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Over View on Journey of Antimalrials and Its Resistance

Ch.N V S Mastanrao[1*], Dr.R.Margret Chandira,[2]
1. Research Scholar, Vinayaka Missions Research Foundation, Salem, Tamilnadu, India- 636008.
2. Professor Department of pharmaceutics, Vinayaka Mission's Research Foundation,Sankari Main Road, Ariyanur, Tamil Nadu -636308.
3.Assistant professor nalanda institute of pharmaceutical sciences, kantepdi,sattenapalli,Guntur,522403

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I. INTRODUCTION:

Malaria is a complex disease that varies widely in epidemiology and clinical manifestation in different parts of the world. This variability is the result of factors such as the species of malaria parasites that occur in a given area, their susceptibility to commonly used or available antimalarial drugs, the distribution and efficiency of mosquito vectors, climate and other environmental conditions and the behavior and level of acquired immunity of the exposed human populations. In particular, young children, pregnant women, and non-immune visitors to malarious areas are at greatest risk of severe or fatal illness. Many malaria control strategies exist, but none are appropriate and affordable in all contexts. Malaria control and prevention efforts need to be designed for the specific environment in which they will be used and need to take into account the local epidemiology of malaria and the level of available resources and political will.

Malaria is caused by infection with a single-cell parasite, Plasmodium. Four Plasmodium spp. cause malaria in human beings: Plasmodium falciparum, P. vivax, P. ovale, and P. malariae. P. falciparum is the most important because it accounts for the majority of infections and causes the most severe symptoms. Antimalarials are used in three different ways: prophylaxis, treatment of falciparum malaria, and treatment of non-falciparum malaria. Prophylactic antimalarials are used almost exclusively by travelers from developed countries who are visiting malaria endemic countries. Treatment protocols for falciparum malaria vary, depending on the severity of the disease; fast-acting, parenteral drugs are best for severe, life threatening disease. In addition, treatment protocols for falciparum malaria vary geographically and depend on the resistance profiles for strains in particular regions. Non-falciparum malarias, in contrast, rarely are drug resistant. In addition, P. vivax and P. ovale have dormant liver stages that can cause relapses months to years after an infection is cleared, so they need to be treated with an additional agent that can clear this stage. The antimalarials in common use come from following classes of compounds: the quinolines (chloroquine, quinine, mefloquine, amodiaquine, primaquine), the antifolates (pyrimethamine, proguanil and sulfadoxine),the artmisinin derivatives (artemisinin, artesunate, artemether, arteether) and hydroxynaphthaquinones (atovaquine).

This review looks at the drugs in common use and their treatment regimens, pharmacokinetic properties, mechanism of action and resistance, a status of resistance.

Drug resistance has been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease had been eradicated. Drug resistance has also played a significant role in the occurrence and severity of epidemics in some parts of the world. Population movement has introduced resistant parasites to areas previously free of drug resistance. The economics of developing new pharmaceuticals for tropical diseases, including malaria, are such that there is a great disparity between the public health importance of the disease and the amount of resources invested in developing new cures (1, 2). This disparity comes at a time when malaria parasites have demonstrated some level of resistance to almost every antimalarial drug currently available, significantly increasing the cost and complexity of achieving parasitological cure. The purpose of this review is to describe the state of knowledge regarding drug- resistant malaria and to outline the current thinking regarding strategies to limit the advent, spread, and intensification of drug resistant malaria**.**

1.1 Causative agents:

In humans, malaria infection is caused by one or more of four species of intracellular

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protozoan parasite. Plasmodium falciparum, P. vivax, P. ovale, and P. malariae differ in geographical distribution, microscopic appearance, clinical features (periodicity of infection, potential for severe disease, and ability to cause relapses), and potential for development of resistance to antimalarial drugs. To date, drug resistance has only been documented in two of the four species, P. falciparum and P. vivax

Diagnosis :

Direct microscopic examination of intracellular parasites on stained blood films is the current standard for definitive diagnosis in nearly all settings. However, several other approaches exist or are in development and will be described here.

1.2 Microscopy:

Simple light microscopic examination of Giemsa stained blood films is the most widely practised and useful method for definitive malaria diagnosis. Advantages include differentiation between species, quantification of the parasite density, and ability to distinguish clinically important asexual parasite stages from gametocytes which may persist without causing symptoms. These advantages can be critical for proper case-management and evaluating parasitological response to treatment. Specific disadvantages are that slide collection, staining, and reading can be time-consuming and microscopists need to be trained and supervised to ensure consistent reliability. While availability of microscopic diagnosis has been shown to reduce drug use in some trial settings, in practice, results are often disregarded by clinicians. Any programme aimed at improving the availability of reliable microscopy should also retrain clinicians in the use and interpretation of microscopic diagnosis. A second method is a modification of light microscopy called the quantitative buffy coat method (QBCTM, Becton-Dickinson). Originally developed to screen large numbers of specimens for complete blood cell counts, this method has been adapted for malaria diagnosis. The technique uses micro haematocrit tubes pre coated with fluorescent acridine orange stain to highlight malaria parasites. With centrifugation, parasites are concentrated at a predictable location. Advantages to QBC are that less training is required to operate the system than for reading Giemsa-stained blood films, and the test is typically quicker to perform than normal light microscopy. Field trials have shown that the QBC system may be marginally more sensitive than conventional microscopy under ideal conditions. Disadvantages are that electricity is always required, special equipment and supplies are needed, the per-test cost is higher than simple light microscopy, and species-specific diagnosis is not reliable.

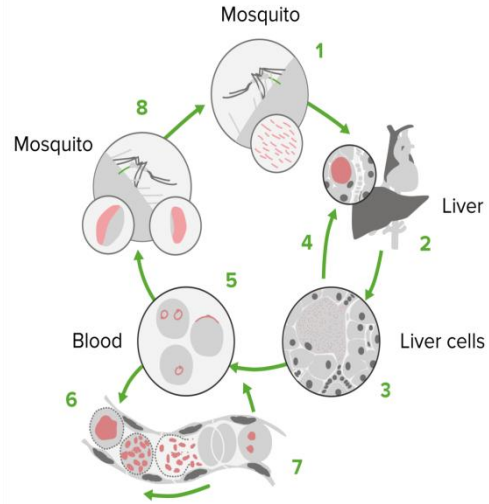

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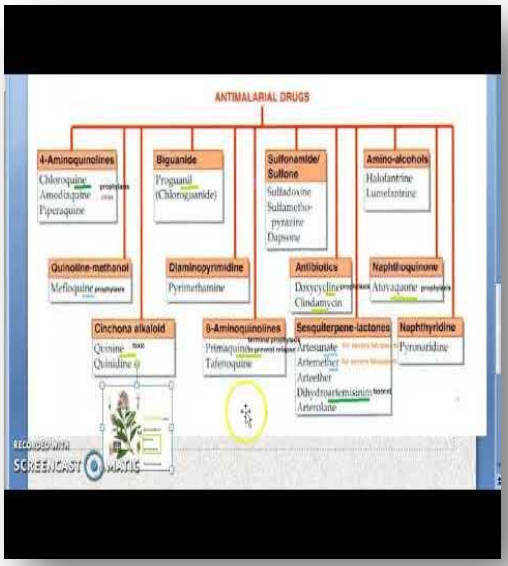
Figure no.1 life cycle of plasmodium species

1.3 Drugs available for treatment of malaria:

There are only a limited number of drugs which can be used to treat or prevent malaria. The most widely used are quinine and its derivatives and antifolate combination drugs.



Antimalarials are classified

1. According to anti malarial activity
2. According to the structure

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1.3.1 According to anti malarial activity:

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. Pyrimethamine and Primaquine have this activity. However since it is impossible to predict the infection before clinical symptoms begins; this mode of therapy is more theoretical than practical.

2. Tissue schizonticides for preventing relapse: These drugs act on the hypnozoites of P. vivax and 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, halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracycline's etc.

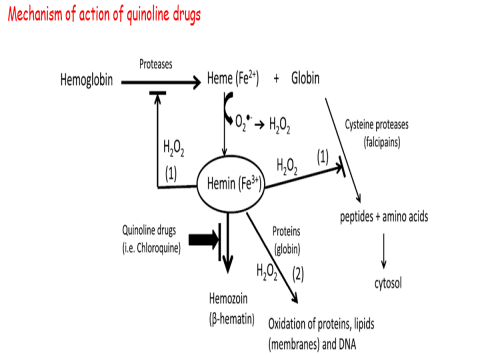
4. Gameto cytocides: These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have Gametocytocides activity against P. vivax and P. malariae, but not against P. falciparum. Primaquine has gametocytocidal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

5. Sporontocides: These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action. • Thus in effect, treatment of malaria would include a blood schizonticide, a gametocytocide and a tissue schizonticide (in case of P. vivax and P. ovale). • A combination of chloroquine and primaquine is thus needed in ALL cases of malaria

1.3.2 According to the structure:

1. Aryl amino alcohols: Quinine, guanidine (cinchona alkaloids), mefloquine, halofantrine.
2. 4-aminoquinolines: Chloroquine, amodiaquine.
3. Folate synthesis inhibitors:
4. Type 1 – competitive inhibitors of dihydropteroate syntheses – sulphones, sulphonamides;
5. Type 2 – inhibit dihydrofolate reductase – biguanides like proguanil and chloroproguanil; di amino pyrimidine like pyrimethamine
6. 8-aminoquinolines: Primaquine
7. Antimicrobials: Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones
8. Peroxides: Artemisinin derivatives and analogues – artemether, arteether, artesunate, artelinic acid
9. Naphtho quinines: Atovaquone 8. Iron chelating agents: Desferrioxamine

Mechanism of action of atimalarials:



Mechanism of action of quinoline drugs inhibiting hemozoin in the digestive vacuole of Plasmodium inside erythrocytes or in other organisms that use hemoglobin as food. This inhibition enhances the levels of free hemin which promote peroxidase reactions with H2O2 arising from heme (Fe2+) oxidation. Hemin and peroxidase reactions inhibit cysteine proteases needed for degradation of proteins used for parasite growth (1), and may also oxidize proteins (enzymes), lipids and DNA resulting in parasite damage (2).

Herraiz T, Guillén H, González-Peña D, Arán VJ. Antimalarial Quinoline Drugs Inhibit β-Hematin and Increase Free Hemin Catalyzing Peroxidative Reactions and Inhibition of Cysteine Proteases. Sci Rep. 2019 Oct 28;9(1):15398. PMID: 31659177.

Artemisinin:

- Artemisinin is a natural product that can be extracted from the leaves of Artemisia annua
- Formula : C15H22O5
- Molar mass : 282.332 g/mol
- Density : 1.24 ± 0.1 g/cm3
- M.P : 152 to 157 °C (306 to 315 °F)
- Artemisinin The therapeutic utility of the lead itself is limited by poor physicochemical properties such as poor oil & water solubility Artemisinin
- Artemisinin serve as a lead compound for the development of new antimalarials with improved properties • The lactone group can be reduced & form dihydroartemisinin which is used to prepare semi synthetic prodrug that are more water & oil soluble
- The hydroxyl group can be alkylated to give oil soluble ether derivatives such as artemether & arteether • Esterification of the hydroxyl with succinic acid gives the water soluble derivative , artesunate SAR Of Artemisinin
- Studies of artemisinin analogues such as deoxy artemisinin which do not contain the Endoperoxide Bridge showed vastly reduced biological activity.

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Quinine & Related Compounds:

The bark of the cinchona tree contains antimalarial compounds, most notably the highly fluorescent compound, quinine.

• The bark of the cinchona tree, if made into an aqueous solution was able to treat most cases of malaria.

• The active principle quinine was first isolated from the bark during the early 19th century.

• Quinine is the compound that contributes to the bitter taste of tonic water.

4-aminoquinolines

Increasing concern about cinchona supplies and the desire to find quinine alternatives with reduced side effects led to a massive search for novel antimalarials.

• Chloroquine was one of the drugs successfully developed. The drug was first used during the 1950s.

• Chloroquine is effective against erythrocytic forms of the Plasmodium parasite. Like chloroquine, the drugs amodiaquine and hydroxychloroquine belong to a class of quinine analogues called 4-aminoquinolines.4-aminoquinoline.

1.4 Drug designed of Chloroquine as prototype drug:

It consists of 4- aminoquinoline pharmacophore.

• The structural analogues of chloroquine have been designed in such a way that it will show more drug likeness score than the prototype molecule but having the same pharmacophore essential for the antimalarial activity. The side chain present at 4 position of chloroquine has been modified with alteration of halogen atom in some cases at position 8 to get increased drug likeness score.

• In case of designed molecules the chlorine molecule at position 8 has been replaced by –F atom to increase the drug likeness score than the prototype molecule chloroquine.

• The position of R1 and R2 in the 4- amino quinolone ring are modified in these designed molecules to get increased drug likeness score.

8-aminoquinolines

Drugs in this group have amino group at position 8 of quinoline ring

• Such drugs have OCH3 group at position 6

• Pamaquine, primaquine, and tafenoquine are antimalarial drugs that belong to a family named 8-aminoquinolines.

• Pamaquine is closely related to primaquine. • Compared to primaquine, pamaquine is more toxic and less effacacious.

• Tafenoquine is currently in late clinical trials.• When side chain is introduced at amino group antimalarial activity is intensified • It causes hemolysis of RBCs Diethyl amino pentyl side chain Pamaquine

• It contains tertiary amino group and when it is converted into primary amino group the compound is called primaquine, which is – Less toxic – Well tolerated It is the most commonly used agent in this group in the treatment of malaria Primaquine

• OCH3 is not necessary for antimalarial activity but when replaced by OC2H5 the compound became – less active – Toxic in nature

• OCH3 when replaced by CH3 the compound become inactive

• Introduction of halogens increases toxicity.

• Presence of quinoline ring is necessary for antimalarial activity. When pyridine ring is converted to piperidine (saturated) the compound became inactive

• Pentyl side chain gives maximum activity, increase or decrease of chain result is reduction of activity.

• The branched side chain when converted into straight chain pentaquine is obtained • It has less antimalarial activity as compared to both pamaquine and primaquine.

1.5 Antifolate combination drugs:

These drugs are various combinations of dihydroolate-reductase inhibitors (proguanil, chlorproguanil, pyrimethamine, and trimethoprim) and sulfa drugs (dapsone, sulfalene, sulfamethoxazole, sulfadoxine, and others). Although these drugs have antimalarial activity when used alone, parasitological resistance can develop rapidly. When used in combination, they produce a synergistic effect on the parasite and can be effective even in the presence of resistance to the individual components. Typical combinations include sulfadoxine/ pyrimethamine (SP or Fansidar1), sulfalene pyrimethamine (metakelfin), and sulfamethoxazole-trimethoprim (co-trimoxazole). A new antifolate combination drug is currently being tested in Africa.

This drug, a combination of chlorproguanil and dapsone, also known as LapDap, has a much more potent synergistic effect on malaria than existing drugs such as SP. Benefits of this combination include

1) a greater cure rate, even in areas currently experiencing some level of SP resistance,

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2) a lower likelihood of resistance developing because of a more advantageous pharmacokinetic and pharmacodynamic profile, and
3) Probable low cost (currently estimated at less than US$ 1 per adult treatment course)

1.6 Combination therapy with antimalarials:

The use of two antimalarials simultaneously, especially when the antimalarials have different mechanisms of action, has the potential for inhibiting the development of resistance to either of the components. The efficacy of a combination of a 4-aminoquinoline drug (either chloroquine or amodiaquine) with sulfadoxine/pyrimethamine has been reviewed (43). The results of this review suggested that the addition of either chloroquine or amodiaquine to SP marginally improved parasitological clearance (compared with SP alone). The studies reviewed were mostly done in areas and at times when both SP and chloroquine/amodiaquine retained a fair amount of efficacy, and it is not clear from these studies how well such a combination would act in areas where one of the components was significantly compromised. Additionally, to date, there are no data to suggest whether this slightly improved clearance would translate into prolonged useful life span for either drug. Another combination therapy approach, combining an artemisinin derivative with other, longer half-life antimalarials.

1.7 Current status of drug-resistant malaria:

Resistance to antimalarial drugs has been described for two of the four species of malaria parasite that naturally infect humans, P. falciparum and P. vivax. P. falciparum has developed resistance to nearly all antimalarials in current use, although the geographical distribution of resistance to any single antimalarial drug varies greatly. P. vivax infection acquired in some areas has been shown to be resistant to chloroquine and/or primaquine (44, 45). Chloroquine-resistant P. falciparum malaria

1.8Mechanisms of antimalarial resistance:

In general, resistance appears to occur through spontaneous mutations that confer reduced sensitivity to a given drug or class of drugs. For some drugs, only a single point mutation is required to confer resistance, while for other drugs, multiple mutations appear to be required. Provided the mutations are not deleterious to the survival or reproduction of the parasite, drug pressure will remove susceptible parasites while resistant parasites survive. Single malaria isolates have been found to be made up of heterogeneous populations of parasites that can have widely varying drug response characteristics, from highly resistant to completely sensitive (51). Similarly, within a geographical area, malaria infections demonstrate a range of drug susceptibility. Over time, resistance becomes estabilished in the population and can be very stable; persisting long after specific drug pressure is removed. The biochemical mechanism of resistance has been well described for chloroquine, the antifolate combination drugs, and atovaquone.

1.9 Conclusion:

Because of the realities of health care infrastructure and the influence of the private sector, approaches to malaria therapy, especially in sub-Saharan Africa, will probably favour increased access to drugs (and, therefore, loss of control over how they are used) over restricted access (and, therefore, more control over how they are used). If this proves to be true, while only minor advances against antimalarial drug resistance can be expected, short-term reductions in malaria morbidity and mortality may be achieved. Long-term success of this strategy, however, will depend on a continuous supply of new and affordable drugs and on the development of effective and implementable control measures to reduce overall burden of disease. A more cautious approach would be to avoid placing too much faith in future scientific advances and technology and to invest in methods to improve the way people and antimalarial drugs interact in an environment of essentially uncontrolled use. The objective of this investment would be to prolong the useful life span of drugs enough to increase the likelihood that new drugs or other methods of malaria control will indeed be developed and implemented. Significant advances against antimalarial drug resistance are probably unlikely without major change in health infrastructure leading to higher quality services that are more readily available.

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