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Review

Analytical sample preparation strategies for the determination of antimalarial drugs in human whole blood, plasma and urine

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ABSTRACT

Antimalarial drugs commonly referred to as antimalarials, include a variety of compounds with different physicochemical properties. There is a lack of information on antimalarial distribution in the body over time after administration, e.g. the drug concentrations in whole blood, plasma, and urine, which must be improved in order to advance curing the parasitic disease malaria. A key problem also lies in that pharmacokinetic studies not always are performed in patient groups that may benefit most of the treatment such as children, pregnancy and lower-weight ethnic populations. Here we review the available sample preparation strategies combined with liquid chromatographic (LC) analysis to determine antimalarials in whole blood, plasma and urine published over the last decade. Sample preparation can be done by protein precipitation, solid-phase extraction, liquid–liquid extraction or dilution. After LC separation, the preferred detection tool is tandem mass spectrometry (MS/MS) but other detection methods have been used e.g. UV, fluorescence and electrochemical detection. Major trends for sample preparation of the different groups of antimalarials for each matrix and its detection have been summarized. Finally, the main problems that the researchers have dealt with are highlighted. This information will aid analytical chemists in the development of novel methods for determining existing antimalarials and upcoming new drugs.

Contents

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1. Introduction

Malaria is a health problem of major concern worldwide. In 2009 there were an estimated 247 million cases of malaria and nearly one million deaths [1,2]. The pathogenic agent of malaria is four species of *Plasmodium* parasites [3,4]. Sexual reproduction occurs in mosquitoes, acting as parasite vectors, while asexual reproduction occurs in humans acting as hosts for the parasite [5]. Malaria can be categorized as uncomplicated or severe. The former is defined as a symptomatic infection without signs of severity or evidence of organ dysfunction [2], while the latter is life-threatening and results from organ dysfunction. Once humans are infected and the symptoms of malaria observed, antimalarial pharmaceuticals (antimalarials) are prescribed for treatment [4,6]. Currently used antimalarials can be classified into seven groups [4] (Table 1); sesquiterpene endoperoxides (artemisinin based drugs), 4-aminoquinolines, arylaminoalcohols, 8-aminoquinolines, antifolates, hydroxynaphtoquinones, and tetracyclines. Tetracyclines, however, have been excluded from this paper since these have been covered elsewhere [7,8]. Today most malaria treatments have changed from the less effective chloroquine/sulfadoxine–pyrimethamine mix to the artemisinin-based combination therapies (ACT's) recommended by the World Health Organization (WHO) [9]. These consist of artemisinin-based compounds combined with a variety of antimalarials that have lost efficacy as monotherapeutics [10]. Available ACT's are; artemether/lumefantrine, artesunate/amodiaquine, artesunate/mefloquine, and artesunate/sulfadoxine–pyrimethamine [11]. Other common treatments are combinations of sulfadoxine–pyrimethamine with chloroquine, amodiaquine or quinine [11]. Quinine monotherapy (applied for 300 years) is still in use for treatment of certain resistant parasites, but show strong side effects [2,10]. Additionally, quinine can be combined with clindamycin, doxycyclin or tetracycline as recommended by the WHO [10,11]. The mixture chlorproguanil/dapsone, was proven efficient, but withdrawn in 2008 due to its haematological side-effects [12]. Instead the combination of proguanil/atovaquone has lately proved to be efficient but high costs limits its accessibility, being mostly used for treatment by Western travellers and military personnel [10,11]. Despite the large number of antimalarials prescribed worldwide for many years, there is still today often a lack of knowledge on antimalarial concentrations reached in the body over time after the administration, which is essential to understand pharmacokinetics [13]. There is also data deficiency on the relationship between blood concentrations and the therapeutic response in patients which is crucial for evaluating the cause of treatment failure such as parasite resistance or to insufficient drug levels in the blood [13]. Additionally, the majority of the antimalarials have not been developed using stringent pharmacokinetic–pharmacodynamic studies, as this most often is not easily performed in field trials. Consequently, some patients are most likely not adequately dosed. This may lead to under-dosing promoting parasite resistance or it may lead to over-dosing triggering intoxication [14]. One obstacle in determining patient antimalarial levels during treatment has been the lack of sensitive, reliable and robust analytical methods [14]. However, the improvement of liquid chromatography–mass spectrometry (LC–MS) systems has aided in generating results for pharmacokinetic studies that are more reliable than previous simpler chemical or chromatographic assays and bioassays [13]. Within the last decade several analytical methods have been published for the determination of antimalarials in human body fluids. The aim with this review is to identify and assess recent scientific articles applying liquid chromatographic (LC) methods for the determination of antimalarial drugs in whole blood, plasma and urine. Major focus is given to sample preparation strategies, which often is overseen despite that this often is the part of the analytical chain most prone to errors such as poor recoveries due to losses during sampling, storage, extraction and evaporation.

2. Physicochemical properties of antimalarials

The chemical structure and size of the antimalarials differ to a large extent causing a great variation in physicochemical parameters (Table 1). Two key parameters are water solubility (S_w) and octanol–water partitioning coefficient (K_{ow}) showing the substances ability to be solubilized in hydrophilic and lipophilic compartments, respectively. The large differences between the log K_{ow} and water solubility for antimalarials are illustrated in Fig. 1. For a majority of the antimalarials in Table 1 the identified physicochemical data are relatively consistent, however a few of them show relatively large spans of S_w and K_{ow}, for the same compound, depending on source. The reason for such deviations is not always obvious but might be a result of the nature of the molecules,

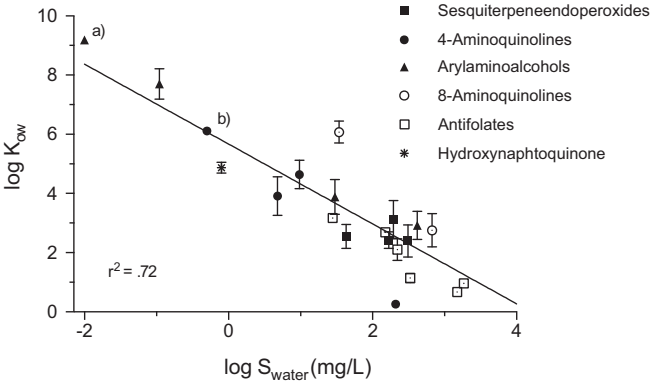

Fig. 1. Relation between water solubility and log K_{ow} for various groups of antimalarials, showing the large variation in physicochemical properties for this heterogeneous group of pharmaceuticals. Data from Table 1. (a) S_w was fixed to 0.01 mg/L for lumefantrine. (b) S_w was fixed to 0.50 mg/L for piperaquine.