Review Article

Resistant Malaria : Current Concepts and Therapeutic Strategies

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Introduction

Malaria is by far the world's most important tropical parasitic disease, and kills more people than any other tropical disease except tuberculosis. 40% i.e. 500 million persons of the world's population live in malaria endemic zone. There are 300-500 million new cases of malaria annually. Every year, there are 1.5-2.7 million deaths due to malaria, globally. 200-300 children die every hour. Between 1981 and 1996 there were 20-40 million deaths due to malaria alone as against 2.5 million deaths due to HIV infection [1]. Most deaths are due to delay in diagnosis and treatment. The disease affects the otherwise vulnerable section of the society, the children and the poor.

Drug Resistance

WHO (1967) has defined "Resistance as the ability of the parasite strain to survive and / or to multiply despite administration and absorption of a drug in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject" [2].

Grading of Resistance

Sensitive : Complete clearance of blood film of asexual parasite within 7 days of initiation of therapy without subsequent recrudescence within 28 days.

R-I Resistance : Clearance of asexual parasite in 7 days followed by recrudescence within 28 days.

R-II Resistance : More than 75% clearance of asexual parasitemia within 48 hours.

R-III Resistance : Less than 75% reduction in asexual parasitemia within 48 hours.

Plasmodium Resistance

The resistance to anti malarials was first observed

in 1910 when Quinine resistance was reported from Brazil. In 1948, Proguanil failed to exhibit expected therapeutic response in patients with *Plasmodium falciparum* (Pf) and *Plasmodium vivax* (Pv) malaria from Malaya. Other drugs to which resistance has been reported are Pyrimethamine (1962) Venezuela, Mepacrine (1980's) Thailand, and the African countries, Sulfadoxin-pyrimethamine (1980's) Thailand, South East Asia, South America, South Africa and Mefloquine failure has been reported from Thailand, Burma and Cambodia in 1988 [3].

Emergence of resistance to Chloroquine of plasmodium strains was suspected in Thailand in 1967 and confirmed in Pf malaria in Colombia in 1969. In 1989, Rickmann KH et al reported a chloroquine resistant strain of Pv in Papua, New Guinea. Subsequently Schwartz et al (1991) from Indonesia and CN Potkar (1994) from Mumbai too reported similar strains [4].

Drug Resistance in India

Chloroquine resistance, in India, was first reported from Diphu area of Karbi Anglong district of Assam in 1973. In 1974 another resistant focus was detected in Nowgaon district too, of Assam state. Thereafter, several tests were carried out in the states of Orissa, Tamilnadu, Karnataka and Madhya Pradesh from 1973 to 1977, but did not reveal any focus of resistance. A large number of tests carried out in the North-Eastern parts of India, indicated that chloroquine resistance in Pf was quite wide spread in the states of Assam, Arunachal Pradesh, Mizoram and Nagaland. These observations necessitated the monitoring of drug sensitivity on a wider scale. A systematic study on monitoring of drug resistance throughout the country was initiated by Government of India from 1978.

Under the operational research scheme of directorate of National Malaria Eradication Programme

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(NMEP), 13 teams are monitoring the sensitivity status of Pf to chloroquine and other antimalarial drugs from 1978. One of these teams is for conducting trials of alternate drugs. From 1978 to end of 1998, these teams have studied in vivo 13,614 Pf cases [3].

In vivo drug resistance studies with sulfa-pyrimethamine have shown resistance to this drug combination in low proportion in the North Eastern states, West Bengal, Kolar District of Karnataka, Bhopal city of Madhya Pradesh and Tripura. In vivo-resistance to quinine at RI and RIII level has been reported from Sairang Primary Health Centre (PHC) of Lunglei district in Mizoram.

In vitro tests were conducted with chloroquine, amodiaquine, sulfa-pyrimethamine combination, quinine and mefloquine. Resistance to mefloquine was observed in the district of Surat in 26.3% of isolates but in East Godavari, only one isolate was studied and was found resistant.

In an epidemic in Rajasthan in 1994, 95% of isolated Pf strains were resistant to chloroquine [5]. In a study from Mumbai, an increase every year in the number of cases showing in-vivo resistance to chloroquine has been reported. The figures were 36.78% in 1994, 45% in 1995, and 53% in 1996 with in-vitro figures of 41.17%, 54.28% and 66.6% in the same years [6]. In another study, 61 out of 90 Pf tested were found to be chloroquine resistant (49 were RI, 8 were RII and 4 were considered RIII). Interestingly, despite supervised primaquine treatment, 4 of the 15 chloroquine sensitive patients and 32 of the 49 RI resistant had gametocytes on day 29 [7].

Antimalarials used in Resistant Malaria

An ideal new antimalarial should have the following properties :

- (a) Fast fever (FCT) and parasite clearance time (PCT).
- (b) A single dose administration should be sufficient.
- (c) There should be no cross resistance amongst the drugs.
- (d) It should be cheap.
- (e) It should have no or minimal side effects.
- (f) It should be safe in pregnancy and childhood.

Chloroquine, which meets most of these requirements, is slowly going out of use in various countries due to development of resistance against Pf.

Quinine has been in use for over three centuries but it had gone out of use due to cinchonism. With the emergence of resistance to chloroquine it is recom-

mended for resistant malaria. Quinine acts on the ring, trophozoite and schizont forms of the intraerythrocytic stage of all malarial parasites [8]. Quinidine, the dextrorotatory diastereoisomer, is more active than quinine, but is also more cardiotoxic and expensive. The cinchona alkaloids are active against all species of malaria including chloroquine resistant strains of Pf. National Anti Malaria Programme (NAMP) recommends its use in severe and complicated Pf malaria and chloroquine and sulfa+pyrimethamine combination resistant Pf malaria. Dosage :-

(a) Quinine : Routine ECG monitoring is not required when quinine is used in patients with previously normal heart. Loading dose of 20 mg/kg salt in 300 ml of dextrose water infused over 4 hours should be used in severe infections. Alternatively 5-7 mg/kg salt may be given by infusion pump over 30 minutes. Maintenance dose is 10mg/kg in 4 hours, given eight hourly. Total duration of IV and oral drug is 7 days. The drug has a narrow therapeutic ratio though serious central nervous and cardiovascular system toxic effects during anti malarial treatment are rare. It should never be given by bolus injection as it can lead to fatal hypotension. Principal side effect is hyperinsulinemic hypoglycaemia.

(b) Sulphonamide (500 mg) and Pyrimethamine (25 mg) combination is effective against drug resistant Pf. Sulphonamides act on the intra-erythrocytic forms while pyrimethamine acts on the primary tissue phase. Dose is three tablets once in adults. Resistance to this drug is however widespread.

(c) Maloprim : It is a combination of dapsone (100 mg) and pyrimethamine (25mg). It is indicated for use in drug resistant Pf. Major side effect is Steven Johnson syndrome. Resistance to this drug is widespread.

(d) Primaquine (8-aminoquinoline) interferes with function of plasmodia DNA. It is effective against the primary tissue phase and gametocytes of Pf. It is used for gametocidal action against Pf. Dose is 45 mg stat for gametocidal action. Side effects include hemolysis in G6PD deficient individuals. Resistance to the drug has been reported. It should not be given with metakelfin, on the same day, as they can precipitate severe haemolysis in G6PD deficient individuals. It is contraindicated in pregnancy.

(e) Mefloquine is a synthetic aryl-amino alcohol compound related to quinine. It forms toxic complexes with free haem that damages membrane of parasite. It has a strong schizonticidal action against all four species and is gametocidal for *P vivax*, *ovale* and *malariae* but not *falciparum*. It is indicated for chemo-

prophylaxis and treatment of drug resistant Pf. Dose (WHO) is 15 mg/kg. Where the dose exceeds 1,000mg it should be administered in two divided doses 8 hours apart. An additional dose of 10 mg/kg is required after 6-8 hours where high degree of chloroquine resistance exists. The side effects include acute brain syndrome, gastrointestinal upset and prolongation of Q-T interval. Neuropsychiatric reactions have been reported in 0.5%-1% of Europeans and Africans, and approximately 0.1% of Southeast Asian patients [9,10]. It should be avoided in patients on beta-blockers, pregnancy, epileptic and psychiatric patients.

(f) Halofantrine : is a synthetic phenanthrene methanol. It is schizonticidal for all four species. It has no action against hypnozoites. It is more active than mefloquine [11]. However, its oral bioavailability is poor and variable. It is effective against drug resistant Pf. Dose is 500 mg 6 hourly for 3 doses. Side effects include neuropsychiatric disturbance. It induces a concentration dependent delay in AV conduction and ventricular repolarization. It is contra-indicated in patients with abnormally prolonged QT interval. It should not be used to treat early recrudescence (within 28 days) following mefloquine treatment, because it increases their cardiac and central nervous system (CNS) effects. It is contra-indicated in pregnancy and breast feeding.

(g) Artemisinins (Qinghaosu) are derived from the Chinese herb Qinghao or sweet worm-wood (*Artemisia annua*). Its derivatives developed as pharmaceutical agents in China, are the most rapidly acting of all antimalarials. They concentrate in parasitised RBC's, where they produce free radicals that damage the parasite membrane. They have the shortest FCT of 30.08 hours and PCT of 40.32 hours of all antimalarials [12,13]. Four compounds have been used in artemisinin, a water soluble derivative artesunate, and two oil soluble ethers, artemether and arteether. The ethers are metabolised to a biologically active metabolite di-hydro-artemisinin [14]. Artemisinin and its derivatives have a broader window period of effectiveness than other anti-malarials during 48 hour asexual life cycle of the parasite. Anti-parasitic effects on the younger ring forms prevent them from developing into the more mature pathogenic forms. They are short acting and so not useful for chemoprophylaxis and not effective against gametocytes and hypnozoites. Doses:-

(i) Artemether is available as Inj (80 mg, vial) and capsules (40 mg). A loading dose of 3.2mg/kg IM on day 1, followed by 1.6 mg/kg IM from days 2-5.

(ii) Artesunate 2.4 mg/kg IV or IM, 1.2 mg/kg at 12 and 24 hours and later 1.2 mg/kg daily for 3 days. Artesunic acid is available as a vial containing 60 mg of dry powder. It is dissolved in 0.6 ml of 5% sodium bicarbonate and diluted in 3-5 ml of 5% distilled water. It is 20-100 times more potent than artemether.

(iii) Arteether is available as Inj (150 mg in 2 ml vial). The dose is 150 mg deep IM daily for 3 days.

Loading dose is contra-indicated if quinine/quinidine has been given in the preceding 24 hours or mefloquine in preceding 7 days. Artesunate is the most rapidly acting of the available compounds. Suppositories of artemisinins are now available and are as effective as parenteral drug.

In some parts of Southeast-Asia where failure rate of treatment with high dose mefloquine alone in falciparum malaria now exceeds 40%, oral artesunate given for three to five days in combination with mefloquine still remains highly effective [15,16,17].

In two recent comparative studies of patients with severe falciparum malaria (which had more than 1000 patients), treatment with IM artemether accelerated parasite clearance but slightly prolonged recovery from coma and did not reduce mortality significantly in comparison with quinine. The result of this trial confirms that artemether is an acceptable and well-tolerated alternative to quinine in severe malaria but a final assessment with respect to mortality should await a systematic overview of these and other recent studies [12,17]. The safety of artemisinin and its derivatives has not been established during first trimester of pregnancy.

WHO recommends for multidrug resistant (MDR) malaria : artemether by mouth 40 mg capsules for minimum of three days with single dose of mefloquine. This strategy gives a rapid initial therapeutic response, meanwhile, protecting artemether compound from resistance, since other antimalarial drugs should eliminate residual parasite [17].

(h) Pyronaridine (Malaridine) was developed by Chinese Academy of Preventive Medicine in 1970. It is effective against Pv, Pf and MDR strains. It inhibits haemoglobin degradation by the parasite. The first clinical trial outside China was published in Lancet (1996). FCT was 3 days and PCT was 4 days for this drug. Dose is a total of 1.2 gm; 0.3 gm IM/IV, 2 doses 8 hours apart on day 1 and 0.3 gm OD on days 2 and 3.

(i) Malarone : is a combination of atovaquone (250 mg) and proguanil (100 mg). Atovaquone was used

for the treatment of *Pneumocystis carini* pneumonia. It was first introduced in Australia in 1998. The combination is synergistic and very effective. Side effects are mild and rare. The dose is 4 tablets daily for 3 days.

(j) Desferoxamine chelates iron. Iron is an essential nutrient for Pf. It enhances clearance of Pf. When used alone the recrudescence rates are high. It may be combined with quinine. It speeds up arousal in cerebral malaria patients.

(k) Etacrine is a newly developed long acting primaquine like drug. It may be available soon for radical cure.

(l) Other antimalarials : include tetracycline, doxycycline, clindamycin, mepacrine, erythromycin, benflumentol, hydroxypipraquine, trioxanes, tetraoxanes, peroxides and azithromycin.

(m) Multidrug resistant malaria : Drugs recommended for use are mefloquine, halofantrine and quinine with tetracycline. A three day course of clindamycin with quinine has proved effective in areas of endemic disease but there is insufficient evidence of their effectiveness in non-immune individuals [18].

(n) Drugs that reverse chloroquine resistance: Rapid excretion of chloroquine from Pf causes resistance to the drug. Calcium channel blockers like nifedipine and verpamil, tricyclic compounds and H1 receptor blockers like cyproheptadine can effectively overcome this limitation. However, there has been no clinical trial to demonstrate the practical utility of these drugs for the purpose stated.

(o) Combination Chemotherapy : with various antimalarials is more promising in terms of efficacy and to retard the development of resistant strains. Drug combinations recommended are given below :

Quinine combination : tetracycline, clindamycin

Artesunate combination : tetracycline, mefloquine

Pyronaridine combination : sulfadoxine + pyrimethamine, primaquine

Supportive therapy and treatment of complications

The clinical manifestations of severe malaria depend on age [19]. Hypoglycaemia, convulsions and severe anaemia are relatively more common in children [20,21]; acute renal failure (ARF), jaundice and pulmonary edema are more common in adults. Cerebral malaria, shock and acidosis, which may terminate in respiratory arrest, may occur at any age.

Hypoglycaemia occurs in about 8% of adults and 25% of children, a maintenance infusion of 5 to 10% glucose should be given to all patients. In patients hav-

ing hypoglycaemia, IV injection of 50% glucose is given followed by continuous infusion of 5% or 10% glucose.

Incidence of seizures ranges from more than 80% in infants to less than 20% in adults. Seizures should be treated promptly with IV diazepam (0.15 mg/kg of body weight, maximum 10 mg for adults) or IM injection of paraldehyde (0.1mg/kg)

Haemolysis is extensive and anaemia develops rapidly. Blood should be transfused if the haematocrit falls below 20%. Transfusion of fresh blood is preferable particularly if there is pronounced bleeding due to DIC or stress ulceration. Exchange transfusion should be started when the parasitemia exceeds 15%. It may also be considered for parasitemia between 5 to 15% when there are other signs of poor prognosis.

Adults are more vulnerable to fluid overload and non-cardiogenic pulmonary edema, yet the dehydration and hypovolemia contribute to hypotension and shock (particularly in children) and may hasten ARF arising from acute tubular necrosis (particularly in adults). After rehydration, the CVP should be maintained at approximately 5 cm of water (pulmonary artery occlusion pressure, less than 15 mm Hg).

When hyper catabolic ARF develops with other evidence of vital organ dysfunction, dialysis should be started immediately. Renal function (restoration of urine flow to more than 20 ml per kg per day) returns after a median of four days although some patients would require dialysis for more than one week.

Bacterial infections are common and may lead to septicaemia. This should be treated with appropriate antibiotics along with haemodynamic correction.

Pregnancy and Malaria

Pregnancy lowers the immunity to malaria. Severe malaria is more common resulting in high foetal and maternal mortality. Hypoglycaemia is a common and dreaded complication and should be closely monitored. Safe drugs in pregnancy include chloroquine, quinine and proguanil. There is also evidence that mefloquine and sulfadoxine-pyrimethamine is safe in second and third trimesters. Contraindicated drugs include primaquine and halofantrine [16].

Present Recommendations of National Anti Malaria Programme-Drug Policy (Apr-1996)

NAMP was first drafted in 1982 to combat the increasing level of resistance to chloroquine detected in Pf [17]. A committee of medical experts from different specialities-clinical, pharmacology, malariology etc. was constituted by the Director General Health

Services under his chairmanship. Based on the recommendations of the expert committee the directorate of NAMP has revised its drug policy since April 1996.

Present strategy involves stratifying rural areas into high and low risk PHC's. Criteria for identifying high-risk areas:

- Recorded deaths due to malaria
- Slide positivity rate (SPR)
 - (i) Doubling of SPR in the last 3 years with SPR 4% or more in the 2nd and 3rd year.
 - (ii) No doubling but average SPR in the last 3 years is 5% or more
- Pf proportion is 30% or more and SPR is 3% during any of the last 3 years.
- Area with chloroquine resistant focus
- Topical aggregation of labour in endemic or vulnerable areas.

Urban Malaria Scheme covers towns with a population of 50,000 or more, with an average SPR of 5% over the last three years and a case proportion of malaria of 30% or more.

Presumptive treatment : All suspected malaria / clinical malaria cases should be presumptively administered :

- (a) In low risk of resistance areas : Chloroquine phosphate 600 mg (4 tablets) single dose
- (b) Resistant Pf areas : Chloroquine 10 mg/kg-600 mg on day 1 & 2 and 5 mg/kg-300 mg on day 3 along with primaquine 0.75 mg/kg - 45 mg on day 1.

Radical treatment : Radical treatment should be administered after microscopic confirmation of species :

- (a) Pv : chloroquine (600 mg)+primaquine 0.25 mg/kg (15 mg) OD for 5 days.
- (b) Pf in areas of low risk of resistance : chloroquine (1500 mg) over 3 days + primaquine 45 mg stat on day 1.
- (c) Pf in areas of high risk of resistance :
 - (i) Day 1 : sulphalene 1500 mg plus pyrimethamine (75 mg) (Fansidar)
 - (ii) Day 2 : primaquine 45 mg.

These drugs should not be given on the same day as it may precipitate severe haemolysis in G6PD deficient individuals.

Amodiaquine has no advantage over chloroquine in chloroquine resistant areas and considering its toxicity, amodiaquine has been withdrawn from the programme and private sector from April 1996.

Management of complicated *P falciparum* : In

cases resistant to above drugs and in severe and complicated Pf malaria, IV quinine dihydrochloride is given in the doses as under [18] :-

- (a) 10 mg/kg x 8 hourly in 5% dextrose solution over 4 hours. After regaining consciousness the same dose schedule is given orally to complete 7 days.
- (b) Pregnant women are managed with IV quinine in appropriate doses. It does not induce abortion in recommended doses. In delayed treatment, abortion occurs due to foetal hypoxia.

Use of new anti malarials by registered medical specialist:

- (a) Mefloquine for chloroquine resistant Pf cases only with ring stage (not gametocyte alone) to be issued on the prescription by a qualified registered medical specialist supported by laboratory report from qualified parasitologist.
- (b) Artemisinin and its derivatives in injectable form only (to prevent misuse) in Pf areas of resistant foci for severe and complicated Pf cases. Careful monitoring of distribution to be ensured [22].

New Targets of Chemotherapy

In view of the ability of the malarial parasite to develop resistance to the available drugs there is a pressing requirement to develop new and potent anti-malarials. Some of the drugs likely to be introduced in the near future are as under :

- (a) WR-33063 (9-phenanthrene methanol) cured 80% volunteers with MDR strains, while WR - 30090 cured 90% of volunteers.
- (b) Malarial proteases inhibitors are the targets for development of future drugs. Proteases appear to be required for the rupture and subsequent reinvasion of erythrocytes by merozoite - stage parasites and for the degradation of haemoglobin by intra-erythrocytic trophozoites. Inhibitors of aspartic and cysteine proteases have synergistic effects on inhibiting the growth of cultured malarial parasites [23] and these proteases also act synergistically to degrade haemoglobin in vitro [24]. Therefore, the combination of inhibitors of malarial cysteine and aspartic proteases may provide the most effective chemotherapeutic regimen and best limit the development of parasite resistance to proteases.
- (c) WR-238, 605 is a new 8-amino quinoline developed by Walter Reed Army Institute of Research in Washington DC. It is ten times more active as a hypnozoitocidal drug than primaquine and also has blood schizonticidal activity. Phase I trials have already been launched.

Conclusion

It will require more than just the development of new-antimalarials to combat the global menace of malaria. A multilateral effort involving political, administrative and health agencies directed towards vector control, prevention of transmission and early detection with prompt treatment will be required to achieve even a semblance of control. However, drug development will always remain an important component of this effort to reduce morbidity and mortality due to this disease. Drug resistance will continue to be a problem for future. It is unlikely that an ideal anti-malarial with no possibility of resistance will ever be manufactured. Responsible use of new drugs is essential, if they are not to become as clinically compromised as chloroquine is today.

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