

CLARITHROMYCIN



“The Sense of Taste” from the La Dame a la Licorne, Late 15th Century Flemish Tapestry in wool and silk, Musée Nationale du Moyen Age, Paris.

The other senses may be enjoyed in all their beauty when one is alone, but taste is largely social. Humans rarely choose to dine in solitude, and food has a powerful social component. The Bantu feel that exchanging food makes a contract between two people who then have a “clanship of porridge”. We usually eat with our families, so it’s easy to see how “breaking bread” together would symbolically link an outsider to a family group. Throughout the world the stratagems of business take place over meals; weddings

end with a feast; friends reunite at celebratory dinners; children herald their birthdays with ice-cream and cake; religious ceremonies offer food in fear, homage, and sacrifice; wayfarers are welcomed with a meal. As Brillat-Savarin says “every...sociability...can be found assembled around the same table: love, friendship, business, speculation, power, importunity, patronage, ambition, intrigue...”.

If an event is meant to matter emotionally, symbolically, or mystically, food will be close at hand to sanctify and bind it. Every culture uses food as a sign of approval or commemoration, and some foods are even credited with supernatural powers, others eaten symbolically, still others eaten ritualistically, with ill fortune befalling dullards or skeptics who forget the recipe or get the order of events wrong. Jews attending a Seder eat a horseradish dish to symbolize the tears shed by their ancestors when they were slaves in Egypt. Malays celebrate important events with rice, the inspirational center of their lives. Catholics and Anglicans take communion of wine and wafer. The ancient Egyptians thought onions symbolized the many layered Universe, and swore oaths on an onion, as we might on a Bible. Most cultures embellish eating with fancy plates and glasses, accompany it with parties, music, dinner theater, open air barbecues, or other forms of revelry. Taste is an intimate sense. We can't taste things at a distance. And how we taste things, as well as the exact makeup of our saliva, may be as individual as our fingerprints...Throughout history, and in many cultures, taste, has always had a double meaning. The word comes from the Middle English “tasten” to examine by touch, test, or sample, and continues back to the Latin “taxare”, to touch sharply. So a taste was always a trial or test. People who have taste are those who have appraised life in an intensely personal way and found some of it sublime, the rest of it lacking. Something in bad taste tends to be obscene or vulgar. And we defer to professional critics of wine, food, art, and so forth, whom we trust to taste things for us because we think their taste more refined or educated than ours. A companion is “one who eats bread with another”, and people sharing food as a gesture of peace or hospitality like to sit around and chew the fat.

The first thing we taste is milk from our mother's breast, accompanied by love and affection, stroking, a sense of security, warmth, and well-being, our first intense feelings of pleasure. Later on she will feed us solid food from her hands, or even chew food first and press it into our mouths, partially digested. Such powerful associations do not fade easily, if at all. We say “food” as if it were a simple thing, an absolute like rock or rain to take for granted. But it is a big source of pleasure in most lives, a complex realm of satisfaction both physiological and emotional, much of which involves memories of childhood. Food must taste good, must reward us, or we would not stoke the furnace in each of our cells. We must eat to live, as we must breathe. But breathing is involuntary, finding food is not; it takes energy and planning, so it must tantalize us out of our natural torpor. It must decoy us out of bed in the morning and prompt us to put on constricting clothes, go to work, and perform tasks we may not enjoy for eight hours a day, five days a week, just to “earn our daily bread” or be “worth our salt”, if you like, where the word “salary” comes from. And, because we are omnivores, many tastes must appeal to us, so that we'll try new foods. As children grow they meet regularly throughout the day - at mealtimes - to hear grown-up talk, ask questions, learn about customs, language, and the world. If language didn't arise at mealtimes, it certainly evolved and became more fluent there, as it did during group hunts.

We tend to see our distant past through a reverse telescope that compresses it: a short time as hunter-gatherers, a long time as “civilized” people. But civilization is a recent stage of human life, and, for all we know, it may not be any great achievement. It may not even be the final stage. We have been alive on this planet as recognizable humans for about two million years, and for all but the last two or three thousand we’ve been hunter-gatherers. We may sing in choirs and park our rages behind a desk, but we patrol the world with many of the hunter-gatherer’s drives, motives, and skills. These aren’t knowable truths. Should an alien civilization ever contact us, the greatest gift they could give us would be a set of home movies: films of our species at each stage in our evolution.

Consciousness, the great poem of matter, seems so unlikely, so impossible, and yet here we are with our loneliness and our giant dreams. Speaking into the perforations of a telephone receiver as if through a screen of a confessional, we do sometimes share our emotions with a friend, but usually this is too disembodied, too much like yelling into the wind. We prefer to talk in person, as if we could temporarily slide into their feelings. Our friend first offers us food, drink. It is a symbolic act, a gesture that says: “This food will nourish your body as I will nourish your soul” in hard times, or in the wild, it also says, “I will endanger my own life by parting with some of what I must consume to survive”. Those desperate times may be ancient history, but the part of us forged in such trials accepts the token drink and piece of cheese and is grateful.

Diane Ackerman, “A Natural History of the Senses”, 1990

A majority of people prefer to interpret history as the unfolding of a supernatural design, to whose author we owe obeisance. But that comforting interpretation has grown less supportable as knowledge of the real world has expanded.... In traditional explanations of the past, religious creation stories have been blended with the humanities to attribute meaning to our species’ existence. The time has come to consider what science might give to the humanities and the humanities to science in a common search for a more solidly grounded answer than before to the great riddle of our existence. To begin, biologists have found that the biological origin of advanced social behavior in humans was similar to that occurring elsewhere in the animal kingdom. Using comparative studies of thousands of animal species, from insects to mammals, we’ve concluded that the most complex societies have arisen through eusociality - meaning, roughly, the “true” social condition. By definition, the members of a eusocial group cooperatively rear the young across multiple generations. They also divide labor through the surrender by some members of at least part of their personal reproduction in a way that increases the “reproductive success” (lifetime reproduction) of other members.

Eusociality stands out as an oddity in a couple of ways. One is its extreme rarity. Out of hundreds of thousands of evolving lines of animals on the land during the past four hundred million years, the condition, so far as we can determine, has arisen only nineteen times, scattered across insects, marine crustaceans, and subterranean rodents. The number is twenty, if we include human beings....Furthermore, the known eusocial species arose very late in the history of life. It appears to have occurred not at all during the great Paleozoic diversification of insects, 350 to 250 million years before the present,

during which the variety of insects approached that of today. Nor is there as yet any evidence of eusocial species alive during the Mesozoic Era until the appearance of the earliest termites and ants between 200 and 150 million years ago. Humans at the *Homo* level appeared only very recently, following tens of millions of years of evolution among the Old World primates. Once attained, advanced social behavior at the eusocial grade found a major ecological success....

The history of eusociality raises a question: Given the enormous advantage it confers, why has this advanced form of social behavior been so rare and long in coming? The answer appears to be the special sequence of preliminary evolutionary changes that must occur before the final step to eusociality can be taken. In all of the eusocial species analyzed to date, the final step before eusociality is the construction of a protected nest, from which foraging trips are launched and within which the young are raised to maturity. The original nest builders can be a lone female, a mated pair, or a small and weakly organized group. When this final preliminary step is attained, all that is needed to create a eusocial colony is for the parents and offspring to stay at the nest and cooperate in raising additional generations of young. Such primitive assemblages then divide easily into risk-prone foragers and risk-averse parents and nurses.

What brought a single primate line to the rare level of eusociality? Paleontologists have found that the circumstances were humble. In Africa roughly two million years ago, one species of the primarily vegetarian australopithecines evidently began to shift its diet to include a much higher reliance on meat. For a group to harvest such a high-energy, widely dispersed source of food, it did not pay to roam about as a loosely organized pack of adults and young in the manner of present-day chimpanzees and bonobos. It was more efficient to occupy a campsite (thus, the nest) and send out hunters who could bring home meat, both killed or scavenged, to share with others. In exchange, the hunters received protection of the campsite and their own young offspring kept there. From studies of modern humans, including hunter-gatherers, whose lives tell us so much about human origins, social psychologists have deduced the mental growth that began with hunting and campsites. A premium was placed on personal relationships geared to both competition and cooperation among the members.....Today, at the terminus of this evolutionary process, our immense memory banks are smoothly activated to join past, present, and future. They allow us to evaluate the prospects and consequences of alliances, bonding, sexual contact, rivalries, domination, deception, loyalty, and betrayal. We instinctively delight in the telling of countless stories about others, cast as players upon our own inner stage. The best of it is expressed in the creative arts, political theory, and other higher-level activities we have come to call the humanities

Edward O Wilson, "The Meaning of Human Existence" 2014.

The magisterial Edward O. Wilson makes an impassioned plea for the humanities and the sciences to work together to give meaning to human existence. Ms Dianne Ackerman in her splendidly sensuous book "A Natural History of the Senses" answers this call with her enchanting narrative of the sense of taste - a truly human insight to "eusociality".

Sadly the antibiotic agent clarithromycin, has the unusual and not uncommon side effect of disturbing the evolutionary miracle of our "social sense".

CLARITHROMYCIN

Introduction

Clarithromycin is a semi-synthetic **macrolide** antibiotic for **oral** use.

It can be prescribed for people who have an allergy to the penicillins or the cephalosporins.

It is better tolerated orally than erythromycin, and only requires twice daily dosing compared to erythromycin which is generally taken 6 - 8 hourly.

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

History

Clarithromycin was developed by researchers at the Japanese drug company Taisho Pharmaceutical in the 1970s.

It was developed in an effort to overcome the GIT effects of the prototype macrolide, erythromycin.

It came into widespread clinical use in Japan in the 1990s and in Europe and the USA in the mid- 2000s.

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.

Preparations

Clarithromycin as:

Tablets:

- 250 mg
- 500 mg.

Liquid:

- 50 mg/mL (as powder for reconstitution)

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.

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:
 - 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*.
 - Clarithromycin also has specific activity against **mycobacteria ulcerans**, (but is usually used in combination with rifampicin for this infection).

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

- Enteric Gram-negative rods.
- Pseudomonas aeruginosa

Pharmacokinetics

Absorption:

- Clarithromycin is administered orally.
- The absolute bioavailability of 250 mg tablets is approximately 50%.

Distribution:

- Clarithromycin distributes readily into body tissues and fluids, though animal studies indicate that its penetration into the CNS is poor.
- Because of high intracellular concentrations, tissue concentrations may be higher than serum concentrations.³
- Protein binding of clarithromycin in plasma averages about 70%
- Clarithromycin can cross the human placenta
- Clarithromycin is excreted into human breast milk

Metabolism and excretion:

- The principal metabolite of clarithromycin is 14-hydroxy-clarithromycin.
- Approximately 20 - 30 % (depending on the dose given) of clarithromycin is excreted unchanged in the urine.

Indications

It can be 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
4. Prevention and treatment of pertussis
5. Prevention and treatment of *Mycobacterium avium* complex (MAC) and other non-tuberculous mycobacterial infections, with other agents
6. Clarithromycin can also be used in combination with other drugs in the eradication of *Helicobacter pylori* infection. ¹

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 clarithromycin (or other macrolides).
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. 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

Clarithromycin is a category B3 drug with respect to pregnancy.

Category B3 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 shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Clarithromycin use during pregnancy has not been associated with a significant increased risk of major malformations or congenital cardiovascular malformations.

Clarithromycin is considered safe to use during pregnancy if it is the medicine of choice, but consultation with an Infectious Diseases Specialist or Clinical Microbiologist for further advice is recommended if required.

Breast feeding

Small amounts of clarithromycin are excreted into the breast milk, but adverse effects have not been reported in breastfed infants.

Clarithromycin is safe to use at the recommended doses. However, observe the breastfed infant for potential adverse effects such as diarrhoea, vomiting, skin rashes 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. Taste disturbance:
 - An unusual, but relatively frequent, minor adverse effect of clarithromycin is altered taste perception, often described as “metallic”.
4. 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.

5. Drug interactions:

- Erythromycin (and clarithromycin) are potent inhibitors of the cytochrome P450 (CYP3A4) enzyme system, so they can have significant drug interactions with drugs that are metabolized by these this enzyme system.

Azithromycin and roxithromycin cause less inhibition of the cytochrome P450 (CYP3A4) enzyme system.

6. Azithromycin, erythromycin and clarithromycin may prolong the QT interval

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:

- **Clarithromycin 500 mg orally 12 hourly**

Children: 7.5 mg/kg (maximum 500 mg) twice daily.

Daily maximum is 1 gram twice daily.

References

1. eTG - June 2017
 - Antibiotic Therapeutic Guidelines 15th ed 2014.
2. Clarithromycin in Australian Medicines Handbook Website, Accessed August 2014.
3. Clarithromycin in MIMs Website 1 July 2012
4. Clarithromycin in RWH Pregnancy & Breast feeding Guidelines, 17 January 2017

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