**RENAL TUBULAR SECRETION AND CARDIAC DISTRIBUTION OF DOFETILIDE IS DEPENDENT ON MATE1 FUNCTION**

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**Introduction**

Dofetilide is a delayed rectifier potassium channel inhibitor used to treat patients with atrial fibrillation and flutter, and its use is associated with a risk of QT prolongation and *Torsades de Pointes*. The mechanisms involved in dofetilide’s renal tubular secretion and its uptake into cardiomyocytes remain unknown. Previously reported drug-drug interaction (DDI) studies of dofetilide with cimetidine, ketoconazole, and megestrol suggest the involvement of organic cation transporters. Here, we investigated the contribution of organic cation transporters (OCT2; *SLC22A2)* and multidrug and toxin extrusion protein 1 (MATE1; *SLC47A1*) to the pharmacokinetics (PK) of dofetilide to gain insight into its DDI potential.

**Methods**

*In vitro* and *ex vivo* transport kinetics of dofetilide were determined in HEK293 cells stably transfected with OCT2 or MATE1, and in isolated cardiomyocytes, respectively. *In vivo* PK, DDIs, and mass balance studies were performed in wild-type, OCT1,2-, and MATE1-deficient mice receiving a single dose of dofetilide (5 mg/kg, p.o.; 2.5 mg/kg, i.v.), and contraindicated drugs. Concentrations of dofetilide in plasma and urine were determined by UPLC-MS/MS. PK parameters were calculated using Phoenix® WinNonlin®, while urinary excretion was calculated as a ratio of dofetilide recovery to the dose administered.

**Results**

*In vitro* studies demonstrated that dofetilide is a substrate of MATE1.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 in cardiomyocytes was increased by 2-fold in MATE1-deficient females, and pre-incubation with the MATE1 inhibitor cimetidine significantly reduced dofetilide uptake in wild-type cardiomyocytes. Several contraindicated drugs listed in the dofetilide prescribing information, including cimetidine, ketoconazole, increased dofetilide plasma exposure in wild-type mice by >2.8-fold.

**Conclusion**

Renal secretion of dofetilide is mediated by MATE1 and is highly sensitive to inhibition by many widely used prescription drugs that can cause clinically relevant DDIs. Deficiency of MATE1 also increases accumulation in the heart which may contribute to individual variation in response to dofetilide.