THE NORTHERN HOSPITAL

RIFAMPICIN

"Sofa Rouge", Lithograph, c. 1985 Rene Gruau (1909-2004).

"Take the vitriol of Venus...and add thereto the elements water and air. Resolve, and set to putrefy for a month according to the instructions...Separate and you will soon see two colours, namely white and red. The red is above the white. The red tincture of vitriol is so powerful that it reddens all white bodies...which is truly wondrous".

Paracelsus, "The Water-Stone of the Wise Men: Describing the matter of, and manner of how to attain the Universal Tincture" in "The Treasure of Treasures for Alchemists", c.1530.

"Never before or since the Middle Ages was colour so central to chemistry. We can recognize through their colour changes the transformations, albeit half-obscured by the alchemist's secretive terminology, that these proto-chemists were conducting in their elaborate alembics and pelicans. For all its mythical resonance, vitriol of Venus was nothing other than the blue copper sulphate, familiar from many a school laboratory…. There is good reason to argue that red is the primary hue of both Medieval chemistry and Art. Alchemy accords red a special significance: it is the "colour" of gold (which was more beautiful when more ruddy) and it signifies the culmination of the Great Work: the creation of the Philosopher's stone. "Red is last on the work of Alkimy", said the Fifteenth century alchemist Norton of Bristol. Colour underpins the alchemical belief in transmutation. A substance's colour was deemed an outward manifestation of its inner properties. Lacking much information beyond this superficial characteristic, alchemists had every reason to suppose that a metal with the appearance of gold was none other than gold itself".

Philip Ball, "Bright Earth: the invention of colour", Penguin Viking, 2001.

Colour was one of the supreme guiding principles of the medieval alchemists. As the magisterial Philip Ball points out, without the detailed and sophisticated knowledge of chemistry that we posses today, the superficial colour changes that were observed with alchemical reactions were often taken as proof of various "transmutations". The closer the colour to a known compound - then the more assured was the success of a transmutation. Many an alchemist were convinced that they had produced gold from a "base" metal. They guarded their secret recipes and processes accordingly and recorded their findings in indecipherable alchemical language and arcane symbolism. For the alchemists red vermillion was one of the most prized substances in their arsenal. It was produced in various ways from quicksilver and sulphur. The earliest record we have of the fabled vermilion occurs in the Eighth or early Ninth century, where the Arabic alchemist, Jabir ibn Hayyan, describes the formation of a red substance from the union of quicksilver and sulphur.

Art took a lead from alchemy. The most prized pigments of the Artist's pallets were taken from the crucibles of the alchemists. Apart from lapis lazuli, it was vermilion, the most brilliant form of red, that was one of the most prized pigments of all. Daniel Thomason regarded the production of vermillion as one of the great medieval innovations in painting. He wrote: "No other scientific invention has had so great and lasting an effect upon painting practice as the invention of this colour…If the Middle Ages had not had this brilliant red, they could hardly have developed the standards of coloring which they upheld: and there would have been less use for the inventions of other brilliant colors, which come on the scene in and after the Twelfth century". Vermilion we now know today to be none other than the highly toxic compound, mercuric sulfide.

In a less enlightened age, a sign of red tears could have been interpreted as the divine stigmata of tears of blood. Fortunately today our knowledge of the biological sciences allows us a far deeper understanding of superficial appearances. The sign of vermilion tears, we can be reassured, is not a miraculous stigmata, but a rather more boring phenomenon - a benign and temporary side effect of the antibiotic rifampicin.

RIFAMPICIN

Introduction

Rifampicin is a bactericidal antibiotic drug of the rifamycin group.

Rifamycins are effective against both gram positive and gram negative bacteria and are particularly effective against mycobacteria, (and are therefore used to treat **tuberculosis, leprosy,** and **mycobacterium avium complex (MAC)** infections).

Due to the rapid emergence of resistance, these drugs are usually used in combination with antimicrobials from a different class.

History

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.

A research group headed by Professor Piero Sensi (1920-2013) and Dr. Maria Teresa Timbal (1925 - 1969) analyzing this sample discovered a bacterium hitherto unknown.

The new bacterium immediately sparked great interest as it produced a novel class of molecules with antibiotic activity.

At the time Sensi, Timbal and the other researchers of their team 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 semisynthetic products, a new molecule with high efficacy and good tolerability was produced in 1959 and was named "rifampicin".

Chemistry

The **rifamycins** are a group of antibiotics that are synthesized either naturally by the bacterium ***Amycolatopsis rifamycinica*** or artificially.

They are a subclass of the larger family of ansamycins.

Rifampicin is a semisynthetic antibiotic derivative of rifamycin B

Classification

The rifamycin group includes the "classic" rifamycin drugs as well as the rifamycin derivatives:

- **Rifampicin**

- Rifabutin
- Rifaximin
- Rifapentine
- Rifalazil.

Preparation

Tablets/ Capsules: 150 mg, 300 mg, 600 mg

Oral liquid: 20 mg/mL, 60 mL

Ampoule: 600 mg (powder & solvent)

Mechanism of Action

Rifampicin inhibits DNA dependent RNA polymerase activity in susceptible cells.

Specifically, it interacts with **bacterial** RNA polymerase, but does not inhibit the mammalian enzyme.

Pharmacokinetics

Absorption:

- Rifampicin can be given orally or IV

  It *cannot* be administered IM

  Rifampicin is readily absorbed from the stomach and the duodenum.

  Peak serum concentrations occur about 2 - 4 hours after an oral dose of 600 mg on an empty stomach.

Distribution:

- Rifampicin is widely distributed throughout the body.
- It is present in effective concentrations in many organs and body fluids, including **cerebrospinal fluid.**
- Rifampicin is about 80% protein bound. Most of the unbound fraction is not ionised and, therefore, diffuses freely in tissues.
- Rifampicin crosses the placenta and serum levels in the fetus equal 15 to 96% of the maternal levels.

- It also appears in breast milk.

Metabolism and excretion:

- Rifampicin is rapidly eliminated in the bile and an enterohepatic circulation ensues.

  During this process rifampicin undergoes progressive deacetylation so that nearly all the drug in the bile is in this form in about six hours. This metabolite retains essentially complete antibacterial activity.

- Intestinal reabsorption is reduced by deacetylation and elimination is facilitated.

- Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

- In normal subjects the biological half-life of rifampicin in serum averages about 3 hours after a 600 mg dose.

Pharmacodynamics

Rifampicin (and **rifabutin)** are active against:

1. Gram-positive bacteria (including staphylococci)
2. Gram-negative bacteria
3. Mycobacteria
   - Tuberculosis
   - Leprosy
   - Mycobacterium avium complex (MAC)

Note however that while rifampicin is bactericidal, resistance develops rapidly if used as the sole agent

Indications

Indications for rifampicin (often in combination with other agents) include: [1]

1. Tuberculosis, (in **combination** with other antituberculous agents).
2. Non-tuberculous mycobacteria, including:
   - Mycobacterium avium complex (MAC)

- M. ulcerans
- Leprosy

3. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection, (with other agents).

4. Epiglottitis.

5. **Prophylaxis** in contacts of patients with:
   - Haemophilus influenzae type b
   - Meningococcal disease.

Contraindications/ Precautions

These include:

1. Hepatic impairment:
   - Contraindicated in jaundice
   - Rifampicin may worsen hepatic impairment; use cautiously (a slightly lower dose may be necessary)
   - Treatment with hepatotoxic drugs may also increase the risk of hepatotoxicity (hepatitis is common when taken with isoniazid).

2. Allergy to any rifamycins in general

3. Drug interactions:
   - Rifampicin and rifabutin interact significantly with many other drugs.
   - Consult an appropriate text on drug interactions when starting or stopping these drugs in patients taking other medicines.

4. Pregnancy (contraindicated - see below).

Pregnancy

Rifampicin is a class C drug with respect to pregnancy.

Class C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without

causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Breast feeding

Compatible; but may cause diarrhoea in infant. Monitor infant for jaundice

Adverse Effects

These include:

1. **Hepatic:**

    - Rifampicin can cause hepatitis, so liver function should be checked before starting treatment.

2. Reddish discoloration of body tissues:

    - Warn patients that rifamycins can cause orange discoloration of bodily fluids, including **urine, sweat** and **tears,** and that **soft contact lenses** can also become stained.

3. Drug interactions:

    - Rifampicin and rifabutin interact significantly with many other drugs.

      In particular rifampicin can reduce the effectiveness of the contraceptive pill. Extra precautions will need to be taken.

      Consult an appropriate text on drug interactions when starting or stopping these drugs in patients taking other medicines.

    - Rifampicin induces several hepatic and intestinal CYP enzymes as well as transporter proteins such as P-glycoprotein, decreasing the concentration and reducing the activity of many drugs.

      It takes about a week for maximum induction to occur, and this lasts for about 2 weeks after stopping rifampicin. [2]

4. GIT upset

5. Dermatological reactions

6. Allergic reactions

7. Clostridium difficile-associated disease, (as for many other antibiotics).

Dosing

Tuberculosis:

The current *standard short-course oral therapy* is for tuberculosis is:

- 2 months of treatment with **isoniazid, rifampicin, pyrazinamide** and **ethambutol.**

Followed by:

- 4 months of treatment with isoniazid and rifampicin

Note however there are a great variety of regimens, depending on the exact nature of the infection being treated.

See latest Antibiotic Therapeutic Guidelines for full prescribing details.

Neisseria meningitidis (meningococcus) chemoprophylaxis: [1]

A suitable oral regimen for *Neisseria meningitidis* (meningococcus) chemoprophylaxis is:

- **Rifampicin 600 mg (neonate: 5 mg/kg; child: 10 mg/kg up to 600 mg) orally, 12 hourly for 2 days.**

Haemophilus influenzae type b chemoprophylaxis: [1]

A suitable oral regimen for Haemophilus influenzae type b (Hib) chemoprophylaxis is:

- **Rifampicin 600 mg (neonate: 10 mg/kg; child: 20 mg/kg up to 600 mg) orally, daily for 4 days.**

References

1. eTG - November 2014

    - Antibiotic Therapeutic Guidelines, 15th ed. 2015.

2. Rifampicin in Australian Medicines Handbook Website, Accessed December 2014.

3. Rifampicin in MIMs 1 April 2009.

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