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QUESTIONS
Classify the antimalarial agents and state the mechanism of action of each class of drug listed
ANSWER
Classes of antimalarial agents include:

1) **4-Aminoquinolines** : Amodiaquine
   Chloroquine
2) **Quinoline methanol:** Mefloquine
3) **Cinchona alkaloid:** Quinidine
   Quinine
4) **Biguanides:** Proguanil
   (Chloroguanide)
5) **Diaminopyrimidines:** Pyrimethamine
6) **8-Aminoquinoline:** Primaquine
   Tafenoquine
7) **Sulfonamides & sulfone:** Sulfadoxine
   Sulfamethopyrazine
   Dapsone
8) **Antibiotics:** Tetracyclins
   Doxycycline
9) **Sesquiterpine lactones** : Artesunate
   Artemether
   Arteether
10) **Amino alcohols:** Halofantrine
    Lumefantrine
11) **Naphthyridine:** Pyronaridine
12) **Naphthoquinone:** Atovaquone

Mechanism of action:

1) **4-Aminoquinolines** : Amodiaquine
   Chloroquine

The mechanism of action of 4-aminoquinolines is characterized by the concentration of the drug in the digestive vacuole of the intraerythrocytic parasite. Various hypotheses have been advanced to explain the specificity of action on the parasite; the most recent one is the inhibition of the haem polymerase of the parasite, leading to the accumulation of soluble haem toxic for the parasite. Chloroquine-resistant parasites accumulate the drug to a lesser extent than do sensitive parasites. Recent findings have shown that chloroquine resistance can be reversed by various tricyclic drugs, which are able to restore the

effective concentrations of chloroquine in the infected erythrocyte, but intrinsic mechanisms of action of these reversing agents are unknown. Four-aminoquinolines are extensively distributed in tissues and characterized by a long elimination half-life. Despite similarities in their chemical structures, these drugs show differences in their biotransformation and routes of elimination: chloroquine is partly metabolized into a monodesethylderivative and eliminated mainly by the kidney. In contrast, amodiaquine is a prodrug and amopyroquine is poorly metabolized; both drugs are excreted mainly in the bile.

2) **Quinoline methanol:** Mefloquine

Quinoline-containing antimalarial drugs, such as chloroquine, quinine and mefloquine, are mainstays of chemotherapy against malaria. The parasite degrades hemoglobin, in an acidic food vacuole, producing free heme and reactive oxygen species as toxic by-products. The heme moieties are neutralized by polymerisation, while the free radical species are detoxified by a vulnerable series of antioxidant mechanisms. Chloroquine, a dibasic drug, is accumulated several thousand-fold in the food vacuole. The high intravacuolar chloroquine concentration is proposed to interfere with the polymerisation of heme and/or the detoxification of the reactive oxygen species, effectively killing the parasite with its own metabolic waste. Chloroquine resistance appears to arise as a result of a decreased level of chloroquine uptake, due to an increased vacuolar pH or to changes in a chloroquine importer or receptor. The more lipophilic quinolinemethanol drugs mefloquine and quinine do not appear to be concentrated so extensively in the food vacuole and may act on alternative targets in the parasite. Resistance to the quinolinemethanols is thought to involve a plasmodial homolog of P-glycoprotein.

3) **Cinchona alkaloid:** Quinidine
Quinine

Quinine is theorized to be toxic to the malarial pathogen, Plasmodium falciparum, by interfering with the parasite's ability to dissolve and metabolize hemoglobin. As with other quinoline antimalarial drugs, the mechanism of action of quinine has not been fully resolved. The most widely accepted hypothesis of its action is based on the well-studied and closely related quinoline drug, chloroquine. This model involves the inhibition of hemozoin biocrystallization in Heme Detoxification pathway, which facilitates the aggregation of cytotoxic heme. Free cytotoxic heme accumulates in the parasites, causing their deaths. Quinine may target malaria's purine nucleoside phosphorylase enzyme.

4) **Biguanides:** Proguanil
(Chloroguanide)

Biguanides do not affect the output of insulin, unlike other hypoglycemic agents such as sulfonylureas and meglitinides. Therefore, they are effective in Type 2 diabetics; and in Type 1 diabetes when used in conjunction with insulin therapy.

Mainly used in Type II diabetes, metformin is considered to increase insulin sensitivity in vivo, resulting in reduced plasma glucose concentrations, increased glucose uptake, and decreased gluconeogenesis.

However, in hyperinsulinemia, biguanides can lower fasting levels of insulin in plasma. Their therapeutic uses derive from their tendency to reduce gluconeogenesis in the liver, and, as a result, reduce the level

of glucose in the blood. Biguanides also tend to make the cells of the body more willing to absorb glucose already present in the blood stream, and there again reducing the level of glucose in the plasma.

5) **Diaminopyrimidines:** Pyrimethamine

Pyrimethamine interferes with the regeneration of tetrahydrofolic acid from dihydrofolate by competitively inhibiting the enzyme dihydrofolate reductase. Tetrahydrofolic acid is essential for DNA and RNA synthesis in many species, including protozoa. It has also been found to reduce the expression of SOD1, a key protein involved in amyotrophic lateral sclerosis.

6) **8-Aminoquinoline:** Primaquine
Tafenoquine

Primaquine is lethal to *P. vivax* and *P. ovale* in the liver stage, and also to *P. vivax* in the blood stage through its ability to do oxidative damage to the cell. However, the exact mechanism of action is not fully understood.

7) **Sulfonamides & sulfone:** Sulfadoxine
Sulfamethopyrazine
Dapsone

Sulfadoxine is a sulfa drug, often used in combination with pyrimethamine to treat malaria. This medicine may also be used to prevent malaria in people who are living in, or will be traveling to, an area where there is a chance of getting malaria. Sulfadoxine targets Plasmodium dihydropteroate synthase and dihydrofolate reductase. Sulfa drugs or Sulfonamides are antimetabolites. They compete with para-aminobenzoic acid (PABA) for incorporation into folic acid. The action of sulfonamides exploits the difference between mammal cells and other kinds of cells in their folic acid metabolism. All cells require folic acid for growth. Folic acid (as a vitamin) diffuses or is transported into human cells. However, folic acid cannot cross bacterial (and certain protozoan) cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid.

8) **Antibiotics:** Tetracyclins
Doxycycline

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. Some studies have shown that tetracyclines may bind to both 16S and 23S rRNAs. Tetracyclines also have been found to inhibit matrix metalloproteinases. This mechanism does not add to their antibiotic effects, but has led to extensive research on chemically modified tetracyclines or CMTs (like incyclinide) for the treatment of rosacea, acne, diabetes and various types of neoplasms. It has been shown that tetracyclines are not only active against broad spectrum of bacteria, but also against viruses, protozoa that lack mitochondria and some noninfectious conditions. The binding of tetracyclines to cellular dsRNA (double stranded RNA) may be an explanation for their wide range of effect. It can also be attributed to the nature of ribosomal protein synthesis pathways among bacteria. Incyclinide was announced to be ineffective for rosacea in September 2007. Several trials have examined modified and unmodified tetracyclines for the

treatment of human cancers; of those, very promising results were achieved with CMT-3 for patients with Kaposi Sarcoma.

9) **Sesquiterpine lactones** : Artesunate
Artemether
Arteether

Artemether is an artemisinin derivative and the mechanism of action for artemisinins is.

Artemether interact with ferriprotoporphyrin IX (heme) or ferrous ions in the acidic parasite food vacuole, and generates cytotoxic radical species.

The accepted mode of action of the peroxide containing drug involve its interaction with heme (byproduct of hemoglobin degradation), derived from proteolysis of haemoglobin. This interaction results in the formation of toxic oxygen and carbon centered radicals.

One of the proposed mechanisms is that through inhibiting anti-oxidant and metabolic enzymes, artemisinin derivatives inflict oxidative and metabolic stress on the cell. Some pathways affected may concern glutathione and glucose metabolism. As a consequence, lesions and reduced growth of the parasite may result.

Another possible mechanism of action suggests that arteristinin drugs exert their cidal action through inhibiting PfATP6. Since PfATP6 is an enzyme regulating cellular calcium concentration, its malfunctioning will lead to intracellular calcium accumulation, which in turns causes cell death.

10) **Amino alcohols:** Halofantrine
Lumefantrine

Halofantrine is a drug used to treat malaria. Halofantrine's structure contains a substituted phenanthrene, and is related to the antimalarial drugs quinine and lumefantrine. Marketed as **Halfan**, halofantrine is never used to prevent malaria and its mode of action is unknown, although a crystallographic study showed that it binds to hematin *in vitro*, suggesting a possible mechanism of action. Halofantrine has also been shown to bind to plasmpesin, a haemoglobin degrading enzyme unique to the malarial parasites.

11) **Naphthyridine:** Pyronaridine

Artesunate is a prodrug that is rapidly converted to its active form dihydroartemisinin (DHA). This process involves hydrolysis of the 4-carbon ester group via plasma esterase enzyme. It is hypothesized that the cleavage of endoperoxide bridge in the pharmacophore of DHA generates reactive oxygen species (ROS), which increases oxidative stress and causes malarial protein damage via alkylation. In addition, Artesunate potently inhibits the essential *Plasmodium falciparum* exported protein 1 (EXP1), a membrane glutathione S-transferase. As a result, the amount of glutathione in the parasite is reduced.

12) **Naphthoquinone:** Atovaquone

Atovaquone selectively inhibits the malarial cytochrome bc_1 complex in the parasitic electron transport chain, collapsing the mitochondrial membrane potential. The malarial electron transport chain does not contribute significantly to ATP synthesis; thus, it is believed that parasite death is due to the indirect inhibition of dihydroorotate dehydrogenase, which requires transport chain function and is essential to pyrimidine biosynthesis. Proguanil, via its metabolite cycloguanil, functions as a dihydrofolate reductase inhibitor, halting parasitic deoxythymidylate synthesis.