

AZITHROMYCIN



*Saviours of the Western World - Leonidas and the 300, at the Hot Gates - The Battle of Thermopylae
480 B.C (Still from Warner Bros, "300", 2006).*

Spartan soldier: The Persian arrows will be so numerous they will darken the sun.

Leonidas Good - then we shall fight them in the shade!

Plutarch, the Moralia, c. 100 A.D

Xerxes meanwhile, having made libations at sunrise, stayed for some time, until about the hour when the market falls, and then made an advance upon them; for thus it had been enjoined by Epialtes, seeing that the descent of the mountain is shorter and the space to be passed over much less than the going round and the ascent. The Barbarians accordingly with Xerxes were advancing to the attack; and the Hellenes with Leonidas, feeling that they were going forth to death, now advanced out much further than at first into the broader part of the defile; for when the fence of the wall was being guarded, they on the former days fought retiring before the enemy into the narrow part of the pass; but now they engaged with them outside the narrows, and very many of the Barbarians fell: for behind them the leaders of the divisions with scourges in their hands were striking each man, ever urging them on to the front. Many of them were then driven into the sea and perished, and many more still were trodden down while yet alive by one another, and there was no reckoning of the number that perished: for knowing the death which was about to come upon them by reason of those who were going round the mountain, they displayed upon the Barbarians all the strength which they had, to its greatest extent, disregarding danger and acting as if possessed by a spirit of recklessness.

Now by this time the spears of the greater number of them were broken, so it chanced, in this combat, and they were slaying the Persians with their swords; and in this fighting fell Leonidas, having proved himself a very good man, and others also of the Spartans with him, men of note, of whose names I was informed as of men who had proved themselves worthy, and indeed I was told also the names of all the three hundred. Moreover of the Persians there fell here, besides many others of note, especially two sons of Dareios, Abrocomes and Hyperanthes, born to Dareios of Phratagune the daughter of Artanes: now Artanes was the brother of king Dareios and the son of Hystaspes, the son of Arsames; and he in giving his daughter in marriage to Dareios gave also with her all his substance, because she was his only child.

Two brothers of Xerxes, I say, fell here fighting; and meanwhile over the body of Leonidas there arose a great struggle between the Persians and the Lacedemonians, until the Hellenes by valour dragged this away from the enemy and turned their opponents to flight four times. This conflict continued until those who had gone with Epialtes came up; and when the Hellenes learnt that these had come, from that moment the nature of the combat was changed; for they retired backwards to the narrow part of the way, and having passed by the wall they went and placed themselves upon the hillock, all in a body together except only the Thebans: now this hillock is in the entrance, where now the stone lion is placed for Leonidas. On this spot while defending themselves with daggers, that is those who still had them left, and also with hands and with teeth, they were overwhelmed by the missiles of the Barbarians, some of these having followed directly after them and destroyed the fence of the wall, while others had come round and stood about them on all sides.

Such were the proofs of valour given by the Lacedemonians and Thespians; yet the Spartan Dienekes is said to have proved himself the best man of all, the same who, as they report, uttered this saying before they engaged battle with the Medes: -- being informed by one of the men of Trachis that when the Barbarians discharged their arrows they obscured the light of the sun by the multitude of the arrows, so great was the number of their host, he was not dismayed by this, but making small account of the number of the Medes, he said that their guest from Trachis brought them very good news, for if the Medes obscured the light of the sun, the battle against them would be in the shade and not in the sun.

Herodotus, "The Histories", c. 450 - 420 B.C

Over millennia the "West" as we know it today survived about eight critical threats to its very existence. Had any one of these threats not been overcome by extraordinary men in extraordinary circumstances, the world would be a totally different place today. As one goes back in time far enough, an event - even seemingly of the most trivial kind - by dint of the ripple or butterfly effect will have ever exponentially magnifying consequences down through subsequent ages, creating a contemporary Universe that could have had untold alternate realities. With this thought we look far far back to the very first time the cultural heritage we now loosely call the "West" was threatened with extinction - 480 B.C at a place contemporary Greeks called - the "Hot Gates" - the narrowest of the myriad mountain passes that give passage from the East into Greece - a region history would recall as Thermopylae.

In 480 B.C, the Persian Empire was the greatest that had yet existed. It stretched from India to the Hellespont. It was ruled over by Xerxes, who having conquered the entire East, turned his envious eyes to the West. Xerxes' army was said to be over one million - but modern scholars dismiss this as most certainly an extreme exaggeration. The logistics simply did not exist to feed and equip an army

of that size in the Fifth century B.C, indeed armies would not be countered in the millions until the time of the First World War. Nonetheless Xerxes' army was without a doubt by far the biggest ever seen till that time - by some modern estimates perhaps up to 100,000 - 150,000. At Thermopylae fewer than 4000 Greeks faced them - the action at the Hot Gates was in part a rearguard defence - that allowed the escape of the majority of the Greek army back into Greece to reorganize, recoup, and to plan strategies that would not rely on superiority of numbers. The very best of the most elite troops in the world were chosen to defend the mountain passes at Thermopylae - their mission to hold up Xerxes' army for as long as possible, and allow the escape of the bulk of the Greek army - these troops were Spartans to a man, and there would be just 300 of them. The Spartans were few in number, but they were the greatest soldiers in history and at Thermopylae they were led by a brilliant general by the name of Leonidas. The strategy was brilliant - the Greeks were hopelessly - infinitely - outnumbered - but they managed to create a trap that nullified the variable of numbers - and reduced battle to a contest of one on one. On these terms the Spartans were unsurpassed.

At the narrowest point of the mountain passes around Thermopylae at a place called the Hot Gates - Spartan stood shoulder to shoulder with impregnable shields and fearsome spears. For three continuous days they held up the greatest army in history. Xerxes, without any regard whatsoever for the lives of his soldiers, in the "finest" traditions of the First World War - sent wave after wave after wave after wave of his men into the horrific meat-grinder of the Hot Gates. The Spartans slaughtered them all to a man. Herodotus records that over three days they killed 20,000 Persians. Xerxes in a rage forced his men on into the Hot Gates, driving them forward under the lash of battalions behind them. Xerxes' rage was ungoverned, Herodotus records that he even had the Hellespont whipped, "as the waters would not obey him!". His frustration can be imagined. An army of 150,000 in the Fifth century B.C could only survive by constant movement. It survived like a plague of locusts, stripping the land and towns of all resources and food then moving on. To remain still meant to exhaust local resources in very short time - and this would quickly be followed by starvation and infectious disease that could destroy an army far quicker than any opposing army. Every hour lost in stasis brought logistical disaster one step closer to Xerxes. Late on the third day however the Spartans were betrayed by a Greek known as Epialtes, who led the Persians by a circuitous route bypassing the Spartan position. Quickly they were surrounded. Xerxes, with grudging respect offered terms, "surrender your arms" he demanded of the Spartans. Leonidas' famous reply came back, "come and get them!". Immediately Leonidas gave the order to again form up the battle phalanx. Xerxes, outraged, ordered a continuous rain of arrow fire (from a safe long range) - until every Spartan had been killed.

*Though of course technically a "defeat", the rear-guard action at Thermopylae immediately became a glorious symbol of Greek heroism and defiance in the face of overwhelming odds. "Victory" lay not in immediate military terms, but in less tangible long term ones. The inspiring (in the **true** sense of the word- not the modern flogged cliché) defence the Spartans put up at Thermopylae gave strength of spirit to the rest of Greece and enabled it to continue the fight, true to the memory of their heroic comrades. After Thermopylae, serious doubt was put into the mind of Xerxes about whether victory over such a small yet such a formable resistance could be achieved. He would personally withdraw from the campaign, leaving it in the hands of his general Mardonius. Other brilliant generals such as Themistocles, and stunning victories at Salamis and then at Plataea (by a combined Spartan and Athenian force) would deliver ultimate victory to the Greeks. The Greeks achieved final victory, but they would never forget Xerxes' invasion of their homeland. A century and half later they would have their ultimate revenge - in the person of Alexander the Great.*

Over the ensuing millennia, the battle of Thermopylae, came to symbolize the cultural ideals of Western civilization - extremely powerful Western motifs - the honourable fight - not for gold but for duty, the defence of freedom against powers that labour under the lash. The vision of an idea - for a way of life - described so eloquently by John Ruskin's appraisal of democracy as an, "...obedience in its highest form" and "not obedience to a constant and compulsory law, but a persuaded or voluntary yielded obedience to an issued command - freedom proving the stronger idea as the more courageous fighting of the Greeks at Thermopylae, and their later victories at Salamis and Plataea attested". The West carries these same ideals today in the ongoing fight for freedom liberty and democracy against oppression and slavery. A plaque with an epitaph to the 300 is seen today at Thermopylae, with the words of Simonides of Ceos who lived through Xerxes' invasion:

*"Go tell the Spartans, stranger passing by,
That here, obedient to Spartan law, we lie".*

Simonides' epitaph pays homage to an ancient Greek ideal - democracy and the rule of law as a way of life - that resonates down through the countless centuries since - and still remains relevant today.

When overwhelmed by vast hordes of invading microorganisms, we have a most powerful defence at hand in the form of Azithromycin - this agent does not give ultimate victory - rather, just as the Spartans at the Hot Gates, it gives a most invaluable bacteriostatic "holding action" against these invaders -one that will allow time for the body's natural defences to then bring final victory!



"We shall fight them in the shade" - Plutarch

AZITHROMYCIN

Introduction

Azithromycin is a **macrolide bacteriostatic** antibiotic that was derived from erythromycin.

It has a wide spectrum of activity and so is useful for a wide range of conditions.

Azithromycin is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.

History

Azithromycin was developed Pliva, a pharmaceutical company based in Zagreb, Croatia, in 1980.

It was introduced into clinical practice shortly afterwards

Chemistry

Azithromycin is the first of a class of antibiotics designated chemically as **azalides**, a subclass of the **macrolides**.

It was derived from erythromycin chemically, by the insertion of a nitrogen atom into the lactone ring of erythromycin A.

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

Azithromycin as:

Tablets:

- 500 mg, 600 mg.

Oral liquid:

- 40 mg/mL (powder), 15 mL

Ampoules:

- 500 mg powder for reconstitution.

Mechanism of Action

The macrolides including azithromycin 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.

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

They also have some immunomodulatory and anti-inflammatory effects.

Pharmacodynamics

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

1. Gram-positive cocci
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*.

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:

- Azithromycin is given orally or IV (by slow infusion).
It cannot be given by IM injection.
- Bioavailability after oral administration is approximately 37%, but meals can reduce this further.

Distribution:

- Azithromycin is widely distributed throughout the body, although there is poor penetration into the CSF.
- Pharmacokinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the drug is heavily tissue bound.
- Protein binding is variable at 7 -51%
- Azithromycin can cross the human placenta
- Azithromycin is excreted into human breast milk in small amounts.

Metabolism and excretion:

- Biliary excretion is a major route of elimination for unchanged drug, following oral administration.
- Azithromycin has a long tissue half-life, **2 - 4 days**

Indications

Azithromycin because of its broad spectrum of activity is suitable for a wide range of infections.

It may be used alone *or in combination* with other agents for:

1. Pneumonias:

Including many “atypical” pneumonias such as:

- Legionella

- *Mycoplasma pneumoniae*
2. Streptococcal pharyngitis/tonsillitis
 3. Pertussis, (prevention and treatment).
 4. Chlamydial infections:
 - e.g. urethritis, cervicitis, trachoma
 5. STDs including:
 - Gonococcal infection
 - Chancroid (*Haemophilus ducreyi*)
 - Donovanosis (granuloma inguinale - *Klebsiella granulomatis*)
 - Sexually acquired epididymo-orchitis
 - Lymphogranuloma venereum
 - PID
 6. Enteric infections:
 - *Campylobacter* enteritis
 - Cholera
 - *Salmonella* enteritis
 - Typhoid and paratyphoid fevers
 - Traveller's diarrhoea
 7. Mycobacterium infections:
 - *Mycobacterium avium* complex
 - *Mycobacterium marinum*
 8. Australian spotted fevers:
 - Tick typhus: (*Rickettsia australis*, *Rickettsia honei*)
 - Scrub typhus (*Orientia tsutsugamushi*)

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 (including macrolides as a group).
2. Renal impairment:
 - Caution should be exercised when azithromycin is administered to patients with **severe** renal impairment.
3. Hepatic impairment:
 - Use with caution in **severe** impairment; consider dose reduction.
4. Caution in association with other medications known to prolong the QT interval.
5. There is often cross-resistance between macrolides and lincosamides (clindamycin and lincomycin).

Pregnancy

Azithromycin is a class B1 drug with respect to pregnancy.

Class 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.

Azithromycin use during pregnancy has not been associated with an increased risk of major malformations.

Azithromycin is considered safe to use during pregnancy if it is the medicine of choice.

Breast feeding

Small amounts of azithromycin are excreted into breast milk.

Gastrointestinal adverse effects, rash and somnolence have been reported in infants exposed to azithromycin via breast milk.

However, azithromycin is considered safe to use at the recommended doses during breastfeeding, but observe the breastfed infant for adverse effects such as diarrhoea, vomiting and skin rash.

Adverse Effects

These include:

1. CVS:
 - Azithromycin has been associated with prolonged QT interval, (but this is very uncommon).
2. Allergic reactions (uncommon)
3. Dermatologic hypersensitivity reactions:
 - Including serious reactions such as Stevens-Johnson syndrome, DRESS and toxic epidermal necrolysis and AGEP.
4. GIT upset:

As with many antibiotics:

 - Nausea, vomiting, diarrhoea, abdominal pain and cramps

Clostridium difficile associated diarrhoea:

 - Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including azithromycin.
5. Abnormal liver function:
 - Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported. Discontinue azithromycin if signs and symptoms of hepatitis occur.

Dosing

Azithromycin is administered as an intravenous **infusion** over not less than **60 minutes**.

Exact dosing regimens vary according to the condition that is being treated.

In general terms:

Oral:

Adult:

- Oral, 500 mg once on day 1.
Then give 500 mg once daily for 2 days or 250 mg once daily for 4 days.

The higher dose can be given for > 3 days, depending on the infection.

Child:

- > 6 months, oral 10 mg/kg (maximum 500 mg) once on day 1.

Then give 10 mg/kg (maximum 500 mg) once daily for 2 days or 5 mg/kg (maximum 250 mg) once daily for 4 days.

The higher dose can be given for >3 days, depending on the infection.

IV:

The commonest indication for azithromycin in the ED is for the **empiric treatment of pneumonias, in combination with other agents.**

For pneumonia give:

- **Azithromycin 500 mg IV, infused over 1 hour, daily.**



“Many of them were then driven into the sea and perished” - Herodotus

References

1. eTG - July 2018
2. Azithromycin in Australian Medicines Handbook Website, Accessed August 2018.
3. Azithromycin in MIMs Website 1 October 2017.
4. Azithromycin in RWH Pregnancy & Breastfeeding Guidelines, 17 January 2017.

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