Publication

A single LC-tandem mass spectrometry method for the simultaneous determination of 14 antimalarial drugs and their metabolites in human plasma

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Among the various determinants of treatment response, the achievement of sufficient blood levels is essential for curing malaria. For helping us at improving our current understanding of antimalarial drugs pharmacokinetics, efficacy and toxicity, we have developed a liquid chromatography-tandem mass spectrometry method (LC-MS/MS) requiring 200mul of plasma for the simultaneous determination of 14 antimalarial drugs and their metabolites which are the components of the current first-line combination treatments for malaria (artemether, artesunate, dihydroartemisinin, amodiaquine, N-desethyl-amodiaquine, lumefantrine, desbutyl-lumefantrine, piperaquine, pyronaridine, mefloquine, chloroquine, quinine, pyrimethamine and sulfadoxine). Plasma is purified by a combination of protein precipitation, evaporation and reconstitution in methanol/ammonium formate 20mM (pH 4.0) 1:1. Reverse-phase chromatographic separation of antimalarial drugs is obtained using a gradient elution of 20mM ammonium formate and acetonitrile both containing 0.5% formic acid, followed by rinsing and re-equilibration to the initial solvent composition up to 21min. Analyte quantification, using matrix-matched calibration samples, is performed by electro-spray ionization-triple quadrupole mass spectrometry by selected reaction monitoring detection in the positive mode. The method was validated according to FDA recommendations, including assessment of extraction yield, matrix effect variability, overall process efficiency, standard addition experiments as well as antimalarials short- and long-term stability in plasma. The reactivity of endoperoxide-containing antimalarials in the presence of hemolysis was tested both in vitro and on malaria patients samples. With this method, signal intensity of artemisinin decreased by about 20% in the presence of 0.2% hemolysed red-blood cells in plasma, whereas its derivatives were essentially not affected. The method is precise (inter-day CV%: 3.1-12.6%) and sensitive (lower limits of quantification 0.15-3.0 and 0.75-5ng/ml for basic/neutral antimalarials and artemisinin derivatives, respectively). This is the first broad-range LC-MS/MS assay covering the currently in-use antimalarials. It is an improvement over previous methods in terms of convenience (a single extraction procedure for 14 major antimalarials and metabolites reducing significantly the analytical time), sensitivity, selectivity and throughput. While its main limitation is investment costs for the equipment, plasma samples can be collected in the field and kept at 4 degrees C for up to 48h before storage at -80 degrees C. It is suited to detecting the presence of drug in subjects for screening purposes and quantifying drug exposure after treatment. It may contribute to filling the current knowledge gaps in the pharmacokinetics/pharmacodynamics relationships of antimalarials and better define the therapeutic dose ranges in different patient populations
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