CONTRIBUTION OF MATE1 TO DOFETILIDE-INDUCED PROARRHYTHMIA

Muhammad Erfan Uddin¹, Yan Jin¹, Alice A. Gibson¹, Alec Millar², Przemyslaw Radwanski², Cynthia A. Carnes²,³, Shuiying Hu², and Alex Sparreboom¹

¹Division of Pharmaceutics and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, OH
²Division of Outcomes and Translational Sciences, College of Pharmacy, The Ohio State University, Columbus, OH
³Division of Pharmacy Practice and Science, College of Pharmacy, The Ohio State University, Columbus, OH

Background
Dofetilide is a rapid delayed rectifier potassium current (I_{Kr}) inhibitor used to prevent the recurrence of atrial fibrillation and flutter. The clinical use of this drug is associated with increases in QTc interval, which can exacerbate cardiac arrhythmias. The mechanisms involved in dofetilide’s renal tubular secretion and its incidence of QTc prolongation remain unknown. Previously reported drug-drug interaction (DDI) studies of dofetilide suggest the involvement of organic cation transporters which might have been associated with prolonged QTc interval. Here, we investigate the contribution of multidrug and toxin extrusion protein 1 (MATE1; SLC47A1) to the pharmacokinetics of dofetilide to gain insight into its DDI potential, and mechanism of cardiotoxicity.

Methods
In vitro transport kinetics of tetraethylammonium (TEA), metformin, and dofetilide were determined in various transporter overexpressing cell lines. In vivo PK, DDIs, and mass balance studies (urinary excretion) were performed in wild-type, and MATE1-deficient mice receiving a single dose of dofetilide (5 mg/kg, p.o.; 2.5 mg/kg, i.v.) in the presence and absence of various contraindicated drugs. Concentrations of dofetilide in plasma and urine were determined by UPLC-MS/MS. PK parameters were calculated using WinNonlin. Cardiomyocytes from wild-type and MATE1-deficient mice were isolated using a Langendorff perfusion system, and used to examine ex vivo drug uptake. Continuous electrocardiographic (ECG) recordings were obtained in neonatal wild-type and MATE1-deficient mice (1 day old) before and after the treatment of dofetilide (0.5 mg/kg; i.p.) using ADInstruments, and heart rate corrected QT intervals were analyzed using the LabChart 7.3 program. A physiologically-based pharmacokinetic (PBPK) model of dofetilide was developed using SimCYP® (V19) by incorporating data from in vitro, preclinical, and clinical pharmacokinetic studies in healthy volunteers.

Results
In vitro studies demonstrated that dofetilide is a substrate of MATE1 (4.3-fold increase in drug uptake over vector control), and deficiency of MATE1 was associated with increased plasma concentrations of dofetilide and with a significantly reduced urinary excretion (3-fold in females and 5-fold in males, respectively). Dofetilide accumulation within cardiomyocytes was increased by 2-fold in MATE1-deficient mice, and pre-incubation with the MATE1 inhibitor cimetidine significantly reduced dofetilide uptake in wild-type cardiomyocytes. QTc prolongation was significantly increased in MATE1-deficient neonatal mice compared to wild-type, and all MATE1-deficient mice were found to develop second-degree heart blocks (Mobitz I and II) following dofetilide treatment. Several contraindicated drugs listed in the dofetilide prescribing information, including bictegravir, cimetidine, ketoconazole, trimethoprim, verapamil, increased dofetilide plasma exposure in wild-type mice by >1.6-fold. The PBPK model adequately predicted changes in dofetilide exposure after co-administration of cimetidine (65.5% predicted versus 58% observed increase) and ketoconazole (41.1% predicted versus 41% observed increase) as well as reduced renal clearance with cimetidine (38.9% predicted versus 43.7% observed).

Conclusion


This study suggests that renal tubular secretion of dofetilide is dependent on MATE1, and is sensitive to inhibition by widely used prescription drugs. Inhibition of MATE1 function not only reduces urinary excretion of dofetilide but also contributes to its accumulation in the heart which could potentially lead to cause QTc prolongation. Our newly developed PBPK model also predicts clinical DDIs of dofetilide with various MATE1 inhibitors, further supporting the hypothesis that cation transporters are critical determinants of interindividual variation in response to dofetilide.