical work,people should gradually change their mistaken recognition and remove the horror to help patients reach the real physical and mental health.

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