Name: Olumba Cherish Nwadiuto

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Classes of Drugs Used in the Treatment of Malaria

Although vector control has some impact, the control and prevention of malaria largely depends on the use of drug therapies. There are a number of life cycle stages at which therapeutic interventions could be beneficial, however the majority of antimalarial drugs act on the asexual intra- erythrocytic phases of development, which is appropriate as this is the stage of the life cycle associated with clinical symptoms.

These include;

* the quinoline methanols- quinine, mefloquine and the phenanthrene halofan- trine
* the sulfonamides- dapsone, sulfadoxine
* the 8-aminoquinoline- primaquine, tafenoquine, bulaquine
* the 4-aminoquinolines- chloroquine (CQ), and amodiaquine (AMQ), hydroxychloroquine, pyronaridine
* the biguanides- chlorproguanil and proguanil
* the napthoquinones such as atovaquone
* the tetracyclines- tetracycline and doxycycline
* the diaminopyrimidines- pyrimethamine
* the antimalarial endoperoxide derivatives artemether, arteether and sodium artesunate

As noted, asexual blood stages have been targeted for chemotherapeutic interventions. Other approaches also merit attention, such as drugs active against liver stages; drugs preventing gametocyte formation; and drugs with gametocytocidal activity (to prevent transmission). The complexity of the parasites life cycle undoubtedly offers many opportunities for therapeutic attack, however this very same complexity appears to have been a major barrier to the systematic study of the parasites biology. The recent completion of the P. falciparum genome sequencing project should go some way to improving this situation with the promise of many new drugs targeting new parasite processes on the way.

Mechanism of action

* Chloroquine

chloroquine and other similar quinolines (e.g. hydroxychloroquine, quinine) become concentrated in parasite food vacuoles, preventing the polymerization of the hemoglobin product, heme, into hemozoin and thus eliciting parasite toxicity due to the build up of heme.

It is not active against liver stage parasites (and primaquine must be added for the radical cure of these species).

* Quinine

Its precise mechanism as an antimalarial is poorly understood. In Plasmodium falciparum quinine has been found to inhibit nucleic acid synthesis, protein synthesis, and glycolysis; it also binds with hemazoin in parasitized erythrocytes.

Quinine is effective as a malarial suppressant and in control of overt clinical attacks. Its primary action is schizontocidal, no lethal effect is exerted on sporozoites or pre-erythrocitic tissue forms.

Quinine blocks cardiac K & Na channels similar to quinidine.

* Primaquine

Active against the hepatic stages of all human malarial parasites. Some gametocytes are destroyed while others cannot undergo maturation division in the gut of the mosquito. Primaquine’s cellular mechanism of action is still poorly understood: Fourteen primaquine metabolites have been detected, and few have been fully assessed for their biological activity.

Evidence suggests that one or more highly reactive metabolites of primaquine inflict extensive oxidative damage that interferes with mitochondrial electron transport in parasites (NOTE: primaquine is also known to increase the oxidative stress on human red blood cells, an effect that contributes to its hemolytic side effects).

* Mefloquine

Unknown, chemically related to quinidine. Has strong blood schizonticidal activity against P. falciparum and P. vivax, but not against hepatic stages or gametocytes.

* Pyrimethamine + Sulfadoxine

Folic acid antagonists. The rationale for there combination is a synergistic effect to inhibit folic acid synthesis, and a differential requirement between host and parasite for nucleic acid precursors involved in growth. This activity is highly selective against plasmodia and Toxoplasma gondii.

Pyrimethamine is chemically related to trimethoprim. It acts slowly against erythrocytic forms of susceptible strains of all four human malaria species. It is not adequately gametocidal or effective against liver stages.

* Artesunate & Artemether (Artemisinin analogs)

Produces a free radical when it undergoes an iron-catalyzed cleavage of an endoperoxide bond in the parasite food vacuole.

It is a rapidly acting blood schizonticide, with some activity against gametocytes, but no activity against the hepatic stages of the malarial parasite.

* Biguanides

Target the dihydrofolate reductase (DHFR) activity of the parasite’s bifunctional DHFR-thymidylate synthetase (TS) protein, these drugs acting as competitive inhibitors of the natural substrates.

* Atovaquone

It is a broad spectrum anti parasitic drug that collapses the mitochondrial membrane potential. The inhibition of electron transfer in the mitochondrion not only results in a loss of the membrane potential but also impedes pyrimidine biosynthesis, two essential processes whose inhibition leads to parasite death.

* Tetracyclines

Cyclines act by binding to several proteins in the 30S ribosomal small subunit and to different ribonucleic acids in the 16S ribosomal RNA. Their mechanisms of action on Plasmodium have not been as well described, although a number of studies have addressed this issue. tetracycline may directly inhibit mitochondrial protein synthesis and also decrease the activity of a mitochondrial enzyme (i.e., dihydroorotate dehydrogenase) involved in de novo pyrimidine synthesis. Doxycycline inhibits the synthesis of nucleotides and deoxynucleotides in P. falciparum.