Chapter-14

Antimalarial Drugs

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ABSTRACT

Antimalarial drugs are medications used to prevent and treat malaria, a life-threatening disease caused by *Plasmodium* parasites transmitted through the bites of infected Anopheles mosquitoes. These drugs target different stages of the parasite's life cycle, including the liver and blood stages. Common antimalarial drugs include chloroquine, quinine, mefloquine, atovaquone-proguanil, and artemisinin-based combination therapies (ACTs). Chloroquine and mefloquine interfere with the parasite's ability to detoxify heme, a toxic byproduct of hemoglobin digestion. Quinine, a traditional remedy, disrupts the parasite's replication within red blood cells. ACTs, such as artemether-lumefantrine, are highly effective due to the rapid action of artemisinin derivatives combined with a partner drug to prevent resistance. Prophylactic drugs like atovaquone-proguanil and doxycycline are used to prevent infection in travelers to endemic areas. The development of drug resistance, particularly in *Plasmodium falciparum*, poses significant challenges, necessitating ongoing research for new treatments. Effective antimalarial therapy, combined with preventive measures like bed nets and insect repellents, is crucial for controlling and eventually eradicating malaria.

Introduction to Antimalarial Drugs

Malaria is a serious and sometimes fatal disease caused by *Plasmodium* parasites, which are transmitted to humans through the bites of infected Anopheles mosquitoes. The disease remains a major health problem in many parts of the world, particularly in sub-Saharan Africa, Southeast Asia, and parts of South America. Antimalarial drugs are critical in both the treatment and prevention of malaria. These drugs work by targeting different stages of the parasite's life cycle, including the liver and blood stages, to reduce the parasite load and alleviate symptoms. Effective antimalarial therapy, in combination with vector control measures such as insecticide-treated bed nets and indoor residual spraying, is essential in the global fight against malaria.

Classification of Antimalarial Drugs

Antimalarial drugs can be classified based on their chemical structure, mechanism of action, and the stage of the *Plasmodium* life cycle they target. The main classes include:

1. Aminoquinolines
2. Artemisinin Derivatives

3. Antifolate Drugs
4. Hydroxynaphthoquinones
5. Antibiotics
6. Other Antimalarials

1. Aminoquinolines

Examples: Chloroquine, Hydroxychloroquine, Mefloquine

Mechanism of Action: Aminoquinolines interfere with the parasite's ability to detoxify heme, a byproduct of hemoglobin digestion within red blood cells. Accumulation of toxic heme leads to parasite death.

Targeted Stages: Blood schizonticides, effective against asexual erythrocytic forms of *Plasmodium*.

Clinical Use: Chloroquine is used for treating non-resistant *Plasmodium falciparum* and other *Plasmodium* species. Mefloquine is used for both treatment and prophylaxis, particularly in areas with chloroquine-resistant *P. falciparum*.

2. Artemisinin Derivatives

Examples: Artemether, Artesunate, Dihydroartemisinin

Mechanism of Action: Artemisinin derivatives produce free radicals within the parasite by reacting with heme, leading to oxidative damage and death of the parasite.

Targeted Stages: Rapid-acting blood schizonticides, effective against asexual erythrocytic forms and early gametocytes of *Plasmodium*.

Clinical Use: Used in combination therapies (ACTs) to treat uncomplicated and severe malaria. Examples include artemether-lumefantrine and artesunate-mefloquine.

3. Antifolate Drugs

Examples: Sulfadoxine-Pyrimethamine (Fansidar), Proguanil, Pyrimethamine

Mechanism of Action: Antifolate drugs inhibit enzymes involved in folate synthesis, crucial for DNA synthesis and cell division in the parasite.

Targeted Stages: Blood schizonticides and some liver stage activity.

Clinical Use: Used in combination with other antimalarials for treatment and prophylaxis. Sulfadoxine-pyrimethamine is commonly used in intermittent preventive treatment in pregnancy (IPTp).

4. Hydroxynaphthoquinones

Examples: Atovaquone

Mechanism of Action: Atovaquone inhibits the parasite's mitochondrial electron transport chain, disrupting energy production.

Targeted Stages: Blood and liver schizonticide.

Clinical Use: Used in combination with proguanil (atovaquone-proguanil) for both treatment and prophylaxis of malaria.

5. **Antibiotics**

   Examples: Doxycycline, Clindamycin, Azithromycin

   Mechanism of Action: Antibiotics interfere with protein synthesis in the parasite by targeting its ribosomes.

   Targeted Stages: Blood schizonticides; primarily used in combination with other antimalarials.

   Clinical Use: Doxycycline is commonly used for malaria prophylaxis in travelers. Clindamycin is used in combination with quinine or artesunate for treatment.

6. **Other Antimalarials**

   Examples: Quinine, Primaquine, Tafenoquine

   Mechanism of Action

   - **Quinine:** Interferes with heme polymerization, similar to aminoquinolines.
   - **Primaquine and Tafenoquine:** Disrupt mitochondrial function and generate reactive oxygen species.

   Targeted Stages

   - **Quinine:** Blood schizonticide, effective against severe malaria.
   - **Primaquine and Tafenoquine:** Effective against liver stages (hypnozoites of *P. vivax* and *P. ovale*) and gametocytes.

   Clinical Use

   - **Quinine:** Used for severe malaria and as a second-line treatment.
   - **Primaquine and Tafenoquine:** Used for radical cure of *P. vivax* and *P. ovale* to prevent relapse and to prevent transmission.

Chloroquine

Chemical Structure: Chloroquine is a 4-aminoquinoline compound.

Mechanism of Action: Chloroquine acts by inhibiting the heme polymerase enzyme, which converts toxic heme (released during hemoglobin digestion) into non-toxic hemozoin in the parasite's food vacuole. Accumulation of toxic heme results in oxidative damage and death of the parasite.

Pharmacokinetics

- **Absorption:** Chloroquine is well absorbed orally.
- **Distribution:** It is widely distributed in body tissues, including the liver, spleen, kidneys, and lungs. It also accumulates in melanin-containing tissues like the skin and retina.
- **Metabolism:** Metabolized in the liver to active metabolites.
- **Excretion:** Excreted primarily via the kidneys. The elimination half-life is about 1-2 months due to extensive tissue binding.

Therapeutic Uses

- Treatment and prophylaxis of malaria caused by *Plasmodium vivax*, *P. ovale*, *P. malariae*, and chloroquine-sensitive *P. falciparum*.
- Treatment of extraintestinal amebiasis.
- Anti-inflammatory effects for rheumatoid arthritis and lupus erythematosus.

Adverse Effects

- **Common:** Gastrointestinal disturbances, headache, dizziness, and pruritus.
- **Severe:** Retinopathy, cardiotoxicity (especially with long-term use), and potential for hypoglycemia.

Artemisinin

Chemical Structure: Artemisinin is a sesquiterpene lactone containing a peroxide bridge, derived from the sweet wormwood plant (*Artemisia annua*).

Mechanism of Action: The peroxide bridge in artemisinin is activated by iron, leading to the generation of free radicals within the parasite. These free radicals cause extensive oxidative damage to parasite proteins and membranes, leading to rapid parasite death.

Pharmacokinetics

- **Absorption:** Artemisinin and its derivatives (artemether, artesunate) are well absorbed orally and intramuscularly.
- **Distribution:** Widely distributed in the body, including the brain.
- **Metabolism:** Rapidly metabolized in the liver to dihydroartemisinin, the active metabolite.
- **Excretion:** Excreted primarily in the urine. The half-life is relatively short, ranging from 1 to 3 hours.

Therapeutic Uses

- Treatment of uncomplicated and severe malaria caused by *Plasmodium falciparum*.
- Often used in combination with other antimalarials (artemisinin-based combination therapies, ACTs) to prevent resistance.

Adverse Effects

- **Common:** Nausea, vomiting, diarrhea, dizziness.
- **Severe:** Rare but can include neurotoxicity and cardiotoxicity, especially with prolonged use or high doses.

Hydroxychloroquine

Chemical Structure: Hydroxychloroquine is a 4-aminoquinoline, chemically similar to chloroquine but with a hydroxyl group.

Mechanism of Action: Similar to chloroquine, hydroxychloroquine inhibits heme polymerase, leading to the accumulation of toxic heme in the parasite's food vacuole. It also has immunomodulatory effects, making it useful in treating autoimmune diseases.

Pharmacokinetics

- **Absorption:** Well absorbed orally.
- **Distribution:** Extensively distributed in body tissues, including the skin, liver, kidneys, and eyes. It crosses the placenta and is found in breast milk.
- **Metabolism:** Partially metabolized in the liver to active metabolites.
- **Excretion:** Excreted primarily via the kidneys. The elimination half-life is approximately 40-50 days due to extensive tissue binding.

Therapeutic Uses

- Treatment and prophylaxis of malaria, particularly in chloroquine-sensitive areas.
- Treatment of rheumatoid arthritis and systemic lupus erythematosus.
- Potential off-label uses in other autoimmune conditions.

Adverse Effects

- **Common:** Gastrointestinal disturbances, headache, dizziness, and pruritus.
- **Severe:** Retinopathy (risk increases with cumulative dose), cardiotoxicity, muscle weakness, and potential for hypoglycemia.

Artemether

1. Mechanism of Action

- Artemether is a derivative of artemisinin and acts by forming free radicals in the presence of iron. This can damage the proteins and membranes of the malaria parasite, leading to its destruction.

2. Pharmacokinetics

- **Absorption**: Artemether is rapidly absorbed after oral administration.
- **Distribution:** It has a short half-life and is quickly distributed to tissues.
- **Metabolism:** Artemether undergoes metabolism primarily in the liver.
- **Excretion:** The drug and its metabolites are excreted in the urine.

3. Clinical Uses

- Artemether is often used in combination with lumefantrine as part of artemisinin-based combination therapies (ACTs).
- It is specifically effective against Plasmodium falciparum, including drug-resistant strains.
- ACTs, including artemether-based combinations, are recommended as the first-line treatment for uncomplicated falciparum malaria due to their rapid parasite clearance.

Sulfadoxine-Pyrimethamine (SP)

1. Mechanism of Action

- Sulfadoxine: Sulfadoxine is a dihydropteroate synthase inhibitor, which interferes with the synthesis of folic acid in the malaria parasite. Folic acid is essential for the synthesis of DNA and RNA.
- Pyrimethamine: Pyrimethamine inhibits dihydrofolate reductase, another enzyme involved in the synthesis of folic acid. The combination of sulfadoxine and pyrimethamine results in a synergistic effect, disrupting folate metabolism and inhibiting the growth of the malaria parasite.

2. Pharmacokinetics

- **Absorption:** Both components are well-absorbed after oral administration.
- **Distribution:** They are widely distributed in tissues.
- **Metabolism**: Metabolism occurs in the liver.
    - **Excretion:** Both drugs and their metabolites are excreted in the urine.

3. Clinical Uses

- SP has been used for the treatment of uncomplicated malaria caused by Plasmodium falciparum.
- It has also been used for intermittent preventive treatment in pregnant women and infants in areas with high malaria transmission.

Primaquine

1. Mechanism of Action

- Primaquine's exact mechanism of action is not fully understood. It is believed to interfere with the metabolism of the malarial parasite, particularly in the liver stage, and may also induce oxidative stress leading to the destruction of the parasite.

2. Pharmacokinetics

- **Absorption:** Primaquine is well-absorbed after oral administration.
- **Distribution:** It is distributed throughout the body.
- **Metabolism:** Metabolism occurs primarily in the liver.
- **Excretion:** Primaquine and its metabolites are excreted in the urine.

3. Clinical Uses

- Primaquine is primarily used for the radical cure of Plasmodium vivax and Plasmodium ovale malaria, as it targets the liver stages of the parasite.
- It is also used for the prevention of relapse in individuals infected with P. vivax or P. ovale.

Proguanil

1. Mechanism of Action

- Proguanil is a synthetic antimalarial drug that is a prodrug. Its active form is cycloguanil.
- Cycloguanil inhibits the dihydrofolate reductase enzyme of the malaria parasite. This enzyme is essential for the synthesis of purines and pyrimidines, which are necessary for DNA replication and ultimately the survival of the parasite.

2. Clinical Use

- Proguanil is often used in combination with atovaquone, and the combination is known as atovaquone/proguanil (Malarone). This combination is used for both the prevention and treatment of malaria.

3. Pharmacokinetics

- Proguanil is well-absorbed orally.
- It undergoes hepatic metabolism to its active form, cycloguanil.

4. Adverse Effects

- Proguanil is generally well-tolerated, but potential side effects may include gastrointestinal disturbances and mouth ulcers.

Quinine

1. Mechanism of Action

- Quinine is a natural alkaloid derived from the bark of the cinchona tree.
- It acts primarily by inhibiting the hemozoin biocrystallization process within the parasitized erythrocyte. Hemozoin is a byproduct of hemoglobin digestion by the malaria parasite, and its inhibition leads to the accumulation of toxic heme within the parasite, causing its death.

2. Clinical Use

- Quinine has been used for many years in the treatment of malaria. It's often used in combination with other antimalarial drugs to reduce the risk of resistance.

3. Pharmacokinetics

- Quinine is administered orally or intravenously.
- It undergoes hepatic metabolism, and its elimination half-life varies.

4. Adverse Effects

- Quinine can cause a range of side effects, including cinchonism (headache, nausea, vomiting, tinnitus), hypoglycemia, and, in rare cases, serious adverse events like cardiac arrhythmias.

Doxycycline

1. Mechanism of Action

- Doxycycline is a tetracycline antibiotic.
- It inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit, preventing the addition of amino acids to the growing peptide chain.

2. Clinical Use

- In the context of malaria, doxycycline is often used for the prevention of malaria in travelers to areas where certain types of malaria parasites are resistant to other antimalarial drugs.
- It is also used for the treatment of malaria in combination with other antimalarial drugs.

3. Pharmacokinetics

- Doxycycline is well-absorbed after oral administration.
- It has a relatively long half-life, allowing for once-daily dosing.

4. Adverse Effects

- Common side effects include gastrointestinal disturbances, photosensitivity, and the risk of yeast infections.
- It should not be used in pregnant women or young children due to the risk of tooth discoloration.

Mefloquine

1. Mechanism of Action

- Mefloquine is a synthetic antimalarial drug.
- Its exact mechanism of action is not completely understood, but it is believed to interfere with the parasites' ability to detoxify heme, leading to the accumulation of toxic heme metabolites within the parasite.

2. Clinical Use

- Mefloquine is used both for the prevention and treatment of malaria.
- It is particularly useful in areas where malaria parasites are resistant to other antimalarial drugs.

3. Pharmacokinetics

- Mefloquine is well-absorbed after oral administration.
- It has a long half-life, allowing for weekly dosing for malaria prophylaxis.

4. Adverse Effects

- Adverse effects may include gastrointestinal disturbances, dizziness, headache, and vivid dreams.
- Rarely, mefloquine can cause neuropsychiatric side effects, such as anxiety, depression, and seizures. Therefore, individuals with a history of psychiatric disorders may be advised against using mefloquine.

Clindamycin

1. Mechanism of Action

- Clindamycin is a lincosamide antibiotic.
- It inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit and preventing the addition of amino acids to the growing peptide chain.

2. Clinical Use

- Clindamycin is primarily used for the treatment of bacterial infections, especially those caused by anaerobic bacteria.
- In the context of malaria, it is sometimes used as an alternative treatment for severe cases or when other medications are not well-tolerated.

3. Pharmacokinetics

- Clindamycin is available in oral, intravenous, and topical formulations.
- It is well-absorbed after oral administration, and it penetrates well into various tissues, making it effective against infections in different body systems.

4. Adverse Effects

- Common side effects include gastrointestinal disturbances, rash, and the risk of Clostridium difficile infection.
- Severe allergic reactions are rare but can occur.

Lumefantrine

1. Mechanism of Action

- Lumefantrine is an artemisinin-based combination therapy (ACT), specifically combined with artemether in the medication Coartem.
- It works in conjunction with artemether to disrupt the growth and reproduction of the malaria parasites in the erythrocytic stage.

2. Clinical Use

- Lumefantrine, in combination with artemether, is used for the treatment of uncomplicated malaria, particularly caused by Plasmodium falciparum.
- ACTs are recommended by the World Health Organization as a first-line treatment for uncomplicated malaria due to their efficacy.

3. Pharmacokinetics

- Lumefantrine is administered orally.
- It has a relatively long elimination half-life, which helps to sustain therapeutic levels in the body.

4. Adverse Effects

- Common side effects include gastrointestinal symptoms, headache, and dizziness.
- It is generally well-tolerated, but allergic reactions and rare instances of QT interval prolongation have been reported.

Piperaquine

1. Mechanism of Action

- Piperaquine is a bisquinoline antimalarial agent.
- It inhibits heme polymerase activity, preventing the detoxification of heme and leading to the accumulation of toxic heme metabolites in the malaria parasite.

2. Clinical Use

- Piperaquine is often used in combination with other antimalarial drugs, such as dihydroartemisinin, in artemisinin-based combination therapies (ACTs).
- ACTs are recommended as first-line treatments for uncomplicated malaria caused by Plasmodium falciparum.

3. Pharmacokinetics

- Piperaquine is administered orally.
- It has a long elimination half-life, allowing for once-daily dosing in combination therapies.

4. Adverse Effects

- Common side effects include gastrointestinal symptoms, dizziness, and changes in electrocardiogram (ECG) readings.
- It is generally well-tolerated, but prolonged QT interval on ECG has been reported in some cases.

Pyrimethamine

1. Mechanism of Action

- Pyrimethamine is a dihydrofolate reductase inhibitor.
- It inhibits the enzyme dihydrofolate reductase, which is involved in the synthesis of tetrahydrofolic acid, a precursor to DNA synthesis in the malaria parasite.

2. Clinical Use

- Pyrimethamine is often used in combination with sulfadoxine, forming a combination known as sulfadoxine/pyrimethamine (SP).
- This combination is used for the intermittent preventive treatment of malaria in pregnant women and infants in areas with high levels of malaria transmission.

3. Pharmacokinetics

- Pyrimethamine is administered orally.
- It undergoes hepatic metabolism and has a relatively long elimination half-life.

4. Adverse Effects

- Common side effects include gastrointestinal disturbances, rash, and allergic reactions.
- Pyrimethamine should be used with caution in individuals with folate deficiency, as it can exacerbate folate deficiency symptoms.

Atovaquone

1. Mechanism of Action

- Atovaquone is a hydroxynaphthoquinone.
- It inhibits the mitochondrial electron transport chain in the malaria parasite, specifically targeting the cytochrome bc1 complex. This disruption interferes with the parasite's ability to generate adenosine triphosphate (ATP) and leads to the death of the parasite.

2. Clinical Use

- Atovaquone is commonly used in combination with proguanil (atovaquone/proguanil or Malarone) for the prevention and treatment of malaria.
- It is also used in the treatment of Toxoplasma gondii and Pneumocystis jirovecii infections in certain patient populations.

3. Pharmacokinetics

- Atovaquone is well-absorbed orally.
- It has a relatively long elimination half-life, allowing for once-daily dosing.

4. Adverse Effects

- Common side effects include gastrointestinal symptoms such as nausea, vomiting, and diarrhea.
- It is generally well-tolerated, but elevated liver enzyme levels have been reported in some cases.

Artemether-Lumefantrine (Coartem)

1. Mechanism of Action

- Artemether is an artemisinin derivative that rapidly clears the majority of parasites, while lumefantrine, a derivative of aryl-amino alcohol, has a slower action and helps to eliminate remaining parasites.
- Artemether-lumefantrine (Coartem) is an artemisinin-based combination therapy (ACT) used for the treatment of uncomplicated malaria.
- The combination works by rapidly reducing the parasite burden (artemether) and then eliminating residual parasites over a longer period (lumefantrine).

2. Clinical Use

- Coartem is a first-line treatment for uncomplicated malaria, especially in areas where Plasmodium falciparum is prevalent.
- ACTs, including Coartem, are recommended by the World Health Organization due to their high efficacy.

3. Pharmacokinetics

- Artemether-lumefantrine is administered orally.
- Lumefantrine has a relatively long elimination half-life, allowing for a specific dosing schedule.

4. Adverse Effects

- Common side effects include gastrointestinal symptoms, headache, and dizziness.
- It is generally well-tolerated, but rare instances of QT interval prolongation have been reported.