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Review Article

Chloroquine-Resistance Malaria

B. Akshaya Srikanth[1], Nesrin Mohamed Abd alsabor Ali[2], S.Chandra Babu[3]

[1]Pharm.D Intern, P.R.R.M.College of Pharmacy, Kadapa, A.P, India

[2]Faculty of Pharmacy, Assuit University, Egypt

[3]Asst.Professor of Medicine, Rajiv Gandhi Institute of Medical Sciences, Kadapa, A.P, India

*Corresponding author: akshaypharmd@gmail.com

ABSTRACT

Malaria is the major health problem in developing countries including India. Resistance to antimalarial drugs is proving to be a challenging problem in malaria control in most parts of the world. Chloroquine resistance has emerged independently less than ten times in the past 50 years and the most of the chloroquine resistance targets are localized in the acid food vacuole of the malaria. Resistance to *P.falciparum* may be due to increased capacity of the parasite to expel chloroquine to reach levels required for inhibition of the heme-polymerization. Resistance to sufadoxime-pyrimethamine, quinine and mefloquine is much higher than the chloroquine. Increased chloroquine treatment failure has led to change the drug policy to artesunate combined therapy (ACT) as first line of malaria treatment. The artesunate-based combination currently used in the established multidrug-resistant areas on different parts of world. With emerging resistance there is a urgent need of a fully synthetic drug such as arterolane, which has an activity profile that is similar to that of the artemisinins, provides an important potential in such an endeavor.

Keywords: Malaria, Chloroquine, Resistance, ACT, India

1. INTRODUCTION

Malaria is caused by infection of red blood cells with protozoan parasite of the genus *Plasmodium*. The parasites are inoculated into the human host by feeding female anopheline mosquito. The four *Plasmodium* species that infect human are *P.falciparum, P.vivax, P.ovale and P.malaria*. Increasingly, human infections with the monkey malaria parasite, *P.knowlesi*, have also been reported from the forested regions of South-East Asia.[1]

Globally 300-500 million people are infected and 1.5-1.7 million people die of malaria every year [2] and in India, over the past two decades, malaria incidence has been fluctuating between 2 to 3 million cases per year [3, 4]. At late 1934, chloroquine was discovered by Hans Andersang in Germany. Subsequent work by the British and the United States Armies during World War II showed the drug was a very promising antimalarial. In 1945, Chloroquine replaced quinine as the first-line treatment for malaria due to low cost, straightforward synthesis and low toxicity and first resistance case to chloroquine was documented in 1957 [5, 6]. Onset of chloroquine resistance marked the beginning of new chapter in the history of malaria.

2. DRUG RESISTANCE IN MALARIA

Resistance to antimalarial drugs is proving to be a challenging problem in malaria control in most parts of the world. Resistance to antimalaria drugs has been a particular problem with *P.falciparum* in which widespread resistance to chloroquine, sulphadoxine-pyrimethamine and mefloquine has been observed [Figure 1]. For instance, as per estimates in the past decades, 50% of the strains of *P.falciparum* are resistant to chloroquine [7] and resistant strains of *P.vivax* are also increasing in different parts of India [8]. Antifolate and chloroquine resistance has developed in P. vivax in several areas, and chloroquine resistance in P. malariae has also recently been reported [9].

3. CHLOROQUINE RESISTANCE MECHANISM

Chloroquine resistance is associated with a decrease in the amount of chloroquine that accumulates in the food vacuole, the site of action for chloroquine. [Figure 2] The mechanism for this decreased accumulation is controversial. Some studies have shown that the decrease in drug accumulation is due to an increase in drug efflux [10] [Figure 3]. Whereas other studies suggest that diminished levels of chloroquine accumulation is more important [11]. The observation that verapamil and related drugs can reverse the chloroquine resistant phenotype has led to speculation that an ATP dependent transporter plays a role in drug efflux and chloroquine resistance, similar to the multidrug resistance (MDR) in cancer. A MDR-like transporter, designated *Plasmodium falciparum Multidrug resistance* 1 (PfMDR1), has been identified on the food vacuole membrane. However, no definitive correlations between

PfMDR1 and chloroquine resistance could be demonstrated. An ancillary role for PfMDR1 in chloroquine resistance cannot be ruled out though.

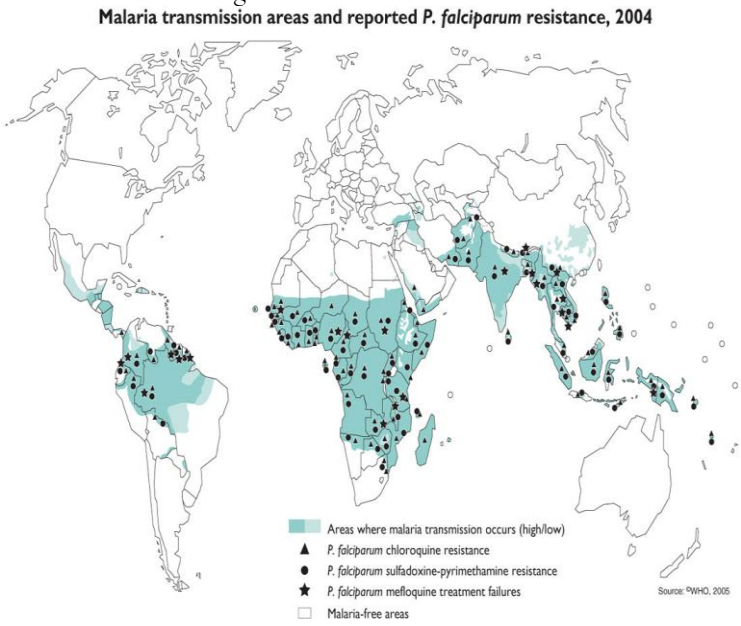

Figure 1 description: *Malaria transmission areas and the distribution of reported resistance or treatment failures with selected antimalarial drugs, September 2004 (mefloquine resistance in Africa is currently being further reviewed)*

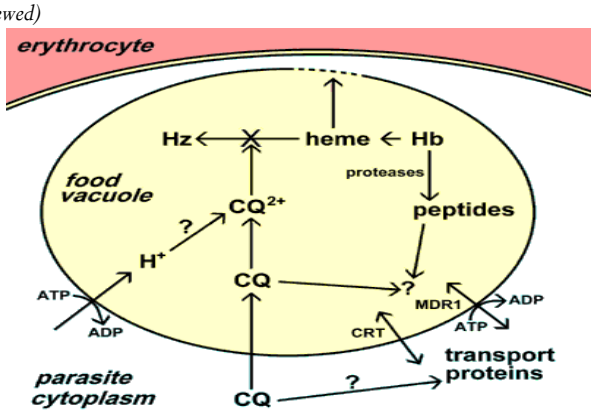

Figure 2 description: *Chloroquine (CQ) accumulates in the food vacuole of the parasite. This accumulation may involve ion trapping following protonation, specific transport, and/or binding to a receptor (eg., heme). The major action of chloroquine is to inhibit the formation of hemozoin (Hz) from the heme released by the digestion of hemoglobin (Hb). The free heme then lyses membranes and leads to parasite death. Chloroquine resistance is due to a decreased accumulation of chloroquine in the food vacuole. Two different transporters (CRT and MDR1) have been implicated in resistance. The functions of these transporters and their exact roles in chloroquine resistance are not known.*

The genetic locus of chloroquine resistance was identified through a genetic cross and mapping experiment. A 400 kb region on chromosome 7 was found to segregate with chloroquine resistance and further analysis suggested that a single gene, called Pfcrt, was responsible for chloroquine resistance. Out of a total of 10 polymorphisms identified in this gene, only a single mutation is perfectedly associated with the chloroquine resistance phenotype. This mutation results in a lysine at residue 76 being changed to a threonine (K76T). Several field studies have demonstrated an association between Pfcrt-K76T and chloroquine resistance using both in vivo and in vitro methods. It has been recently suggested that there have been at least 4 founder mutations in the Pfcrt gene associated with different geographical regions: Asia/Africa, Papua New Guinea, Brazil/Peru, and Colombia [12]. Presumably the use of chloroquine resulted in the subsequent selection and spread of the resistant phenotype. Current molecular studies of *P.falciparum* isolates suggested that few gene loci are associated with chloroquine resistance to *P.falciparum*. [2, 13].

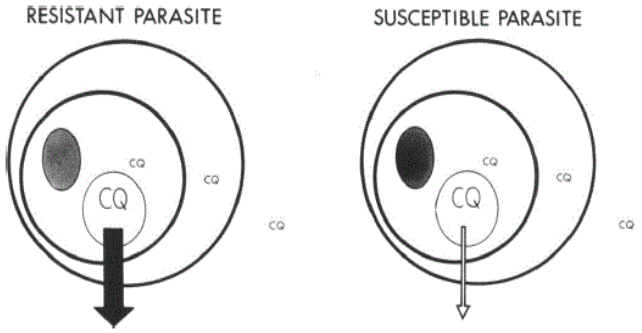

Figure 3 description: *The resistant P.falciparum parasite releases chloroquine 40-to 50-fold more rapidly than the susceptible parasite (shown by bold arrow). This difference in their rate of chloroquine release in consistent with the differences in their steady-state accumulations of chloroquine and in their chloroquine 50% effective doses. These data suggested that the critical difference between resistant and susceptible parasites may be the rate at which they release chloroquine.*

4. TRACKING THE SPREAD OF CHLOROQUINE RESISTANCE

From 1940s-1990s, chloroquine was the mainstay of malaria therapy worldwide. Selection of *P.falciparum*-resistant isolates was first reported in Southeast Asia (Thai-Cambodian border) and South America (Colombia) in the 1950s [14, 15]. In Africa, the resistance is currently less severe in west and central Africa than in east Africa, but even in west Africa, its intensity varies from an advanced stage with severe effects on mortality and morbidity in focal areas of Senegal [16, 17]. Chloroquine-resistant parasites in Africa were though by some to share the same origin as the Indochina strains, but by others to have developed locally as a result of mass drug administration plus intrinsic entomological, epidemiological, and parasitological factors that promoted local resistance selection [18]. Current molecular studies suggest the Asian origin of African isolates, but at least four different foci of chloroquine resistance have so far been identified [19, 20]. Since then chloroquine resistance has spread far beyond the first focus and is now found in all parts of the world where malaria is endemic [21]. Chloroquine resistance has emerged independently less than ten times in the past 50 years [9] [Figure 4].

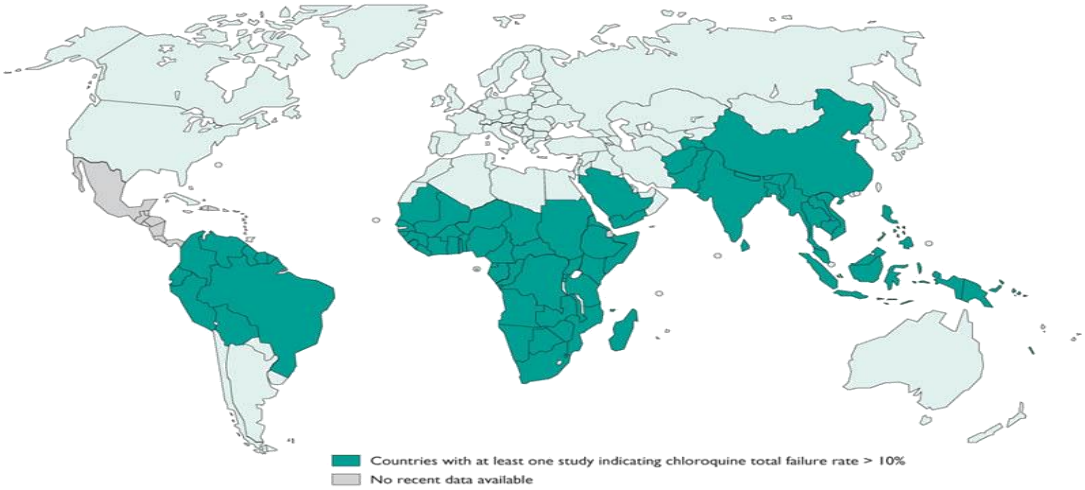

Figure 4 description: *Distribution of chloroquine resistance in Plasmodium falciparum*

5. CHLOROQUINE RESISTANCE; THE INDIAN SAGA

In India chloroquine resistance was first detected in 1973 and in 1974 in karbi-Anglong district of Assam and Nowgong district of Assam respectively. Gradually it spread towards the west and south, covering almost the entire country [22, 23]. Currently chloroquine resistance is severe in Northeast and South-eastern regions with high morbidity and mortality [Figure 5].Several reports of chloroquine resistance in P.vivax are documented. This has been spread from Papua New Guinea [24]. Resistance in P.vivax is more serious as hypnozoites will cause relapse of resistant parasites and P.vivax is a mixture of various strains with respect to incubation period, relapsing pattern and response to primaquine since sulfa drugs are not effective in its treatment [2, 25].

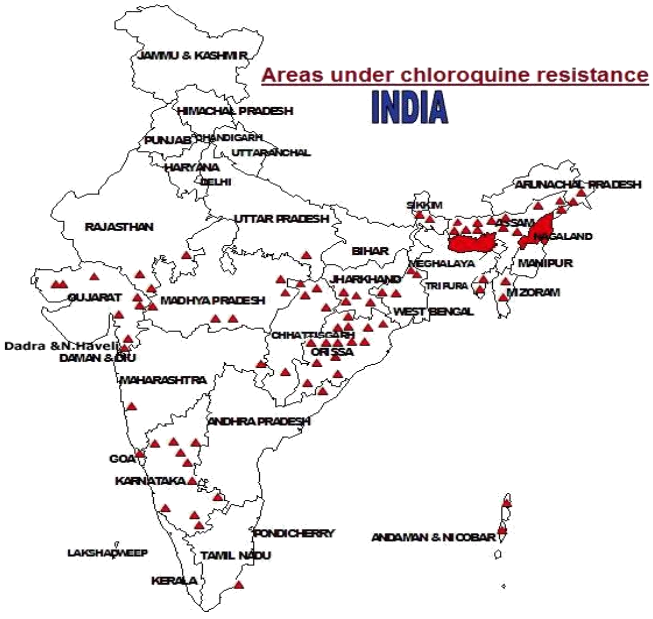

Figure 5 description: *Areas showing in red (triangle and patches) where chloroquine in Plasmodium falciparum has been confirmed.*

6. RESISTANCE TO OTHER ANTIMALARIALS IN INDIA

6.1. Sulfadoxine-pyrimethamine: Resistance to sulfa drugs has been reported from *P.falciparum* predominated areas like Northeast states and Orissa [26]. Resistance is likely to progress geographically and in intensity at an alarming rate if nothing is done to interrupt its course.

6.2. Quinine: Resistance has emerged against quinine in North-eastern states and Kolar districts of Karnataka [27].

6.3. Mefloquine: Mefloquine resistance is frequent in parts of Southeast Asia and resistance in *P.falciparum* to mefloquine in India was detected in Surat district of Gujarat state [28].

7. EVOLUTION OF STRATEGIES TO OVERCOME DRUG-RESISTANT MALARIA

In 1973, chloroquine resistance has been reported in East-Africa, owing to high intensity chloroquine resistance, chloroquine had to be replaced by the combination of sulfadoxine-pyrimethamine (SP) or combination of chloroquine and sulfadoxine-pyrimethamine as a first-line drug for the treatment of uncomplicated malaria in many parts of the world. Due to widespread use of SP combination resulted in loss of sensitivity started declining in the late 1980s. Resistance is likely to progress geographically and in its intensity at an alarming rate if nothing is done to interrupt its course. In 1985, eventually SP was replaced by mefloquine. The rapid development of resistance to mefloquine leads to introduction of artemisinin as a combination drug in the mid-1990s [2]. Artemisinin and its derivatives like aremether, artesunate, and dihydroartemisinin are associated with high rate of recrudescences after monotherapy, probably because of the pharmacodynamic properties of these agents [29]. Some of the

Artemisinin based combination therapies (ACT's) recommended by world health organisations (WHO) are artesunate and mefloquine, artesunate and sulfadoxine-pyrimethamine, artesunate and amodiaquine, artemether-lumefantrine [30]

8. EMERGING ARTEMISININ-RESISTANT MALARIA

The global implementation of ACTs, clinical treatment failures with ACTs came from observational studies in the early 2000s of artesunate-mefloquine use [31]. The evidence of emerging of artemisinin resistance came from the study published in mid-2009 by Dondorp *et al*. [32], stating the delayed parasite clearance rates comparing with artesunate monotherapy or artesunate-mefloquine combination therapy. The artesunate-mefloquine combination currently used in the established multidrug-resistant areas of Thailand cannot be expected to offer similarly favorable operational prospects for Africa. Parasites resistant to artemisinin-based combination therapies take 3 or 4 days to clear as compared with less than 2 days for artemisinin-sensitive parasites. This delayed clearance could be a step towards high-level resistance and frank treatment failure. Artemisinins have very short half-life [33]. This loss of potency also renders the more slowly eliminated drugs that are parts of combination therapies vulnerable to development of resistance. The gravity of this threat has been recognized and an ambitious program to contain artemisinin has been launched under the guidance of the World Health Organization (WHO) [34].

9. CONCLUSION

Drug resistance is probably the greatest challenge that most malarial endemic countries and the problem of drug resistance malaria are worldwide. Development of high level resistance to the chloroquine in *P.falciparum* has forced to introduce artesunate combination therapy. In view of the emerging resistance against the existing anitmalarial agents and increased parasite clearance time following artemisinin-based combination therapy, there is an urgent need to develop new alternative drugs. A fully synthetic drug such as arterolane, which has an activity profile that is similar to that of the artemisinins, provides an important potential in such an endeavor.

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