Evaluation of the relationship between polymorphisms in CYP2C19 and pharmacokinetics of the proton pump inhibitors.

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INTRODUCTION: Cytochrome P450 CYP2C19 mediates the major metabolic transformations of the proton pump inhibitors (PPIs). Genetic polymorphisms of CYP2C19 can lead to significant phenotypic variation in the activity of this isoenzyme and thus in the metabolism of PPIs. The aim of this study was to evaluate the possible association between polymorphisms in the CYP2C19 (CYP2C19*2 and CYP2C19*3) and the pharmacokinetics of omeprazole, rabeprazole and pantoprazole under fasting and fed conditions.

METHODS: The study population included 111 (66 male and 45 female) healthy volunteers from 4 single dose clinical trials under fed conditions and 100 (50 male and 45 female) healthy volunteers from 3 single dose clinical trials under fasting conditions. 55 volunteers participated both in fed and fasting studies. DNA was extracted from blood samples and single-nucleotide polymorphisms in the CYP2C19 gene were evaluated using real-time polymerase chain reaction (LightSNiP Roche®). Plasma concentrations were measured by high performance liquid chromatography coupled to mass spectrometry. The pharmacokinetics parameters were calculated by a non-compartmental method using WinNolin 2.0 program. The relationship between the pharmacokinetic parameters and genotype were analyzed by t-test using SPSS 16.0 comparing wild type and *2 carriers.

RESULTS: CYP2C19 genotype frequencies were 77% for CYP2C19*1/*1, 22% for *1/*2 and 1% *2/*2 in fasting studies and 78.4% for *1/*1, 20.7% *1/*2 and 0.9% *2/*2 under fed studies. No CYP2C19*3 allele carriers were found. Both in fasting and fed studies, CYP2C19*2 carriers showed a higher AUC_, AUC_, Cmax, half-life and a lower Cl than wild type subjects (p≤0.05). Under fasting conditions AUC_ was increased by 61.27% in pantoprazole, 84.65% in rabeprazole and 81.84% in omeprazole. Under fed conditions AUC_ was increased by 69.97% in pantoprazole, 64.67% in rabeprazole and 90.36% in omeprazole.

CONCLUSIONS: These results show an association between CYP2C19*2 and the pharmacokinetics parameters of omeprazole, pantoprazole and rabeprazole both under fasting and fed conditions. This effect is similar for the three drugs and causes an increase of 60-90% in AUC that could be related with a higher efficacy in CYP2C19*2 carriers.