Pharmacology assignment 17/mhs01/246

Classify the antimalarial agents and state the mechanism of action of each class of drug listed

i) Quinine:

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 that chloroquine however, it is still very effective and widely used in the treatment of acute casesof severe p.falciparum. Doses can be given by oral, intravenous or intramuscular routes.

Quinmax and quinidine are the two most commonly used alkaloids related to quinine in the treatment and prevention of malaria.

Mechanism of action:

It is the interference with the parasites ability to digest heamoglobin. Quinine and quinidine also inhibit the spontaneous formation of beta-haematin which is a toxic product of the digestion of haemoglobin by parasites.

ii) 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 level of toxicity.

Mechanism of action:

It inhibits the action of heme polymerase in malarial trophozoites, preventing the conversion of heme to hemazoin, it passively diffuses through cell membranes and into endososomes, lysosomes and golgi vesicles, where it becomes protonated, trapping the chloroquine in the organelle and raising the surrounding pH. It prevents virus particles from utilizing their activity for fusion and entry into the cell.

iii) Amodiaquine :

It is a 4-aminoquinolone anti-malarial drug similar in structure and mechanism of action to chloroquine.it has tended to be administered in areas of chloroquine resistance while some patients prefer its tendency to cause less itching than chloroquine.

Mechanism of action:

It is not completely certain like other quinoline derivatives, it is thought to inhibit heme polymerase activity. This results in the accumulation of free heme, which is toxic to parasites.

iv) Pyrimethamine

It is used in the treatment of uncompleted 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.

Mechanism of action:

It inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication.

v) Proguanil:

It is a biguanide; a synthetic derivative of pyrimidine.it 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.

Mechanism of action:

It inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.

vi) Sulfonamides:

It act on the schizont stages of the erythrocytic(asexual cycle). When administered alone sulfanomides are not efficacious in treating malaria but coadministration with the antifolate pyrimethamine, most commonly as fixed dose sulfadoxine-pyrimethamine, produces synergistic effects sufficient to cure sensitive strains of malaria

Mechanism of action:

It is a competitive inhibitor of bacterial enzyme dihydropteroate synthetase. The enzyme normally uses pare-aminobenzoic acid for synthesizing the necessary folic acid. It is normally necessary in these organisms for the synthesis of folic acid, without it bacteria cannot replicate.

vii) Mefloquine :

It is chemically related to quinine. It is a very potent blood shizonticide with a long half-life. It is thought to act by forming toxic heme complexex that damage parasitic

food vacuoles.it is effective in prophylaxis and for acute therapy. It can only be taken for a period up to six months due to side effects.

Mechanism of action:

It has been found to produce swelling of the plasmodium falciparum food vacuoles. It may act by forming toxic complexes with free heme that damage membranes and interact with other plasmodial components.

viii) Atovaquone :

It is commonly used in prophylaxis by travelers and used to treat falciparum malaria in developed countries. A liquid oral suspension of atavaquone is available under the name mepron.

Mechanism of action:

It has not been fully elucidated, in plasmodium species the site of action appears to be cytochrome bc1 complex(complex iii).inhibition of electron transport by atovaquone will result in indirect inhibition of these enzymes.

ix) Primaquine :

It is 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.

<u>Mechanism of action</u>

It is not fully understood but it is thought to block oxidative metabolism in plasmodia. It can also be combined with methylene blue. It may be acting ny generating reactive oxygen species or by interfering with the electron transport in the parasite, also although its mechanism of action is unclear, primaquine may bind to and alter the properties of protozoal DNA

x) Artemisinin and derivatives:

It has a very rapid action and the vast majority of acute patients treated showing significant improvement within 1-3 days of receiving treatments.it has demonstrated the fastest clearance of all anti-malarials currently used and acts primarily on the trophozoite phase, thus preventing progression of the disease.

- Artemether is a methyl ether derivative of dihydroartemesinin, it is similar to artemisinin mode of action but demonstrates a reduced ability as a hypnozoiticidal compound, instead acting more significantly to decrease gametocyte carriage
- Artesunate is a hemisuccinate derivative of the active metabolite dihydroartemisin.
- Dihydroartemisinin is the active metabolite to which artemesinin is reduced.it is the most effective artemesinin compound and the least stable.

- Other derivatives are arteether etc.
  Mechanism of action:
  It appears to involve the heme-mediated decomposition of the endoperoxide bridge to produce carbon-centered free radicals. The involvement of heme explains why the drugs are selectively toxic to malaria parasites.

xi) Halofantrine:

Despite being effective against drug resistant parasites, halafantrine is not commonly used in the treatment of malaria due to its high cost, it has very variable bioavailability and has been shown to have potentially high levels of cardiotoxicity.

Mechanism of action:

The mechanism of action may be similar to that of chloroquine, quinine and mefloquine; by forming toxic complexes with ferritoporphyrin IX that damage the membrane of the parasite.

xii) Lumefantrine:

it is a relative of halofantrine that is used in some combination antimalarial regimens.

Mechanism of action:

The exact mechanism by which lumefantrine exerts its antimalarial effect is unknown, howeverit suggests that lumefantrine inhibits the formation pf beta-hematin by forming a complex with hemin and inhibits nucleic acid and protein synthesis.

xiii) Doxycycline:

It is a tetracycline compound derived from oxytetracycline. It is used in combination for the treatment of acute cases of p.falciparum infections, this is due to the slow onset, unlike doxycyline it is not used chemoprophylaxis.

Mechanism of action:

It is thought to inhibit translation by binding to the 16S rRNA portion of the ribosome preventing binding of tRNA to the RNA-3oS bacterial ribosomal subunit, which is necessary for the delivery of amino acids for protein synthesis, it stops the replication of bacteria and produces a bacteriostatic effect.

xiv) Clindamycin:

It is s aderivative of lincomycin, with a slow action against blood schizonticides.

Mechanism of action:

It onhibits bacterial protein synthesis by binding to 23S RNA of the 50S subunit of the bacterial ribosome. It impedes both the assembly of the ribosome and the translation process. The mechanism through which topical clindamycin treats acne vulgar is unclear, but may be related to its activity against propionibacterium acnes, a bacteria that has been associated with acne.