Resistance of Plasmodium falciparum

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Introduction

Resistance of Plasmodium falciparum to antimalarial drugs is emerging as one of the two most important technical factors obstructing the worldwide effort to eradicate, or at least control the disease. The other major factor is entomological – the diminishing efficacy of residual insecticidal spraying of dwellings. There are two reasons for the diminishing impact of spraying on vector populations: physiological resistance of certain vectors to insecticides and strain differences or adaptive mechanisms in some anophelines resulting in the avoidance of sprayed surfaces.

Depending heavily on anti-vector techniques, the Malaria Eradication Programmes established in the late 1950s did not generally employ antimalarial drugs as attack measures, using them strategically instead for elimination of parasite reservoirs. In certain countries, however, drug administration alone may be the only method available for any degree of malaria control.

Antimalarial drug action

In a discussion of the development of parasite resistance to chemotherapeutic agents, it may be useful to review the sites at which drugs act to interrupt the life cycle of plasmodia. Antimalarial drugs may be divided into the following categories:

1) causal prophylactic agents (acting against primary tissue stages);
2) anti-relapse drugs (acting against latent tissue stages);
3) blood schizontocides;
4) gametocytocides;
5) sporontocides.

Drugs to which activity against primary tissue (liver) stages of the parasite has been attributed include the antifolates proguanil and pyrimethamine, possibly the sulfas, tetracycline (although adequate field testing of this application is far from complete), and primaquine, although it is thought that doses of this drug required for prophylactic activity would be toxic.

Primaquine and some of its more toxic analogues are the only available agents which act against the latent tissue stages (hypnozoites) of the relapsing malarias, Antimalarial drug action with haem binders to a toxic chloroquine-FP complex, Primaquine also has schizontocidal activity, but only at toxic doses.

The gametocytes of P. vivax, P. malariae, and presumably P. ovale, are killed by usual doses of the effective blood schizontocides, but mature gametocytes of P. falciparum are not affected. Primaquine, which kills gametocytes of all species, is particularly useful for interrupting transmission of P. falciparum. Primaquine, as well as pyrimethamine and proguanil (against susceptible strains), is known to prevent development of oocysts and sporozoites in the vector mosquito.

Mechanisms of drug action

Surprisingly little is known with certainty about the mechanisms of antimalarial drug activity. Research in this area has been especially difficult due to the obligate intracellular nature of the parasites, and, until recent years, the inability to work in vitro or in animal models. However, a large body of information is now being accumulated on the distribution of various substances in the life stages of the plasmodia, parasite nutritional requirements, and the metabolic pathways utilized.

It is known that nucleic acid metabolism in plasmodia is similar to that in other eukaryotic organisms, and that both DNA and RNA are synthesized during nuclear growth and division. It is clear that antifols and sulfonamides exert their antimalarial action through inhibition of parasite enzymes involved in the synthesis of folate cofactors. In experimental avian malaria, nuclear division is seen to be interrupted at metaphase. The antifols (such as pyrimethamine) act by binding dihydrofolate reductase and the sulfonamides by inhibiting dihydropterate synthetase. Potentiation occurs when the two classes of drugs are used simultaneously. Important information is being collected concerning the mode of action of the 4-aminoquinolines. It is known that a number of blood schizontocides, including 4-aminoquinolines, mepracine, quinoline methanols such as mefloquine, and phenanthrene methanols are concentrated in infected red cells through a saturable, energy-dependent process involving high-affinity binding sites. Red cells harboring chloroquine-resistant parasites concentrate this drug to a much lesser extent obviously due to a deficiency in the binding mechanism.

Fitch and his coworkers, in work of major importance, have identified a product of hemoglobin degradation, ferriprotoporphyrin IX (FP), as a high-affinity receptor for chloroquine. It is hypothesized that chloroquine acts by diverting FP from non-toxic complexes with haem binders to a toxic chloroquine-FP complex, resulting in membrane damage, ion-gradient alteration,
and eventual cell lysis. These investigators theorize that resistant parasites may contain haem binders which preferentially bind FP either because of increased affinity or amount of these binders, or that FP sequestration in pigment may be increased in resistant parasites. This work appears to be corroborated by the results of Jeamprapat et al., who also demonstrated binding of quinacrine and mefloquine as well as chloroquine to haemopozoin and protoporphyrin IX. Yuthavong et al. has demonstrated a difference in the distribution of binding sites between infected and uninfected cells and showed that most of the binding occurring in infected cells takes place in the parasites, further supporting this hypothesis for the mechanism of drug effect.

The possibility that 4-aminoquinolines (and quinine) intercalate with parasite DNA is still disputed, although, in any case, this is not considered to be a major factor in their parasitocidal action.

Possible mechanisms for the antimalarial activity of antibiotics are being explored. A recent report suggests that tetracycline and erythromycin inhibit \( P. falciparum \) through actions on mitochondrial synthesis or function. These workers also provide supporting information for the clinically observed slowness of action of tetracycline in falciparum infections. In their in vitro system, parasites exposed to tetracyclines (or to erythromycin) for 48 h were killed by the drug only at concentrations somewhat higher than those observed therapeutically. When exposure was extended to 96 h, lethal effects were observed at concentrations within the therapeutic range.

History and current status of resistance

The earliest reports of antimalarial drug resistance came from Brazil in 1910, when failures of quinine were reported. Whether this situation reflected naturally low levels of sensitivity of the local parasite population to this drug or true resistance selected by large scale suppressive use is unclear. It is known that strains of \( P. falciparum \) encountered in Southeast Asia, the Pacific, and the Americas are by nature relatively less susceptible to quinine than strains found in India and westward including the African continent. On the other hand, experimental evidence indicates that resistance can be selected through serial passage of falciparum isolates under drug pressure. Solid evidence of clinical refractoriness to quinine is accumulating from Thailand, where usual 7–10-day courses of quinine produce low rates of radical cure of infections acquired at the Kampuchean border. Studies of malaria in Thai children also indicate changing patterns of susceptibility. The Thai antimalaria program is documenting evidence of increasing resistance using in vitro test systems of Rieckmann (Laksami Suebsaeng, personal communication). Although quinine, at least in Thailand, is gradually losing its ability to provide radical cure of falciparum infections, it is still a dependable agent for producing relatively rapid initial reduction in parasitemia, retaining its life-saving value in cerebral and other complicated or severe manifestations of falciparum malaria.

The earliest of the synthetic blood schizontocides, Atabrin (now known as mecaprine or quinacrine), was developed in the early 1930s. This is a toxic drug, and is now obsolete, having been replaced by a related series of compounds, the 4-aminoquinolines, particularly chloroquine and amodiaquine. Although chloroquine was initially synthesized in Germany in 1934, its importance was not fully appreciated until 10 years later when clinical studies proved it to be an excellent antimalarial. Amodiaquine was shown to have similar efficacy and tolerance.

Chloroquine became the mainstay of antimalarial chemotherapy, and is still the most widely used schizontocidal drug. However, in the late 1950s, clinical treatment failures were noted in Thailand. At about the same time, two reports from South America indicated resistance in falciparum infections acquired in Colombia. Since that time, resistance has spread widely to involve most malaria-endemic regions of the world. In Asia, the most seriously-affected regions include Thailand, Burma, Vietnam, Kampuchea, Laos, and southern China. Also involved are India (originally limited to the east coast, but now widely reported), Bangladesh, Malaysia, Indonesia, the Philippines, Papua-New Guinea, the Solomon Islands and Vanuatu (formerly New Hebrides).

In most areas of South America where transmission of \( P. falciparum \) continues, resistance to chloroquine is prevalent, although the problem has not increased in severity or distribution to the extent seen in Asia during the same period of time. Especially affected are parts of Brazil, Colombia, French Guiana, Guyana, and Suriname. Resistance is present but focal in Bolivia, Equador, Venezuela and southern Panama.

In Africa, resistance to the 4-aminoquinolines has been well documented in cases acquired in Kenya, Tanzania, the Comoro Islands, Uganda, Madagascar, the Sudan, Zambia, and Malawi. There are reports of cases, though not fully confirmed, from Rwanda, Burundi, Ethiopia, Somalia, Nigeria, and Zaire. Although most cases have been reported in non-immune travellers to the continent, resistance has now been detected in presumably semi-immune indigenous populations in Tanzania and Zanzibar.

The antifolate drugs proguanil and pyrimethamine were developed in 1945 and 1951, respectively. At the end of the Second World War, proguanil was widely used as an effective and well-tolerated causal prophylactic drug, although it was never a potent therapeutic agent. The development of pyrimethamine was considered to be an important advance, since it was more potent than proguanil, had a longer half-life in man and a wide margin of safety between effective and toxic doses. However, resistance to pyrimethamine was found to develop extremely rapidly – within a year or two of its introduction – and crossresistance between proguanil and pyrimethamine was demonstrated. Currently, resistance to pyrimethamine by both \( P. falciparum \) and \( P. vivax \) is widely distributed throughout nearly all endemic regions. There is an apparent association with prior application of mass drug distribution techniques (e.g., medicated salt).

An unresolved question concerns the efficacy of antifolates as causal prophylactic agents in the face of resistance of asexual blood forms. It has been assumed...