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IMPACT OF PHARMACOGENOMICS ON PHARMACOKINETIC OF BETA BLOCKERS

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Beta adrenergic blockers (β-blockers) antagonize beta-1, beta-2 adrenergic receptors, and have been widely used for cardiovascular therapy, as well as treatment of disorders such as anxiety, thyrotoxicosis and glaucoma. Clinical response to β-blockers depends on various factors, including individual genetic polymorphisms, which affect pharmacokinetic (PK) and pharmacodynamic (PD) of this class of drugs [4]. Cytochrome p450 2D6 (CYP2D6) enzyme is of great importance for pharmacogenetic (PG), and involves in metabolism of non-selective and selective β_1-blockers such as Metoprolol, Carvedilol, Propranolol, Nebivolol, Timolol, and Labetalol. Depending on the CYP2D6 gene alleles, that carry individuals, there are four different types of phenotypes, expressing the range of the enzyme activity. In spite of establishment of clinical recommendations for CYP2D6 genotypes and prescribing metoprolol by Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC), due to the differences of sympathetic tone in patients, this theory needs more investigations to be validated in practice. According to evidences for metoprolo therapy, CYP2D6 ultrarapid metabolizer phenotypes are exposed to an increased metabolism of metoprolol, leading

to a decreased drug concentration. However, there is no dosing recommendation, due to a lack of sufficient evidences. CYP2D6 normal and moderate metabolizers are recommended to initiate standard dosing. CYP2D6 poor metabolizers are exposed to a high blood drug concentration, resulting in an increased risk of adverse events (decreased blood pressure and heart rate). For this phenotype, initial therapy with lowest recommended starting dose is necessary and dose titration upward to clinical effect or guidelinerecommended dose should be performed carefully. Worth noting, guideline recommendations related to CYP2D6 genotypes and β-blockers doses are associated with the health status of individuals and presence of comorbidities (for instance, impaired hepatic metabolism), which affect PK of the drugs. Moreover, concomitant use of CYP2D6 inhibitors such as SSRI fluoxetine and metoprolol may cause phenoconversion (drug-drug interaction), inducing bradycardia. Notably, there is a lack of sufficient data related to the plasma concentration of propranolol, carvedilol and related adverse events in CYP2D6 poor metabolizers [2, 3]. Bisoprolol is a highly selective β1-blocker administered orally for the treatment of hypertension, heart failure and ischemic heart disease, with increasing prescription rate in Europe. Bisoprolol response association with genetic polymorphisms in CYP2D6 remained controversial. Results of a study didn't reveal any association between CYP2D6 genotypes and drug response. While, results of another study showed a correlation between CYP2D6*2A CC genotype with higher systolic and diastolic arterial blood pressure and lower bisoprolol blood concentration compared to GG or GC alleles. Additionally, higher frequencies of side effects such as tiredness, chest pain and dyspnea in GG allele carriers were reported [1]. In conclusion, most of data regarding association of PK of β-blockers and CYP2D6 genetic variability are focusing on metoprolol. Hence, organizing further investigations to assess the association of CYP2D6 genes and other β-blockers seems necessary.

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