Original Research

Lack of Clinically Relevant Drug–Drug Interaction Between Empagliflozin, a Sodium Glucose Cotransporter 2 Inhibitor, and Verapamil, Ramipril, or Digoxin in Healthy Volunteers

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ABSTRACT

Background: Empagliflozin is a sodium glucose cotransporter 2 inhibitor in clinical development as a treatment for type 2 diabetes mellitus.

Objective: The goal of this study was to investigate potential drug–drug interactions between empagliflozin and verapamil, ramipril, and digoxin in healthy volunteers.

Methods: The potential drug–drug interactions were evaluated in 3 separate trials. In the first study, 16 subjects were randomized to receive single-dose empagliflozin 25 mg alone or single-dose empagliflozin 25 mg with single-dose verapamil 120 mg. In the second study, 23 subjects were randomized to receive empagliflozin 25 mg once daily (QD) for 5 days, ramipril (2.5 mg on day 1 then 5 mg QD on days 2–5) for 5 days or empagliflozin 25 mg with ramipril (2.5 mg on day 1 then 5 mg QD on days 2–5) for 5 days. In the third study, 20 subjects were randomized to receive single-dose digoxin 0.5 mg alone or empagliflozin 25 mg QD for 8 days with single-dose digoxin 0.5 mg on day 5.

Results: Exposure of empagliflozin was not affected by coadministration with verapamil ($AUC_{0-\infty}$: geometric mean ratio [GMR], 102.95%; 90% CI, 98.87–107.20; C_{max}: GMR, 92.39%; 90% CI, 85.38–99.97) or ramipril (AUC over a uniform dosing interval τ at steady state [$AUC_{\tau,ss}$]: GMR, 96.55%; 90% CI, 93.05–100.18; C_{max} at steady state [$C_{max,ss}$]: GMR, 104.47%; 90% CI 97.65–111.77). Empagliflozin had no clinically relevant effect on exposure of ramipril ($AUC_{\tau,ss}$: GMR, 108.14%; 90% CI 100.51–116.35; $C_{max,ss}$: GMR, 103.61%; 90% CI, 89.73–119.64) or its active metabolite ramiprilat ($AUC_{\tau,ss}$: GMR, 98.67%; 90% CI, 96.00–101.42; $C_{max,ss}$: GMR, 98.29%; 90% CI, 92.67–104.25). Coadministration of empagliflozin had no clinically meaningful effect on digoxin $AUC_{0-\infty}$ (GMR, 106.11%; 90% CI, 96.71–116.41); however, a slight increase in C_{max} was observed that was not considered clinically relevant (GMR, 113.94%; 90% CI, 99.33–130.70). All treatments were well tolerated. There were no serious adverse events or adverse events leading to discontinuation in any of the studies.

Conclusions: No dose adjustment of empagliflozin is required when coadministered with ramipril or verapamil, and no dose adjustment of digoxin or ramipril is required when coadministered with empagliflozin. ClinicalTrials.gov identifiers: NCT01306175 (digoxin), NCT01276301 (verapamil), and NCT01284621 (ramipril). (*Clin Ther*. 2013;35:226–235)

Key words: digoxin, drug–drug interaction, empagliflozin, ramipril, SGLT2 inhibitor, type 2 diabetes, verapamil.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is an increasing global problem, with prevalence rates that have more than doubled over the past 3 decades and continue to increase.[1,2] There are several pharmacologic treatment options for T2DM, including metformin, sulphonylureas, thiazoli-

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dinediones, glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, and insulin. Due to the progressive nature of the disease, treatment with multiple antidiabetic therapies is often required.[3,4] Current antidiabetic therapies are often limited by adverse effects such as weight gain and hypoglycemia,[3,4] and new approaches for antidiabetic therapies are being investigated.

One approach for new antidiabetic therapies is the inhibition of the sodium glucose cotransporter 2 (SGLT2). In healthy individuals, ~180 g per day of glucose is filtered by the kidneys, almost all of which is reabsorbed via SGLT2.[5] In patients with T2DM, SGLT2 is overexpressed,[6] resulting in increased renal glucose reabsorption, which contributes to the maintenance of hyperglycemia.[7] Empagliflozin is a potent, selective SGLT2 inhibitor[8] in clinical development for the treatment of T2DM. Empagliflozin exhibits linear pharmacokinetics, and ~11% to 19% of the administered dose is excreted unchanged in urine.[9] Empagliflozin increases urinary glucose excretion in healthy volunteers[9] and in patients with T2DM,[10,11] decreases plasma glucose levels in patients with T2DM,[10–13] and is well tolerated.[9–13] In addition, preliminary evidence suggests that empagliflozin reduces body weight[12,13] and systolic blood pressure (BP)[13] in patients with T2DM.

Patients with T2DM are at risk of developing cardiovascular (CV) complications and often have concurrent CV disease.[14–17] Hypertension is a common comorbid condition, estimated to be up to 3 times as common in patients with diabetes compared with individuals who do not have the disease.[18] Patients with diabetes have also been shown to be at increased risk of atrial fibrillation[19,20] and heart failure[21,22] and to have a 6 times higher risk of stroke.[23] Death rates due to CV disease in patients with diabetes are 3- to 4-fold higher than in individuals without diabetes.[14]

Verapamil is approved for the treatment of angina, arrhythmia, and essential hypertension.[24] It is an inhibitor of P-glycoprotein (P-gp) and is extensively metabolized by the cytochrome P-450 (CYP) 3A4,[25,26] CYP1A2,[27] CYP3A5,[26] and CYP2C8 enzymes,[26] as well as by demethylation and dealkylation reactions.[28] Approximately 70% of the administered verapamil dose is excreted as metabolites in urine,[28] 16% as metabolites in feces,[24] and 3% to 4% unchanged in urine.[28]

Ramipril is indicated for the treatment of hypertension and to reduce the risk of myocardial infarction, stroke, and CV-related death in patients at high risk of a major CV event.[29] Ramipril is almost completely metabolized via hepatic esterases to its active diacid metabolite, ramiprilat.[29] Approximately 60% of ramipril and its metabolites are eliminated in urine, with 40% recovered in feces.[29]

Digoxin is indicated for the treatment of mild to moderate heart failure and for the control of ventricular response rates in patients with chronic atrial fibrillation.[30] Digoxin is a P-gp substrate.[31] Studies have shown that 50% to 70% of the administered dose of digoxin is excreted unchanged in urine and 16% is metabolized in the liver via hydrolysis, oxidation, and conjugation to produce a number of metabolites.[30]

Given the CV comorbidities associated with T2DM, drugs used for the treatment of patients with T2DM are commonly coadministered with CV drugs. Three studies were undertaken to evaluate potential drug–drug interactions between empagliflozin and verapamil, ramipril, or digoxin in healthy volunteers.

METHODS

Subjects

Screening was performed up to 21 days before study drug administration in all studies. Healthy male and female volunteers aged 18 to 50 years (digoxin and verapamil studies) or 18 to 55 years (ramipril study) and with a body mass index in the range of 18.5 to 29.9 kg/m^2 were eligible to participate in these studies. Major exclusion criteria were: evidence of any clinically relevant concomitant disease; gastrointestinal, hepatic, renal, respiratory, CV, metabolic, immunologic, or hormonal disorders; history of relevant orthostatic hypotension, fainting spells, or blackouts; drug/alcohol abuse or regularly smoking >10 cigarettes/day; and any laboratory values outside of the reference range and of clinical relevance. Subjects in the verapamil study were excluded if they had systolic BP <90 mm Hg, pulse rate <50 beats/min, or any degree of atrioventricular block at screening. Subjects with a history of relevant low BP, supine systolic BP <110 mm Hg and diastolic BP <60 mm Hg at screening, or a history of angioneurotic edema were excluded from the ramipril study. Subjects in the digoxin trial were excluded if they had abnormal electrocardiogram (ECG) findings at screening (eg, heart rate <50 beats/min, atrioventricular block). All participants provided written informed consent before any study-related procedure.

Study Designs

All 3 trials were randomized, open-label, crossover studies in healthy volunteers. The study protocols were