

DOXYCYCLINE



Napoleon Visiting the Plague House in Jaffa, March 11 1799, oil on canvas, 1804, Jean Antoine Gros, Louvre Museum.

...The general walked through the hospital and its annexe, spoke to almost all of the soldiers who were conscious enough to hear him, and for one and a half hours, with the greatest calm, busied himself with the details of the administration. Finding himself in a very cramped and overcrowded room, he helped to lift, or rather carry, the hideous corpse of a soldier whose torn uniform was soiled by the spontaneous bursting of an enormous abscessed bubo...

Nicolas Rene Desgenettes, Chief Medical Officer, Jaffa, March , 1799.

In April of 1798, the ruling Directory of France were worried. A brilliant young General by the name of Napoleon Bonaparte had apparently come from nowhere and was winning stunning victory after stunning victory against battle hardened Austrian generals in Northern Italy. Naturally they were delighted that this young soldier had almost single headedly saved Republican France from Austrian invasion, and by so doing had also saved the Revolution. His fame in Paris had become immense, indeed it had become almost Alexander the Great-like, when Jean Antoine Gros had depicted him leading his men across the bridge at Arcola in his famous painting of 1796.

By 1798, even though no one in Paris had even seen him, the fame of the dashing young general had become so great, the Directory had come to see him as a possible rival for political power and in consequence had begun to fear for its very existence. They devised a plan to send him on an impossible mission, but if he should succeed, then at least it would strike a great blow against their intractable enemies, Great Britain. Napoleon would be sent to Egypt with a moderate sized army of around 38,000 troops, to defeat the ruling Mamelukes who had effectively ruled Egypt since the Thirteenth century and were legendary, apparently invincible, and fearless warriors. By so doing they would break Britain's strong relationship with the Mamelukes and so block her trade routes to India and re-establish their own commerce with the Levant. Of course if Napoleon should fail, then at least his reputation would be destroyed and a dangerous political rival would have been eliminated. Napoleon enthusiastically accepted the mission and saw it a great adventure. Things would not exactly go according the Directory's plans.

From the moment Napoleon set foot in Egypt near Alexandria, he was like, what later rival generals would refer to him as, a "torrent". He led with an inspirational vigor and energy that his subordinate commanders could only marvel at. In short order he led his army southward where in July 1798 he confronted the main Mameluke army very near the Great Pyramid of Cheops. The Mamelukes with their antiquated weapons and tactics were no match for a modern European army, let alone the finest army then in Europe. Napoleon always cognizant of history and "la gloire" of France, famously inspired his generals, by screaming out to them, "From the heights of those Pyramids, forty centuries look down on us" - which was the signal to begin the battle. The Mameluke army was annihilated. Napoleon rode into Cairo master of all of Egypt. The Directory had badly miscalculated. If Napoleon's fame was great before, now it positively exploded like a supernova. Across Europe all the nations opposing France stood up and took notice - asking "who is this man?"

Though the Directory had not succeeded in dampening Napoleon's reputation, neither did Napoleon have things all his own way. While the French army was now unrivaled in the world, on the high seas it was Britannia that ruled the waves. And as Napoleon was the greatest commander in Europe on land, Horatio Nelson was the greatest commander at sea. Smarting at the loss of Egypt, Nelson was sent with a large fleet to Egypt to seek out the French fleet and try to engage it. On the 1st of August, 1798 Nelson brilliantly ambushed the French expeditionary fleet whilst in anchor in Aboukir Bay, about 20 miles northeast of Alexandria. The Royal Navy annihilated the French fleet just as thoroughly as Napoleon had annihilated the Mamelukes. The Battle of the Nile, for the British, became just as legendary as the Battle of the Pyramids for the French. The British could not challenge the French in Egypt itself, but now Napoleon found himself trapped in

Egypt with his army. He merely shrugged his shoulders and decided to extend his conquests deep into the lands of the Ottomans, by invading their Syrian Provinces. He would reach Acre, and besiege it but as supplies ran out and reinforcements could not be sent from France, he was unable to take it. Just at this time the plague catastrophically broke out in several Syrian cities and also began to infect the French army. With casualties mounting from sickness, no prospect of relief from France, and with disturbing news from Paris that Austrian and German armies had once again attacked France and were having some success, Napoleon finally decided that to remain in Egypt any longer was pointless. In August 1799, he secretly left Cairo in a small flotilla, handing over command of the army to General Kléber. Within seven weeks he was back in Paris. The French army in Egypt would hold out for a further two years, before finally surrendering to the British. In Paris Napoleon was hailed as a savior, as France's enemies closed in. On 9th of November 1799, Napoleon led a successful coup against the Directory, known according to the Revolutionary calendar as the coup of 18 Brumaire. Although the new Consulate consisted of three, Napoleon as "First Consul", was now master of France in all but name.

Napoleon's victory at the Battle of the Pyramids came to be seen as a romantically heroic episode in French military history, every bit as exotic as Julius Caesar's expedition to the mysterious island of Britain in 55 B.C. If Gros' "Bridge at Arcola" had made Napoleon famous in Paris, the subsequent works of painters depicting him in Egypt turned him into a legend. Perhaps the best example is Jean Antoine Gros' monumental "Napoleon Visiting the Plague House in Jaffa, March 11 1799" painted in 1804, which today hangs in the Louvre Museum. Napoleon is depicted at Jaffa (modern day Tel Aviv) where the victims of the Plague were gathered at the Pest House. Gros however does not show a moment of despair and defeat, but rather spins the situation into a moment of grand heroism. Napoleon is showing his compassion for the sick soldiers by visiting them and comforting them. Indeed he does more than merely give words of encouragement, he dramatically reaches out to them, even touches them, much to the horror of one of his aids, who stands directly behind him holding a handkerchief to his mouth and nose to keep the plague away and block out the stench of the diseased bodies all around them. By this grand gesture, Gros is showing Napoleon's great empathy for the suffering of his troops, echoing the motif of the centuries old tradition of the "King's touch". It was believed, among the common people, that the touch of the Monarch could cure subjects of diseases such as tuberculosis (or scrofula - as it was often know as). Napoleon is imitating the great Monarchs of France. Artistically the work, with its use of dramatic gestures, lighting, and its exotic setting, may be seen as a harbinger of Romanticism in France.

The catastrophic plague that broke out among Napoleon's Army of the Orient, in Acre in March 1799 took a fearful toll, and greatly contributed to the failure of the siege of that city and the eventual withdrawal of the French back to Egypt. The simple 21st century antibiotic doxycycline, could have cured many.

DOXYCYCLINE

Introduction

Doxycycline is a broad spectrum long acting tetracycline antibiotic.

It is effective against both gram positive and gram negative organisms, as well as a wide range of “atypical” organisms, including **rickettsia, mycoplasma, chlamydia**, and some **plasmodium** species.

Many gram positive and gram negative strains however are resistant and doxycycline remains most useful for atypical organisms.

It is contraindicated in children and pregnancy and children.

It is on the World Health Organization’s current List of Essential Medicines, a list of the most important medications needed in a basic health system.

History

Benjamin Minge Duggar (1872 - 1956) was an American Botanist who in 1945 discovered chlortetracycline, the first tetracycline antibiotic, extracted from a soil bacterium *Streptomyces aureofaciens*.

Oxytetracycline was discovered shortly afterwards by AC Finlay et al. and was extracted from a similar soil bacterium named *Streptomyces rimosus*.

Robert Burns Woodward, an American Organic Chemist (1917 - 1979) determined the structure of Oxytetracycline which then enabled Lloyd H. Conover to discover tetracycline and then produce it synthetically in 1952.

Doxycycline was developed from Oxytetracycline and first marketed for clinical use in 1967.

Chemistry

Doxycycline is a broad spectrum antibiotic synthetically derived from oxytetracycline.

The tetracyclines are so named for their 4 central carbon rings.

Classification

The tetracycline group of antibiotics includes:

- Tetracycline
- Demeclocycline

- Doxycycline
- Minocycline

Doxycycline is generally the best tolerated of the tetracycline antibiotics.

Preparation

Tablets: 50mg, 100 mg.

Capsules: 50mg, 100 mg.

There is an injection formulation but this is only available in Australia via the Special Access Scheme.

Mechanism of Action

The tetracyclines are **bacteriostatic** antibiotics.

They inhibit bacterial protein synthesis by reversibly binding to **30S subunit** of the bacterial ribosome.

Note that the effect of tetracyclines in acne vulgaris also involves mechanisms other than their antimicrobial activity.

Pharmacokinetics

Absorption:

- Doxycycline is administered orally.

It is almost completely absorbed.

IV doxycycline is not registered for use in Australia but is available via the Special Access Scheme. The IV infusion however is painful, and so doxycycline should be administered orally if possible.

Distribution:

- Serum protein binding of doxycycline varies widely (from 23 - 93 %).

Metabolism and excretion:

- The metabolism of doxycycline in the human body has not been well studied.
- More than 90 % of an oral dose of doxycycline is eliminated from the body within 72 hours of drug administration by renal and GIT excretion.

- Its half life is long at 15 - 25 hours, allowing for once or twice daily dosing.

Pharmacodynamics

The tetracyclines, including doxycycline, have a broad spectrum of activity that includes:

- Gram-positive bacteria:
 - ♥ Although many strains are resistant and so empiric doxycycline is not the preferred treatment option here unless susceptibility has been established.

- Gram-negative bacteria:

Including:

- ♥ *Vibrio* species (cholera); *Brucella* species (brucellosis (in conjunction with streptomycin)), *Yersinia pestis* (plague); *Francisella tularensis* (tularemia); *Bartonella bacilliformis* (bartonellosis);
- Chlamydia
- Rickettsia
- Mycoplasma
- Spirochaetes
- Some non-tuberculous mycobacteria
- Some protozoa (including *Plasmodium* species causing malaria).

Indications

Indications for doxycycline include:

1. Lower respiratory tract infections:
 - Community-acquired pneumonia
 - Exacerbation of chronic bronchitis
2. Acute bacterial sinusitis
3. Infections caused by *M. pneumoniae*
4. Chlamydial infections:

- Including lymphogranuloma venereum and other non-gonococcal genital tract infections.
 - Trachoma
5. Rickettsial infections:
 - Including Q fever and typhus.
 6. PID (usually in combination with other agents).
 7. Melioidosis (with other agents)
 8. Sexually acquired epididymo-orchitis (with ceftriaxone)
 9. Chronic prostatitis
 10. Malaria:
 - Prophylaxis of malaria in areas of widespread mefloquine or chloroquine resistance, or in people in whom mefloquine or chloroquine is not tolerated
 - Treatment of *P. falciparum* malaria with quinine
 11. Dermatological:
 - Acne
 - Rosacea (severe cases or failure of topical treatment)

When penicillin is contraindicated, doxycycline is also an alternative drug in the treatment of infections due to:

- *Treponema pallidum* (syphilis)
- *Treponema pertenue* (yaws)
- *Neisseria gonorrhoea*

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. Serious allergy to tetracyclines (contraindicated).
2. **Tetracyclines are contraindicated in children < 8 years:**
 - The principle period of risk is during tooth development which occurs in the latter half of pregnancy, infancy and childhood to the age of 8 years)
 - Note however that because dentine development continues in some children after this age, some practitioners avoid the use of tetracyclines in children up to the age of **12 years**.¹

Pregnancy

Tetracyclines are classified as class D drugs with respect to pregnancy.

Class D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Tetracyclines however are safe for use during the first 18 weeks of pregnancy (16 weeks post conception) after which they may affect the formation of the baby's teeth and cause discolouration.

Breast feeding

Compatible for short courses (e.g. 10 days) if an alternative drug is not appropriate

May cause diarrhoea in infant

Adverse Effects

These principally include:

1. GIT upset, (as with most antibiotics).
2. Allergic reactions
3. Tetracyclines given to children can:
 - Discolour teeth
 - Cause enamel dysplasia, which increases the risk of dental caries.
 - Be deposited in bone, causing deformities and inhibiting bone growth.
4. Dermatological:

- Photosensitivity rashes (depends on the tetracycline, the dose and degree of sun exposure)
 - Occasionally severe reactions such as Stevens-Johnson syndrome.
5. Pseudomembranous colitis:
- Pseudomembranous colitis has been reported with nearly all antibacterial agents, including tetracyclines, and may range in severity from mild to life-threatening.
- Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.
6. Oesophageal ulcers:
- Due to *partly* swallowed tablets or capsules

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:

- **Doxycycline 100 mg orally daily or 12 hourly**

Duration may range from 5 - 14 days depending in the condition being treated



“The Battle of the Pyramids”, oil on canvas, 1808 Louis-François Baron Lejeune.

References

1. eTG - November 2014
 - Antibiotic Therapeutic Guidelines, 15th 2015.
2. Doxycycline in Australian Medicines Handbook Website, Accessed December 2014.
3. Doxycycline in MIMs 1 April 2013.

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