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**COURSE TITLE: SYSTEMIC PHARMACOLOGY IN NURSING PRACTICE**

**TOPIC: CHEMOTHERAPY OF MALARIAL PARASITES**

**CLASSIFICATION OF ANTIMALARIAL AGENTS AND THEIR MECHANISM OF ACTION**

The currently available antimalarials fall into three categories according to their chemical structure and mode of action

1. ARYL AMINOALCOHOL COMPOUNDS: Quinine, Quinidine, Chloroquine, Mefloquine, Lumefantrine etc.
2. ANTIFOLATE COMPOUNDS (ANTIFOLS): Pyrimithamine, Proguanil, Trimethoprin etc
3. ARTHEMISININ COMPOUNDS: Arthmisinin dehydroartemisinin, Arthemeter, Artesunate.

**MECHANISM OF ACTION AND DRUG RESISTANCE**

1. ARYL AMINOALCOHOL COMPPUNDS

* CHLOROQUINE: One of its most dramatic characteristics is its ability to concentrate itself from Nano molar (10^4) levels outside the parasite to levels 1 million times higher in the food vacuole of the parasite inside RBC. Chloroquine works by interfering with the dimerization, detoxifying biochemical process within the malaria parasite that normally yields malaria pigments (hemozoin).

Reduced intracellular drug concentration accompany chloroquine resistance, however, chloroquine resistance was found to be reversible by VERAPAMIL which are calcium channel blockers.

1. ANTIFOLATE DRUGS:

* Pyrimethamine and Biguanides such as cycloguanil interfere with folic acid synthesis, inhibiting the parasite enzyme known as dihydrofolate reductase-thymidilate synthase (DHFR). Sulfonamides act at the previous step in the folic acid pathway, inhibiting the parasite enzyme dihydropteroate synthase (DHPS). There is marked synergy between these two classes of drugs when they are taken together. However, resistance to pyrimethamine is *P.falciparum* developed within a few years of its introduction due to point mutations in the DHFR gene which cause 100-1000 fold reduced affinity of the enzyme complex to the drug.

1. ARTEMISININS

* Of the available antimalarials, the artemisinins are effective at killing the broadest range of asexual stages of the parasite, ranging from medium sized rings to early schizonts; they also produce the most rapid therapeutic responses by accelerating clearance of circulating ring staged parasites. Artemisinin’s chemical structure is unlike any other known antimalarial. It includes an endoperoxide bridge necessary for its antimalarial action. Artemisinin treatment of membranes, especially in the presence of heme, causes lipid peroxidation; this event may occur as a result of the drug’s interaction with intracellular heme or iron. With respect to artemisinin’s direct effect on the malaria parasite, recent work suggests that artemisinin specifically inhibits PfATp6, the SERCA orthologous of *plasmodium falciparum,* a calcium ATPase.

In vivo, artemisinins kill malaria parasites within host erythrocytes, after which dead parasites are culled by the spleen, leaving formerly infected red blood cells intact and circulating. It is not yet clear which asexual parasite lifecycle stages are most sensitive to artemisinin derivatives. Artemisinin derivatives kill early stage gametocytes and are more active over a boarder range of the parasite life cycle than any other antimalarial drug currently in use.

Three derivatives are widely used:

* The oil-soluble methyl ether, artemether (artemotil is a closely related compound).
* The water soluble hemi-subsedrate derivatives, artesunate.
* Dihydroartemisinin (DHA)

Artesunate, artemether are synthesized from DHA and are converted back to it within the body.

NB:

* Artemisisnin is available as capsules of powder, or as suppositories.
* Artemether is formulated in peanut oil for intramuscular injection and in capsules or tablets for oral use
* Artesunate is formulated either tablets, in a gel enclosed in gelatin for rectal administration, or as a dry powder of artesunic acid for injection, supplied with an ampoule of 5% sodium bicarbonate.