THE NORTHERN HOSPITAL

RIAMET (ARTEMETHER AND LUMEFANTRINE)

"Artemis", Roman marble, copy of a Greek original, possibly by Cephisodotus, Fourth Century BCE, Musei Capitolini, Rome.

"Take one bunch of Qinghao, soak this in two sheng of water, wring it out to obtain the juice and ingest it in its entirety"

Prescriptions for Emergency Treatments
Ge Hong, Jin Dynasty, 3rd/4th Century A.D

On the 23rd of May 1967, during the darkest days of the Cultural Revolution and the Vietnam War, a top secret meeting was held by the highest levels of the Chinese Communist government. The war against the West in Vietnam was not going well. Even worse, chloroquine resistant malaria had arisen in the jungles of the North, and it was taking a fearful toll on the troops. The North Vietnamese sent an urgent message to Chairman Mao pleading for urgent medical assistance. As a result of the subsequent meeting a secret project, known only as "Protect 523" was established.

Over five hundred scientists in over sixty laboratories and institutes went to work, in what essentially amounted to a botanical "Manhattan project". Different approaches were taken, but one team in particular took a daring approach. Professor Youyou Tu, led her team in closely examining the ancient recipes and practices of millennia of Chinese traditional medicine. Amoung the countless number, one stood out to her from an almanac of the time of the Jin Dynasty..."Take one bunch of Qinghao, soak this in two sheng of water, wring it out to obtain the juice and ingest it in its entirety". It was known that this concoction had been used at least up until the Sixteenth century for the treatment of certain fevers. In a stunning achievement she managed to isolate a chemical from the Qinghaosu plant that was an extremely potent anti-malarial agent.

In 2011, Youyou Tu was awarded the prestigious Lasker DeBakey Clinical Research Award for her discovery of the Artemisinins, the most potent natural anti-malarial agents discovered since the time of the discovery of quinine by South American Jesuits in the Sixteenth century. Many synthetic anti-malarial agents have burst onto the scene, only to quickly fall into obsolesce in face of rapid evolution of resistance in the malaria parasite. Only the naturally occurring quinine has stood the test of centuries of longevity. It is to be hoped that the Artemisinins may the same longevity.

An important message from the lesson of the life saving chemicals to be found in the plant kingdom, is that it is the diversity of nature that drives evolution. We must strive to preserve as much of this diversity as we possibly can - in the future we will no doubt face terrible new biological threats - and it will be more than likely that our delivery from these will come from the incredible diversity of life on planet Earth - providing this diversity still exists!

Most ancient cultures and religions recognize the critical relationship of humanity with the natural world. Many have creation mythology that describes a deity that nurtures the balance of nature for the benefit of all humanity. One of the most ancient of all these deities was the Greek goddess Artemis, goddess of the animals, of the plants, of all nature. Our contract with the goddess is to preserve nature and she will in return preserve humanity. We honour Artemis by invoking her name in the latest life-saving anti-malarial agent - the Artemis-inins.

RIAMET (ARTEMETHER AND LUMEFANTRINE)

Artemisia annua, is a native to temperate regions of Asia.

"…I will argue that every scrap of biological diversity is priceless, to be learned and cherished, and never to be surrendered without a struggle….We should preserve every scrap ….while we learn to use it and come to understand what it means to humanity".

Edward O Wilson.

Introduction

Riamet (Artemether and Lumefantrine) is a dual combination drug used in the treatment of malaria.

It is the current drug of first choice for the treatment of uncomplicated *Plasmodium falciparum* malaria. [1]

The combination is also active against all other forms malaria, including ovale, malariae, vivax and knowlesi.

It is thus the drug of choice for the empirical treatment of suspected malaria.

Its most important contraindication however is **pregnancy.**

The antimalarial activity of the combination of lumefantrine and artemether in Riamet is greater than that of either substance alone.

Monotherapy is discouraged by the World Health Organization, as this increases the risk of drug resistance.

History

The genus name *Artemisia* is derived from the Greek goddess **Artemis.**

The medicinal value of the "Qinghaosu**"** plant as it is known in China, had been known by the Chinese for at least two millennia.

In 1596 Li Shizhen recommended tea made from Qinghaosu specifically to treat malaria symptoms.

Professor Youyou Tu, was awarded the **Lasker DeBakey Clinical Research Award** in 2011 for her discovery of the Artemisinins.

Chemistry

Artemisinin and its derivatives are a group of drugs that possess potent anti-malarial activity against all malaria parasites, including *Plasmodium falciparum*.

Artemisinin was first isolated from the plant *Artemisia annua*, (more commonly known as **sweet wormwood** or **sweet Annie)** a herb that had been employed in Chinese traditional medicines.

It is now produced using genetically engineered yeasts.

Chemically, artemisinin is a sesquiterpene lactone that contains an unusual peroxide bridge. This peroxide bridge is believed to be responsible for the drug's mechanism of anti-malarial action. Few other natural compounds are known that have such a peroxide bridge.

Preparation

Tablets Regular:

- **Artemether 20 mg** and **lumefantrine 120 mg**

Riamet **dispersible** tablets are available for:

- Infants and children weighing 5 kg to < 35 kg.

Or

- Aged greater than or equal to 3 months up to 12 years.

Mix the tablet(s) in about 10 mL water per tablet and then take

Mechanism of Action

Artemether and lumefantrine are blood schizontocide agents.

The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment.

Artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron.

Lumefantrine is thought to interfere with the polymerisation process.

Both artemether and lumefantrine also have secondary actions involving inhibition of nucleic acid synthesis within the malarial parasite.

Pharmacodynamics

The antimalarial activity of the combination of lumefantrine and artemether in Riamet is greater than that of either substance alone.

Pharmacokinetics

Absorption:

- Riamet is given orally:
    - ♥ Artemether is absorbed rapidly, with peak plasma concentrations reached about two hours after dosing.
    - ♥ Absorption of lumefantrine, a highly lipophilic compound, starts after a lag time of up to two hours, with peak plasma concentration about six to eight hours after dosing.
- Food **enhances** the absorption of both artemether and lumefantrine.

Distribution:

- Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (97.9 and 99.9%, respectively).

- It is thought likely that artemether and lumefantrine can cross the human placenta

- It is thought likely that artemether and lumefantrine are excreted into human breast milk.

Metabolism and excretion:

- Artemether is rapidly and extensively metabolised by the liver (including substantial first-pass metabolism)

  Human liver microsomes metabolise artemether to the biologically active main metabolite **dihydro-artemisinin** predominantly through the enzyme CYP3A4/5.

  Lumefantrine is metabolized, in human liver microsomes

- Artemether (and dihydro-artemisinin) are rapidly cleared from plasma, with an elimination half-life of about two hours.

  Lumefantrine is eliminated very slowly, with a terminal half-life of two to three days in healthy volunteers and four to six days in patients with falciparum malaria.

Indications

These are:

1. Drug of first choice for the treatment of uncomplicated *Plasmodium falciparum* malaria.

2. Drug of first choice for the empirical treatment of suspected malaria.

Contraindications/ Precautions

These include:

1. Pregnancy (contraindicated) - see below.

2. As Riamet is contraindicated during the first trimester of pregnancy, **women should not conceive while on this treatment for malaria**

3. Patients with known hypersensitivity to artemether or lumefantrine (or any of the excipients).

4. Patients with conditions causing prolonged QTc interval or on drugs which prolong the QTc interval (this is a relative contraindication - no clinical adverse event attributable to QTc prolongation (e.g. syncope, sudden death) has been reported).

5. Riamet is not indicated for, and has not been evaluated for, malaria prophylaxis.

Pregnancy

Artemether and lumefantrine are contraindicated in pregnancy, particularly the first trimester.

They are classed as group 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. Specialized texts should be consulted for further details.

There is very limited information available describing the use of artemether with lumefantrine during the first trimester of pregnancy. However, artemether with lumefantrine is considered safe to use for the treatment of uncomplicated P.falciparum malaria in the second and third trimester of pregnancy.

During the second and the third trimester, treatment may be considered *if the expected benefit to the mother outweighs the risk to the fetus. Expert opinion should be sought.*

Consultation with an Infectious Diseases specialist or Clinical Microbiologist for further advice is recommended when considering artemether with lumefantrine during pregnancy.

Breast feeding

Information on the use of artemether with lumefantrine during breastfeeding has not been located.

The amount of artemether and lumefantrine excreted into breast milk is unlikely to pose adverse effects in the breastfed infant as the medicine is highly protein bound.

Artemether with lumefantrine has been used in infants and young children requiring treatment for malaria, with mild adverse effects. Therefore, infants exposed to artemether with lumefantrine via breast milk should be observed for signs of gastrointestinal adverse effects such as vomiting.

Adverse Effects

The important ones include:

1. **Toxic effects on fetus, (particularly first trimester)**

    - Artemisinins are known to be embryotoxic and teratogenic in animals, causing cardiovascular and skeletal deformities.

    - Based on this evidence from animal studies, Riamet is contraindicated in pregnancy, (especially in the first trimester).

2. GIT upset

3. Allergic/ hypersensitivity reactions, (rare).

Dosing

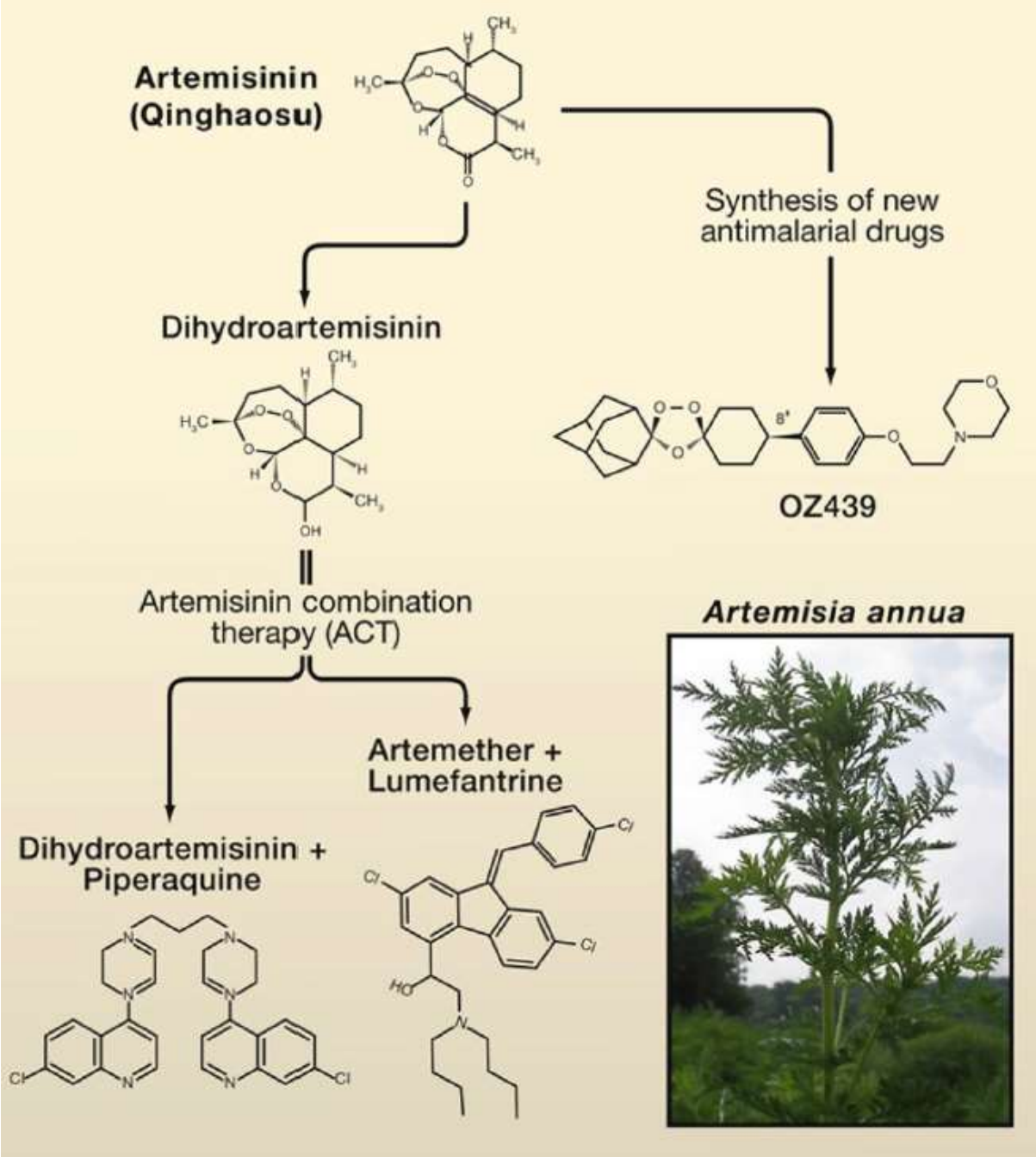
Artemether and lumefantrine tablets (20 mg and 120 mg).

For Adults and children > 34 kg:	4 tablets
Child 5 - 14 kg:	1 tablet.
Child 15 - 24 kg:	2 tablets.
Child 25 to 34 kg:	3 tablets

Tablets are best given with fatty food or full-fat milk

Doses are given at **0, 8, 24, 36, 48** and **60 hours**, making a total adult dose of 24 tablets in 6 doses, (i.e. 4 x 6 tablets).

Appendix 1



Discovery of the Antimalarial Drug Artemisinin (Qinghaosu): *Since the discovery of artemisinin from Artemisia annua L., a plant used in traditional Chinese medicine, by Youyou Tu and colleagues, many derivatives have been synthesized, including dihydroartemisinin, which is more active than artemisinin. To protect this important antimalarial drug, combination therapy with another antimalarial drug is the only treatment used today. The future synthesis of new antimalarial drugs may be possible, originating from the endoperoxide bridge that is required for artemisinin's Antimalarial activity (Charman et al., 2011*

References

1. eTG - March 2014

2. Riamet in Australian Medicines Handbook, October 2013

3. Riamet in MIMs October 2013.

4. Artemether + lumefantrine in RWH Pregnancy & Breastfeeding Guidelines, 17 January 2017.

Further reading:

Louis H. Miller, Xinzhuan Su. Artemisinin: Discovery from the Chinese Herbal Garden. Cell. 2011 September 16; 146 (6): 855 - 858.

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