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Development and Validation of a GC-MS Method for the Quantitation of Nanoformulated Primaquine in Whole Blood and Plasma of Mouse Model

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ABSTRACT

A Gas chromatography-mass spectrometry (GC/MS) method was developed and validated for the quantitation of the antimalarial drug, nanoformulated Primaquine (PQ), in whole blood and plasma. The analyte was extracted using a protein precipitation method followed by chromatographic separation on a Waters Xterra, RP C8, 2.5µm, 50mm x 4.6mm analytical column with a mobile phase consisting of A: 0.5% Formic acid in 20mM NH_4COOH, B: Methanol pH adjusted to 3.0 with FA at a ratio of 3:7 (v/v), delivered at a constant flow rate of 0.5 ml/min. Mefloquine (MEF) was used as the internal standard. Compound reaction monitoring was performed using 260.4 Da for precursor ion and 175. 2 and 379.2 Da for product ions for the quantification of PQ and 379.2 Da for precursor ion and 175.2 and 379.2 Da for product ions for the quantification, respectively. Calibration curves were constructed over the concentration range 16.7–4300 ng/ml. The mean intra- and inter-assay accuracy values for the analysis of PQ in WB was 104% (%CV = 5.6) and 98.6% (%CV = 5.7), respectively. The mean intra- and inter-assay accuracy values for the analysis of PQ in plasma was 92.7% (%CV = 3.7) and 93.7% (%CV = 5.4), respectively. No significant matrix effect was observed during the method validation. The validated method was applied to an absorption study in mice, to determine and compare PQ concentrations in whole blood and plasma samples. Results of the statistical analysis using a linear mixed effects growth curve model concluded that there was no significant difference (p-value = 0.688) between WB and plasma PQ concentrations. This method utilizes a small sample volume of 20 µl, facilitating low blood collection volumes and a short chromatographic run time of 3 min which allows for high sample through put analysis.

KEYWORDS

Mefloquine, Nanoformulated Primaquine, Plasma, Whole Blood

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1. INTRODUCTION

Malaria is a dual-host haemoprotozoan infection caused by plasmodium parasites and transmitted to humans by certain species of the female anopheles mosquito. Malaria continues to be an enormous social, economic, and ill health, notably in tropical countries. The disease kills between one and three million individuals; the bulk of who are young children (Snow et al., 2005). Efforts to regulate protozoal infection have enclosed tries within the development of effective vaccines, destruction of dipteran vectors, and development of recent medicine. protozoal infection parasites have incontestable some level of resistance to nearly each antiprotozoal drug obtainable (Bloland PB, 2016), with a number of the medicine in use having serious facet effects. The failure of dipteran destruction, drug resistance, and therefore the non-availability of a good antiprotozoal drug vaccinum herald the requirement for various antiplasmodial medical care, a quest for novel antiprotozoal drug compounds, or improvement of the prevailing antimalarials(WHO, 2011).Antimalarial (PQ) is one among the foremost wide used antiprotozoal drug medicine and is that the solely obtainable drug thus far for combating the lapse variety of protozoal infection, particularly within the case of malaria parasite and P. ovale (Baird et al., 2004).PQ contains a distinctive and powerful role within the bar and cure of protozoal infection. though its mechanism of action isn't however absolutely understood, (Fernando et al., 2011)[a] it's thought to interfere with the respiration of the parasite by generating O free radicals and release the electron transport (Hill et al.,2006). PQ may be a tissue schizonticide 8-aminoquinoline cluster of drug that destroys exoerythrocytes and hypnozoites within the liver, (Fernando, 2011)[b] so preventing relapse and irruption. However, the drug has serious facet effects as well as nausea, vomiting, abdomen cramps, and haemolytic anaemia (Kilawa and Ntoumi, 2009). This prohibits its use in key teams, adore pregnant girls (Fernando et al., 2011)[a]. The PQ dose-limiting facet effects as well as acute haemolyticanaemia in people with glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency), methemoglobinemia, leukocytopenia, blood disease, canal disturbances, and abdominal cramps (Baird and Rieckmann, 2003) are partially because of the nonspecific targeting and short half-life that necessitates frequent dosing. as an instance, for P. vivax, the indefinite quantity is thirty mg daily for fourteen days, whereas for P. ovale, the indefinite quantity is fifteen mg daily for fourteen days (Baird et al., 2004). The drug is additionally an informal prophylactic, particularly for travelers to endemic areas, (Alving et al., 1985) however the dose frequency is additionally comparatively frequent because the indefinite quantity involves thirty mg once daily, beginning the day before travel and continues up to seven days once returning. PQ oral bioavailability is additionally restricted because of pre-systemic metabolism and excretion (Singh and Vingkar, 2008). The plasma concentration of PQ is the considered the principal determinant of treatment efficacy of AL (artemether + lumefantrine) (Ezzet et al., 1998 and Price et al., 2006). The blood or plasma concentration of PQ at treatment day 7 is considered as a valuable pharmacokinetic predictor of therapeutic efficacy. Patients with day 7 PQ concentrations of <175 ng/ml were reported to have a substantially higher risk of therapeutic failure (Ezzet et al., 1998 and Price et al., 2006). For the purpose of definitively predicting therapeutic efficacy based on drug PK, it would be useful to ascertain that the concentration of PQ, determined by GC/MS methods, is comparable between blood and plasma. Validating bioanalytical methods for analyte quantification in a specific biological matrix (blood, plasma, urine, etc.), ensures that the method is robust and reproducible for analyzing samples of unknown concentrations. There are five published LC/MS methods for the quantification of PQ in human plasma and one for the quantification of PQ in rat plasma (Wahjuddin et al., 2009, Hodell et al., 2009, Mundal et al., 2010, Cesar et al., 2011, Sethi et al., 2011 and Wang et al., 2012). There seems to be no GC/MS methods for the quantification of PQ in WB or plasma. The aim of this study was to develop and validate a

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