

Abstract

Carvedilol, a drug available as a racemic mixture, is eliminated as hydroxyphenylcarvedilol (OHC) by CYP2D6 and O-desmethylcarvedilol (DMC) by CYP2C9 followed by conjugation to glucuronides. In contrast to other β -adrenergic receptor antagonists, carvedilol does not induce insulin resistance or worsen glycaemic control in the diabetic hypertensive patients. This study aims to investigate the implications of type 2 diabetes (T2DM) on the pharmacokinetics of carvedilol enantiomers using an integrated population pharmacokinetic modelling approach. In total, 14 T2DM patients with good glycaemic control receiving standard doses of metformin and glibenclamide were evaluated along with a control group of 13 healthy subjects. Serial blood samples were collected up to 24 hours after administration of a single 25 mg dose of racemic carvedilol. A multicompartmental population pharmacokinetic model describing the enantioselective disposition of the parent compound, OHC and DMC was developed in NONMEM v7.2. Even though data are limited, it appears that despite inhibition of CYP2C9 by long-term glibenclamide administration to T2DM patients, overall there is no differences in the total clearance of carvedilol when compared to healthy volunteers (43.1 vs 45.9 L/h for (S)-(-)-carvedilol and 29.0 vs 33.1 L/h for (R)-(+)-carvedilol). These results provide evidence for a compensatory mechanism to the inhibition of CYP2C9, with higher contribution of CYP2D6 to the elimination of carvedilol. Therefore, no dose adjustment for carvedilol is recommended in T2DM patients receiving glibenclamide and metformin.