Atovaquone–Proguanil Combination

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INTRODUCTION

Development of an atovaquone–proguanil combination, trademarked Malarone, during the 1990s has been a major step in addressing the need for antimalarial drugs with targets different from those of agents for which resistance is already rampant in the field (1). Atovaquone affects parasite mitochondrial functions in a selective manner (2,3) and, thus, constitutes an entirely new class of antimicrobial agents. While atovaquone as a single agent has been used for treating Pneumocystis carinii pneumonia and toxoplasmosis in immunodeficient patients (4,5), it met with unacceptable rates of treatment failure when used against malaria (6,7). The inclusion of proguanil as a synergistic agent with atovaquone appears to have overcome the high rate of treatment failure, and the resulting drug, Malarone, has been approved for treatment of falciparum malaria in more than 30 countries. This chapter aims to provide a perspective on the development of this new drug and its clinical efficacy. Furthermore, recent studies on mechanisms of action as well as resistance to this drug will be discussed. It is important to note that the atovaquone–proguanil combination may be one of the few antimalarials for which significant details of drug action and resistance are available before its widespread introduction. This information may prove useful in devising strategies for drug usage as well as in the development of the next generation of antimalarials with mitochondrion-specific modes of action.

DEVELOPMENT OF ATOVAQUONE

Atovaquone is a naphthoquinone belonging to a family of compounds that have been investigated as antimalarials for over 50 yr. Early investigations on naphthoquinones as antimalarials have been previously reviewed in some detail elsewhere (8,9). Hooker (10) was the first to recognize the presence of naphthoquinones in plant extracts and to synthesize lapachol, a 2-alkylnaphthoquinone, in 1936. Efforts to find substitutes for quinine during World War II included investigations on naphthoquinones, and hydrolapachol (see Fig. 1 for structures) was found to have antimalarial activity. This led to collaborative efforts between academic and industrial scientists, resulting in synthesis of hundreds of hydrolapachol analogs and their testing as antimalarials in a duck malaria model (11). The most promising compound to emerge from this early study, lapinone, was found to be effective in treating vivax malaria but needed to be
given parenterally in large doses (12). The advent of chloroquine as an inexpensive orally available antimalarial at about the same time diminished interest in developing hydroxynaphthoquinones as antimalarials. In the 1960s, coinciding with the emergence of chloroquine resistance, there was a renewed interest in naphthoquinones as antimalarials (8,13,14). One compound, menoctone, was chosen for clinical testing but proved to be disappointing against malaria (15). Menoctone, however, was effective against Theileria parva infection in cattle (16), which then led to extensive structure–activity studies. Parvaquone was identified as an effective and economic antitheilerial agent from these investigations with about a 90% cure rate in field studies (17). Modifications of the cyclohexyl moiety of parvaquone were extensively investigated and found to have broad-spectrum antiparasitic activities (18). One such compound, BW58C80, was tested in humans but found to be rapidly converted to an inactive red-colored metabolite that was secreted in the urine and, thus, was dropped from further development (1). Modification of the 4′-position of the cyclohexyl ring by a chlorophenyl moiety resulted in compound 566C80, which was metabolically stable and had broad-spectrum activity against a number of eukaryotic pathogens, including malaria parasites (1). The compound 566C80 was named atovaquone and has been registered as Mepron.

ATOVAQUONE AS AN ANTIMALARIAL

Cultured Plasmodium falciparum isolates from different parts of the world were inhibited by atovaquone at low nanomolar concentrations (median inhibitory concentration [IC₅₀] 0.7–4.3 nM) regardless of the relative resistance of the isolates to other antimalarials (1). Oral doses of the drug to Aotus monkeys infected with P. falciparum and mice infected with P. yoelii and P. berghei were highly effective in curing malaria infection (1). Following a phase I evaluation of toxicity, a single dose of 500 mg atovaquone was given to patients with P. falciparum malaria in the United Kingdom and was found to give prompt clinical response with removal of asexual parasites from the blood smears (6). Most of these patients, however, developed recrudescent malaria (6). In larger studies done in Thailand (7) as well as in Zambia (reviewed in ref. 19), atovaquone was tested as a single agent in varying doses for its ability to cure uncom-