THE NORTHERN HOSPITAL

ROXITHROMYCIN

Frida Kahlo, Vogue Magazine, January 1937, (Antoinette Frissell Bacon).

"....From the bright woollen strings that she plaits into her black hair and the colour she puts into her cheeks and lips, to her heavy antique Mexican necklaces and her gaily coloured Tehuana blouses and skirts, Madame Rivera seems herself a product of her art, and, like her work, one that is instinctively and calculatingly well composed...."

Bertram D. Wolfe, "The Rise of Another Rivera", US Vogue, 1 November 1938.

Despite her miseries, Frida did participate in the "surrealistic" pleasures of Paris. She got to know such luminaries of Surrealist circles as the poet Paul Eluard and Max Ernst, whose intense blue eyes, white hair, and beaky nose appealed to her, and whose painting she liked, but whose personality she found a little inaccessible - like dry ice. Her new friends escorted her to artist's cafes and to nightclubs like the Boeuf - sur - le - Toit, where she listened to jazz....Already proficient at the cadavre exquis, she now became an expert at other Surrealist games. Breton's favourite - and he took it very seriously, becoming irate if anyone spoke out of turn - was the jeux de la verite (truth or consequences). People who refused to tell the truth were asked to do things like crawl into the room blindfolded and on all fours and then guess who it was that had kissed them. On one occasion Frida refused to answer the question, "What's your age?", and the punishment was: "You must make love to the armchair". One player remembered, "Frida.....did it ....beautifully...."

The world of haute couture embraced her too. Schiaparelli was so taken with her Tehuana costumes that she designed a "robe Madame Rivera" for fashionable Parisians, and Frida's beringed hand appeared in the cover of Vogue.....

Hayden Herrera, "Frida", 1983.

From 1930 to 1934 Frida Kahlo lived in America with her famous husband, the Mexican Muralist, Diego Rivera. At this time Diego was world famous, but Frida had been totally unknown before she arrived. But once in America she captured the imagination of high society, the press and the general public at large, with her outgoing flamboyant personality and her incredibly colourful Mexican Tehuana costumes, that were a glittering stand out on the drab streets of Depression era New York City. She turned heads wherever she went. But it was not only her vital personality and her exotic dress that astonished Americans, it was also her Art. Frida painted alongside her husband to pass the time - and her work was like nothing most Americans had ever seen. It was left to "high-cultured" Europeans such as Andre Breton, to explain her work to uncomprehending Americans - "Frida is a self-made Surrealist" he pronounced loudly to all. Breton was so taken with Fridas work he invited her to Paris for her own exhibition. She did exhibit - but she never much cared for the Surrealists. Frida's fame started to rise - the great fashion houses began to copy her dress style, she was even featured in Vogue magazine. But it was not only for high fashion that Frida was being noticed - by now it was becoming apparent that Frida did not simply follow in the shadow of her husband - she was increasingly being seen as a great Artist, in her own right!

The macrolides are justly famous as effective antibiotics, however they have other admirable attributes not so widely appreciated. Though they reduce inflammation through their antibacterial effect, they are also effective anti inflammatory agents - "in their own right!"

ROXITHROMYCIN

Introduction

Roxithromycin (trade name in Australia, "Rulide" amoung others) is a semi-synthetic **macrolide** antibiotic for **oral** use.

It is often prescribed for people who have an allergy to the **penicillins** or the **cephalosporins**.

Oral preparations of roxithromycin tend to cause less GIT upset compared to oral erythromycin.

It is primarily used for upper and lower respiratory tract infections and skin infections.

History

Roxithromycin was introduced to clinical practice in in 1987.

Chemistry

Roxithromycin is derived from erythromycin, and contains the same 14-membered **lactone ring**.

Classification

The macrolide antibiotics include:

1. **Azithromycin**
2. **Clarithromycin**
3. **Erythromycin**
4. **Roxithromycin**

The newer macrolides have more reliable absorption and longer half-lives (azithromycin > roxithromycin > clarithromycin > erythromycin) allowing less frequent dosing.

They attain high intracellular concentrations that confer theoretical benefits in the treatment of infections due to intracellular pathogens.

Preparation

Roxithromycin as:

Tablets:

- 50 mg ("Rulide D"):

The 50 mg tablets are administered to children weighing < 40 kg as an aqueous suspension that is made by adding either a half, one or two tablets to a spoonful of water.

After waiting 30 - 40 seconds for the tablet(s) to disintegrate into fine granules, the suspension is given to the child. A drink of water should follow the dose.

Only the 50 mg tablets are designed to be mixed with water. The 150 mg and 300 mg **film coated** tablets must be swallowed whole with a drink

- 150 mg
- 300 mg.

Mechanism of Action

The macrolides including roxithromycin are **bacteriostatic** agents, (as opposed to bactericidal agents). Bacteriostatic agents inhibit bacterial reproduction, without necessarily killing them. Once inhibited from reproducing the body's natural immune system can kill the organism. Bactericidal agents directly kill bacteria.

Roxithromycin may be **bactericidal** at **high** concentrations.

The macrolides inhibit **bacterial protein synthesis** by binding to the **50S ribosomal subunit** and preventing translocation of peptides.

The macrolides as a group also have some direct **immunomodulatory** and **anti-inflammatory** effects.

Pharmacodynamics

The macrolides in general have a wide spectrum of antibiotic activity that includes: [1]

1. Gram-positive cocci:
    - Including Streptococcus pneumoniae, Streptococcus pyogenes,
2. Gram-negative cocci
3. Anaerobes (both Gram-positive and Gram-negative
4. They also have activity against many so-called "atypical" organisms including:
    - *Legionella*
    - *Corynebacteria*
    - *Mycoplasma*

- *Chlamydia*
- *Bordetella*.

Haemophilus influenzae and Staphylococcus aureus, (except methicillin resistant Staph. aureus - MRSA) are partially sensitive in vitro to roxithromycin.

The macrolides do **not** have significant activity against:

- Enteric Gram-negative rods.
- Pseudomonas aeruginosa

Azithromycin is less active than erythromycin against Gram-positive pathogens, but has activity against a few Gram-negative bacteria, some anaerobes, non-tuberculous mycobacteria including MAC, and also against some parasites (e.g. *Toxoplasma gondii*).[1]

Pharmacokinetics

Absorption:

- Roxithromycin is administered orally.

  It has an absolute bioavailability of approximately 50%.

Distribution:

- Roxithromycin is highly bound to plasma proteins, (up to 96 %).
- Roxithromycin can cross the human placenta.
- Roxithromycin is distributed into human breast milk in small amounts only.

Metabolism and excretion:

- Roxithromycin undergoes limited metabolism in the body, presumably in the liver - the major metabolite being descladinose roxithromycin.
- Approximately 7% of a dose is excreted unchanged in the urine and 13% is eliminated via the lungs.
- Faecal excretion, (which represents the unabsorbed fraction) and a small proportion excreted by the liver, accounts for approximately 53% of the dose.
- The mean half-life of roxithromycin is approximately 12 hours in young adults and 20 hours in children.

  The half-life is prolonged to 25 hours in patients with impaired hepatic function.

The half-life is prolonged to 18 hours in patients with renal insufficiency.

The half-life in elderly patients may be a prolonged as approximately 27 hours.

Indications

It is often prescribed for people who have an allergy to the penicillins or the cephalosporins.

Usual indications include:

1. Upper respiratory tract infections
2. Lower respiratory tract infections
    - Including community-acquired pneumonia
3. Skin infections

Note that, as for all antibiotics, the prevalence of bacterial resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

Contraindications/ Precautions

These include:

1. Known hypersensitivity (to macrolides in general).
2. Caution in those with risk factors for prolonged QT interval
    - Roxithromycin has been associated with prolonged QT interval.
3. Hepatic impairment:
    - Caution in severe hepatic impairment; reduce dose.
4. Cross-resistance:
    - There is a high degree of cross-resistance between erythromycin and the other macrolides.
    - There is often cross resistance between macrolides and lincosamides (clindamycin and lincomycin).
5. Concomitant therapy with vasoconstrictive ergot alkaloids (contraindicated).

- Reactions of ergotism with possible peripheral necrosis have been reported after concomitant therapy of macrolides with vasoconstrictive ergot alkaloids, particularly ergotamine and dihydroergotamine.

Pregnancy

Roxithromycin is a category B1 drug with respect with pregnancy.

Category B1 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Maternal use of roxithromycin has not been associated with an increased risk of birth defects or adverse pregnancy outcomes.

Roxithromycin is safe to use during pregnancy.

Breastfeeding

Small amounts of roxithromycin are excreted into breast milk, but these amounts are unlikely to pose harm to the breastfed infant.

Roxithromycin is safe to use during breastfeeding at the recommended doses and observe the breastfed infant for potential adverse effects such as diarrhoea, vomiting, skin rash or thrush.

Adverse Effects

These include:

1. Allergic reactions

2. Dermatologic hypersensitivity reactions:

    - Including serious reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

3. GIT upset:

    As with many antibiotics:

    - Nausea, vomiting, diarrhoea, abdominal pain and cramps

        Roxithromycin induced GIT upset tends to be tend dose-related.

    Clostridium difficile associated diarrhoea:

- Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including azithromycin.

Dosing

Exact dosing and the duration of dosing depends on the condition being treated as well as the severity of the condition and illness.

See latest Antibiotic Therapeutic Guidelines for full prescribing details.

In *general* terms:

- **Roxithromycin 150 mg orally 12 hourly.**

Alternatively:

- **Roxithromycin 300 mg once daily.** [2]

  A prolonged postantibiotic effect has been observed with roxithromycin. Whilst the clinical significance of this remains uncertain, it supports the rationale for once daily dosing. Although clinical data have demonstrated the efficacy and safety of once daily dosing in adults, these have not been demonstrated in children. [3]

Frida Kahlo, Vogue Magazine, January 1937, (Antoinette Frissell Bacon).

References

1. eTG - July 2019

2. Roxithromycin in Australian Medicines Handbook Website January 2019.

3. Roxithromycin in MIMs Website 1 September 2018.

4. Roxithromycin in RWH Pregnancy & Breastfeeding Guidelines, 18 January 2019.

5. Brygida Kwiatkowska, Maria Maslinska: Macrolide Therapy in Chronic Inflammatory Diseases. Mediators of Inflammation, Volume 2012, Article ID 636157.

    - doi:10.1155/2012/636157

Dr J. Hayes
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