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Pharmacology assignment

1. 4-Aminoquinolines    Chloroquine                   Amodiaquine

2) Quinoline methanol Mefloquine

3) Cinchona alkaloid      Quinine

                   Quinidine

4)  Biguanides        Proguanil                                (Chloroguanide)

           Diaminopyrimidines      Pyrimethamine

• 8-Aminoquinoline        Primaquine

                         Tafenoquine

•Sulfonamides & sulfone    Sulfadoxine                                  Sulfamethopyrazine                              Dapsone

•Antibiotics                  Tetracyclins

                             Doxycycline

Sesquiterpine lactones Artesunate                            Artemether                            Arteether

Amino alcohols        Halofantrine                            Lumefantrine

Naphthyridine        Pyronaridine

Naphthoquinone        Atovaquone

Chloroquine.

Amodiaquine is a mannich base 4-aminoquinoline that exhibits clinical efficacy and toxicity that although there is crossresistance, it is effective against some chloroquine-resistant strains of P. falciparum. It is rapidly and extensively converted to a pharmacologically active metabolite, diethyl-amodiaquine. Its adverse effects are similar to those of chloroquine.

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 Amodiaquine.

Primaquine is an 8-aminoquinoline compound which is effective against intrahepatic forms of all types of malaria parasites. It has been a drug of choice for the treatment of P. vivax and P. ovale infections. With an unknown mechanism of action, it is readily absorbed from the gastrointestinal tract. However, the most known adverse effects are hemolytic anemia, leukocytosis, leukopenia, nausea, vomiting, epigastric distress, and abdominal cramps.

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Artemisinin Compounds

Artemisinin, a sesquiterpene lactone is extracted from the leaves of Artemisia annua. It is currently grown in China, Vietnam and parts of Africa and it is used for treatment of fever. Artemisinin has a labile peroxide bridge. The peroxide bridge is responsible for generating free radicals that rapidly undergo alkylating reaction and parasite membranes are particularly sensitive to the oxidative damage. It is effective against all Plasmodium species and exhibit broad activity against asexual parasites, killing all stages from young rings to schizonts . In P. falciparum malaria, it kills all the stages of gametocytes. Artemisinin and its derivatives have a low level of toxicity thus they are safe and well tolerated. However, mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopenia, neutropenia, and elevated liver enzyme values have been reported in some patients.

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Antibiotics

Antibiotics such as tetracycline and doxycycline are very potent antimalarial drugs and are used for both treatment and prophylaxis. They are often used in combination with quinine to improve cure rates.

Other Antimalarial Drugs

Sulfadoxine: Sulfadoxine is a slowly eliminated sulfanamide. Sulfonamides are analogs and competitive antagonists of p-aminobenzoic acid. When combined with pyrimethamine, it is considered to be more effective in treating malaria caused by P. falciparum than that caused by P. vivax . It is readily absorbed from the gastrointestinal tract. Its adverse effects include nausea, vomiting, anorexia, and diarrhea.

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Sulfadoxine.

Pyrimethamine: Pyrimethamine is a diaminopyridine (Fig. 7.8) that was once used extensively for chemoprophylaxis because of its long half-life and safety in pregnancy. However, resistance has become so widespread that it is now mainly used in combination with sulfadoxine and with dapsone. It inhibits plasmodial dihydrofolate reductase by indirectly blocking the synthesis of nucleic acids in the malaria parasite . It is effective against all human malaria, although resistance has emerged rapidly. It is generally well tolerated. However, acute overdose can cause gastrointestinal effects and stimulation of the central nervous system with vomiting, excitability, and convulsions.

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FiPyrimethamine.

Lumefantrine (Benflumetol): Lumefantrine is a racemic fluorine derivative developed in China .It is highly effective against multidrug-resistance P. falciparum. It is well tolerated and its reported adverse effects are generally mild which include: nausea, abdominal discomfort, headache, and dizziness.

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Lumefantrine.

Proguanil: Proguanil is a biguanide compound and it is metabolized in the body by the polymorphic cytochrome P450 enzyme CYP2C19 to the active metabolite, cycloguanil . Cycloguanil inhibits plasmodial dihydrofolate reductase. Proguanil renders the gametocytes noninfective to the mosquito vector because of its sporontocidal activity . It develops resistance quickly and to overcome resistance, it is used in combination with atovaquone . Side effects associated with proguanil hydrochloride are diarrhea, hair loss, mild gastric intolerance, and aphthous ulceration . Overdosage results in hematuria, epigastric discomfort, and vomiting.

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Proguanil.

Chlorproguanil: Chlorproguanil is a biguanide and is given as a hydrochloride salt. Its mechanism of action and properties are very similar to proguanil. It is available only in combination with a sulfone such as dapsone.

Artemether-lumefantrine

•   Both protect each other from plasmodial

      resistance

•  High clinical efficacy

•   Active even in multidrug resistant Plasmodium

      falciparum areas

•  Artemether – Quickly reduces parasite biomass

                               and resolves symptoms

     Lumefantrine – Prevents recrudescence

•   Gametocyte population is checked

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Quinine and its Analogues

Malaria is a major scourge of humanity, and the discovery of new antimalarial drugs is a worldwide health imperative. The alkaloid quinine, isolated from the bark of the South American tree Cinchona officinal is and other trees of the same genus, was the first effective antimalarial agent to be discovered, and it has been called “the drug to have relieved more human suffering than any other in history”. It served humanity well for about 300 years, although resistance to the drug was first noted in 1910, and it is no longer recommended by the WHO as a first line treatment for malaria. It was largely replaced in the mid-20th century by the synthetic analogue chloroquine , but resistance to this drug emerged in 1957, and it is no longer of value in many areas of the world. Several other synthetic antimalarial agents have been based on the quinine pharmacophore, including mefloquine , primaquine, mepacrine, and amodiaquine, but each of these has its own disadvantages, including drug resistance and—in the case of mefloquine—psychotic side effects in some individuals.