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DEPTARTMENT: NURSING
LEVEL: 300LEVEL

PHARAMACOLOGY ASSIGNMENT
QUESTION:
1. CLASSIFY THE ANTIMALARIAL AGENTS AND STATE THE MECHANISM OF ACION OF EACH CLASS OF DRUG LISTED

Classification of antimalarial drugs :
1. 4-Aminoquinolines
2. Cinchona alkaloid
3. 8-aminoquinoline
4. Quinolone methanol
5. Diaminopyrimidines
6. Sulphonamides & sulfone
7. Sesquiterpine lactones
8. Biguanides
9. Antibiotics
10. Amino alcohols
11. Naphthoquinone
12. Tissue schizonticides

1)4-Aminoquinolines: e.g chloroquine
Chloroquine is a 4-aminoquinolone compound with a complicated and still unclear mechanism of action. It is believed to reach high concentrations in the vacuoles of the parasite, which, due to its alkaline nature, raises the internal pH. It controls the conversion of toxic heme to hemozoin by inhibiting the biocrystallization of hemozoin, thus poisoning the parasite through excess levels of toxicity. Other potential mechanisms through which it may act include interfering with the biosynthesis of parasitic nucleic acids and the formation of a chloroquine-haem or chloroquine-DNA complex.

2)Cinchona Alkaloid: e.g Quinine is an alkaloid that acts as a blood schizonticidal and weak gametocide against Plasmodium vivax and Plasmodium malariae. As an alkaloid, it is accumulated in the food vacuoles of Plasmodium species, especially Plasmodium falciparum. It acts by inhibiting the hemozoin biocrystallization, thus facilitating an aggregation of cytotoxic heme. Quinine is less effective and more toxic as a blood schizonticidal agent than chloroquine; however, it is still very effective and widely used in the treatment of acute cases of severe P. falciparum. It is especially useful in areas where there is known to be a high level of resistance to chloroquine, mefloquine, and sulfa drug combinations with pyrimethamine. Quinine is also used in post-exposure treatment of individuals returning from an area where malaria is endemic.

3)8-aminoquinoline: Primaquine is a highly active 8-aminoquinolone that is effective against P. falcipaum gametocytes but also acts on merozoites in the bloodstream and on hypnozoites, the dormant hepatic forms of P. vivax and P. ovale.It is the only known drug to cure both relapsing malaria infections and acute cases. The mechanism of action is not fully understood but it is thought to block oxidative metabolism in Plasmodia. It can also be combined with methylene blue.

4)Quinolone Methanol e.g mefloquine is chemically related to quinine. It was developed to protect American troops against multi-drug resistant P. falciparum. It is a very potent blood schizonticide with a long half-life. It is thought to act by forming toxic heme complexes that damage parasitic food vacuoles. Mefloquine is effective in prophylaxis and for acute therapy. It is now used solely for the prevention of resistant strains of P. falciparum (usually combined with Artesunate) despite being effective against P. vivax, P. ovale and P. marlariae. Chloroquine/proguanil or sulfa drug-pyrimethamine combinations should be used in all other plasmodia infections.

5) Diaminopyrimidines: e.g Pyrimethamine
Pyrimethamine is used in the treatment of uncomplicated malaria. It is particularly useful in cases of chloroquine-resistant P. falciparum strains when combined with sulfadoxine. It acts by inhibiting dihydrofolate reductase in the parasite thus preventing the biosynthesis of purines and pyrimidines, thereby halting the processes of DNA replication, cell division and reproduction. It acts primarily on the schizonts during the erythrocytic phase, and nowadays
is only used in concert with a sulfonamide.

6)Sulfonamide and sulfone:eg Sulfadoxine
Sulfadoxine and sulfamethoxypyridazine are specific inhibitors of the enzyme dihydropteroate synthetase in the tetrahydrofolate synthesis pathway of malaria parasites. They are structural analogs of p-aminobenzoic acid (PABA) and compete with PABA to block its conversion to dihydrofolic acid. Sulfonamides act on the schizont stages of the erythrocytic (asexual) cycle. When administered alone sulfonamides are not efficacious in treating malaria but co-administration with the antifolate pyrimethamine, most commonly as fixed-dose sulfadoxine-pyrimethamine (Fansidar), produces synergistic effects sufficient to cure sensitive strains of malaria.

7) Sesquiterpine lactones e.g Artesunate
Artesunate is a hemisuccinate derivative of the active metabolite dihydroartemisin. it is the most frequently used of all the artemesinin-type drugs. Its only effect is mediated through a reduction in the gametocyte transmission. It is used in combination therapy and is effective in cases of uncomplicated P. falciparum. The mechanism of artesunate is thought to involve cleavage of the endoperoxide bond through reaction with haeme . This produces free radicals which alkylate parasitic proteins. It has been shown to inhibit an essential parasite calcium adenosine triphosphatase enzyme. Artesunate inhibits malaria proteins EXP1, a glutathione S-transferase, responsible for breaking down cytotoxic hematin . It is unknown to what extent this inhibition contributes to the action of artesunate.

8)Biguanide: e.g Proguanil

Proguanil (chloroguanide) is a biguanide; a synthetic derivative of pyrimidine. It has many mechanisms of action but primarily is mediated through conversion to the active metabolite cycloguanil. This inhibits the malarial dihydrofolate reductase enzyme. Its most prominent effect is on the primary tissue stages of P. falciparum, P. vivax and P. ovale. It has no known effect against hypnozoites therefore is not used in the prevention of relapse. It has a weak blood schizonticidal activity and is not recommended for therapy of acute infection. However it is useful in prophylaxis when combined with atovaquone or chloroquine (in areas where there is no chloroquine resistance).

9) Antibiotics : e g tetracycline

Tetracycline antibiotics are protein synthesis inhibitors. They inhibit the initiation of translation in variety of ways by binding to the 30S ribosomal subunit, which is made up of 16S rRNA and 21 proteins. They inhibit the binding of aminoacyl-tRNA to the mRNA translation complex.

10) Amino alcohols: eg Halofantrine

It is a phenanthrene methanol, chemically related to Quinine and acts acting as a blood schizonticide effective against all Plasmodium parasites. Its mechanism of action is similar to other anti-malarials. Cytotoxic complexes are formed with ferritoporphyrin XI that cause plasmodial membrane damage. Despite being effective against drug resistant parasites, halofantrine is not commonly used in the treatment (prophylactic or therapeutic) of malaria due to its high cost. It has very variable bioavailability and has been shown to have potentially high levels of cardiotoxicity.

11)Naphthoquinone : eg atovaquone

In Plasmodium species, the site of action appears to be the cytochrome bc1 complex (Complex III). Several metabolic enzymes are linked to the mitochondrial electron transport chain via ubiquinone. Inhibition of electron transport by atovaquone will result in indirect inhibition of these enzymes. The ultimate metabolic effects of such blockade may include inhibition of nucleic acid and ATP synthesis. Atovaquone also has been shown to have good in vitro activity against Toxoplasma gondii. It is commonly used in prophylaxis by travelers and used to treat falciparum malaria in developed countries

12)Tissue Schizonticides: e.g Proguanil

Proguanil (chloroguanide) is a biguanide; a synthetic derivative of pyrimidine.It has many mechanisms of action but primarily is mediated through conversion to the active metabolite cycloguanil. This inhibits the malarial dihydrofolate reductase enzyme. Its most prominent effect is on the primary tissue stages of P. falciparum, P. vivax and P. ovale. It has no known effect against hypnozoites therefore is not used in the prevention of relapse. It has a weak blood schizonticidal activity and is not recommended for therapy of acute infection. However it is useful in prophylaxis when combined with atovaquone or chloroquine (in areas where there is no chloroquine resistance).