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Review on Anti Malarial Drug

D.R. Gite, Raviraj Rathod, Shaikh Shahebaj, Krishna Pawar.
Raosaheb Patil Danve College Of Pharmacy Badnapur, Jalna

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ABSTRACT:-
Plasmodium, which infectsred bloodcells. Newantimalarial drugisafixed dose combination of two antimalarial active ingredients arterolane maleate and piperaquine phosphate. Arterolane undergoes reductive cleavage in the food vacuolebyferrous ironto generate freeradicals whichinhibitPfATP6, asarcoplasmicendoplasmicreticulumcalciumATPa Malariaisaninfectious disease caused by a parasite, se encoded by P. Falciparum. Piperaquine produces inhibition of the heme-digestion pathway in the parasite food vacuole. Both the drugs are well absorbed orally with Peak plasma concentrationsbetween3-5hourspostdoseforarterolaneand4-6hourspost doseforpiperaquineandbotharehighlyplasmaprotein boundwithextensive volume ofdistribution. The major metabolic pathway is the oxidation ofthe adamantane moiety for arterolane. Overall contribution of CYP3A4 to Arterolane metabolismis30%.CYP3A4 is theprimaryisozymeresponsible for the metabolism of both arterolane as well as piperaquine. Observed metabolites fromlivermicrosomesare monooxygenationanddioxygenation productsforpiperaquine.Arterolaneisrapidlyeliminat edfrombloodplasma. Hence, the combination provides rapid clearance of parasitemia and most malaria-related symptoms, coupled with prevention of recrudescence.

Keywords:-
Sarcoplasmic,ATPase,monooxygenation,dioxygenat ion.

I. INTRODUCTION

Malaria is an infectious disease caused by a parasite, Plasmodium,whichinfectsredbloodcells.Malariahasi nfectedhumanssince thebeginningofmankind.The name"malaria"(meaning"badair"inItalian) wasfirstused in1740byH.Walpole.Thetermwasshortenedto"malar ia"in the 20th century. C. Laveran in 1880 was the first to identify the parasites in human blood. The five species that cause malaria are • Plasmodium falciparum: The most serious type, can be life-threatening • Plasmodium vivax: generally less serious and are usually not life-threatening. • Plasmodium malariae,:generally less serious and are usually not life- threatening. • Plasmodium ovale :generally less serious and are usually not life-threatening.•Plasmodiumknowlesi:dangerous,found onlyinlong-tailed and pigtail macaque monkeys, can be lifethreatening1 . SIGN AND SYMPTOMS : The symptoms characteristic of malaria include-

1. Flulikeillnesswithsystemicfever
2. Chills,Sweating
3. Muscleaches(Fatigue, Pain)
4. Centralheadache.
5. Nausea
6. Vomiting
7. DryCough
8. Diarrhea
9. Spleenenlargement

Sometimes symptoms may occur later in those individuals who have taken antimalarialmedications.Initialpropagationaresimila rtoflu-likesymptoms, septicemia, gastroenteritis and viral diseases. They also may include headache, fever, shivering, joint pain, vomiting, -jaundice, hemoglobin urea, retinal damage, convulsions and hemolytic anemia,The mainclassic symptomis cyclicaloccurrence of suddencoldness followed by shivering and then fever and sweating, which is known as paroxysm. • Paroxysm occurring every two days in P. vivax and P. ovale infections. • Paroxysm occurring every three days for P. malariae. P. falciparum infection can cause recurrent fever every 36–48 hours or a continuous fever.

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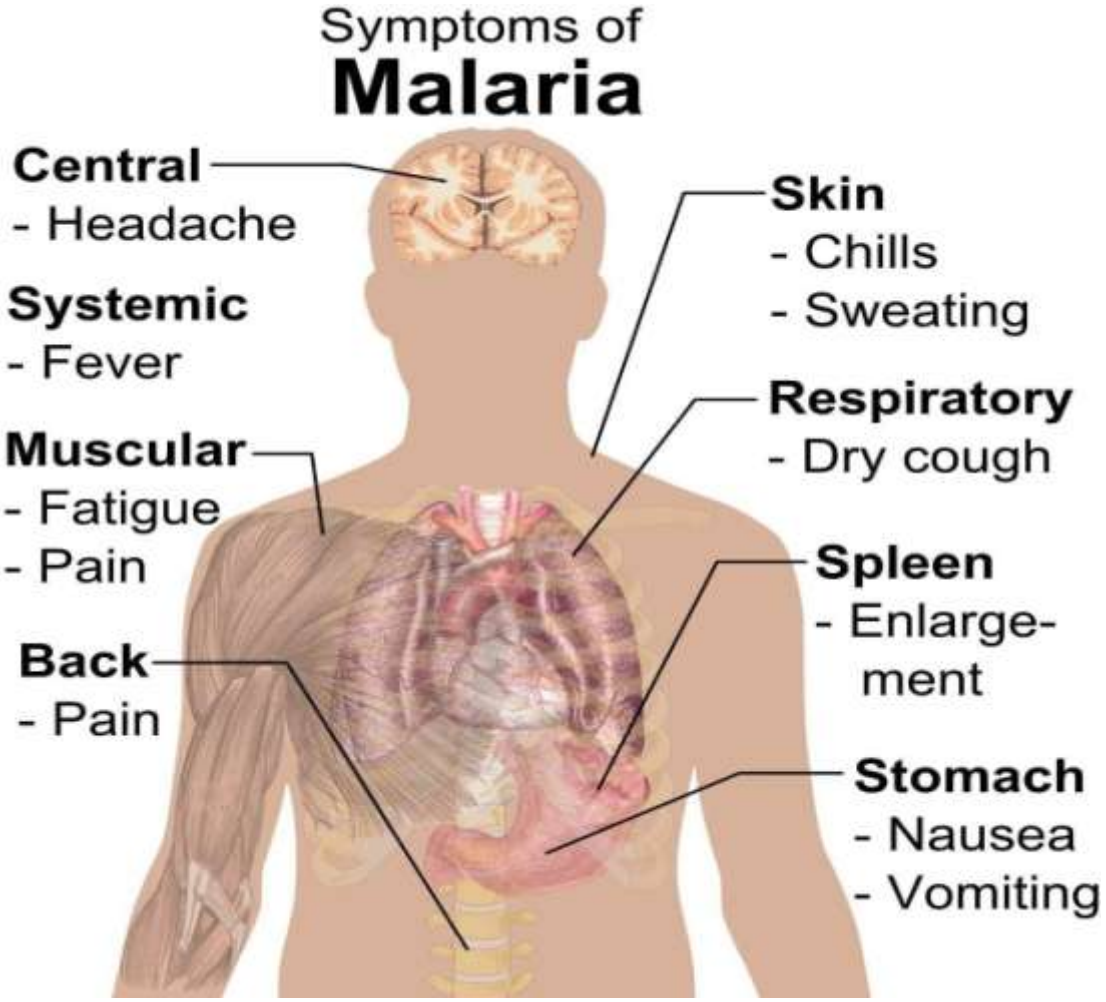

Fig 1.Symptomsofmalaria

Complications:-

Themaincomplicationisthedevelopmentofrespiratorydistress,due to respiratorycompensationof metabolic acidosis, Concomitant pneumonia, noncardiogenicpulmonary oedemaandsevereanaemia.Acuterespiratory distresssyndromeoccursin5–25%ofadultsandupto29%ofpregnant women.7InfectionofHIVwithmalaria increasesthechancesofdeath.8Due to infection with P. falciparum Cerebral malaria may occur. Which is associatedwithretinal whitening(ausefulclinical signin distinguishing malariafrom othercausesoffever.)9.Splenomegaly,liverenlargement, hypoglycemia,severeheadache,andhemoglobinurea withrenalfailuremay occur.4 Malaria may cause stillbirths, infant mortality and low birth weight duringthepregnancy,10particularlyinP.falciparum& P.vivaxinfection.11

Causesofmalaria:-

Malaria iscausedbyP.falciparum,P. malariae,P.ovale,P.vivaxin humans12,13 P. falciparum is the most common species identified (~75%) followedbyP. vivax(~20%).3AlthoughP. falciparumtraditionallyaccounts for the majority of deaths,14 Recent evidence suggests that P. vivax malaria isassociatedwithpotentiallylife-threateningconditionsaboutasoftenaswith a diagnosis of P. falciparum infection.15 P. vivax proportionally is more common outside of Africa.16 P. knowlesi is a zoonotic species that causes malaria inmacaques13, theseare mostlyoflimitedpublic healthimportance.

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Lifecycleofthemalariaparasite:-

The life cycle ofthe malaria parasite (Plasmodium) is complicated and involves two hosts, humans and Anopheles mosquitoes. The disease is transmitted to humans when an infected Anopheles mosquito bites a person and injects the malaria parasites (sporozoites) into the blood. Sporozoites travel through the bloodstream to the liver, mature, and eventually infect the human red blood cells. While in red blood cells, the parasites again develop until a mosquito takes a blood meal from an infected human and ingests human red blood cells containing the parasites. Then the parasites reach the Anopheles mosquito's stomach and eventually invade the mosquito salivary glands. When an Anopheles mosquito bites a human, these sporozoites completeandrepeatthecomplexPlasmodiumlifecycle .P.ovaleandP.vivax can further complicate the cycle by producingdormant stages (h ypnozoites) that may not develop for weeks to years.

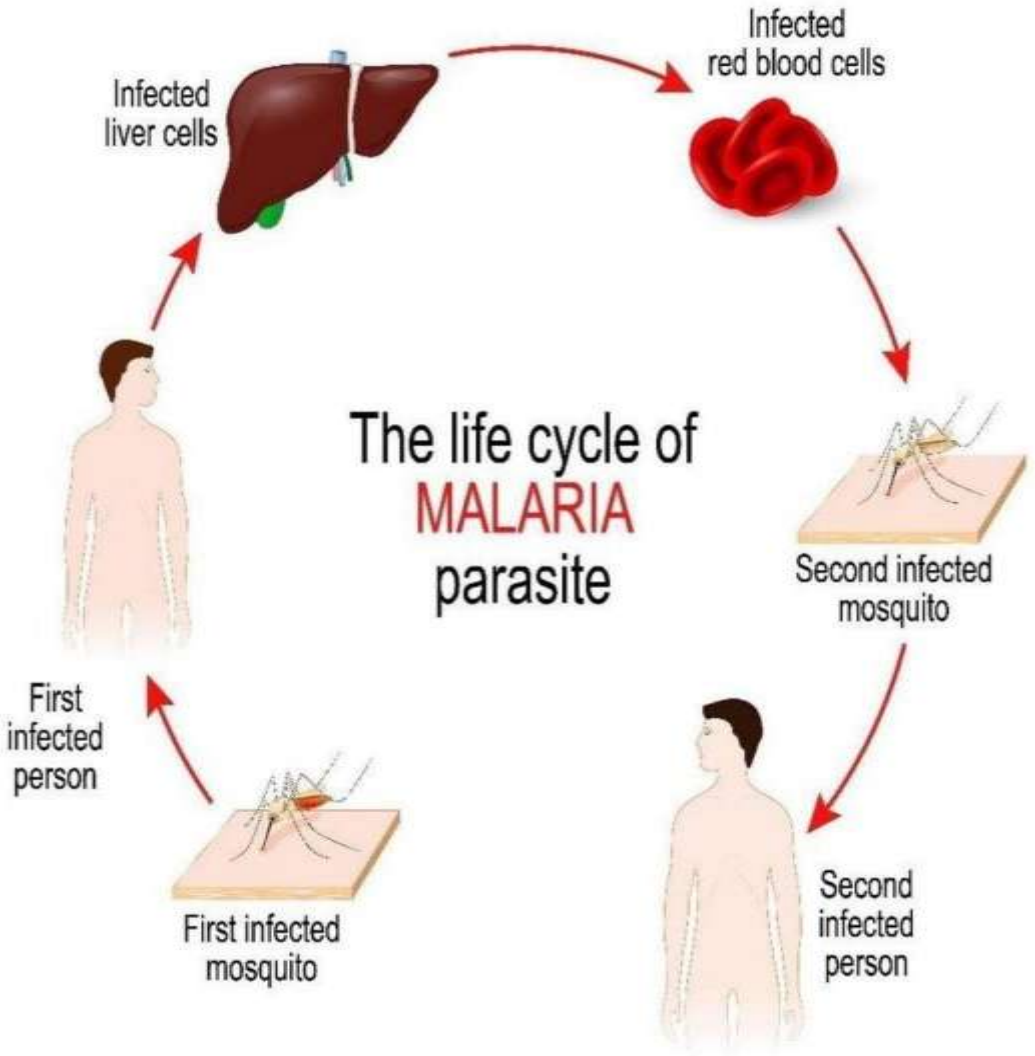

Fig2. Lifecycleofmalariaparasite

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Diagnosisofmalaria:-

Diagnosis of malaria in non-endemic areas requires a high degree of suspicion, which might be elicited by any of the following: recent travel history, enlarged spleen, fever, low number of platelets in the blood, and higher-than-normal levels of bilirubin in the blood combined with a normal level of white blood cells.

Microscopy :-

Malariaisusuallyconfirmedbythemicroscopicexaminationormicroscopy ofblood films orbyantigenbasedrapiddiagnostic tests(RDT).20,21 About 165millionbloodfilmsweremicroscopicallyexaminedformalariain2010.

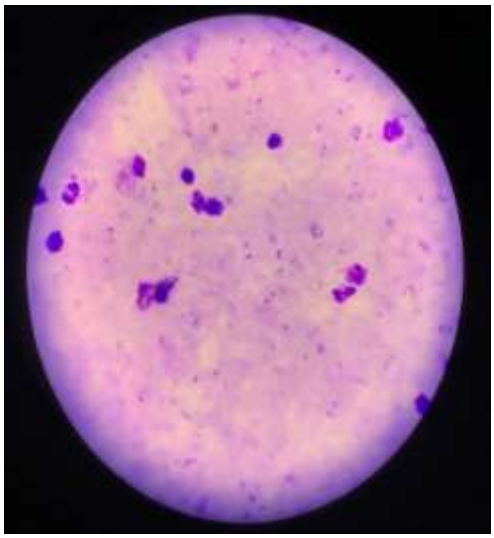

Fig3.Microscopyofmalarialparasite

Classificationofmalaria:-

WorldHealthOrganization(WHO)classifiedMalariaintotwotypes:-

1. Severemalaria
2. Uncomplicated malaria.

Theseveremalariaisdeclaredwhenanyofthefollowing criteriaarepresent, otherwise it is considered as uncomplicated malaria.

1. Decreasedconsciousness
2. Significantweaknesssuchthatthepersonisunable to walk
3. Inabilitytofeed
4. Twoormoreconvulsions
5. Lowbloodpressure(lessthan70mmHginadults and 50 mmHg in children)
6. Breathingproblems
7. Circulatoryshock
8. Kidneyfailureorhemoglobininthe urine
9. Bleedingproblems,orhemoglobinlessthan50g/L (5 g/dL)
10. Pulmonaryoedema
11. Bloodglucoselessthan2.2mmol/L(40mg/dL)
12. Acidosisorlactatelevelsofgreaterthan5mmol/L
13. Aparasitelevelinthebloodofgreaterthan 100,000permicrolitre(µL)inlow-intensitytransmissionareas,or250,000 per µL in high-intensity transmission areas.

Classificationofmalaria:-

000perµLinhigh-intensityWorldHealthOrganization(WHO)classified Malaria into two types:

1. Severemalaria
2. Uncomplicated malaria.

Thesevere malariaisdeclaredwhenanyofthefollowingcriteriaare present, otherwise it is considered as uncomplicated malaria.[24]

1. Decreasedconsciousness
2. Significantweaknesssuchthatthepersonisunable to walk
3. Inabilitytofeed
4. Twoormoreconvulsions
5. Lowbloodpressure(lessthan70mmHginadults and 50 mmHg in children)
6. Breathingproblems
7. Circulatoryshock
8. Kidneyfailureorhemoglobininthe urine
9. Bleedingproblems,orhemoglobinlessthan50g/L (5 g/dL)
10. Pulmonaryoedema
11. Bloodglucoselessthan2.2mmol/L(40 mg/dL)
12. Acidosisorlactatelevelsofgreaterthan5mmol/L
13. Aparasitelevelinthebloodofgreaterthan

100,000permicrolitre(µL)inlow-intensitytransmissionareas,or250, transmission areas.

Methodsofmalariaprevention:-

Therearevariousmethodsusedtopreventmalaria which are such as:

1. Medications
2. Mosquitoelimination
3. Preventionofbites

Atpresentthere is no vaccine available for malaria.Malaria occurs inanarea where the combination ofhigh human population density,

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high anopheles mosquito population density and high rates of transmissionfrom humans to mosquitoes and from mosquitoes tohumans available. If any of these is lowered sufficiently, the parasite will eventually disappear from thatarea. However, unless the parasite is eliminated from the whole world, it could become re-established if conditions revert to a combination that favours the parasite's reproduction. Furthermore, the cost per person of eliminating anopheles mosquitoes rises with decreasing population density, making it economically possible in some areas.26

Prevention of malaria may be more cost-effective than treatment of the disease inthe longrun, but the initialcosts required are out ofreachof many of the world'spoorestpeople.Chinagovernmentannounceda strategytopursue malaria elimination which required small proportion of investment of public expenditure onhealth. Whereas asimilarprograminTanzania wouldcostan estimated one-fifth of the public health budget.[27]

Vectorcontrol:

Vector control methods used to decrease malaria by reducing the levels of transmission by mosquitoes.For individual protection, the most effective vector control methods are • Insect repellents are based on DEET or picaridin.28 • Insecticide-treated mosquito nets (ITNs) • Indoor residual spraying (IRS) have beenshownto be highlyeffective inpreventing malaria among children in areas where malaria is common.29,30 • Prompt treatment ofconfirmedcaseswithartemisininbasedcombination therapies(ACTs)may also reduce transmission.31

Insecticide-treated mosquitonets(ITNs):

Mosquitonetshelpkeepmosquitoesawayfro mpeopleandreduce infection rates andtransmissionofmalaria.

Netsarenotaperfectbarrierandareoften treatedwithaninsecticidedesignedtokillthe mosquitobefore it has timeto find a way past the net. Insecticide-treated nets are estimated to be twice as effective as untreated nets and offer greater than 70% protection compared withno net.32Between2000 and 2008, the use ofITNs saved the lives ofan estimated250,000infantsinSubSaharanAfrica.33Ab out13%ofhouseholds in SubSaharan countriesown ITNs.34In 2000,1.7million (1.8%)African childrenlivinginstablemalariaendemicconditionswe reprotectedbyanITN.

Thatnumberincreasedto20.3million(18.5%)African childrenusingITNs in2007,leaving89.6millionchildrenunprotected.35A nincreasedpercentage of African households (31%) are estimated to own at least one ITN in 2008. Most nets are impregnated with pyrethroids, a class of insecticides with low toxicity.Arecommendedpracticeforusageistohangal arge"bednet"above the center of a bed to drape over it completely with the edges tucked in. Pyrethroid-treated netsand long-lastinginsecticide-treated netsofferthebest protection, and are most effective when used from dusk to dawn.36

Indoorresidualspraying(IRS):

Indoor residual spraying is the spraying of insecticides on the walls inside a home.Afterfeeding, manymosquitorestonanearbysurfacewhiledigesting the bloodmeal, so if the walls of houses have been coated with insecticides, the resting mosquitoes can be killed before they can bite another person and transfer the malaria parasite.37 As of 2006, the World Health Organization recommends12insecticidesin IRSoperations,including DDTandthe pyrethroidscyfluthrin and deltamethrin.38Thispublichealth useof small amountsofDDTispermittedundertheStockholmCon vention,which prohibitsitsagriculturaluse.39Oneproblemwithallfor msofIRSis insecticide resistance. Mosquitoes affected by IRS tend to rest and live indoors,andduetotheirritationcausedbyspraying,thei rdescendantstendto rest and live outdoors, meaning that they are less affected by the IRS.

MedicationofMalaria :

Eachantimalarialdrugisconsideredbychemicalstruct ureand mechanismof action.

Quinineandrelatedagents:

Quinine is an alkaloid obtained fromcinchona acts as a blood schizonticidal and weak gametocide against Plasmodium vivax and Plasmodium malariae. QuinineisaccumulatedinthefoodvacuolesofPlasmod iumspecies, especially Plasmodium falciparum and inhibit the hemozoin biocrystallization,thus facilitatinganaggregationofcytotoxicheme.Quinine is very effective and widely used inthe treatment ofacute cases ofsevere P. falciparumbut it isless effective and more toxic than chloroquine. Mostly

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usefulinareaswhere highlevelofresistancetochloroquine, mefloquine,and sulfadrugcombinationswithpyrimethamine.TheWorldHealthOrganization recommendation for quinine by oral, intravenous or intramuscular routes, is 20mg/kgfirsttimesand10mg/kg8hrfor5dayswhereasinquinine sensitivity quinine may combined with doxycycline, tetracycline or clindamycin.Useof quinineischaracterisedby afrequentlyexperienced syndromecalledcinchonism. Tinnitus, rashes, vertigo, nausea, vomiting and abdominalpainarethemostcommonsymptoms.Quininecancause hypoglycemia through its action of stimulating insulin secretion. This effect can be exaggeratedinpregnancy and therefore additional care in administeringandmonitoringthedosageisessential.Repeatedorover-dosagecanresultinrenalfailureanddeaththroughdepressionofthe respiratory system. 05

Quininerelatedagents:

Quinimax and quinidine are the two most commonly used alkaloids. Quinimax is a combination of four alkaloids (quinine, quinidine, cinchoine and cinchonidine). Due to a synergistic action between the four cinchona derivatives this combination has been shown more effective than quinine. Quinidine is a distereoisomer ofquinine withsimilar anti-malarialproperties andrecommendedonlyforthetreatmentofseverecases ofmalaria.Warburg's Tincture was a febrifuge developed by Dr Carl Warburg in 1834, which includedquinineasakeyingredient.Warburg'sTincturewashighlyregarded by many eminent medical professionals who considered it as being superior to quinine (e.g. Surgeon-General W. C. Maclean, Professor of Military Medicine at British Army Medical School, Netley). Warburg's Tincture appeared in Martindale: The complete drug reference from 1883 until about 1920. The formula was published in The Lancet 1875.49

Chloroquine:

Chloroquinewasleastexpensive,besttested, safestandthe mostwidelyused anti-malarial. It was the original prototype from which most methods of treatment are derived. The emergence of drug-resistant parasitic strains is rapidlydecreasingitseffectiveness.NowChloroquineissuggestedtousedin combination with other antimalarial drugs to extend its effective usage. Popular drugs based on chloroquine phosphate (also called nivaquine) are Chloroquine FNA, Resochin and Dawaquin. Chloroquine is a 4-aminoquinolonecompoundwhichis believedtoreachhighconcentrations in thevacuolesoftheparasiteandraisestheinternalpH.Itcontrolstheconversion of toxic heme to hemozoin by inhibiting the biocrystallization of hemozoin, thus poisoning the parasite through excess levels of toxicity. Childrenand adults should receive 25 mgofchloroquine perkggivenover 3 days,recommendedbytheWHO, involvesgivinganinitialdoseof10 mg/kg followed 6–8 hours later by 5 mg/kg, then 5 mg/kg on the following 2 days.

Amodiaquine:

Amodiaquine is a 4-aminoquinolone anti-malarial drug similar in structure and mechanism of action to chloroquine. Amodiaquine has tended to be administered inareas ofchloroquineresistancewhilesome patientsprefer its tendency to cause less itching than chloroquine. Amodiaquine is now available in a combined formulation with artesunate (ASAQ) and is among the artemisinin-combination therapies recommended by the World Health Organisation. The drug should be given in doses between 25 mg/kg and 35 mg/kg over 3 days in a similar method to that used in chloroquine administration

Pyrimethamine:

Pyrimethamineisusedinthetreatmentofuncomplicatedmalaria,particularly in cases of chloroquineresistant 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 processesofDNAreplication,celldivisionandreproduction.Itactsprimarily onthe schizonts during the erythrocytic phase, and nowadays is only used in concert with a sulfonamide.

Proguanil :

Proguanil (chloroguanide) is a biguanide ,a synthetic pyrimidine derivative. It has many mechanisms of action but primarily is mediated through conversion to the active metabolite cycloguanil. This inhibits the malarial dihydrofolate reductase enzyme. It has a weak blood schizonticidal activity and is not

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recommended for therapy of acute infection. However it is useful in prophylaxis when combined with atovaquone or chloroquine (in areas where there is no chloroquine resistance). 3 mg/kg is the advised dosage per day, (hence approximate adult dosage is 200 mg). There are very few side effectstoproguanil,withslighthairlossandmouthulcersbeingoccasionally reported following prophylactic use.

Sulfonamides:

Sulfadoxineandsulfamethoxypyridazineare specificinhibitorsoftheenzymedihydropteroatesynthetaseinthetetrahydrofolatesynthesispathway ofmalariaparasites.Sulfonamidesactontheschizontstagesofthe erythrocyticcycle.Whensulfonamidesareco-administrationwiththeantifolate pyrimethamine, most commonly as fixed-dose sulfadoxine- pyrimethamine (Fansidar), produces synergistic effects sufficient to cure sensitive strains of malaria.

Mefloquine:

Mefloquine is a very potent blood schizonticide act by forming toxic heme complexes thatdamage parasitic foodvacuoles. Itis now usedsolelyforthepreventionofresistantstrainsofP.falciparumdespitebeingeffectiveagainst P.vivax,P.ovaleandP.marlariae.Mefloquineiseffectiveinprophylaxisand for acute therapy. It is now strictly used for resistant strains and is usually combined with Artesunate. Mefloquine is recommended as a dose of 15–25 mg/kg,dependingontheprevalenceofmefloquineresistance.The increased dosageisassociatedwitha muchgreaterlevelofintolerance, mostnoticeably in young children; with the drug inducing vomiting and oesophagitis. It was not recommended for use duringthe first trimester, although considered safe during the second and third trimester.

II. NEED OF STUDY

1. **GLOBALHEALTHPROBLEM:-**

Malaria remains one of the most serious public health challengesworldwide,especiallyintropicalandsubtropical regions such as Africa, Southeast Asia, and parts of South America.

2. **HighMortalityandMorbidity:-**

Children under five, pregnant women, and immunocompromisedindividualsaremostvulnerable to malaria-related deaths.

3. **EmergenceofDrugResistance:-**

Themajorchallengeinmalariatreatmentisresistanceto conventional drugs such as chloroquine, sulfadoxine– pyrimethamine, and partially to artemisinin.

4. **NeedforNewDrugDiscovery:-**

Theevolutionofmultidrug-resistantPlasmodiumfalciparum necessitates the discovery of new chemical entities and combination therapies

5. **PharmacologicalUnderstanding:-**

Adetailedstudyofantimalarialdrugshelpsin understanding mechanisms of action, pharmacokinetics, and pharmacodynamics.

6. **AcademicandResearchSignificance:-**

Forpharmacystudents,studyingantimalarial drugsprovides scientific understanding of drug development, resistance mechanisms, and clinical applications.

7. **PharmacologicalUnderstanding:-**

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10. **AcademicandResearchSignificance:-**

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III. AIM:-A REVIEW REPORT ON ANTIMALARIAL DRUGS

OBJECTIVE:-

1. **UnderstandingMalariaEtiologyandLifeCycle:-**

Tostudythecausativeagentsofmalaria(Plasmodium species) and the role of Anopheles

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mosquitoes in transmission.

2. UnderstandingMalariaEtiologyandLifeCycle:-

Toclassifyantimalarialdrugsbasedon:

Chemicalstructure:quinolines,artemisininderivatives, antifolates, etc.

Stageofaction:bloodschizonticides,tissueschizonticides, gametocidal agents, and sporontocides.

3. MechanismofAction:-

Tostudythebiochemicalandpharmacologicalmechanisms by which antimalarial drugs act on parasites.

4. PharmacokineticsandPharmacodynamics:-

Toexamineabsorption,distribution,metabolism,and excretion (ADME) of key antimalarial drugs.

5. DrugResistanceStudy:-

Tostudytheemergenceofdrugresistanceinplasmodium falciparum and other species.

6. RecentAdvancesinAntimalarialTherapy:-

ToexplorenewdrugcandidateslikeTafenoquine,OZ439, KAF156, and novel formulations.

Tounderstandtheroleofnanotechnology,targeteddrug delivery, and multistage antimalarial compounds.

IV. CONCLUSION

The combination of Arterolane and Piperaquine act as blood schizonticides with rapid clearance of parasitemia and most malaria-related symptoms, coupled with prevention of recrudescence. The combination provides high clinical efficacyas assessedby PCR corrected ACPR(Adequate Clinical and Parasitological Response), fever clearance time and parasite clearance time. Arterolane maleate and piperaquine phosphate was as well tolerated as artemether and lumefantrine, and had a similar safety profile. Arterolane maleate and Piperaquine phosphate is a synthetic drug and hence easier to manufacture with better predictability and reliability of supplies.

V. SUMMARY

Malaria is one of the most widespread infectious diseases, especially in tropical and subtropical regions. It is mainly caused by Plasmodium falciparum and Plasmodium vivax, transmitted by the female Anopheles mosquito. Antimalarial drugs play a key role in the prevention, control and treatment of malaria. Over the years, several antimalarial agents such as chloroquine, artemisinin derivatives, quinine, primaquine and combination therapies have been developed to reduce morbidity and mortality.

However, increasing drug resistance has become a major global challenge. Chloroquine-resistant P. falciparum has spread in manycountries, leading to the development ofArtemisinin-based CombinationTherapies (ACTs), which are currently the most effective treatment. Continuous monitoring of drug efficacy,developmentofnewmolecules,andvaccinere searchareessentialto overcome emerging resistance.

The review highlights the mechanisms of action of different antimalarial drugs, their therapeutic uses, side effects, resistance patterns and recent advancements. New research focuses on next-generation antimalarials, transmission-blocking agents and long-acting injectable formulations.

Strengtheningsurveillanceprogramsandimprovingclinicalmanagementcan significantly contribute to malaria eradication efforts.

VI. FUTURE SCOPE:-

1. Accelerate development and regulatory review of non-artemisinin combinations(e.g.,ganaplacide+lumefantrine)toprovidealternativeswhere ACTs fail.
2. Expandpipelineinvestmentin compoundswithnovel targets(protein- transport disruption, PfATP4 inhibitors, etc.).
3. Developsingle-doseradicalcuresforbothfalciparumandvivaxinfections to improve adherence.
4. Scaleaffordablepoint-of-careG6PDtestssotafenoquinecanbedeployed safely at scale.
5. Investin transmission-blocking drugstoreducecommunity spreadand complement vaccines.
6. Real-timegenomicsurveillancenetworksforresistance markersintegrated into national malaria programs.

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