ABSTRACT

Influence of CYP2C9 genetic polymorphisms in the PK/PD study of naproxen in saliva samples by LC MS/MS

Individual responses to non-steroidal anti-inflammatory drugs (NSAIDs) are influenced by a combination of pharmacokinetic and pharmacodynamic factors (PK/PD) that may be under the regulatory influence of some genetic factors, which is the path for personalizing the prescription today, with satisfactory efficacy and minimal side effects. Polymorphisms in *CYP2C9* can significantly interfere with the PK and PD parameters of non-steroidal anti-inflammatory drugs (NSAIDs), including naproxen. The synthesis of prostaglandin E2 (PGE2) is modulated by the enzyme cyclooxygenase-2 (COX-2) and changes in PGE2 can be used to quantify the inhibition of COX-2 after the administration of NSAIDs, which is a good target for investigation. The present research aimed to study the PK/PD parameters of naproxen and its metabolite, 6-O-desmethylnaproxen, associated with allelic variations of *CYP2C9*. In our study, a fast, selective and sensitive method of liquid chromatography coupled to mass spectrometry (LC-MS/MS) was developed and validated, according to ANVISA standards, for the determination of naproxen, its main metabolite, 6- O-desmethylnaproxen and PGE_2 in saliva. Saliva collections (4 mL) were sequential in times: before and 0.25; 0.5; 0.75; 1; 1.5; two; 3; 4; 5; 6; 8; 11; 24; 48; 72 and 96 h after taking a naproxen tablet (500 mg). The PGE_2 analysis proved to be effective and sensitive for the analysis of PD parameters. Both naproxen and its main metabolite, 6-O-desmethylnaproxen, and PGE_2 in saliva can be effectively quantified using LC-MS/MS following an oral dose of naproxen. Our method proved to be effective and sensitive to determine the lower limit of quantification of naproxen, its metabolite, 6-O-desmethylnaproxen, and PGE_2 in saliva (2.4 ng/mL). All validation data, such as accuracy, precision, and intra- and inter-assay repeatability, were less than 15%. Allelic variations of *CYP2C9* may be considered relevant in the pharmacokinetics of naproxen, its main metabolite, 6-0-desmethylnaproxen and PGE_2.

Keywords: Pharmacogenetics; naproxen; CYP2C9; Mass spectrometry; Prostaglandin E2