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Macrolide Antibiotics - A Class Of Effective Antibacterial Drugs

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Abstract: Macrolides represent a huge family of protein synthesis inhibitors of great therapeutic interest because of their applicability to human medicine.its a class of drugs used to manage and treat various bacterial infection. Azithromycin,clarithromycin,erythromycin, are some member of this family. Macrolides are composed of a Macrocyclic Lactone of different ring sizes, to which one or more Deoxy-sugar or Amino sugar Residues are Attached. Macrolides act as Antibiotics by binding to Bacterial 50S ribosomal sub unit and Interfering with protein synthesis. The high Affinity of Macrolides for bacterial ribosomes, Together with the highly Complex structure of Ribosomes across virtually all of the bacterial species is Consistent with their broad spectrum Activity. Since the Discovery of the progenitor Macrolide, Erythromycin, in 1950, Many derivatives have been Synthesised, leading to compounds with better Bio-availability and Acid stability and improved Pharmacokinetics. These Efforts led to the Second generation of macrolides, including well known Members such as Azithromycin and Clarithromycin. Subsequently, in order to Address increasing Antibiotic Resistance, a third generation of macrolides displaying improved Activity against many Macrolide resistant strains was Developed. However, these improvements were Accompanied with serious side Effects, leading to disappointment and causing many researchers to stop working on macrolide derivatives, Assuming that this procedure had reached the End. In contrast, a Recent published breakthrough Introduced a New chemical platform for synthesis and Discovery of a wide Range of diverse Macrolide antibiotics. This chemical Synthesis revolution, in Combination with reduction in the side Effects, Namely, 'Ketek effects', has led to a macrolide renaissance, increasing the hope for novel and safe therapeutic agents to Combat Serious Human Infectious diseases.

Introduction - Macrolide antibiotics such as erythromycin, clarithromycin, and azithromycin have been used widely to combat primarily respiratory Diseases caused by Gram-positive pathogens and fastidious Gram-negative pathogens. The Popularity of this class of antibiotics is largely due to their spectrum of activity and their Relative safety. The second-generation macrolides, clarithromycin and azithromycin, are derived from erythromycin, and have a broader spectrum of activity and improved Pharmacokinetic properties. Macrolide antibiotics inhibit bacterial protein synthesis by interfering with ribosome function, and details of the inhibitory mechanisms have been clarified by recent advances in the x-ray structure of the ribosome–macrolide complexes. The widespread use of These antibiotics had catalyzed the emergence of macrolide-resistant strains, Especially among *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus*. In response to these resistant pathogens, third-generation macrolides, represented by the ketolide telithromycin, are being developed. These derivatives have increased Affinity for the Bacterial ribosome and a reduced propensity to be efflux pump substrates compared with the first- and second-generation macrolides. Discovery of telithromycin and its introduction into the market triggered a renewed interest in the chemistry of macrolide antibiotics In recent years. As a result, a large Number of Novel and potent analogs were synthesized and are under investigation. In this chapter, the major classes of macrolide antibiotics as well as the newer analogs are reviewed. Included are descriptions of their syntheses, their mechanism of action, resistance mechanisms, structure–activity relationship (SAR), and their pharmacokinetic and safety properties.

The Macrolides are a class of Antibiotics possessing a large lactone ring to which sugars are attached. Erythromycin, Clarithromycin, and azithromycin are the macrolides Currently available for use in the United States. Although spiramycin has been used extensively in France, experience with it in North America is Limited. Troleandomycin is An older macrolide that is, for the most part, no longer Employed. Clarithromycin, azithromycin, and dirithromycin are newer agents with several Distinct advantages over erythromycin. Thus, they produce less Gastrointestinal irritability, Are more stable in gastric acid, and are better absorbed from the gastrointestinal tract. The newer agents Also have better tissue penetration and display longer half-lives than erythromycin, permitting once- or twice-daily administration.

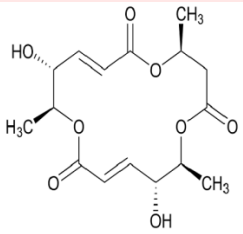
Key words –

1. CAP community acquired pneumonia
2.MIC minimum inhibitory concentration
3 MLS$_B$ macrolide–lincosamide–streptogramin B
4. NPET nascent peptide exit tunnel
5. PTC peptidyl transferase centre

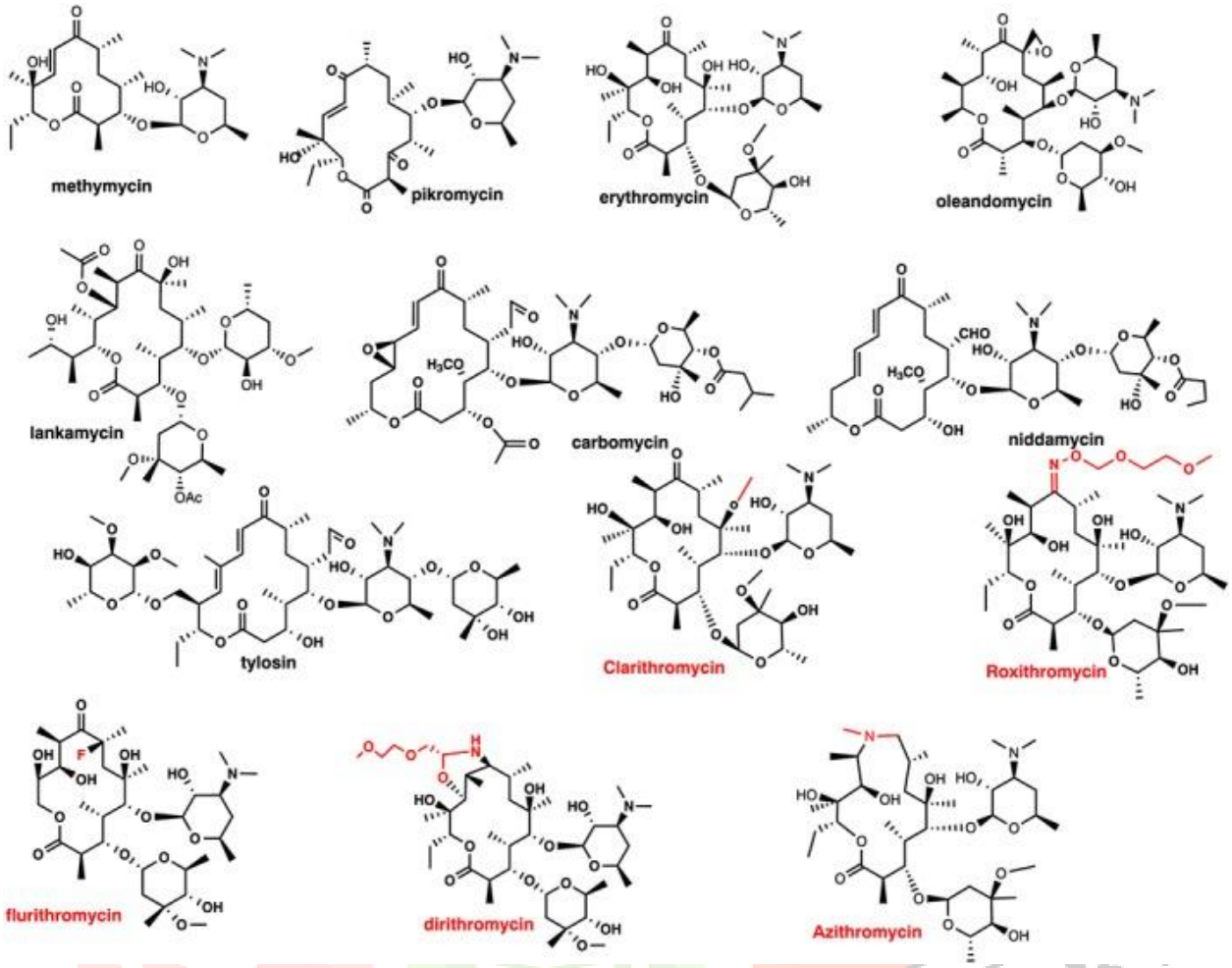
Objectives:

- Identify the mechanism of action of the macrolide class of antibiotics.
- Describe the potential adverse effects of the macrolide class of antibiotics.
- Review the appropriate monitoring necessary for patients on agents in the macrolide class of antibiotics.
- Describe interprofessional team strategies for improving the proper administration and management of macrolide antibiotics.

Natural macrolide and their structures



1.Structure of a macrolide



2.[Macrolide structures. First generation: 12-membered (methymycin), 14-membered (pikromycin, erythromycin, oleandomycin and lankamycin) and 16-membered (carbomycin, niddamycin and tylosin), all natural products. Second generation: 14-membered (clarithromycin, roxithromycin, flurithromycin dirithromycin) and 15-membered (azithromycin). Red colour indicates modifications inserted in the erythromycin molecule to generate the second generation of 14- and 15-membered macrolides.]

Isolation Of Macrolides - The first macrolide antibiotic was isolated from a *Streptomyces* strain in 1950 and was named pikromycin due to its bitter taste (from the ancient Greek word pikro meaning bitter) (Brockmann and Hekel, **1951**). The main chemical characteristic of pikromycin which is common to all later isolated macrolides is the presence of a macrocyclic lactone ring from which the macrolide name derives, as proposed by Woodward in 1950 (see Omura, **2002**). Macrolide antibiotics are classified according to the size of the macrocyclic lactone ring as being either 12-, 14-, 15- or 16-membered ring macrolides (Figure **1**). The majority of macrolides contain amino sugar and/or neutral sugar moieties connected to the lactone ring via a glycosylic bond.

Almost all macrolides are produced by strains of *Streptomyces.* However, several species of the genus *Micromonospora* were found to produce either 14- or 16-membered macrolides (Weinstein *et al*., **1969**; Wagman *et al*., **1972**). Because the antibiotic productivity of *Actinomyces* isolated from a soil sample is very low, higher yields were obtained by examination of various cultural conditions and by improvement of the producing strain using mutational approaches. Industrial yields of macrolide antibiotics are presumed to reach 10 $mg \cdot mL^{-1}$, although the exact details are not known due to company secrecy. Today, although the total synthesis of erythromycin has been reported (Woodward *et al*., **1981**), the fermentation production is preferred due to higher yields.

In this short review, we describe the historical development of macrolides and their mode of action, which has been completely revised during the past few years. Moreover, all resistance mechanisms that render pathogens resistant to macrolides and are responsible for their decreased usage are presented. Finally, the latest developments that have returned this antibiotic family to the forefront of science are discussed, leading to the conclusion that the next-generation macrolide family members will be highly active with reduced toxicity and will therefore re-enter the market in the near future.

Antimicrobial activity and chemical derivatization

In general, macrolide antibiotics are active mainly against Gram-positive bacteria and have only limited activity against Gram-negative bacteria (Nakayama, **1984**). Macrolides are very active against *Staphylococcus*, *Streptococcus* and *Diplococcus* Gram-positive bacteria, and among Gram-negative cocci, *Neisseria gonorrhoea*, *Haemophilus influenzae*, *Bordetella pertussis* and *Neisseria meningitis*. Additionally, they are also extremely active against various *Mycoplasmas*, although there are some susceptibility differences between 14- and 16-membered macrolides

Although macrolides display excellent antibacterial activity, their generally poor bioavailability, unpredictable pharmacokinetics and low stability in the acidic pH of the stomach prompted early searches for new derivatives with improved properties. This resulted in the second generation of macrolides, which were semisynthetic derivatives of the first, natural product, generation. Five derivatives of erythromycin were developed and marketed, namely, clarithromycin (Omura *et al*., **1992**), dirithromycin (Counter *et al*., **1991**), **roxithromycin** (Chantot *et al*., **1986**), flurithromycin (Toscano *et al*., **1983**; Gialdroni-Grassi *et al*., **1986**) and **azithromycin** (Girard *et al*., **1987**; Retsema *et al*., **1987**) (Figure **1**)

Mechanism of Action

Macrolides mechanism of action can be represented as:

Macrolide binds to 50S ribosomal unit →→Stops the formation of polypeptide chain →→Stops mRNA being translated →→Inhibits the protein synthesis →→Prevents the growth of bacteria

Macrolies inhibit bacterial protein synthesis. The mechanism of action of macrolides revolves around their ability to bind the bacterial 50S ribosomal subunit causing the cessation of bacterial protein synthesis. Once it binds, the drug prevents the translation of mRNA, specifically the growing peptide chain, by preventing the enzyme peptidyltransferase from adding the subsequent amino acid attached to the tRNA. Since the bacterial ribosomal structure is highly conserved across most, if not all, bacterial species, it is considered broad-spectrum. Macrolides are bacteriostatic agents as they only inhibit protein synthesis, although, at high doses, they can be bactericidal. [

The anti-inflammatory and immunomodulatory effects of macrolides, particularly azithromycin, are attributed to interactions with phospholipids as well as transcription factors AP-1, NF-kappaB, and other inflammatory cytokines. Later changes seen in macrophages that interact with macrolides include inhibition of cell function, cellular transport, and surface receptor expression regulation. All of these culminate in the immunomodulatory effects of macrolides in the body

Due to the overprescription of antibiotics, there has been tremendous growth in resistance to many mainstay therapies. Macrolides are no exception to this situation, and many organisms are excessively resistant to them. The primary cause of macrolide bacterial resistance is post-transcriptional methylation of the bacterial 23S ribosomal RNA. This acquired resistance can occur via two mechanisms: it can be plasmid-mediated chromosomal. Studies show a solid link to genetic mutations in bacteria and the ability to spread these genes via transposable elements. The gene in question allows bacteria to be resistant to macrolides, lincosamides, and streptogramin groups of antibiotics at once

The Appropriate Use Of Macrolides

Macrolides are a class of antibiotic that includes erythromycin, roxithromycin, azithromycin and clarithromycin. First-line indications for macrolides include the treatment of atypical community acquired pneumonia, *H. Pylori* (as part of triple therapy), chlamydia and acute non-specific urethritis. Macrolides are also a useful alternative for people with penicillin and cephalosporin allergy.

- Macrolides are effective against gram-positive (excluding enterococci) and some gram-negative bacteria. They are also active against *Mycoplasma pneumoniae, Treponema pallidum, Bordetella pertussis, Chlamydia trachomatis, Chlamydophila pneumoniae, Legionella spp., Campylobacter spp. and Borrelia spp.*
- Pertussis - Erythromycin is considered the medicine of choice for treatment and prophylaxis of pertussis as it is active against the causative organism - *Bordetella pertussis*. Infants aged under three months treated with erythromycin are at increased risk of developing pyloric stenosis. As the risk associated with pertussis in a young infant is considerably greater, erythromycin is still indicated, but the infant should be monitored for complications for four weeks after completion of treatment.[4]

- Community-acquired pneumonia: a typical infection

- Severe cases of pneumonia require hospitalisation. The first-line treatment choice for pneumonia treated in the community is amoxicillin (to cover *Streptococcus pneumoniae*). Erythromycin (or roxithromycin) should be added to the treatment regimen when atypical infection is known to be circulating in the community. Erythromycin and roxithromycin provide coverage for *Mycoplasma pneumoniae, Legionella spp. and Chlamydophilia pneumoniae.*

- Pneumonia in children

- **Amoxicillin is the first-line antibiotic for the treatment of pneumonia in children managed in the community. Erythromycin (10 mg/kg, four times daily, for seven days) may be used instead of amoxicillin in children aged over five years, if treatment fails or if atypical infection is known to be circulating in the community. Atypical infection is unlikely in children aged less than five years. Erythromycin may also be used as an alternative to amoxicillin in any child with an allergy to penicillin.**

- Helicobacter pylori infection
- Resistance to clarithromycin is increasing worldwide, therefore it is recommended that clarithromycin should not be used as part of "triple therapy" if it has been used in the last year for any other infection.[8]

- Chlamydia

Azithromycin is the treatment of choice for *Chlamydia trachomatis* infection

A "test of cure" should be requested four to five weeks after treatment with azithromycin if the patient is pregnant, has a rectal infection or if amoxicillin or erythromycin have been used for treatment.[9]

Sexual contacts from the past two months of a symptomatic person and from the past six months of an asymptomatic person who has tested positive for chlamydia should also be treated. Patients should be advised not to have unprotected sex for one week after treatment and until partners have completed treatment.

Resistance of *Chlamydia trachomatis* to azithromycin is increasing, although the extent to which this is occurring is unknown.[10] Some guidance suggests that doxycycline should be considered first-line instead of azithromycin, in order to avoid overuse.[10]

- Azithromycin is also added to the treatment regimen for gonorrhoea (ceftriaxone 250 mg IM + azithromycin 1 g stat) because co-infection with chlamydia is common. Monotherapy with azithromycin 1 g is not adequate treatment for both pathogens.

- Acute non-specific urethritis

Non-specific urethritis is a diagnosis of exclusion. Symptoms include erythema, discomfort and pain in the urethra and penile discharge.

A first void urine sample and urethral swab* should be taken to test for gonorrhoea and chlamydia. Empirical treatment with azithromycin is given on the presumption that the patient has uncomplicated urethritis, due to *Chlamydia trachomatis*. If a purulent discharge is present, treat as for gonorrhoea

Sexual contacts from the past two months should also be treated and tested. This is still

In the majority of cases of campylobacteriosis, antibiotic treatment is not required as diarrhoea will resolve with symptomatic treatment only. Antibiotics have limited effect on the duration and severity of infection, but

can remove the infection from the stool and therefore reduce transmission to others. Treatment with erythromycin 400 mg (children 10 mg/kg), four times daily, for five days, is indicated for people with severe or prolonged infection, in pregnant women nearing term and may be considered for food handlers, childcare workers and people caring for patients who are immuno-compromised

Second-line indications for macrolides

Erythromycin is an alternative antibiotic for people with a history of penicillin allergy in the treatment of otitis media, pharyngitis and boils (when treatment is indicated for these conditions), cellulitis, mastitis and syphilis.

Azithromycin can be used instead of ciprofloxacin as a second-line treatment for severe traveller's diarrhoea, when antibiotics are required. Azithromycin is recommended for pregnant women (ciprofloxacin is contraindicated) or in areas where there is quinolone resistance, e.g. South East Asia. Azithromycin is also recommended for young children with traveller's diarrhoea (ciprofloxacin is not recommended in children), but a liquid formulation is not available in New Zealand. Erythromycin is an alternative. N.B. Azithromycin is not funded for this indication.

Azithromycin 1 g stat can be used instead of doxycycline to treat pelvic inflammatory disease (plus ceftriaxone), when chlamydia is present, especially if compliance is likely to be a problem.

Adverse Effects

Like any other antibiotic, macrolides carry a certain level of risk from typical adverse effects like nausea, vomiting, abdominal pain, and diarrhea. Abdominal symptoms are largely the result of macrolides being motilin agonists causing an increased risk of gastrointestinal upset and side effects.[11] Besides, the enteric gut flora is susceptible to the effects of macrolides; therefore, it can cause an imbalance between commensal bacteria native to the human gut and pathogenic bacteria to be kept in check.,. Symptoms are dose dependent and are more common in children.[1] Erythromycin is associated with a higher incidence of gastrointestinal adverse effects than other macrolides, with 5 - 30% of patients reporting symptoms.[2] Erythromycin ethyl succinate has a lower incidence of gastrointestinal adverse effects compared to other forms of erythromycin. More frequent daily dosing may alleviate gastrointestinal effects.

Another common adverse effect of macrolide use is their propensity to prolong the QT and QTc interval in the cardiac cycle. Erythromycin has the highest tendency, and azithromycin has the lowest. The increase in the intervals puts patients at risk of cardiac arrhythmias like Torsades de pointes, ventricular tachycardia, and ventricular fibrillation. The most common arrhythmia arising from the use of macrolides would be Torsades de Pointes.[12]

Recent studies on macrolides have also shown that the use of these drugs correlates with sensorineural hearing loss. While the majority of cases were reversible with cessation of the drug, few cases resulted in irreversible sensorineural hearing loss. Studies have shown that hearing loss can occur both at standard doses and increased doses.[13]

Serious side effects like Stevens-Johnsons syndrome and toxic epidermal necrolysis, although rare, are a possibility and should be kept in mind while prescribing these drugs.[14]

Erythromycin also has correlations with hepatotoxicity in pregnant women. Moreover, these drugs increase the chances of pyloric stenosis in newborns.[4]

Contradictions

Overall, macrolides are a safe group of antibiotics to take, but relative contraindications exist due to the adverse effects profile and their ability to interact with other drugs. Patients with prolonged QT intervals on electrocardiograms should avoid macrolides due to their arrhythmogenic characteristics. Further, patients with congenital conditions like long QT syndrome type 2 should also avoid these drugs. Patients taking Class Ia and Class III antiarrhythmic agents should also avoid macrolides as both of these drug classes cause an increase in QT interval and induce arrhythmias.[15]

Macrolides can exhibit adverse interactions with some commonly used drugs. Carbamazepine, cyclosporin, terfenadine, astemizole, and theophylline interactions are the most frequently encountered with macrolide antibiotics. As a CYP3A4 inhibitor, erythromycin is more prone to drug-drug interactions mediated by CYP3A4; clarithromycin is much less apt to interact in this manner azithromycin does not participate in these interactions.[16]

Pregnant women should also try to avoid using macrolides, specifically erythromycin, due to possible side effects affecting the mother or the newborn.[17]

Due to the increasing rate of antibiotic resistance, macrolides should be prescribed with caution, and the prescriber should take into account the local resistance status of common pathogens.

Conclusions

The resistance of bacterias and pathogens to antibiotics is a serious and persistent therapeutic problem today, with a fast development of new effective and safe antibiotics are only answer to this problem. Macrolides are a family of valuable versatile antibiotics with great contribution to therapy, which is gradually becoming ineffective because of increasing resistance.so, the development of new generations of macrolides is required, as soon as possible.in addition, this development has to be combine with safety issues to overcome problems related to the use of the newest generation of macrolides (Kim *et al*., **2012**; *Telithromycin*, **2014**).in the starting of the previous decade, there was a revolution in the development of new macrolides and a great enthusiasm found after approval of telithromycin by the FDA.but, telithromycin usage was accompanied by serious side effects. This led to disappointment and caused many researchers to stop searching on macrolide derivatization, assuming that this procedure had reached the end. after then, the discovery of modular macrolide polyketide synthasis initiated new research to alter the activities of the enzyme domains, for the purpose of changing the structure of the corresponding aglycone and the linked sugars (Khosla and Zawada, **1996**; Khosla, **2009**). This procedure allow recombinant genes to be introduced into the macrolide producers to create desired changes to the structure of macrolides obtain (Katz and McDaniel, **1999**; McDaniel *et al*., **2005**). The few fully elaborated new macrolides produced by genetic engineering has not fulfilled the original promise yet (Park *et al*., **2010**). Therefore, it is still too early to assess that this avenue of discovery will be effective. The new findings that many of scientists PKSs either do not produce the expected compounds, or search at levels too low to be useful, indicate that greater understanding of the biochemical details of polyketide biosynthesis is essential before full exploitation of their chemical potential can be feel.. Fortunately, this inability of genetic manipulation produce very fast new compounds designed on the huge amount of available crystal structure, data has been recently overcome by chemical macrolide synthesis procedures, which have opened new horizons into the synthesis of novel macrolide compounds (Seiple *et al*., **2016**). On the other hand, the recent findings in the 'ketek effects' also provided answers to the second critical issue, which is, the safety of macrolides in clinical use (Andrade and Tulkens, **2011**; Fernandes *et al*., **2016**), and therefore, macrolide antibiotics are back again in the forefront of science, and new, versatile ,important, effective and safe macrolides are expected very soon to re-enter the market.

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