36. THE PHARMACOGENETICS ASPECTS OF NEBIVOLOL

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Introduction. The pharmacokinetic and pharmacodynamic properties of β-blockers depend on the variation in genes that contribute to a wide variability of the response between patients. Nebivolol is a cardioselective third-generation β–blocker that is metabolised primarily by the liver by CYP2D6, a metabolic pathway that is under polymorphic genetic regulation. Nebivolol is marketed as a racemic mixture of D- and L-enantiomers. D-nebivolol is responsible for the selective β1-adrenergic receptor antagonism and L-nebivolol for the vasodilatory effect.

Aim of study. The aim of this study is to describe the pharmacogenetic factors affecting nebivolol metabolism and response and to determine the role of CYP2D6 phenotypes on the efficacy and tolerability of nebivolol.

Methods and materials. A bibliographic study was performed with the selection and analysis of 25 scientific bibliographic sources from Pubmed databases and journals on the pharmacogenetic characteristics of nebivolol and their influence on pharmacokinetic parameters and pharmacodynamic effects.

Results. Nebivolol is primarily metabolised by the liver by CYP2D6, including the N-dealkylation, hydroxylation, oxidation and glucuronidation. Both aromatic hydroxylated and alicyclic oxidised molecules are pharmacologically active metabolites, while the N-dealkylated metabolite and glucuronides are inactive metabolites. The bioavailability is 12 % in extensive metabolizers and 96 % in poor metabolizers. The half-life of nebivolol is about 10 hours in extensive metabolizers and 30–50 hours in poor metabolizers. Nebivolol reduced significantly the blood pressure of hypertensive subjects characterised either as poor or extensive metabolizers for CYP2D6. The use of nebivolol in hypertensive patients with a genetically impaired CYP2D6 metabolism appears to be as safe and efficient as in those with a normal metabolic capacity. The vasodilatory action of nebivolol has been attributed mainly to the presence of the L-enantiomer and as being dose dependent. In the hypertensive patients with the poor metabolizers phenotype had plasma levels of L-nebivolol up to 15-fold higher than those of extensive metabolizers, but is not associated with an acute or pronounced fall in blood pressure nor with particular toxicity. The β-blocking activity of nebivolol, which has been ascribed mainly to the D-enantiomer, was found equipotent between the parent drug and the metabolite. The genetic defect CYP2D6, the accumulation of the parent drug in plasma, is likely to compensate for the low formation of active hydroxylated metabolites.

Conclusion. Polymorphisms in the gene encoding CYP2D6 significantly influenced the metabolism of nebivolol, but not its antihypertensive efficacy and tolerability. The similar clinical response between extensive metabolizers and poor metabolizers could be explained by the contribution of active hydroxylated metabolites of nebivolol to its antihypertensive actions in extensive metabolizers.