EFFECT OF BEMPEDOIC ACID ON OAT2-MEDIATED UPTAKE OF DRUGS IN MDCK-II CELLS

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BACKGROUND

- Bempedoic acid, a prodrug, is metabolized in the liver by very long-chain acyl-CoA synthetase 1 (ACSVL1) to form the pharmacologically active bempedoic acid-CoA metabolite, a potent and selective inhibitor of ATP-citrate lyase, resulting in upregulation of the low-density lipoprotein (LDL) receptor and decreased LDL cholesterol
- Bempedoic acid is an inhibitor of organic anion transporter 2 (OAT2) in vitro[1–3]; OAT2 contributes to the active uptake of creatinine and uric acid in the renal proximal tubule
- Inhibition of OAT2 by bempedoic acid may explain small and reversible increases in serum creatinine and uric acid observed in phase 3 studies among patients who received bempedoic acid[4]
- The potential for bempedoic acid to interact with drugs that are OAT2 substrates has not yet been investigated

OBJECTIVE

- To identify putative OAT2 substrates and evaluate the ability of bempedoic acid to inhibit OAT2-mediated uptake using MDCK-II cells expressing OAT2

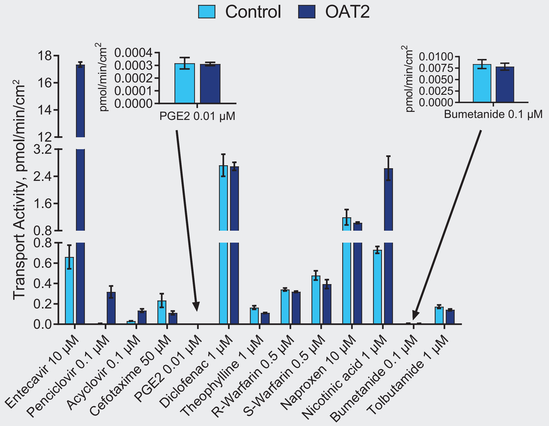
METHODS

- A total of 13 putative substrates of OAT2 were identified from literature sources[5–7]
- Candidate compounds were screened for OAT2-mediated cellular uptake using transiently transfected MDCK-II cells expressing human OAT2
- Inhibition of OAT2-mediated transport by bempedoic acid was determined at the maximum concentration observed clinically after bempedoic acid 180 mg daily dosing (58 µM; 20 µg/mL) and at a 10-fold higher concentration (580 µM; 200 µg/mL)
- Estimates of the half maximal OAT2 inhibitory concentration (IC_{50}) were determined over a range of bempedoic acid concentrations (5.8–1160 µM), nicotinic acid concentrations (1.74–580 µM), and indomethacin 100 µM (positive control)
  - Inhibition at the highest bempedoic acid concentration (1160 µM) was not included in the regression analysis as the solubility of bempedoic acid was incomplete

RESULTS

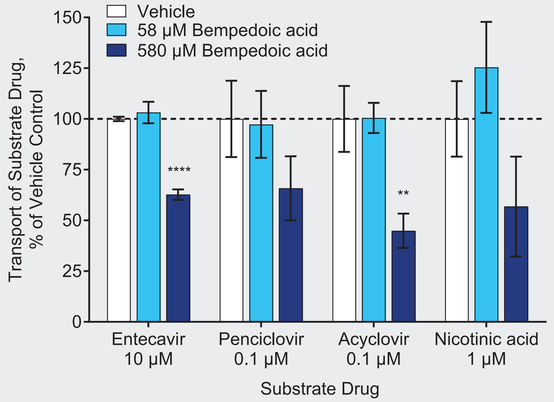
- Putative substrates for OAT2 previously reported in the literature were evaluated in MDCK-II cells expressing the transporter
- The drugs entecavir, penciclovir, acyclovir, and nicotinic acid were identified as OAT2 substrates in MDCK-II cell incubations, as defined by ≥ 2-fold uptake relative to control cells **(Figure 1)**
- At a clinically relevant concentration of 58 µM, bempedoic acid did not inhibit OAT2-mediated uptake of entecavir, penciclovir, acyclovir, and nicotinic acid **(Figure 2)**
  - Bempedoic acid (580 µM) inhibited OAT2-mediated uptake of entecavir by 37.3% ($P < .0001$), penciclovir by 34.2% ($P = .0851$), acyclovir by 55.1% ($P = .0019$), and nicotinic acid by 43.2% ($P = .0908$)
- IC_{50} estimates exceeded 580 µM for the inhibition of OAT2-mediated transport of entecavir, penciclovir, acyclovir, and nicotinic acid by bempedoic acid **(Figure 3)**
  - Individual IC_{50} estimates could not be determined due to insufficient inhibition by bempedoic acid up to 580 µM
  - Maximum mean (SD) transport inhibition with 580 µM bempedoic acid was 36.2% (8.6) for entecavir, 20.6% (0.5) for penciclovir, 48.7% (6.6) for acyclovir, and 39.3% (4.7) for nicotinic acid
- Bempedoic acid is not likely to have clinically relevant pharmacokinetic interactions with entecavir, penciclovir, acyclovir, or nicotinic acid **(Table 1)**

Figure 1. Evaluation of 13 Clinical Drugs as Substrates of Human OAT2 Transport



Data represent the mean (SD) of triplicate samples.OAT2 = organic anion transporter 2; PGE2 = prostaglandin E2.

Figure 2. Inhibition of OAT2-Mediated Transport by Bempedoic Acid



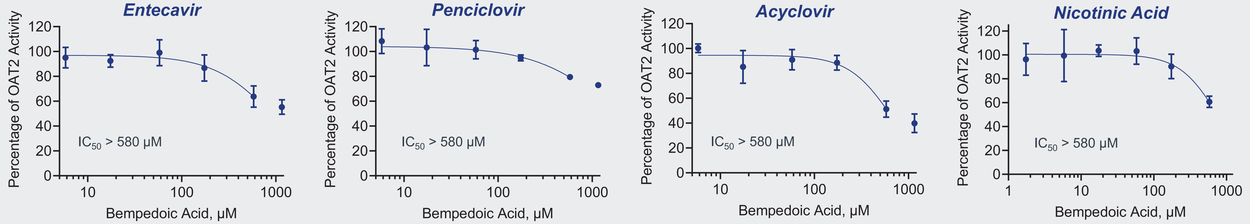
Data represent the mean (SD) of triplicate samples.
Dashed line = 100%. **$P < .01$ and ****$P < .0001$ by one-way analysis of variance post hoc Dunnett test.

Table 1. Inhibition of OAT2-Mediated Substrate Transport by Bempedoic Acid and Estimate of Clinically Relevant Bempedoic Acid Concentrations

Substrate	Substrate Concentration,[a] µM	Substrate Km,[b] µM	Estimated Bempedoic Acid IC_{50}, µM	Estimated IC_{50}/ Bempedoic Acid Unbound Concentration Ratio
Entecavir	10	150[8]	> 580	> 1000
Penciclovir	0.1	284[5]	> 580	> 1000
Acyclovir	0.1	94[5]	> 580	> 1000
Nicotinic acid	1	13.5[9]	> 580	> 1000

[a]Substrate concentration used in transport inhibition experiments.
[b]Reported substrate Km for OAT2.
IC_{50} = half maximal inhibitory concentration; Km = concentration at the half maximal rate of transport.

Figure 3. Determination of IC_{50} Values for Bempedoic Acid Against OAT2-Mediated Transport of Entecavir, Penciclovir, Acyclovir, and Nicotinic Acid



Data represent the mean (SD) of triplicate samples. Highest bempedoic acid concentration (1160 µM) was not included in the regression analyses.
Concentration-dependent inhibition curves were generated using a Hill Equation fixed-bottom nonlinear regression.
IC_{50} = half maximal inhibitory concentration; OAT2 = organic anion transporter 2.

CONCLUSIONS

- Incubations with MDCK-II cells expressing the OAT2 transporter showed entecavir, penciclovir, acyclovir, and nicotinic acid are substrates of OAT2
- Bempedoic acid at 580 µM, a 10-fold greater concentration than observed clinically, was a weak inhibitor of OAT2-mediated uptake of entecavir, penciclovir, acyclovir, and nicotinic acid (all IC_{50} > 580 µM)
- Based on these in vitro findings, bempedoic acid is predicted to have a low potential for clinically meaningful pharmacokinetic interactions with OAT2-substrate drugs

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DECLARATIONS OF INTEREST

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BM Amore and SM Akhtar are current employees of Esperion Therapeutics, Inc., and may own Esperion stock and/or stock options. MG Emery is a consultant for and former employee of Esperion Therapeutics, Inc., and may own Esperion stock and/or stock options. X Zhang and MS Warren are employees of BioIVT, which has a service agreement with Esperion Therapeutics, Inc. JD Unadkat and RG Tirona have served as consultants and/or scientific advisors for Esperion Therapeutics, Inc.

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