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# Current Challenges of Malaria Chemotherapy in Africa: Prospects of Novel Drugs and Combination Therapies

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**The objective of this study was to point out recent undertakings on novel and standard drugs,as single, or combination therapy. The study design was based on aggregation and analysis of data generated in clinical and safety trials, using standard or widely used dosage regimen, acquired through primary publications, secondary or textual and Med-line references. The factors used in data extraction and compilation was length of visit to endemic areas, age, pregnancy, lactation, and idiosyncracy for Malaria chemoprophylaxis; and modes of action, clinical efficacy, safety and structural similarities of antimalarial compounds for chemotherapy. Proguanil/chloroquine combination was thus, found to be a comparatively safe prophylaxis, where there is chloroquine failure. In treatment schedules, chloroquine or artesunate in combination with sulfadoxine/pyrimethamine (S/P) is shown to increase the clinical efficacy of the latter, which reduces drug pressure on quinine. The C-5' modification of pyronaridine and amodiaquine leads to increased potency on one hand and reduced toxicity on the other. This modification is found to be one of the positive developments in drug design. The possibility of development of cross-resistance in structurally modified drugs and their congeners, however, cannot be ruled out. Combination therapies based on the synergistic modes of action as in the case of dapsone/proguanil, and on the complementary kinetics as in the case of artemisinin/mefloquine are recommended. By so doing, recrudescence is avoided and resistance emergence delayed. In conclusion, combining the analgesic/antipyretic features of chloroquine or artesunate with S/P is considered a useful strategy. Prospective prophylaxis and treatment with novel drugs as single or combination therapy are positive developments in face of the challenge in malaria chemotherapy. In line with the experience of quinine and artemisinin, research on herbal medicines is also worth considering.**

## BACKGROUND

Malaria is widely distributed in tropical and developing countries. The incidence of malaria is increasing with reports of 300- 500 million episodes occurring annually [1], out of which 40- 90 % is attributed to *Plasmodium falciparum* [2]. The control of malaria is getting difficult due to the wide spread drug resistance by plasmodium parasites [2]. Resistance to chloroquine now overlaps in the whole area of the species distribution except in America north of the Panama Canal and some areas in Western Asia [1]. In eastern part of Africa, due to chloroquine resistance, sulfadoxine/ pyrimethamine (S/P) has come out as a front line drug against uncomplicated falciparum malaria [3,4]. Foci with S/P resistance are emerging due to exposure to a wider drug pressure for the last few years as a first line drug. S/P failure rate of 20% to 40% is now recorded in Kenya, Tanzania and Malawi [4], followed closely by Ethiopia with 12% rate in 1999, two years after its endorsement as a first line drug (Unpublished document, Malaria Control Unit, Ministry of Health, Ethiopia).

Compared to quinine/quinoline compounds, S/P shows delayed but prolonged response. The importance of such long acting drugs, however, is to combat recrudescence, which makes it ideal for a suppressive-cure therapy [5]. The present recommended administration of antipyretics like paracetamol together with S/P has been of great help in alleviating the problems of delayed fever

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clearance [6]. But quinine/quinolines are reported to have broader analgesic activities including anti-inflammatory properties to malaria symptoms such as myalgia and arthralgia [7]. Besides, though analgestic antimalarial drugs like amodiaquine and quinine have retained a very high cure rate so far [5], and no threatening multi-drug resistance has been reported in Africa, sporadic foci of amodiaquine, quinine and antifolate resistance are now emerging simultaneously in wide apart countries as South Africa, Kenya and Cameroon [8,9]. If this trend continues with increase of quinine resistance, it would have a negative impact, especially in the treatment of severe and complicated malaria in the continent. Besides, due to the failure of chloroquine, and the foetal toxicity, and side effects like pruritus, developing in prolonged administration of S/P [4], a safe prophylactic choice has become limited. In this paper, in view of the current status of drug resistance, feasible research outcomes on standard as well as novel antimalarial drugs, as a single, or combination therapies are discussed.

## Data Aggregation and Terminologies used

In malaria chemoprophylactic aspect, a number of factors affecting prophylactic choice: age, pregnancy, lactation, length of visit to endemic areas and pathological idiosyncrasies related to each drug were reviewed. In malaria treatment, alternative antimalarial drugs to chloroquine were assessed for their present cure rates, their use in complicated and/or uncomplicated malaria, and their pharmacological properties affecting their continued application. Supportive treatment to high malaria risk individuals is based on national and international guidelines [3,4].

Based upon their clinical efficacy, structural similarity and modes of action, data from different trials were compiled to produce expected cross-resistance and clinical use as single or combination drugs. Anticipated clinical use and safety were the major parameters used in dealing with drugs in experimental models or at clinical trial stages. Wherever there are discrepancies as in differing dosage trials, only data based on widely used regimen were included in the study. In the text, safe refers to the absence of observable side effects, at a therapeutic dose of a given drug, while tolerable refers to the ability to withstand the toxic or adverse effects of a drug at its sublethal concentration. The later terminology is used, here, for drugs still under investigation.

Chloroquine, amodiaquine, quinine, mefloquine, sulfadoxine/pyrimethamine, proguanil, halofantrine, and artemisinine & its derivatives are grouped as conventional drugs. Pyronaridine, azitromycine, dapsone, atovaquone, lumefantrine and different drug combinations such as Dapsone/proguanil and Proguanil/atovaquone are grouped as investigational drugs. Primary publications, secondary or textual and Med-line references were used as sources of information in both conventional and investigational drugs.

## Malaria Prophylaxis

Chemoprophylaxis is routinely indicated in high risk individuals in or going to malaria endemic regions. Based on resistance pattern of the area, these include children, pregnant mothers, and adult highlanders or temperate dwellers going to endemic lowlands. As shown in Table 1, for children under 5 years, a weekly chloroquine supplemented with a daily proguanil, and for pregnant women, unlike the other drugs listed, the same choroquine/proguanil with folic acid supplementation is a better recommended combination. This drug combination is not considered to be harmful for lactating mothers, as well.

If there is report of chloroquine resistant malaria, mefloquine or doxycycline can be used as well. A number of factors, such as age, pregnancy, lactation, pathological conditions and length of visit determine the right chemoprophylaxis of choice. As infants and children under 5 years are high-risk groups, Doxycycline should not be used as it tends to stain teeth permanently and inhibits bone growth [4].

**Table 1. Drugs of Chemoprophylaxis use in Chloroquine Resistant Areas**

| Risk Groups | Chloroquine/ Proguanil | Sulfadoxine/ Pyrimethamin | Mefloquine | Doxycycline |
|---|---|---|---|---|
| Children | Recommended | Recommended | Not recommended | Contra-indicated |
| Pregnant Women | Recommended | Not recommended | Contra-indicated | Contra-indicated |
| Lactating women | Recommended | Recommended | Contra-indicated | Not recommended |

Mefloquine should not be used either in children weighing less than 15 kg. Concerning pregnancy, contracting malaria increases the risk of stillbirth, miscarriage, neonatal and maternal death [10]. Chloroquine is recommended in non-resistant cases; and choroquine/proguanil combination with folic acid supplementation is recommended in chloroquine resistant cases [11]. Mefloquine and Doxycycline are contraindicated during pregnancy [12].

In cases of prophylaxis failure, presumptive treatment with the best drug of choice each country has adopted in its guidelines is recommended to be taken at first signs of possible malaria symptoms. These are fever as the main indicator of illness, accompanied by shivering/chill, headache, gastrointestinal symptoms and myalgia and/or arthralgia [7]. But as far as possible, all subjects need be advised to consult a physician after administering presumptive treatment.

The amount of antimalarial agent excreted into breast milk is insufficient to provide adequate protection against malaria in infants [10]. Mefloquine is contraindicated in breast-feeding [13]. Doxycycline is excreted into breast milk in low concentrations and may have adverse effects on the breast-fed infant [10]. Proguanil is excreted into breast milk in insignificant amounts that are not harmful to the infant, but also do not provide any protection to the infant against malaria[12].

A pathological state of the patient is the other factor to be considered in prophylaxis choice Chloroquine and mefloquine are contraindicated in epilepsy, while there are no reports on the contraindications of proguanil and doxycycline [4]. Chloroquine should be used cautiously in liver damage, and the dose has to be reduced in-patients with impaired renal function if it has to be administered for long periods [13]. Mefloquine should be avoided in-patients with renal or hepatic failure [13]. Unlike doxycycline, proguanil is contraindicated in-patients with renal failure and with hepatic damage [4].

As pointed above, prophylactic use is also determined by the length of visit to endemic areas. Mefloquine and Doxycycline can be used as prophylaxis only for a duration of less than 3 or 4 months, respectively [13]. Use of chloroquine should not exceed six years [4]. Only proguanil may be used for long term, prophylaxis of malaria exceeding six years; allopecia is, however, observed in several cases [4]. Such long-term use also calls forth an updated information on drug resistance pattern in areas of visit. Though parasite strains in Africa are still sensitive to antifolates, in South East Asian countries, however, comparison in prophylactic efficacy of proguanil, pyrimethamine and dapsone or their combinations in relation to doxycycline, shows a compromised status of the earlier group of drugs compared to their prophylactic efficacy, two decades ago [14]. Doxycycline was found to be three times more effective than the above pyrimidine inhibitors in use in the region [15]. In Africa as well, an investigation done among 150 British soldiers on exercise in central Kenya taking proguanil/chloroquine prophylaxis for 5 weeks showed a failure rate of 4.67%, suggesting an earlier investigation for more reserve prophylactic drugs [16].

**Table 2. Chloroquine alternative Antimalarial Drugs in use**

| Drug | Current indication | Cure rate | Property | Adverse effects /drawbacks |
|---|---|---|---|---|
| Amodiaquine | Uncomplicated malaria | > 80% | Fast acting and Antipyretic | Agranulocytosis/ chloroquine cross resistance |
| Quinine | Uncomplicated & complicated malaria | > 50% | Fast acting and Antipyretic | Hypoglycemia / resistance emergence |
| S/P | Uncomplicated malaria | > 60% | Slow acting | Fetal toxicity / increasing clinical failure |
| Artemisinine and derivatives | Uncomplicated and complicated malaria | > 87% | Fast acting | Reticulocyte depression |
| Mefloquine | Uncomplicated and complicated malaria | >95% | Fast acting and Antipyretic | Neurologic disorder |
| Halofantrine | Uncomplicated malaria | >80% | Fast acting | Cardiotoxicity/ idiosyncrasy |

## Malaria Chemotherapy

Besides chemoprophylaxis, treatment of malaria is the major challenge in malaria chemotherapy in Africa. Different countries have different treatment guidelines, but generally, besides chloroquine, the conventional drugs in the treatment of uncomplicated malaria include amodiaquine, S/P and quinine, as well as a combination of chloroquine and S/P (Table 2).

Quinine may also be administered in combination with either S/P or doxycycline, for a better clinical outcome. The present experience of multiple drug resistance emergence in Africa (8,9), however, warns against excessive exposure of quinine in uncomplicated falciparum malaria, as these compromise quinine's efficacy in SCM treatment. Quinine or amodiaquine is advised to be used only as an alternative or a second line drug, where there is S/P failure (6). Exploiting the analgesic/antipyretic effect of chloroquine to enhance the clinical efficacy of S/P is a useful strategy to alleviate the drug pressure on the alternative drugs, which otherwise brings about a decline in their cure rate.

The rationale in chloroquine and S/P combination therapy is drug synergism, where Chloroquine's antipyretic/anti-inflammatory effect enhances the clinical outcome of S/P, while the parasiticidal effect of the latter complementarily improves the clinical efficacy of the former by enhancing malaria-induced fever clearance time. Such combination has the additional advantage of treating vivax malaria, as being experienced in rural Ethiopia, where there is laboratory shortage to differentiate vivax from falciparum malaria (3).

Besides, a study carried out in Gambia, on artesunate S/P combination therapy for uncomplicated malaria showed a faster resolution of symptoms, was found safe and more effective than S/P alone. An additional effect of reduction in transmission rates due to the gametocidal effect of artesunate was also observed (18). Presently, a blister package containing one dose of S/P and three doses of artesunate is being developed, possibly with anticipated lower price for public consumption (TDR NEWS No. 64, February 2001).

Uncomplicated as well as complicated malaria cases can best be treated with quinine or in combination with doxycycline (19). Artemisinin derivatives can be considered alternatives to quinine, in resistant and quinine intolerant cases for the treatment of complicated and severe malaria (20). The treatment of malaria should be tailored to individuals at risk. Thus, as pregnant women, are prone to develop hypoglycemia, which is exacerbated by management with quinine (16), intravenous dextrose would be invaluable

during treatment. Chloroquine and quinine are considered safe. S/P needs to be avoided in the first and last trimesters, and doxycycline is totally contraindicated. Children, on the other hand, can well tolerate these antimalarial drugs provided careful adjustment of dosages are made (17).

Due to their high cure rate of >80%, mefloquine, halofantrine and artemisinin can be used against chloroquine resistant malaria. The major draw back in these drugs, however, is their neurologic or cardiotoxic side effects and their high cost for use in mass treatment of patients, especially, ambulatory cases. Hence, mefloquine and artemisinin are better preferred to remain reserve drugs for severe complicated malaria and quinine for resistant cases. Halofantrine can be used for mild to moderate uncomplicated malaria. The drug of choice depends on each country's antimalalarial drug guidelines.

## Novel Drugs Under Trial

In search of novel antimalarial drugs, a number of synthetic and herbal compounds have been tested. As shown in Table 3, a number of drugs are under investigation for use in the treatment of malaria. These drugs include atovaquone, azithromycin, benflumethol or lumefantrine, pyronaridine and the structurally modified amodiaquine. The last two drug families, quinineacridine and aminoquinoline, are expected to show quinoline modes of actions and potency against 4-aminoquinoline resistant cases, and tolerable side effects at their present modified forms. Though expected problems are yet to be determined, preliminary works on artemisinine synergistic effect of lumefantrine, and the protein inhibitory antibiotic azithromycin show both to be tolerable. Atovaquone though considered to be effective against both chloroquine and S/P resistant cases, as a pyrimidine synthesis inhibitor, may develop cross-resistance against antifolates. It, however, is shown to be safe as well.

It was observed that the drug has rapid clinical and parasitological responses [21]. It nevertheless showed a high rate of recrudescence [21]. Treatment of malaria with atovaquone in combination with proguanil was the subject of a recent clinical trial at phase III [22]. Such combination has been shown to be effective in curing chloroquine resistant falciparum malaria [23], while the combination of proguanil with dapsone, was reported to be effective against chloroquine as well as pyrimethamine resistant *P.falciaprum* infections [24].

Pyronaridine, developed in the early 1970s in China, and the only country where it is currently registered, has been tested in Thailand and Cameroon. Results obtained in the latter were encouraging for use in chloroquine as well as in multi-drug resistant malaria [9,25]. However, in Thailand, resistance, with a failure rate of over 35% has already emerged to pyronaridine prior to its release to the world market [26]. This difference between the two countries is considered to be due to differences in background malaria drug resistant profile of quinine/quinoline compounds with which pyronaridine resembles in structure and modes of action, and a local level of earlier exposure to the drug. As to the latter, 5 years of earlier usage of pyronaridine in China/Lao border was found to reduce efficacy by 33% [26].

Lumefantrine, or Benflumethol, is another Chinese drug, which is still at developmental stage. *In vitro* evaluation on Senegalese *P.falciparum* isolates showed that it is potential inhibitory to chloroquine resistant isolates, potentiates artemisinin but without dose response additive effect to pyronaridine, chloroquine, amodiaquine, and quinine [27]. Azithromycin is another drug, which showed antimalarial activity in vitro and animal models.

However, at present, the data available on the antimalarial efficacy of this antibiotic are too insufficient to recommend its wide use as an antimalarial agent [28].

Future undertakings in the field of malaria chemotherapy include structural modifications and combination therapies. The idea of structural modification was to increase efficacy and reduce toxicity of the drugs. In this respect, one of the recent advances refers to bis mannich modification of amodiaquine and pyronaridine.

**Table 3. Drugs Under Experimental and Clinical Trials**

| Drugs | Mode of Action | Anticipated Advantages | Safety |
|---|---|---|---|
| Amodiaquine | Protein and nucleic acid synthesis inhibition | Effective against S/P and low grade Chloroquine resistant strains | Tolerable |
| Pyronaridine | Protein and nucleic acid synthesis inhibition | Effective against S/P & Chloroquine Resistant strains | Tolerable |
| Azithromycin | Protein synthesis inhibition | Effective against S/P & Chloroquine resistant strains | Safe |
| Lumefantrine | Not established | Effective against artemisinine Recrudescent strains | Tolerable |
| Atovaquone | Nucleic acid inhibition | Synergism with sulfones and Antifolates | Safe |

*Refers to a new generation of amodiaquine under investigation (See reference 29-31).

Mannich quinolines are known to undergo oxidation to electrophilic quinineimine metabolites, which deplete the level of cellular glutathione leading to neutrophil cytotoxicity [29]. The bioactivation of these mannich quinolines is also considered to be accompanied by the expression of drug related antigen change on the cell surface, that is recognized by drug specific antibodies [30]. This suggests the precipitation of type II hypersensitivity reaction, producing a cumulative effect with glutathione depletion, towards toxic agranulocytosis.

Thus, the structural modification efforts, at C-5' mannich position, to block such bioactivation that leads to the formation of glutathione conjugates, is one of the positive research developments in drug design. This modification is expected to increase the potency and decrease the toxicity, thereby influencing the clinical outcomes of amodiaquine and pyronaridine [31]. It looks, however, that the emergence of cross-resistance may be inevitable. This is just because so long there is some structural similarity cross-resistance may emanate. To delay resistance and extend the therapeutic life of these compounds may soon be an important challenge to face.

**Combination Therapy**

Combination therapy was first initiated for bacterial infections followed by TB, HIV and malaria chemotherapy. Table 4 shows drug combinations developed as alternative to presently used drugs as in S/P, or as synergistic component regimen to reduce recrudescence as in artemisinine-mefloquine, or artemisinine-lumefantrine. They can also be used as alternatives to quinine failure. Quinine-doxycycline or quinine-tetracycline, however, is another combination therapy used to increase the efficacy and reduce the toxicity of quinine. All the above combinations need a one-week follow up, making compliance their major problem. The main draw back with combination therapies in atovaquone-proguanil or atovaquone-dapsone, on the other hand, is the possible reduction in its

**Table 4. Combination Drugs Against Drug Resistant Strains**

| Drugs | Current Indications | Anticipated Advantages | Expected Problems |
|---|---|---|---|
| Artemisinine-mefloquine | Uncomplicated & Complicated malaria | Increased efficacy and reduced Recrudescence | Non-compliance |
| Artemisinine-lumefantrine | Uncomplicated & Complicated malaria | Increased efficacy, reduced Recrudescence | Non-compliance |
| Quinine-tetracycline | Uncomplicated & Complicated malaria | Increased efficacy, delayed resistance and reduced toxicity | Non-compliance |
| Quinine-Doxycycline | Uncomplicated & Complicated malaria | Increased efficacy, delayed resistance and reduced toxicity | Non-compliance |
| Atovaquone-proguanil-dapsone | Uncomplicated malaria | Delayed resistance emergence | S/P cross resistance |
| Chloroquine-S/P | Uncomplicated malaria | Increased efficacy and delayed Resistance emergence | Not determined |
| Artesunate-S/P | Uncomplicated malaria | Increased efficacy and lowered Gametocyte rate | Not determined |

efficacy due to cross resistance with antifolates already in use. As stated earlier, chloroquine-S/P or artesunate-S/P, are some of the beneficial drug combination to enhance the clinical efficacy of S/P in chloroquine resistant areas, and even the potential to reduce transmission as in artesunate-S/P combination.

The rationale for combining drugs were the following: a/ despite efforts made to develop new antimalarial drugs, these remain scarce, b/ combination regimen are more easily authorized and accepted for treatment than the new chemical entities [32], c/ combination therapy, have also been found more effective than single compounds, and d/ carefully selected drug combinations, have the desired importance of impeding the selection of drug resistant parasites [33].

In a combination of two or more drugs with independent modes and sites of action, resistance emergence could delay, as resistance to two or more drugs is the product of the individual parasite mutation rates [34]. There are some drugs available or under investigation in a fixed combination for malaria chemotherapy. Such combinations include Chloroproguanil/dapsone (registered as LAPDAP) combination presently under investigation in 5 African countries, Gabon, Kenya, Malawi, Nigeria, and Tanzania. The current double blind Phase III clinical trial is underway to measure the efficacy and safety of a 3-day treatment schedule against uncomplicated falciparum malaria (TDR News, No.62, June 2000). The short half-life [t1/2] and rapid elimination is an advantage over S/P with long t1/2 that selects resistant strains. Besides it retains activity against certain pyrimethamine resistant strains [24]. It may be a promising alternative to sulfadoxine/pyrimethamine. It is also affordable by malaria control programs in Africa as 2000 tablets of proguanil and dapsone (100mg) cost only 30USD [35]. Atovaquone/proguanil is another possible combination regimen under investigation.

With combination therapies, hence, avoidance of recrudescence or delaying resistance emergence could be achieved. Development of resistance depends partially on the pharmacokinetics of drugs. Antimalarial drugs with long plasma half-lives are vulnerable to the development of resistance because of the surviving parasites to drug pressure as asexual cycles are exposed to decreasing blood concentrations (36).

Recrudescence was a problem with antimalarial drugs like artemisinin with a rate of 20% (37) and pyronaridine with 12 to 15% recrudescence rates (27). Recrudescence could occur due to rapid termination of action as in the case of artemisinin (21). A long continued treatment >5 days regimen as well as a combined drug regimen would help avoiding recrudescence. In the case of artemisinin, a five to seven days treatment regimen, alone or in combination with a relatively longer acting antimalarial drugs are the options to circumvent resistance emergence. The possible drug combinations are artemisinin/mefloquine, artesunate/mefloquine and artemether/lumefantrine.

The combination regimen of artemisinin/mefloquine is a sequential treatment schedule of 600 mg of artemisinin for 5 days, followed by 1250 mg of mefloquine divided into two doses over 6 hours period. These combinations may also help reduce emergence of resistance by the malarial parasites.

In Africa, high cure rate of > 95% of fever, as well as parasite clearance time of less than 3 and 4 days was observed (17,38), which is a situation comparable to the status of chloroquine in the 1960s. Drug combination trials with pyronaridine shows synergistic effect with primaquine and the 4-aminoquuinolines, but weak antagonism with antifolates, aminoalcohols and artemisinin (39). In a murine model, however, potentiation was observed between pyronaridine and artemisinin (40), which suggests the differences in host and parasite species.

## Conclusion and Recommendations

Presently, as S/P is the 1st line drug in chloroquine resistant areas in the continent, unless the escalating failure of S/P is curbed, the increasing exposure of the clinically efficacious alternative drugs like amodiaquine and quinine in malaria management will be inevitable. This will result in diminishing the precarious reserve antimalarial drugs in Africa. With the present trend of emerging multi-drug resistance, it is obvious that resistance may emerge to the novel drugs as well, even before they are incorporated into the malaria control programs.

It is rational to employ analgesic drugs in combination with sulfadoxine/pyrimethamine (S/P) in view of their antipyretic/anti-inflammatory features. This will help limit the use of the alternative quinine only to patients suspected of genuine S/P resistance, rather than to all cases with inadequate clinical responses. Such S/P combination therapy may delay the alarm of S/P collapse and promote a more rational use of alternative drugs.

In this respect, the investigation to improve the potency and reduce the toxicity of dimannich compounds is also a positive development to strengthen their position as second line drugs. The trial with the combination of proguanil, atovaquone and/ or dapsone is also a welcoming effort as a tertiary alternative. Attention may also need be given to researches on herbal remedies for these may contribute in the development of novel drugs as seen from the experience of quinine and artemisinin.

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