Bioanalysis of antimalarials using liquid chromatography

Wahajuddin, Kanumuri Siva Rama Raju, Isha Taneja

Among the most central aspects of the drug-development process is estimation of drug levels in biological systems, which is an integral part of preclinical and clinical studies. Once the drug is marketed, determination of biological drug levels becomes crucial for therapeutic drug monitoring during treatment regimens and for optimal treatment for individuals. Malaria shows marked variability in treatment outcomes associated with its pharmacogenetic and pharmacogenomic origins and requires personalized dosage regimens.

Technological advancements in bioanalytical chemistry involving liquid chromatography have revolutionized drug analysis. In this article, we review the use of these methods in the bioanalysis of 15 antimalarial drugs, based on papers published since 1988, with emphasis on sensitivity, sample-preparation procedures and detection techniques used.

Keywords: Accelerated mass spectrometry (AMS); Antimalarial; Bioanalysis; Detection; Drug analysis; Liquid chromatography (LC); Matrix; Sample preparation; Sensitivity; Tandem mass spectrometry

Abbreviations: AMQ, Amodiaquine; AMS, Accelerated mass spectrometry; ARM, Artemisinin; ART, Artemether; AS, Aartesunate; ATQ, Atovaquone; CQ, Chloroquine; DHA, Dihydroartimisinin; EC, Electrochemical; GC, Gas chromatography; HPLC, High-performance liquid chromatography; LC, Liquid chromatography; LLE, Liquid-liquid extraction; LLOQ, Lower limit of quantification; LPME, Liquid-phase microextraction; LUME, Lumefantrine; L-ZGP, N-benzyloxycarbonyl-glycyl-L-proline; MQ, Mefloquine; MS, Mass spectrometry; PG, Proguanil; PPT, Protein precipitation; PQ, Piperaquine; PRM, Pyrimethamine; PRN, Pyronaridine; Q, Quinine; SDS, Sodium dodecyl sulfate; SDX, sulfadoxine; SPE, Solid-phase extraction; SPME, Solid-phase microextraction; TBA, Tetrabutylammonium bromide; TCA, Trichloroacetic acid; TEA, Triethylamine; TFA, Trifluoroacetic acid; TOF, Time of flight; UV, Ultraviolet

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1. Introduction

Malaria is a major public health problem in more than 90 countries inhabited by more than 2.4 billion people, accounting for 40% of the world's population. The disease causes up to 250 million new infections worldwide. In 2010, malaria caused 655,000 deaths globally, of which 91% occurred in Africa. About 86% of the victims were children under the age of 5 years [1–5]. The drugs commonly used in antimalarial therapy include quinine, chloroquine, mefloquine, amodiaquine, sulfadoxine, pyrimethamine, atovaquone, proguanil, lumefantrine, and artemisinin and derivatives.

The major obstacle to effective antimalarial therapy has been the emergence of resistance against most first-line drugs used. Resistance has been observed for all currently used antimalarials, including artemisinin derivatives. One of the main reasons attributed to the development of resistance is the variability in the therapeutic concentrations achieved. It has been proved that for chloroquine, doubling the dose could reverse its resistance [6]. Further, the difference in pharmacokinetics of the antimalarial agents could also arise due to pharmacogenetic and pharmacogenomic factors. This obviates the need for therapeutic drug monitoring during ongoing therapy.

Of equal importance is the need for therapeutic drug monitoring during treatment regimens for antimalarials having narrow therapeutic index and dose-dependent adverse effects and in personalized therapy. This necessitates estimation of the biological levels of these drugs. Concentrations of antimalarial drugs are measured in biological matrices, namely plasma, serum, whole blood, capillary blood and urine. This requires reliable, sensitive and reproducible bioanalytical methods. Because of their diverse physicochemical properties, it is becoming increasingly difficult for bioanalysts to develop an analytical method for simultaneous estimation of these

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compounds and their derivatives. Bioanalytical method development for these drugs involves very complex steps of extraction or sample treatment and intricate chromatographic resolution. However, searching the database available for past 25 years, we could find only one review article, published in 1988, discussing analytical aspects in this field [7].

The aim of this review is to summarize HPLC and LC-MS methods published since 1988 for the bioanalysis of 15 antimalarial compounds (chloroquine, atovaquone, quinine, sulfadoxine, pyrimethamine, artemisinin, artemether, dihydroartemisinin, amodiaquine, artesunate, mefloquine, piperaquine, proguanil, pyronaridine, and lumefantrine) used as first-line drugs in malaria therapy. The structures of the compounds discussed are shown in Fig. 1. The scope of this review is restricted to HPLC and LC-MS methods, so neglecting useful but rare GC and GC-MS methods and poorly selective, low-quality spectrophotometric, fluorimetric and electroanalytical methods.

2. Quinoline derivatives

The quinoline derivatives include quinine, chloroquine, mefloquine, amodiaquine and piperaquine whose bioanalytical LC methods are described in Table 1.

2.1. Quinine

Quinine (6-Methoxy-alpha-(5-vinyl-2-quinuclidinyl)-4-quinolinemethanol), the oldest antimalarial drug, has been in use for over 350 years [8]. Its logP value is 3.50

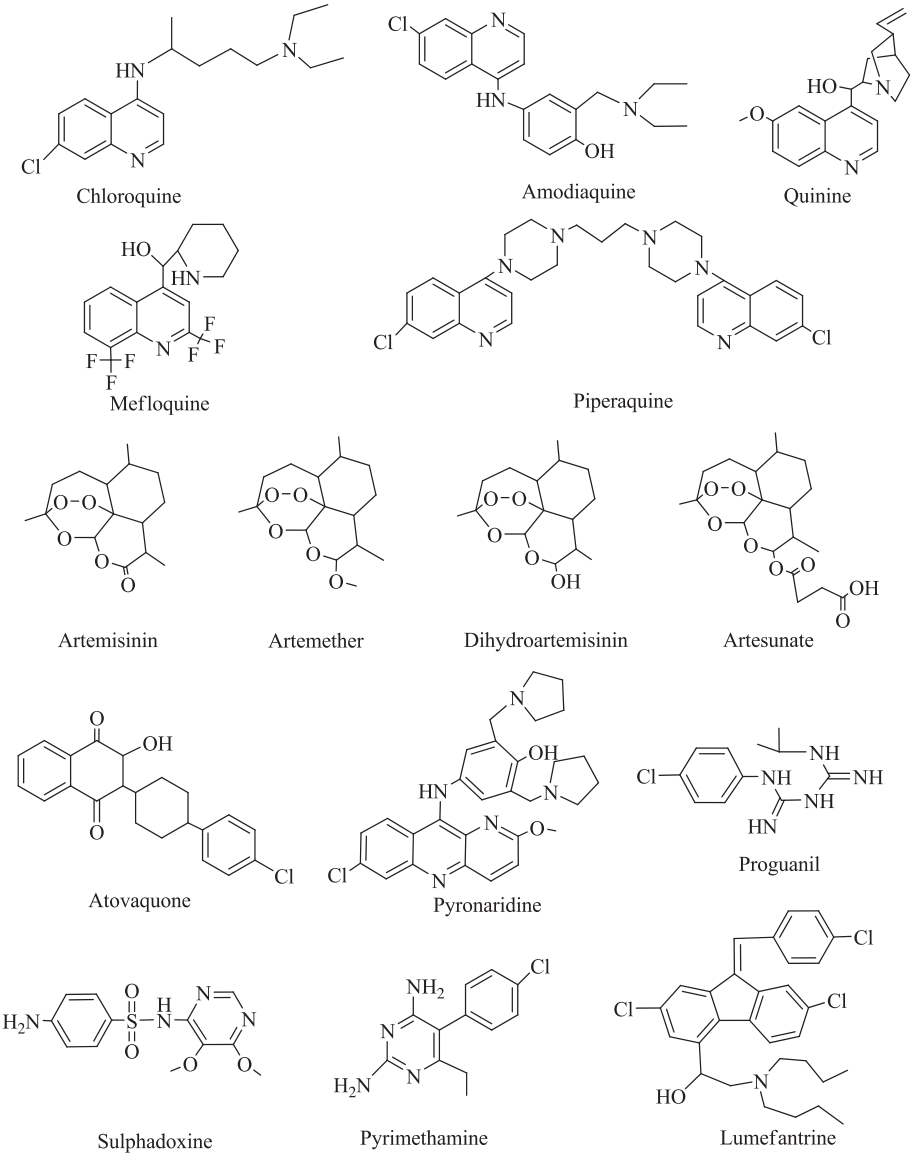

Figure 1. Chemical structures of antimalarial drugs.