

Penicillin and macrolides



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Penicillin and Macrolides – The ANTIBIOTICS Penicillin and Macrolides, each having different properties belong to the same group of medicine called ANTIBIOTICS. Antibiotics refer to the chemical substance secreted or produced by various species of micro-organisms which are capable of inhibiting or killing the bacteria. Antibiotics have enabled the effective treatment of infections including life threatening diseases ranging from respiratory diseases to sexually transmitted diseases (Rang et al. 2007). An antibiotic acts by either limiting or stopping the growth of bacteria. It accomplishes this by probably interfering with the cell wall of the bacteria while having minimal effect on the normal body cells. Classifying bacteria into classes helps in identifying the bacterial species and hence they are classified as gram positive bacteria and gram negative bacteria based upon their staining techniques. Penicillin is the oldest and the best known antibiotic.

Basically, it is an antibiotic compound derived from the moulds *Penicillium notatum* and *Penicillium chrysogenum* and is active in opposition to gram positive bacteria and few gram negative bacteria. Penicillin turns out to have two rings fused together; one being the β -lactam ring and the other Thiazolidine ring (Ref figure 1) (β -Lactam Antibiotics: Penicillins). | Figure 1: General Structure of Penicillin | All Penicillins have the same fundamental structure, only the group R varies. Penicillin is generally classified as bio-synthetic and semi-synthetic.

Bio-synthetic refers to the naturally occurring penicillin. These are the very first agents in the family of penicillin introduced for clinical use. They include

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Penicillin G, Penicillin V and Benzyl Penicillin. These prove to be effective against Gram positive bacteria like meningococcus and also prove useful in patients with oral-cavity infection. Certain chemical alterations in the structure of naturally occurring penicillin results in formation of semi-synthetic penicillins. For example, penicillin V is made by replacing the -CH₂C₆H₅ group in natural penicillin G with -CH₂OC₆H₅ group.

The semi-synthetic class consists of Penicillinase-resistant penicillin and Aminopenicillins. The Penicillinase-resistant penicillin includes Cloxacillin, dicloxacillin, methicilin and Nafcillin while the Aminopenicillins consists of Ampicillin, Amoxicillin and Bacampicillin. Penicillinase-Resistant Penicillin provides a narrower antibacterial spectrum of activity than the natural ones. Aminopenicillins are known to be active against the gram negative bacteria like E. Coli and are used to treat mild infections like sinusitis and bronchitis.

The further classified Extended Spectrum Penicillin provides additional action against the gram negative bacteria (Chain, 1945). Macrolides which are also anti bacterial antibiotics are often used in patients appearing sensitive to penicillin. These are bacteriostatic and work by inhibiting the synthesis of vital proteins in bacteria. The Macrolides were isolated from Streptomyces bacteria, and got their name because they have a macrocyclic lactone chemical structure, also called the macrolide ring. The macrolide molecules are made up of large-ring lactones to which one or more deoxy sugar(s) is attached.

Also they can be 14/15/16 membered (refer table 1). Erythromycin is the best known medicine in this group. Newer members of the group,

azithromycin and clarithromycin, are particularly useful for their high level of lung penetration. Clarithromycin has been widely used to treat *Helicobacter pylori* infections, the cause of stomach ulcers (Chain, 1945).

Table 1: Classification of Macrolides depending upon the size of their rings

14- membered ring| 15-membered ring| 16 membered ring| Erythromycin| Azithromycin| Josamycin| Roxithromycin| | Spiramycin|

Clarithromycin| | Micomycin| Dirithromycin| | | Both Penicillin and Macrolides being anti-bacterial antibiotic in nature are produced by the bacteria itself or are synthesized by genetic modification of the chemical compounds. The period between 1928 and 1940 were the years when the discovery and development of antibacterial antibiotics took place. The antibacterial action of penicillin was discovered at the beginning of World War II. It was discovered accidentally in 1928 by the Scottish bacteriologist Alexander Fleming (1881-1995). In August 1928, Fleming had left a dish of staphylococcus bacterium uncovered forgetfully, and returned a few days later to find an unusual phenomenon: with the entire dish dotted with the bacterial growth apart from a part where it was contaminated with a colony of mould was growing. The mould was discovered to be *Penicillium notatum* later on. This discovery lay undeveloped for a period of 10 years before its clinical manifestation was discovered by other researchers. Later on, Sir Howard Walter Florey and Ernst Boris Chain isolated Penicillin successfully and shared the Nobel Prize with Fleming in year 1945.

This discovery and development of Penicillin played a major role in further development of antibiotics (Lee, 2004). Macrolide Erythromycin also being one of the most successful antibiotics is embodied with a 14-member ringed

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structure, is produced by the fermentation of the fungus *Streptomyces erythreus*. It is the prototype of Macrolides and was first isolated in the year 1952 from the soil samples. Erythromycin was formerly known as Ilotycin after the Philippine region of Iloilo, from where the soil was originally collected.

The antibiotic Clarithromycin was discovered in Taisho Pharmaceutical Company of Japan in 1970s. Currently available Macrolides in use are erythromycin and newer agents include clarithromycin and azithromycin. These 2 macrolides are semi-synthetic derivatives of erythromycin, with structural modification to improve tissue penetration (<http://www.emedexpert.com/compare/macrolides.shtml>). Both Penicillins and Macrolides have different properties making it useful for fighting different types of pathogenic or disease causing microbes and infections.

Penicillins are used to treat a variety of infections. They work by destroying the cell wall of the bacteria. Being a rigid membrane, the bacterial cell wall helps give shape and protection. The mechanism of action of penicillin at the molecular level still remains unknown. However, evidence shows that it is initiated by binding penicillin to the penicillin binding proteins (PBPs) located inside the cell wall. PBPs are the bacterial enzymes catalysing the synthesis of bacterial cell wall. Some PBPs are autolytic enzymes drawn in the last stage of cell wall synthesis called transpeptidation.

These enzymes are exterior to the cell membrane and known to link cell wall components together by joining glycopeptides polymers together to form peptidoglycan/ murein/mucopeptide (Rang et al. , 2007). The cell wall of

bacteria contains peptidoglycan which is absent in eukaryotes. The synthesis of peptidoglycan consists of vulnerable steps and can be blocked at several points. Penicillin is known to inhibit the final transpeptidation by forming covalent bonds with penicillin binding proteins consisting of transpeptidase and carboxypeptidase activities, thus preventing the formation of cross-links.

This in turn results in the lysis of cell wall and the bacterial cell ruptures. This is the final bacteriocidal effect of penicillin (Rang et al. , 2007). The RNA-dependent protein synthesis is inhibited by Macrolides by reversible binding to 50 S ribosomal subunits of susceptible microbes. This causes dissociation of of peptidyl transfer RNA (tRNA) from ribosome during its elongation phase. As a result, this causes suppression of RNA dependent protein synthesis, thereby inhibiting the bacterial growth.

Macrolides are thus mainly bacteriostatic but can be bacteriocidal depending upon the concentration of antibiotic. The following table shows the

comparisons between different Macrolides Table 2: Comparison between major Macrolides. Generic Name| Erythromycin| Clarithromycin|

Azithromycin| FDA approval date| April 09, 1959| October 31st, 1991|

November 1, 1991| Intravenous form| Yes| No| Yes| Fed state affects

absorption| Yes| No| No| Half- life| 1-1. 5 hrs| 3-7 hrs| 40-60 hrs| Potential for

interactions| High| High| Low| Bioavailability| 25%| 55%| 38%|

FDA pregnancy category| B| C| B| Ref: <http://www.emedexpert.com/compare/macrolides.shtml> (retrieved November 18, 2010)

Penicillins are prescription medicines used for treating a variety of bacterial infections, including meningitis, syphilis, sore throats and ear aches. They are also used

for treating infections like arthritis, emphysema, endocarditis, furuncles, mastitis, otitis media, peritonitis, pneumonia, etc. They also help treating infections such as urinary tract infections, septicaemia, meningitis, intra-abdominal infection, gonorrhoea, syphilis, nose and throat infections.

It is also used before and after surgery in order to prevent Streptococcus infections in people with rheumatic heart disease. But penicillins do not act the same way on the viruses, so they do not prove to be effective against viral infections like cold or flu (Goodman and Gilman, 2003). Dosage varies with drug, route of administration, pathogen, site of infection, and severity. Penicillin is administered intravenously mostly; however other routes can be used. Intravenous administration causes rapid absorption, in turn producing maximal concentration of penicillin in blood.

Once absorbed, it can be eliminated from the body rapidly. About 80% of Penicillin is protein-bound and hence cleared only by slow filtration and removed by proximal tubular secretion, its overall rate of elimination is very high (Rang et al. , 2008). Eighty percent of the drug is eliminated through urine within 2 hrs and at the fourth hour the amount of drug remaining in the body is less than 5%. Efforts are being made to delay excretion by combining penicillin with substances of high molecular weight (Rammelkamp and Kirby, 1944).

A number of side effects are related to using of penicillin. These side effects include diarrhoea, upset stomach and certain vaginal yeast infections. Side effects are worse in individual sensitive to penicillin, which include urticaria, hives, swelling of tissues, breathing problems and anaphylactic shock, a life

threatening condition which requires immediate medical treatment.

Generally, breast feeding is not suggested when taking penicillin because of threat of modification to infant's intestinal flora, and risk of masking infection in the infant.

Erythromycin may worsen the weakness of patients with myasthenia gravis.

Azithromycin has rarely being allied with allergic reaction including anaphylaxis, and dermatological reactions including Steven-Johnson syndrome and toxic epidermal necrolysis. Erythromycin administered through injections may cause severe phlebitis. These drugs should be used in concern with patients of liver dysfunction. When one is exposed continually to an antibiotic for an illness of long duration (such as rheumatic fever), the targeted bacteria may develop its own defense against the drug.

Continuous use of penicillins declined slowly because of the spread of antibiotic resistance amongst the bacterium species. Same events were observed for Macrolides Erythromycin. With several studies, it was concluded that antimicrobial resistance arises by two fundamental mechanisms.

Bacteria acquire mutations which reduce susceptibility to the antibiotics or pick up resistant genes from other bacteria by direct DNA transfer. (MacGeer and Low, 2003). Discovery and development of many antibiotics was seen since 1940s.

Some are also based on the similar molecular structure of Penicillin. Bacterial infections were thought to be controlled and conquered. Although in the late 20th century, bacterial resistance to antibiotics including penicillin was recognised which posed a potential threat. However, the incessant

exploration for antibiotics has helped us keep speed with the appearance of many new resistant strains of bacteria. References: * ? -Lactam Antibiotics: Penicillins. " The Merck Manual of Diagnosis and Therapy. Chapter 153. <http://www.merck.com/mrkshared/mmanual/section13/chapter153/153b.jsp> * Chain E. B. (1945) The Chemical Structure of the Penicillins. Nobel Lecture * (<http://nobelprize.org/medicine/laureates/1945/chain-lecture.pdf>) * Lee B. (2004) Penicillin: Its discovery, and early development, Seminars in Pediatric Infectious diseases 15(1), Pages 52-57. * L. S. Goodman and A. Gilman (2003) The Pharmacological Basis of Therapeutics, 5th ed. , Macmillan Publishing Co. , New York, * MacGeer A. And Low D. E. 2003) Is Resistance futile? Nature Medicine 9, 390-392. * Moore, Gregory A. , and Ollie Nygren. (2004) Penicillins. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. (http://ebib.arbetslivsinstitutet.se/ah/2004/ah2004_06.pdf) * Rammelkamp C. And Kirby W. (1944) Factors determining the dosage of penicillin in treatment of infections. The bulletin, pages 656-673. * Rang H. P. , Dale M. M. , Ritter J. M. and Flower R. J. (2007) Pharmacology Sixth Edition Churchill Livingstone Elsevier, China.