Renal Tubular Secretion of Dofetilide is Dependent on MATE1 Function

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Background
Dofetilide is a delayed rectifier potassium channel inhibitor used to treat patients with atrial fibrillation and flutter. The clinical use of this drug is associated with increases in QTc interval, which can exacerbate cardiac arrhythmias. The elimination of dofetilide is predominantly mediated by renal tubular secretion, yet the mechanism by which this occurs remains poorly understood. Previously reported drug-drug interaction (DDI) studies of dofetilide with cimetidine, ketoconazole, and megestrol suggest the involvement of organic cation transporters. Here, we investigate the contribution of organic cation transporter 2 (OCT2; SLC22A2) and multidrug and toxin extrusion protein 1 (MATE1; SLC47A1) to the pharmacokinetics (PK) of dofetilide in examine these mechanisms in the drug’s elimination and its narrow therapeutic window.

Methods
In vitro transport kinetics of tetraethylammonium (TEA), and dofetilide were determined in HEK293 cells stably-transfected with OCT2 or MATE1. 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. Cardiomyocytes from wild-type and MATE1-deficient mice were isolated using a Langendorff perfusion system, and used to examine ex vivo cardiomyocytes uptake.

Results
In vitro studies show that dofetilide is a substrate of MATE1 (4.3-fold increase over vector control). Oral administration of dofetilide increased the plasma concentration (Cmax) and area under the curve (AUC) in MATE1-deficient mice with low plasma clearance. However, MATE1-deficiency in mice was associated with significant 3- and 5-fold reduction of urinary excretion of dofetilide in females and males, respectively, whereas no noticeable differences were observed in OCT2-deficient animals. Accumulation of dofetilide in cardiomyocytes was higher by 2-fold in female mice having MATE1-deficiency than males, while addition of an inhibitor, e.g., cimetidine significantly reduced dofetilide uptake. DDI studies with ketoconazole (50 mg/kg, p.o.) elevated the Cmax in wild-type, OCT1,2-, and MATE1-deficient mice by 181%, 80%, and 54%, respectively, which suggest that transport inhibition is the major mechanism for ketoconazole-induced increases in dofetilide exposure. Several contraindicated drugs listed in the dofetilide prescribing information inhibited MATE1-mediated dofetilide transport by >75%.

Conclusion
This study suggests that the tubular secretion of dofetilide is mediated by MATE1 and occurs independently of OCT2, and is sensitive to inhibition by widely used prescription drugs. Further research is required to identify the transmembrane processes involved in dofetilide uptake into
proximal renal tubular cells. Based on the preliminary data, deficiency of MATE1 not only reduces urinary excretion of dofetilide but also increases accumulation in the heart which may contribute to individual variation in response.
Dofetilide is a delayed rectifier potassium channel inhibitor used to treat 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 elimination of dofetilide is predominantly mediated by tubular secretion, yet the mechanism by which this occurs remains poorly understood. Previously reported drug-drug interaction (DDI) studies of dofetilide with cimetidine, ketoconazole, and megestrol suggest the involvement of organic cation transporters. Here, we investigate the contribution of organic cation transporter 2 (OCT2; SLC22A2) and multidrug and toxin extrusion protein 1 (MATE1; SLC47A1) to the pharmacokinetics (PK) of dofetilide in an effort to elucidate the mechanisms involved in the drug’s elimination and its narrow therapeutic window.

Methods

In vitro transport kinetics of tetraethylammonium (TEA), metformin, and dofetilide were determined in HEK293 cells stably-transfected with OCT2 or MATE1. 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 such as cimetidine, ketoconazole, and megestrol. Concentrations of dofetilide in plasma and urine were determined by UPLC-MS/MS. PK parameters of dofetilide were calculated using Phoenix® WinNonlin® (Version 8.0), while urinary excretion was calculated as a ratio of dofetilide recovery to the dose administered. Cardiomyocytes from wild-type and MATE1-deficient mice were isolated using a Langendorff perfusion system, and performed ex vivo cardiomyocytes uptake.

Results

Functional overexpression of OCT2 and MATE1 in vitro studies was confirmed by >29-fold increased uptake of TEA and metformin in OCT2- or MATE1-transfected cells compared to vector controls. Oral administration of dofetilide increased the plasma concentration (C\text{max}) and area under the curve (AUC) in MATE1-deficient mice with low plasma clearance. However, MATE1-deficiency in mice was associated with significantly reduced by 3- and 5-fold urinary excretion of dofetilide in female and male, respectively, whereas no noticeable differences were observed in OCT2-deficient animals. Accumulation of dofetilide in cardiomyocytes was found higher by 2-fold in female mice having MATE1-deficiency than male while addition of an inhibitor, for example, cimetidine significantly reduced dofetilide uptake. DDI studies with ketoconazole (50 mg/kg, p.o.) elevated the C\text{max} in wild-type, OCT1,2-, and MATE1-deficient mice by 181%, 80%, and 54%, respectively, which suggest that transport inhibition is the major mechanism for ketoconazole-induced increases in dofetilide exposure. Several contraindicated drugs listed in the dofetilide prescribing information inhibited MATE1-mediated dofetilide transport by >75%.

Conclusion

This study suggests that the tubular secretion of dofetilide is mediated by MATE1 and occurs independently of OCT2, and is sensitive to inhibition by widely used prescription drugs. Further research is required to identify the transmembrane processes involved in dofetilide uptake into proximal renal tubular cells.