
BOOK REVIEW

Antimalarial Chemotherapy. Mechanisms of Action, Resistance, and New Directions in Drug Discovery

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Malaria, one of the most ancient human diseases affects 400 million people yearly and causes over 2.5 million deaths, mostly children, in sub-Saharan Africa, where the disease is hyperendemic. Africa accounts for more than 90% of the total cases, followed by India and Brazil, in disease prevalence. In Brazil, malaria remains endemic in the Amazon, with 630,000 cases per year, mostly in adults with a mortality rate of 225 last year, mainly due to late diagnosis, to inadequate treatment or multi-drug resistant parasites. Being an acute disease, with typical symptoms (headache, recurrent fever, among others), individuals affected by malaria in endemic areas often self-medicate with available antimalarial drugs or with medicinal plants.

The book on malaria chemotherapy meets high standards, is enjoyable reading, and presents data on all antimalarial drugs, how they work and mechanisms of drug resistance. It is an excellent guide for searching for new molecules or working with the available ones. It has 20 chapters written by specialists in the field, ideal for specialists, mainly chemists, but certainly helpful to those catching up on the subject (parasitologists, pharmacologists) and to graduate students working on drug discovery. There are not many groups working on drug development, in Brazil, but the fact that several phytochemists have become interested in antimalarial drug discovery and isolating molecules from plants makes these scientists a target for the book.

The book is divided in three parts. Part I - Introduction (5 chapters): the needs for new approaches to antimalarial chemotherapy; the history of antimalarial drugs; the transport and routes in the *Plasmodium* infected red blood cells; the food vacuole of the parasites; clinical and public health implications of antimalarial drug resistance. Part II - Established antimalarial drugs and compounds under clinical development (7 chapters): chloroquine and other quinolines; 8-aminoquinolines; mechanisms of drug resistance; folate antagonists; artemisinin

and derivatives; atavaquone-proguanil combination; antimalarial drug portfolio and research pipeline (ranging from promising lead compounds to those still undergoing research). Part III - New compounds, new approaches and new targets (8 chapters): novel quinolines; trioxanes and endoperoxides; antibiotics, the plasmodial plastid organelle; antimetabolites; iron chelators; protease inhibitors; inhibitors of phospholipid metabolism; and antimalarial drugs based on parasite-induced transport.

The analysis on malaria situation worldwide (Chapter 1) shows that after 50 years of efforts, the control transmission is far from ideal; the disease is still endemic in 56% of the exposed population. The main problem for malaria control, at present, is the antimalarial drug resistance, specially of *P. falciparum*, the most deadly malaria parasite, and also of *P. vivax*, the most common in Brazil. Problems with monotherapy, how drug combinations work, which drugs reverse chloroquine resistance (a hope for chloroquine treatment) are in focus in the book. The approaches described to the discoveries of antimalarial drugs are based on development of analogs from existing agents (chloroquine, amodiaquine, mefloquine, Chapter 6); or on primaquine, an 8-aminoquinoline which prevents late relapses by malaria parasites like *P. vivax*. Its possible substitute, tafenoquine is not commercially available (Chapter 7).

The antimalarial drug discovery so far has been totally based on empiric approaches, and control of the disease still depends on those discoveries from the first half of the twentieth century (Chapter 2) i.e., (i) quinine, the first antimalarial drug discovered in the Western, in the barks of *Cinchona* sp. (a South American tree), used as the basis of most other antimalarial drugs of the quinoline group; and, (ii) artemisinin, a compound isolated and characterized more recently by Chinese scientists from the medicinal plant *Artemisia annua*, (based on its usage in China for millenium). Curiously, both quinine and artemisine derivatives are largely used to treat drug resistant parasites at present. The first report regarding decreased sensitivity of malaria parasites to drugs was on quinine in 1910, in Brazil, but such resistance is not comparable to that of chloroquine, although quinine started being used 250 years ago and chloroquine during the Second World War. Differences in the metabolism of both drugs, among many factors, such as why drug resistance is acquired at different speeds and how to reverse it, have not been elucidated.

The studies on mechanisms of parasite resistance to quinoline drugs, as well as on drugs reversal of chloroquine resistance (Chapter 8), point to the mutations of *pfmdr-1* and *pfcr1*, incriminated as advantageous to the parasite, less important

when malaria acquired immunity exists (like in African hyperendemic countries). Immune adults may clear parasitemia in cases of drug resistance, thus, the presence of *pfprt* mutations *per se* cannot predict drug resistance. How to optimize therapy of drug resistant parasites with the existing agents like artemisinin-derivative combinations, or with the generated mixtures like atavaquone-proguanil (malarone as one of the most promising drugs) and the search for drugs from natural products and their derivatives like quinine, artemisinin are described (Chapter 12) as well as testing compounds like folate antagonists (Chapter 9) antibiotics (Chapter 15) and atavaquone (Chapter 17), active against other diseases.

During decades, chloroquine, a 4-aminoquinoline, was largely used for treatment and prophylaxis of acute malaria with an amazing impact on malaria control. The problems of chloroquine drug-resistant parasites appeared in the early sixties, described in South East Asia and South America, and appeared much later in the African continent. Drug resistant parasites have now spread to most malaria affected countries, including Brazil. Here, the campaign of malaria eradication, based on chloroquine, launched by the World Health Organization and the Ministry of Health in the fifties, reduced transmission in most populated areas, in the Northeast, Southeast and South, but not in the North which is still endemic. As a consequence of drug resistance, the present situation is alarming and new drugs are urgently needed. There is no ideal drug to replace chloroquine or primaquine, there are no vaccines available and no way to block the mosquito transmission at present.

The analyses of clinical and public health implications of antimalarial drug resistance, diagnosis and measurements of drug resistance, and treatment failure (Chapter 5) raise an interesting point about whether money should be used to develop new drugs or to improve access to existing drugs. The argument considers the meager resources allocated for malaria, its prevalence in the developing world, the lack of financial incentives and the consequent lack of interest by the pharmaceutical industry, a crude reality. Since resistance is the prime determinant of a drug's life span, protecting its effective use must be the number one priority in control programs.

Although not all chapters have summaries, they all have an impressive number of references, for example Chapter 6, on chloroquine and other quinoline antimalarial drugs, with 278 references! The book's references are valuable and encompass most of the work published in malaria chemotherapy, including the recent approaches to novel drugs but hardly cited any work from Brazil, where randomized clinical trials have been performed (one example Duarte et al. 1996 *Am J Trop Med Hyg* 54: 197-202) including on mefloquine, tetracycline, artemisine derivatives as well as on experimental work on antimalarial activity of medicinal plants and their molecules (reviewed by Krettli et al. 2001 *Mem Inst Oswaldo Cruz* 96: 1033-1042).

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