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Effect of dronedarone on the pharmacokinetics of carvedilol following oral administration to rats

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ABSTRACT

Dronedarone is a CYP2D6 inhibitor; therefore, it is prudent to exercise caution when concurrently administering CYP2D6-metabolized β-blockers because of a lack of published data on potential drug interactions. The aim of this study was to investigate the effect of dronedarone on the pharmacokinetics of orally administered carvedilol in rats. Twenty male Sprague-Dawley rats were randomly divided into two groups and 10 mg/kg carvedilol was administered to the rat with or without dronedarone pretreatment in a parallel design. Blood samples were collected before and after 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h of drug administration. The plasma concentration of carvedilol was determined using LC-MS/MS. The systemic exposure to carvedilol was significantly increased and elimination of carvedilol was significantly decreased in the dronedarone-pretreated rats than in the vehicle-pretreated rats. The one-compartment model with first-order absorption and elimination was sufficient to explain the pharmacokinetic characters after single oral administration of carvedilol to both vehicle-pretreated and dronedarone-pretreated rats. This study suggests that dronedarone inhibits CYP2D6-mediated carvedilol metabolism, and dose adjustment is needed in carvedilol and dronedarone combination therapy. Further studies are needed to clarify the effect of dronedarone on carvedilol and CYP2D6 substrates in clinical use.

1. Introduction

Carvedilol is a lipophilic vasodilating non-selective β-blocker that lacks intrinsic sympathomimetic activity (McTavish et al., 1993). It is an approved treatment for hypertension, myocardial infarction, heart failure, and atrial fibrillation (Leonetti and Egan, 2012). In particular, ACC/AHA (American College of Cardiology/American Heart Association) and ESC (European Society of Cardiology) guidelines recommend the administration of carvedilol to control heart rate in atrial fibrillation (Camm et al., 2010; January et al., 2014). In addition, a combination therapy of carvedilol and antiarrhythmic agent has been suggested for prevention of cardiac death and relief from various cardiac symptoms, along with clinical benefits when compared with carvedilol therapy alone (Boutitie et al., 1999; Connolly et al., 2006; Toyama et al., 2008).

Dronedarone is a novel antiarrhythmic drug for atrial fibrillation, acting as a multichannel blocker (Hohnloser et al., 2009). The pharmacologic characters of dronedarone are similar to those of amiodarone; however, it is better tolerated than amiodarone because it does not include iodine, and thus does not generate iodine-related adverse reactions (Sun et al., 1999). ACC/AHA and ESC recommend dronedarone as a Class IA drug for maintenance of sinus rhythm in atrial fibrillation patients (Camm et al., 2010; January et al., 2014).

The clinical benefits of carvedilol and dronedarone combination therapy have been suggested to treat and prevent heart failure, atrial fibrillation, myocardial infarction, implantable cardioverter defibrillator shock. Also, carvedilol and dronedarone are widely used medicines as essential cardiovascular treatment. In multi-drug regimen, carvedilol and dronedarone have a strong possibility of co-administration event. A study conducted by eHealthMe based on FDA reports shows that 181 patients were concomitant administered carvedilol and dronedarone from 2009 years (eHealthMe, 2017).

The pharmacokinetic characters of carvedilol have been described in previous studies (Baek et al., 2008). Briefly, the bioavailability of carvedilol is approximately 23% following oral administration, and it is highly protein-bound in plasma. Moreover, carvedilol is extensively metabolized by CYP2D6 (Brodde and Kroemer, 2003), while dronedarone is a CYP2D6 inhibitor (Patel et al., 2009). It is possible to raise the plasma concentration of carvedilol upon concomitant administration of carvedilol and dronedarone. However, pharmacokinetic

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interaction between carvedilol and dronedarone has not been reported in an in vivo model.

Therefore, the aim of this study was to investigate the effect of dronedarone on the pharmacokinetics of carvedilol, following oral administration in rats. The study was performed as a parallel design with dronedarone-pretreatment and vehicle-pretreatment groups. To inhibit CYP2D6, dronedarone was repeatedly administered orally for a five-day pretreatment period. Carvedilol was then administered as a single oral dose on the fifth day. Pharmacokinetic analysis was performed using a non-compartmental analysis and modeling approaches. This study suggested that potential drug–drug interactions between carvedilol and dronedarone might be clinically significant.

2. Materials and methods

2.1. Materials

Carvedilol, dronedarone, and metoprolol tartrate (internal standard, IS) were purchased from Sigma Chemical Co. (St. Louis, MO, USA) for the pharmacokinetic study and determination of plasma carvedilol concentrations using liquid chromatography tandem mass spectrometry (LC-MS/MS). High-performance liquid chromatography grade methanol (MeOH), acetonitrile, and formic acid were obtained from Merck Co. (Darmstadt, Germany).

2.2. Animals

Animal studies were performed according to institutional guidelines for the care and use of laboratory animals, and were approved by the animal ethics committee of Kyungsung University. Twenty male seven-week-old Sprague-Dawley (SD) rats (200–220 g) were purchased from Hyochang Science (Taegu, South Korea). Animals were housed individually in a standard stainless steel cages at the College of Pharmacy, Kyungsung University. Before starting the experiments, animals were acclimated under the following constant standard conditions for at least one week: a temperature of 21–25 °C; humidity of 40–60%; 12 h light/12 h dark cycle; air ventilation rate of 10 times/h. The animals were allowed free access to water and food before the experiment to maintain their normal body condition.

2.3. Study design

SD rats were randomly distributed into two groups and 10 mg/kg carvedilol was oral administered with or without dronedarone pretreatment in a parallel design. Group A (n = 10), the control group, was treated with vehicle (normal saline/dimethyl sulfoxide/polyethylene glycol 400 = 50:10:40) only for five days, followed by orally administration of 10 mg/kg carvedilol. Group B (n = 10) was administered dronedarone dissolved in vehicle orally at a dose of 10 mg/kg once a day for five days. Carvedilol 10 mg/kg was oral administered on the fifth day, following 30 min the last dose of dronedarone. Each dose (10 mg/kg) of carvedilol and dronedarone in rat was set by conversion of human equivalent dose (3.125–50 mg for carvedilol, 100–800 mg for dronedarone) based on body surface area in the US Food and Drug Administration guidelines (Center for Drug Evaluation and Research, 2005). All animals were fasted for about 12 h prior to, and for 2 h following the carvedilol, with free access to water.

To measure plasma concentrations of carvedilol, blood samples (150 μL) were obtained from the jugular vein and stored in heparinized polythene tubes before (0 h) and after 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h of drug administration. The blood samples were centrifuged for 2 min at 10,000 rpm, and the plasma samples were stored at − 70 °C until LC-MS/MS analysis.

Table 1
Main working parameters for tandem mass spectrometry.

Parameter	Value
Scan type	MRM
Ion polarity	Positive
Fragmentor voltage (V)	132
Nebulizer pressure (psi)	30
Drying gas temperature (°C)	350
Dry gas flow (L/min)	12
Dwell time per transition (ms)	150
Collision energy (eV)	34
Ion transition for carvedilol (m/z)	407.3 → 100.0
Ion transition for IS (m/z)	268.1 → 115.9

2.4. LC-MS/MS assay

Plasma concentrations of carvedilol (racemic mixture) were analyzed using an Agilent 1200 series HPLC and interfaced to an Agilent 6410 Triple Quadrupole mass spectrometer (Agilent Technologies, USA) equipped with an electrospray ionization (ESI) source. An Agilent 6410 Triple Quadrupole mass operated in the multiple reaction monitoring (MRM) mode was used for quantitative determination. A turbo electrospray interface was conducted in positive ionization mode. The main mass spectrometer parameters are summarized in Table 1.

Chromatographic separation was performed on a Zorbax SB C_{18} column (50 × 4.6 mm, 5 μm). The mobile phase composition was a mixture of acetonitrile and 10 mM ammonium acetate solution (60:40, v/v), and flow rate was 0.5 mL/min. The column and autosampler were maintained at 30 °C and 10 °C, respectively. All LC-MS/MS data were acquired and analyzed using Agilent 6410 Quantitative Analysis version analyst data processing software.

2.5. Sample preparation

The samples were protein precipitated using methanol to extract analytes from the plasma matrix. Frozen plasma samples were thawed at room temperature. In an Eppendorf tube, 100 μL plasma samples were added 600 μL of methanol containing internal standard (metoprolol 1 μg/mL). After vortex-mixing and centrifugation at 12,000 rpm for 5 min, an aliquot of each supernatant (300 μL) was transferred to a autosampler vial, and 5 μL of samples were injected into the LC-MS/MS system. All samples for method validation and pharmacokinetics were conducted using the same procedure.

2.6. Method validation

Method validation achieved with the United States Food and Drug Administration Bioanalytical Method Validation Guidance (Center for Drug Evaluation and Research, 2001). The calibration curve range of carvedilol was set from 1 to 1000 ng/mL, and the lowest limit of quantification (LLOQ) for carvedilol was 1 ng/mL. The calibration curve was generated by a weighted linear regression ($1/y^2$) of the peak area ratio (peak area analyte/peak area IS) versus concentration. The linear coefficient of correlation for carvedilol > 0.999 for five batches.

Validation samples were analyzed on five batches to evaluate the accuracy and intra- and inter-day precisions of the analytical method. The accuracy and precision was determined by analyzing five replicates at three QC concentration along with one standard curve in each batch. The intra- and inter-day precision for dronedarone were within 15%, and that for accuracy was achieved < 100 ± 15% for three QC samples.

The stability of carvedilol in plasma under the three different conditions was evaluated. QC samples were analyzed for stability by being subjected to short-term stability conditions (room temperature for 6 h), to long-term stability conditions (− 70 °C for one month) and to three