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QUESTION

Classify the antimalarial agents and state the mechanism of action of each classes of drugs listed.

Answers

They can be classified into antimalarial activities and according to their structure

ANTIMALARIAL ACTIVITIES

1. Tissue schizonticides for Causal Prophylaxis:

These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the infection can be theoretically prevented. Pyrethamine and primaquine have this activity. However, since it is impossible to predict the infection before clinical symptoms begin, this mode of therapy is more theoretical than practical.

2. Tissue schiconticides for Preventing Relapse:

These drugs act on the hypnozoites of P. vivaxand P. ovale in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.

3. Blood schizonticides:

These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in anti–malarial chemotherapy. These include chloroquine, quinine, mefloquine, halofantrinepyrimethamine, sulfadoxine, sulfones, tetrac. These include chloroquine, quinine, mefloquine, halofantrine pyrimethamine, sulfadoxine, sulfones, tetracyclines e.t.c

4. Gametocytocides:

These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocytocidalactivity against P.vivax and P. malariae, but not against P. falciparium. Primaquine has gametocytocidal activity against all plasmodia, including P.falciparum.

5. Sporontocides:

These drugs prevent the development of oocytes in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action.

ACCORDING TO STRUCTURE

1. 4 –Aminoquinolines : chloroquine, Aminodiquine
2. Quinolone methanol: mefloquine
3. Cinchona alkaloid :Quinine ,Quinidine

4 . Biguanides :proguanil
5. Diaminopyrimidines: pyrimethanine
6. 8– Aminoquinoline :primaquine
7. Sulfonamides and sulfone :Sulfadoxine,sulfamethopyrazine dapsone
8. Antibiotics :tetracycline , doxcyline
9. Seequiterpinelactories : Artesunate , artemether , arteether
10. Amino alcohols : Halofantrine, lumefanthrine
11. Nepthyridine : atovaquine

1. Quinine and related agents;
Quinine is an alkaloid that acts on the blood schizonticidal and weak gametocyte against plasmodium vivax and plasmodium malariae. As an alkaloid, it is accumulated in the food vacuoles of plasmodium species, especially plasmodium falciparum. Quinine is less effective and more toxic as a blood schizonticidal agent than chloroquine; however, it's still very effective and widely used in the treatment of acute cases of severe plasmodium falciparum. It is useful in areas where there is known to be high level of resistance to chloroquine, mefloquine, and sulfa drugs combination with pyrimethamine. Quinine is a medication used to treat malaria and babesiosis. This includes the treatment of malaria due to Plasmodium falciparum that is resistant to chloroquine when artesunate is not available.
MECHANISM OF ACTION :
The mechanism of action is interference with the parasite's ability to digest hemoglobin. Quinine also inhibit the spontaneous formation of beta–hematin (haemozoinb or malaria pigment) which is a toxic product of the digestion of hemoglobin by parasites. Quinine is rapidly and completely absorbed. The clearance of quinine varies between 1.2–4 ml/min/kg and the mean elimination half–life is 10– 12 hours. Clearance may be reduced in the elderly, smokers and in patients with malaria.

2. Chloroquine;

Description
DescriptionChloroquine is a medication primarily used to prevent and treat malaria in areas where malaria remains sensitive to its effects. Certain types of malaria, resistant strains, and complicated cases typically require different or additional medication. Chloroquine is a medication primarily used to prevent and treat malaria in areas where malaria remains sensitive to its effects.

Chloroquine is also occasionally used for amebiasis that is occurring outside the intestine, rheumatoid arthritis, lupus erythematous.

MECHANISM OF ACTION:

Chloroquine enters the red blood cell by simple diffusion, inhibiting the parasite cell and digestive vacuole. Chloroquine then becomes protonated (to CQ2+), as the digestive vacuole is known to be acidic (pH 4.7); chloroquine then cannot leave by diffusion. Chloroquine caps hemozoin molecules to prevent further biocrystallization of heme, thus leading to heme buildup. Chloroquine binds to heme (or FP) to form the FP–chloroquine complex; this complex is highly toxic to the cell and disrupts membrane function. Action of the toxic FP–chloroquine and FP results in cell lysis and ultimately parasite cell auto–digestion. Parasites that do not form hemozoin are therefore resistant to chloroquine.

3. Pyrimethamine;

Pyrimethamine is a medication used with leucovorine to treat parasite diseases toxoplasmosis and cystoisosporiasis. It was previously used for malaria but no longer recommended due to its resistance.

Description

DescriptionPyrimethamine, sold under the brand name Daraprim among others, is a medication used with leucovorin to treat the parasite diseases toxoplasmosis and cystoisosporiasis. It is also used with dapsone as second–line option to prevent Pneumocystis jiroveci pneumonia in people with HIV/AIDS.

Formula: C12H13ClN

MECHANISM OF ACTION :

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 Superoxide dismutase 1, a key protein involved in amyotrophic lateral sclerosis.

4. Clindamycin;

Clindamycin is an antibiotic used for the treatment of a number of bacterial infections, including bone or joint infections, pelvic inflammatory disease, strep throat, pneumonia, middle ear infections, and endocarditis. In combination with quinine, it can be used for malaria.It is available by mouth, by injection into a vein, and as a cream to be applied to the skin or in the vagina

. Clindamycin is an antibiotic used for the treatment of a number of bacterial infections, including bone or joint infections, pelvic inflammatory disease, strep throat, pneumonia, middle ear infections, and endocarditis. It can also be used to treat acne, and some cases of methicillin–resistant Staphylococcus aureus.
Drug class: Lincosamide antibiotic
Other names: 7–chloro–lincomycin; 7–chloro–7–deoxylincomycin

MECHANISM OF ACTION

Clindamycin prevents peptide bond formation, thereby inhibiting protein synthesis by reversibly binding to 50S ribosomal subunits. Depending on the organism, infection site, and drug concentration, clindamycin may be a bacteriostatic or bactericidal antibiotic. When taken orally, absorption cannot take place until clindamycin palmitate becomes hydrolyzed in the gastrointestinal (GI) tract. It then distributes across the body in tissue and other regions containing blood. Clindamycin cannot efficiently penetrate meninges very well and is therefore not an antibiotic of choice for infections of the cerebrospinal fluid (CSF). As it travels through the bloodstream, clindamycin is primarily bound to protein. Clindamycin is primarily metabolized in the liver by CYP 3A4 (major) and CYP 3A5, which oxidize the antibiotic into clindamycin sulfoxide (primary metabolite) and N–desmethyl clindamycin respectively. When administered orally, the antibiotic peaks within 60 minutes. When given intramuscularly (IM), the drug achieves peak concentrations in 1 to 3 hours. The half–life of clindamycin is approximately 3 hours in adults and approximately 2.5 hours in children, at which point it is excreted in the urine (major) and feces (minor) as active and inactive metabolites.

5. Artemisinin;

Description

DescriptionArtemisinin and its semisynthetic derivatives are a group of drugs used against malaria due to Plasmodium falciparum. It was discovered in 1972 by Tu Youyou, who was co–recipient of the 2015 Nobel Prize in Medicine for her discovery.
Artemisinin and its semisynthetic derivatives are a group of drugs used against malaria due to Plasmodium falciparum. Treatments containing an artemisinin derivative (artemisinin–combination therapies, ACTs) are now standard treatment worldwide for Plasmodium falciparum malaria. Artemisinin is isolated from the plant Artemisia annua, sweet wormwood, a herb employed in Chinese traditional medicine.

DescriptionArtemisinin and its semisynthetic derivatives are a group of drugs used against malaria due to Plasmodium falciparum. It was discovered in 1972 by Tu Youyou, who was co–recipient of the 2015 Nobel Prize in Medicine for her discovery.
Formula: C15H22O5

MECHANISM OF ACTION

Artemisinin and its derivatives are involve the heme–mediated decomposition of the endoperoxide bridge to produce carbon–centred free radicals. The involvement of heme explains why the drugs are selectively toxic to malaria parasites. The resulting carbon–centred free radicals are alkylate heme and proteins, one of which is the translationally controlled tumor protein.

6. Atovaquone/ Proguanil;

Atovaquone/proguanil is a combination of two antimalarial medication atovaquone and proguanil. It is used to treat and prevent malaria, including chloroquine–resistant malaria. It is not recommended for severe or complicated malaria. It is taken by mouth.
DescriptionAtovaquone is a chemical compound that belongs to the class of naphthoquinones. Atovaquone is a hydroxy–1,4–naphthoquinone, an analog of ubiquinone, with antipneumocystic activity. It is manufactured in the US in the liquid form, or oral suspension, under the brand name Mepron.
Formula: C22H19ClO3

MECHANISM OF ACTION

Atovaquone selectively inhibits the malarial cytochrome bc1 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.