Effect of Gemfibrozil, Rifampicin, or Probenecid on the Pharmacokinetics of the SGLT2 Inhibitor Empagliflozin in Healthy Volunteers

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ABSTRACT

Background: Empagliflozin is a potent, oral, selective inhibitor of sodium glucose cotransporter 2 in development for the treatment of type 2 diabetes mellitus.

Objective: The goal of these studies was to investigate potential drug–drug interactions between empagliflozin and gemfibrozil (an organic anion-transporting polypeptide 1B1 [OATP1B1]/1B3 and organic anion transporter 3 [OAT3] inhibitor), rifampicin (an OATP1B1/1B3 inhibitor), or probenecid (an OAT3 and uridine diphosphate glucuronosyltransferase inhibitor).

Methods: Two open-label, randomized, crossover studies were undertaken in healthy subjects. In the first study, 18 subjects received the following in 1 of 2 randomized treatment sequences: a single dose of empagliflozin 25 mg alone and gemfibrozil 600 mg BID for 5 days with a single dose of empagliflozin 25 mg on the third day. In the second study, 18 subjects received a single dose of empagliflozin 10 mg, a single dose of empagliflozin 10 mg coadministered with a single dose of rifampicin 600 mg, and probenecid 500 mg BID for 4 days with a single dose of empagliflozin 10 mg on the second day in 1 of 6 randomized treatment sequences.

Results: In the gemfibrozil study, 11 subjects were male, mean age was 35.1 years and mean body mass index (BMI) was 23.47 kg/m^2. In the rifampicin/probenecid study, 10 subjects were male, mean age was 32.7 years and mean BMI was 23.03 kg/m^2. Exposure to empagliflozin was increased by coadministration with gemfibrozil ($AUC_{0-\infty}$: geometric mean ratio [GMR], 158.50% [90% CI, 151.77–165.53]; C_{max}: GMR, 115.00% [90% CI, 106.15–124.59]), rifampicin ($AUC_{0-\infty}$: GMR, 135.20% [90% CI, 129.58–141.06]; C_{max}: GMR, 175.14% [90% CI, 160.14–191.56]), and probenecid ($AUC_{0-\infty}$: GMR, 153.47% [90% CI, 146.41–160.88]; C_{max}: GMR, 125.60% [90% CI, 113.67–138.78]). All treatments were well tolerated.

Conclusions: Increases in empagliflozin exposure were <2-fold, indicating that the inhibition of the OATP1B1/1B3, OAT3 transporter, and uridine diphosphate glucuronosyltransferases did not have a clinically relevant effect on empagliflozin exposure. No dose adjustments of empagliflozin were necessary when it was coadministered with gemfibrozil, rifampicin, or probenecid. ClinicalTrials.gov identifiers: NCT01301742 and NCT01634100. (*Clin Ther.* 2014;36:280–290)

Key words: drug interactions, empagliflozin, organic anion transporters, uridine diphosphate glucuronosyltransferase.

INTRODUCTION

Empagliflozin, a potent and selective sodium glucose cotransporter 2 (SGLT2) inhibitor,[1] is in development for the treatment of type 2 diabetes mellitus (DM). SGLT2 is found predominantly in the S1/S2 segments of the renal proximal tubule and is reportedly responsible for ~90% of renal glucose reabsorption in animal

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models.[2] Inhibiting SGLT2 reduces renal glucose reabsorption, leading to increased urinary glucose excretion (UGE) and thus reducing hyperglycemia in patients with type 2 DM.[3] Both short- and long-term Phase IIb/III studies with empagliflozin have shown improved glycemic control and reduced weight and blood pressure in patients with type 2 DM.[4–10]

Transporters in epithelial and endothelial barriers have been shown to be important in the absorption and disposition of drugs, and several drug–drug interactions have been attributed to involvement of transporters.[11] Therefore, in addition to the well-recognized metabolic drug–drug interactions, it has become increasingly evident that transporter-based interactions should also be considered during drug development.[12] In vitro studies conducted by using transfected frog oocytes found that empagliflozin is a substrate of organic anion-transporting polypeptide 1B1 (OATP1B1), OATP1B3, and organic anion transporter 3 (OAT3) (data not published). OATP1B1 and OATP1B3 are uptake transporters expressed predominantly in the liver that are involved in the hepatic elimination of many drugs.[13] In addition, several genetic polymorphisms in the gene encoding OATP1B1 (*SLCO1B1*) have been described and may affect transporter function. The 2 common *SLCO1B1* single-nucleotide polymorphisms, c.521T > C (p.Val174Ala) and c.388A > G (p.Asn130Asp), together form 4 functionally distinct haplotypes. Clinically, the *SLCO1B1*5* (c.388A-c.521C) and **15* (c.388G-c.521C) haplotypes are associated with increased plasma exposure to some OATP1B1 substrates, best exemplified by the effect on statins.[14,15] OAT3 is expressed primarily on the basolateral membrane in the renal proximal tubule and is involved in the renal excretion of many drugs.[16,17] Importantly, OATP1B1, OATP1B3, and OAT3 have been shown to cause clinically relevant drug–drug interactions.[11,12,18]

Regulatory authorities recommend the evaluation of potential transporter-mediated drug–drug interactions for new agents that are substrates of OATP1B1/1B3 and OAT3.[12,18] The lipid-lowering agent gemfibrozil, the antibiotic rifampicin, and the uricosuric agent probenecid are recommended as probe inhibitors for such drug–drug interaction studies.[12,19,20] The rationale is that gemfibrozil and its glucuronide metabolite (gemfibrozil 1-O-β-glucuronide) inhibit OATP1B1/1B3 and OAT3 in vitro,[20–22] rifampicin is a potent inhibitor of OATP1B1/1B3,[20] and probenecid is an OAT3 inhibitor.[23]

Two studies were undertaken to determine the effect of OATP1B1/1B3 and OAT3 inhibition on the pharmacokinetics of empagliflozin after coadministration with gemfibrozil, rifampicin, and probenecid. Furthermore, because OAT3-mediated transport of empagliflozin may modulate empagliflozin pharmacodynamics, the effect of probenecid on empagliflozin-induced UGE was investigated. Finally, this study aimed to determine the potential effect of genetic *SLCO1B1* variants on empagliflozin exposure when coadministered with rifampicin. Glucuronidation is the main metabolic pathway for empagliflozin based on the metabolic profile investigated in Phase I studies (data not published). Regulatory authorities also recommend that potential drug–drug interactions via metabolizing enzymes in addition to cytochrome P450 should be considered during drug development, such as uridine diphosphate glucuronosyltransferases (UGTs), particularly if glucuronidation is a predominant pathway of drug elimination.[12,18] In addition to being an inhibitor of OAT3, probenecid also inhibits UGTs.[24] As such, the drug–drug interaction study with probenecid was also used to delineate any potential effect of UGT inhibition on empagliflozin.

SUBJECTS AND METHODS

Two single-center, randomized, open-label, crossover studies were undertaken in healthy subjects, one to determine the relative bioavailability of empagliflozin administered with gemfibrozil (gemfibrozil study) and the other to determine the relative bioavailability of empagliflozin when administered with rifampicin and probenecid (rifampicin/probenecid study). Both clinical trial protocols were approved by the local independent ethics committee (Landesärztekammer Baden-Württemberg, Stuttgart, Germany) and the German Competent Authority (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany). The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice. Written informed consent was provided by each participating subject before enrollment.

Participants

Healthy male or female subjects aged 18 to 55 years (gemfibrozil study) or 18 to 50 years (rifampicin/probenecid study) with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were eligible for enrollment in