Pharmacology Aspect of Antimalaria

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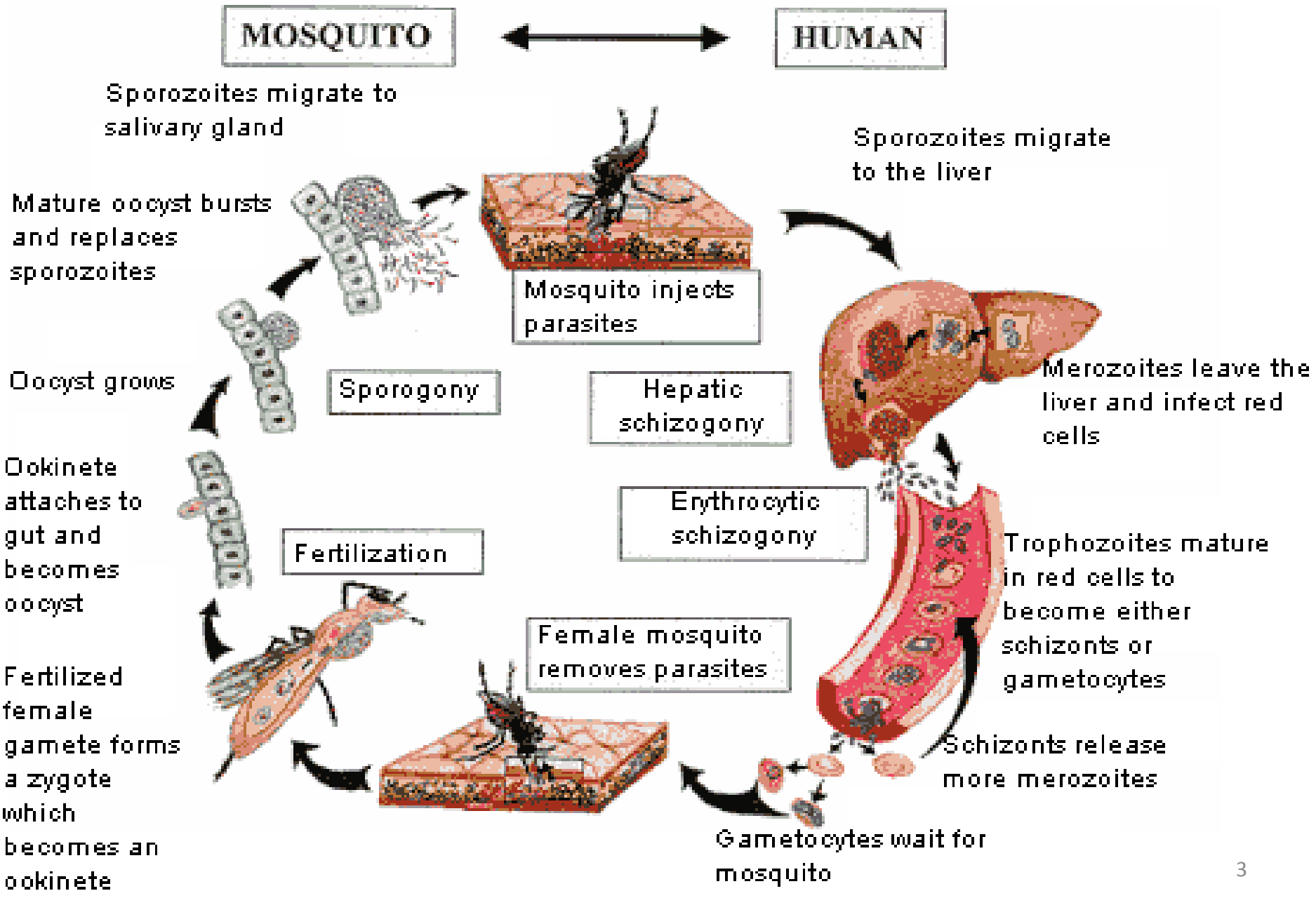
Introduction

- Four species of plasmodium cause human malaria:
  - P *falciparum*,
  - P *vivax,*
  - P *malariae*,
  - P *ovale*.
- Although all may cause significant illness, P *falciparum* is responsible for nearly all serious complications and deaths.
- Drug resistance is an important therapeutic problem, most notably with P *falciparum*.

THE LIFE CYCLE OF MALARIA



Parasite Life Cycle

- An anopheline mosquito inoculates plasmodium sporozoites to initiate human infection.
- Circulating sporozoites rapidly invade liver cells, and exoerythrocytic stage tissue schizonts mature in the liver.
- Merozoites are subsequently released from the liver and invade erythrocytes.
- Only erythrocytic parasites cause clinical illness.
- Repeated cycles of infection can lead to the infection of many erythrocytes and serious disease.
- Sexual stage gametocytes also develop in erythrocytes before being taken up by mosquitoes, where they develop into infective sporozoites.

Parasite Life Cycle

- In P *falciparum* and P *malariae* infection, only one cycle of liver cell invasion and multiplication occurs, and liver infection ceases spontaneously in less than 4 weeks.

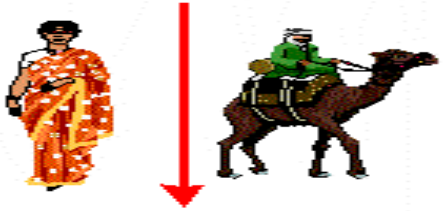
→ Thus, treatment that eliminates erythrocytic parasites will cure these infections.

- In P *vivax* and P *ovale* infections, a dormant hepatic stage, the hypnozoite, is not eradicated by most drugs, and subsequent relapses can therefore occur after therapy directed against erythrocytic parasites.

→ Eradication of both erythrocytic and hepatic parasites is required to cure these infections.

THE LIFE CYCLE OF *PLASMODIUM* SPP.
(CAUSING MALARIA IN HUMANS)

The mosquito injects sporozoites into the human when it feeds.



The sporozoites enter the cells of the liver, reproduce asexually, and finally enter the blood stream..

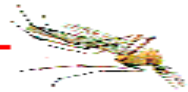
The parasites enter the red blood cells.

The parasites reproduce asexually in the red blood cells. The blood cells burst releasing merozoites.

In the red blood cells, some merozoites will develop into male and female gametocytes.

The gametocytes are ingested by a mosquito when it feeds on blood.

The gametocytes fuse in the vector's gut, sporozoites are produced, and the sporozoites migrate to the vector's salivary glands.



This process continues, destroying significant numbers of red blood cells and causing the paroxysms ("chills and fever") characteristic of malaria infections.

(Parasites and Parasitological Resources)

Drug Classification

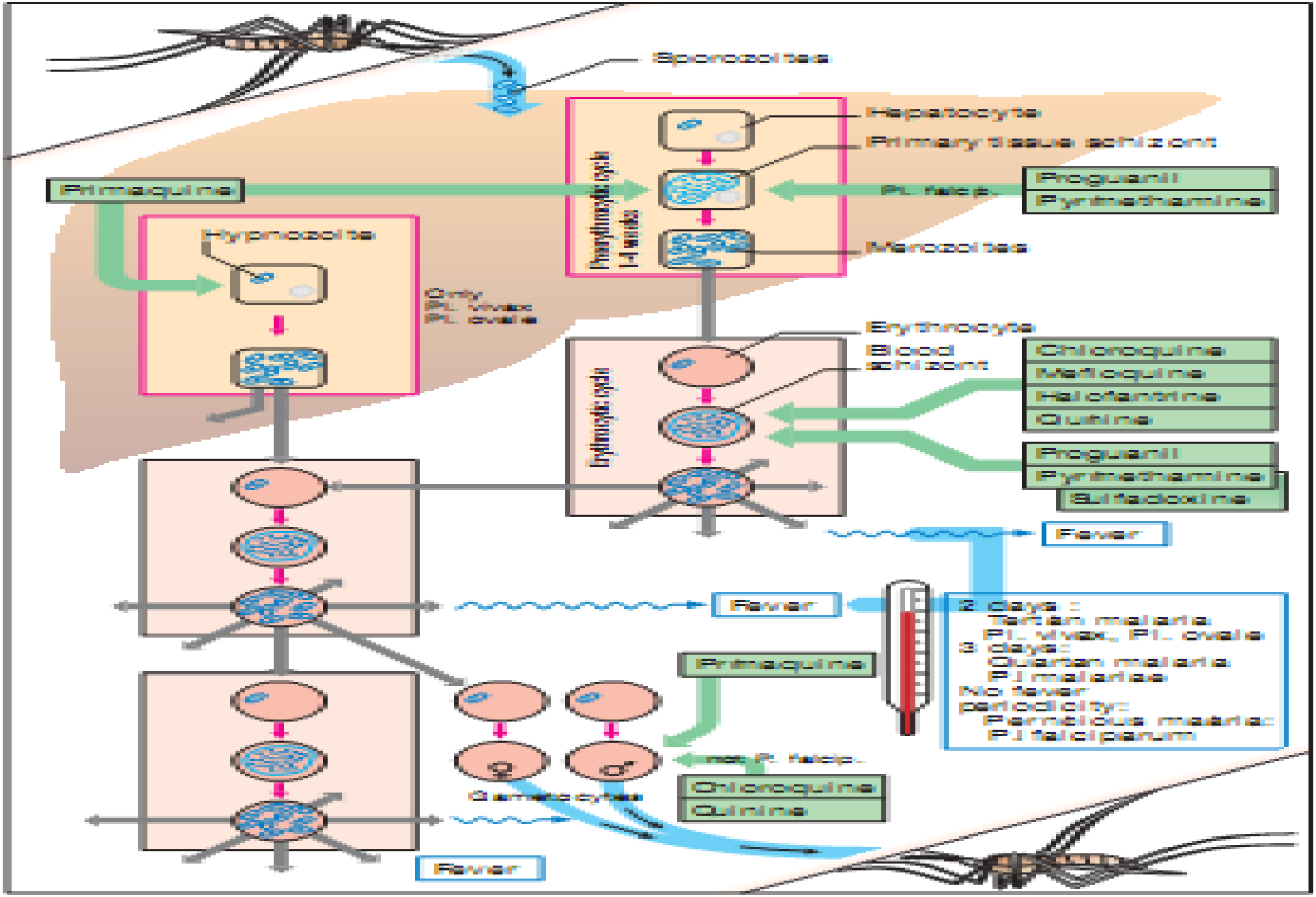
- **Tissue schizonticides** : Drugs that eliminate developing or dormant liver forms
- **Blood schizonticides** : those that act on erythrocytic parasites
- **Gametocides:** those that kill sexual stages and prevent transmission to mosquitoes .
- No one available agent can reliably effect a **radical cure**, ie, eliminate both hepatic and erythrocytic stages.
- Few available agents are **causal prophylactic** drugs, ie, capable of preventing erythrocytic infection.
- However, all effective chemoprophylactic agents kill erythrocytic parasites before they grow sufficiently in number to cause clinical disease.

Drug Classification

Drug	Class	Use
Chloroquine	4-Aminoquinoline	Treatment and chemoprophylaxis of infection with sensitive parasites
Amodiaquine[1]	4-Aminoquinoline	Treatment of infection with some chloroquine-resistant *P falciparum* strains
Quinine	Quinoline methanol	Oral treatment of infections with chloroquine-resistant *P falciparum*
Quinidine	Quinoline methanol	Intravenous therapy of severe infections with *P falciparum*
Mefloquine	Quinoline methanol	Chemoprophylaxis and treatment of infections with *P falciparum*
Primaquine	8-Aminoquinoline	Radical cure and terminal prophylaxis of infections with *P vivax* and *P ovale*
Sulfadoxine-pyrimethamine (Fansidar)	Folate antagonist combination	Treatment of infections with some chloroquine-resistant *P falciparum*
Proguanil[1]	Folate antagonist	Chemoprophylaxis (with chloroquine)

Drug Classification

Doxycycline	Tetracycline	Treatment (with quinine) of infections with *P falciparum;* chemoprophylaxis
Halofantrine[1]	Phenanthrene methanol	Treatment of infections with some chloroquine-resistant *P falciparum*
Lumefantrine[1]	Amyl alcohol	Treatment of *P falciparum* malaria in fixed combination with artemether (Coartem)
Artemisinins[1]	Sesquiterpene lactone endoperoxides	Treatment of infection with multidrug-resistant *P falciparum*
Atovaquone-proguanil (Malarone)	Quinone-folate antagonist combination	Treatment and chemoprophylaxis of *P falciparum* infection



A. Malarial stages of the plasmodial life cycle in the human

Chloroquine

- Synthetic 4-aminoquinoline formulated as the phosphate salt for oral use
- **Phkinetic**:
  - rapidly , almost completely absorbed from the gastrointestinal tract, distributed to the tissue
  - Excreted in the urine
- Blood schizontocide
- Moderately against gametocytes of P. *vivax*, P *ovale* and P. *malariae,* but not P *falciparum*
- Not active against liver stage parasites

Chloroquine

MoA:

- Concentrating in parasite food vacuoles, preventing the polymerization of the hemoglobin breakdown product, heme, into hemozoin and thus eliciting parasite toxicity due to the build up of free heme.

Adverse Effects:

- Common: Pruritus
- Uncommon: Nausea, Vomiting, Abdominal pain, Headache, Anorexia, Malaise, Blurring of vision, Urticaria

Chloroquine

Resistance:

- Common: P. *falciparum*

→ mutations in a putative transporter, PfCRT

- Uncommon: P.*vivax*

Chloroquine : MoA

Inside the red blood cells, the malarial parasite must degrade the hemoglobin for the acquisition of essential amino acids, which the parasite requires to construct its own protein and for energy metabolism. This is essential for parasitic growth and division inside the red blood cell. It is carried out in the digestive vacuole of the parasite cell.

During this process, the parasite produces the toxic and soluble molecule heme. The heme moiety consists of a porphyrin ring called Fe(II)-protoporphyrin IX (FP). To avoid destruction by this molecule, the parasite biocrystallizes heme to form hemozoin, a non-toxic molecule. Hemozoin collects in the digestive vacuole as insoluble crystals.

Chloroquine enters the red blood cell, inhabiting parasite cell, and digestive vacuole by simple diffusion. Chloroquine then becomes protonated (to CQ2+), as the digestive vacuole is known to be acidic (pH 4.7); chloroquine then cannot leave by diffusion. Chloroquine caps hemozoin molecules to prevent further biocrystallization of heme, thus leading to heme buildup. Chloroquine binds to heme (or FP) to form what is known as the FP-Chloroquine complex; this complex is highly toxic to the cell and disrupts membrane function. Action of the toxic FP-Chloroquine and FP results in cell lysis and ultimately parasite cell autodigestion. In essence, the parasite cell drowns in its own metabolic products.

Chloroquine: Resistance

-The effectiveness of chloroquine against the parasite has declined as resistant strains of the parasite that effectively neutralized the drug via the mechanism that drains chloroquine away from the digestive vacuole evolved.[

-CQ-Resistant cells efflux chloroquine at 40 times the rate of CQ-Sensitive cells, this is related to a number of mutations that trace back to transmembrane proteins of the digestive vacuole, including an essential mutation in the PfCRT gene (Plasmodium falciparum Chloroquine Resistance Transporter).

- This mutated protein may actively pump chloroquine from the cell. Resistant parasites frequently have mutated products or amplified expression of ABC transporters that pump out the chloroquine, typically PfMDR1 and PfMDR2 (Plasmodium falciparum Multi-Drug Resistance genes).

- Resistance has also been conferred by reducing the lower transport activity of the intake mechanism, so less chloroquine is imported into the parasite.

Quinine and Quinidine

- QUININE:
  - The bark of the cinchona tree
  - Rapidly acting, highly effective **blood schizonticide** against the four species of human malaria parasites
  - **Gametocidal** against P vivax and P ovale but not P. Falciparum
  - Not active against liver stage parasites
  - **MoA**: unknown
- QUINIDINE: dextrorotatory stereoisomer of quinine

Quinine and Quinidine

- **PO**: rapidly absorbed
  peak plasma levels in 1-3 hours
  widely distributed in body tissues
- **Ph'kinetic**: varies among population
  metabolized in the liver
  excreted in the urine
- Individuals with malaria:
  protein binding ↑
  → higher plasma level
  → but toxicity is not ↑
- Quinidine: shorter t1/2 than quinine

Quinine:

Adverse Effects

- Cinchonism → tinnitus, headache, nausea, dizzines, flushing, visual disturbances
- After prolongoed th/: visual and auditory abnormalities, vomiting, diarrhea, and abdominal pain.
- Hematologic abnormalities (esp. G6PD def)
- Hypoglicemia
- Uterine contraction
- Severe hypotension: Alpha adrenergic blocker
- QT prolongation

Quinine :

Contraindication

- Quinine/quinidine: should be discontinued if :

  - signs of severe cinchonism, hemolysis, or hypersensitivity occur

  - underlying visual or auditory problems

- Not be given concurrently with mefloquine

Primaquine

- **Drug of choice** of dormant liver forms of P *vivax* and P *ovale*
- A synthetic 8-aminoquinoline
- Well **absorbed** orally, reaching peak plasma levels in 1-2 hours
- **Distributed** to the tissues
- The metabolites have less antimalarial activity but more potential for inducing hemolysis than the parent compound

Primaquine

- Active against hepatic stages of all human malaria parasites
- Active against the dormant hypnozoite stages of P *vivax* and P *ovale*
- Gametocidal against the four human malaria species
- **MoA**: unknown

Inhibitor of Folate Synthesis

- PYRIMETHAMINE:
  - t1/2: 3.5 days → administered once a week
- PROGUANIL:
  - biguanide derivative
  - t1/2: 16 hours → administered daily for chemoprophylaxis
  - pro drug: only its triazine metabolite, cycloguanil, is active
- Pyrimethamine and proguanil selectively inhibit plasmodial dihydrofolate reductase
- **Fansidar**: fixed combination of the sulfonamide sulfadoxine (500 mg/tab) and pyrimethamine (25 mg/tab)

Atovaquone

- Atovaquone is a unique naphthoquinone with broad-spectrum antiprotozoal activity.
- It is effective in combination with proguanil for the treatment and prevention of malaria
- A structural analog of protozoan ubiquinone, a mitochondrial protein involved in electron transport.
- It is a highly lipophilic molecule with very low aqueous solubility.
- Atovaquone is protein bound (>99%) but causes no significant displacement of other highly protein-bound drugs.
- However, concomitant administration of atovaquone with rifampin leads to a 40 to 50% reduction in atovaquone levels.

Atovaquone

- For treatment and prophylaxis of malaria it has been combined with the biguanide proguanil in a fixed combination
- **MoA**:

  - Atovaquone has broad-spectrum activity against *Plasmodium* spp., *P. carinii*, *Babesia* spp., and *Toxoplasma gondii*.

  - Its mechanism of action has been most completely elucidated for *Plasmodium* spp.

  - The drug is structurally similar to the inner mitochondrial protein ubiquinone (also called coenzyme Q), which is an integral component of electron flow in aerobic respiration

Artemisinin & Its Derivative

- Artemisinin (qinghaosu):

→a sesquiterpene lactone endoperoxide, the active component of an herbal medicine that has been used as an antipyretic in China for over 2000 years

- Insoluble and can only be used orally
- **Analog**:

  - Artesunate

    (water-soluble, useful for oral, IV, IM, rectal)

  - Artemether

    (lipid soluble, useful for oral, IM, & rectal administration)

Artemisinin & Its Derivative

- The compounds are rapidly metabolized into the active metabolite dihydroartemisinin
- Very rapidly acting blood schizontocides against all human malaria parasites.
- Has no effect on hepatic stages.
- **MoA:** probably results from the production of free radicals that follows the iron catalyzed cleavage of the artemisinin endoperoxide bridge in the parasite food vacuole.

What Is Antimalarial Drug Resistance?

- Ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject" (WHO, 1973).
- The drug must gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action (WHO, 1986).
- Drug resistance ≠ treatment failure

  (host and/or parasite factors)

Consequences of Antimalarial Drug Resistance

- Increased morbidity and mortality
  - including anaemia, low birth weight
- Increased of transmission
  - switch to effective drug combinations in situations of low to moderate endemicity has always resulted in a dramatic decrease in transmission
- Economic impact
  - increases cost to health services (to both provider and patient) because of returning treatment failures
- Greater frequency and severity of epidemics
- Modification of malaria distribution
- Greater reliance on informal private sector
  - With the risk of using monotherapies, sub-standard and counterfeit medicines which in turn will increase drug resistance.

Surveillance of Antimalarial Drug Resistance

1. Avoiding emergence of drug resistance
2. Monitoring drug efficacy
3. Containing of drug resistance

Strategies to Avoid Drug Resistance

- Use of combination therapy
- Effective ACTs of good quality
  - widely accessible
  - correctly used, particularly in the private sector, which includes:
    - education of the practitioners
    - increase compliance by use of co-package or co-formulated ACTs.
    - supervised drug administration can help to back up adherence (similar to DOT)
  - Better diagnosis of the disease to avoid misuse of the medicines
  - Fight against drugs of poor quality
- Transmission control to reduce the burden and the use of antimalarial drugs (less drug pressure)
    - vector control and bed-nets (South Africa)
    - reduction of reservoir of infection (responsible for the spread of drug resistance) in improving therapeutic practice, in particular early diagnosis, effective treatment, and use of gametocytocidal drugs.
    - vaccine

Monitoring Drug Efficacy

- Countries must closely monitor the efficacy of antimalarial medicines recommended in their treatment guidelines and rapidly change drug policy when no longer effective, to avoid emergence of multidrug-resistance.

Rationale for Antimalarial Combination Therapy

- Advantages of combining two or more antimalarial drugs:
  - First cure rates are usually increased.
  - Second, in the rare event that a mutant parasite which is resistant to one of the drugs arises de-novo during the course of the infection, it will be killed by the other drug. This mutual protection prevents the emergence of resistance.
- Both partner drugs in a combination must be independently effective.
- **Risks**: Increased costs and increased side effects

The Choice of Artemisinin Combination Therapy (ACT)

Combinations which have been evaluated:

artemisinin + mefloquine, piperaquine

artemether + mefloquine, lumefantrine

dihydroartemisinin + mefloquine, **piperaquine**, naphthoquine

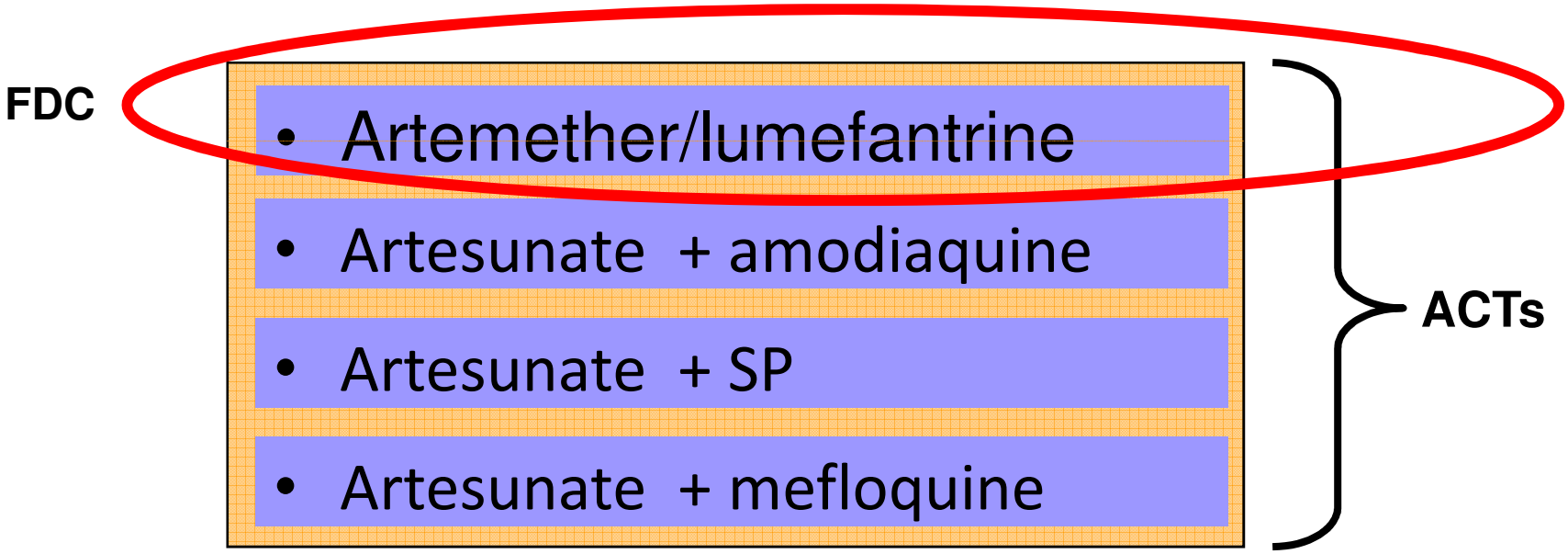
artesunate +

- chloroquine
- amodiaquine
- sulfadoxine-pyrimaethaminine
- mefloquine
- proguanil-dapsone
- chlorproguanil-dapsone
- atovaquone-proguanil
- clindamycin
- tetracycline
- doxycycline

There are now more trials involving artemisinin and its derivatives than other antimalarial drugs, so although there are still gaps in our knowledge, there is a reasonable evidence base on safety and efficacy from which to base recommendations.

Response to increasing resistance :
Combination therapies Recommended by WHO

WHO Technical Consultation on
"Antimalarial Combination Therapy" – April 2001



Remember about ACT's

- Short shelf life (24 months)
- Increased costs
- Longer lead time for deliveries
- Challenging implementation

but also…

- Strong commitment from all the partners
- Upscaled production from the manufacturers
- Shared knowledge and experience
- Global building capacity

Case Management: Drug Efficacy in Pregnancy

- Effective drugs are needed for *P. falciparum* malaria as it can be fatal to both mother and child.
- Drug of choice depends on the geographic drug resistance profile:
  - Chloroquine is the drug of choice in few areas where it is still effective
  - SP often next choice
  - Quinine is the drug of choice for complicated malaria

Drugs that should not be used during pregnancy

- **Tetracycline**
  - Cause abnormalities of skeletal and muscular growth, tooth development, lens/cornea
- **Doxycycline**
  - Risk of cosmetic staining of primary teeth is undetermined
  - Excreted into breast milk
- **Primaquine**
  - Harmful to newborns who are relatively Glucose-6-Phosphatase-Dehydrogenase (G6PD) deficient
- **Halofantrine**
  - No conclusive studies in pregnant women
  - Has been shown to cause unwanted effects, including death of the fetus, in animals


THANKS