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

approved by the local Independent ethics committee (the State Medical Council of Baden-Württemberg [Landesärztekammer Baden-Württemberg], Stuttgart, Germany) and the German Competent Authority (the Federal Institute for Drugs and Medical Devices [Bundesinstitut für Arzneimittel und Medizinprodukte], Bonn, Germany). The studies were conducted at the Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany, in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Verapamil Study

Subjects received 2 treatments: a single dose of empagliflozin 25 mg (treatment A) and a single dose of verapamil 120 mg with a single dose of empagliflozin 25 mg given 1 hour after verapamil administration (treatment B). Subjects were randomly assigned to 1 of 2 treatment sequences (AB or BA) with a washout period of ≥7 days between treatments. Subjects were screened before treatment A and attended an end-of-study examination 3 to 10 days after treatment B.

Ramipril Study

Subjects received 3 treatments: empagliflozin 25 mg once daily (QD) for 5 days (treatment A), ramipril (2.5 mg on day 1 and 5 mg QD on days 2–5) for 5 days (treatment B), and empagliflozin 25 mg QD with ramipril (2.5 mg on day 1 and ramipril 5 mg QD on days 2–5) for 5 days (treatment C). Subjects were randomly allocated to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA) with a washout period of ≥7 days between treatments. Subjects were screened before the first treatment period and attended an end-of-treatment examination ≤14 days after the last pharmacokinetic sampling of the last treatment period.

Digoxin Study

Subjects received 2 treatments: a single dose of digoxin 0.5 mg (treatment A) and empagliflozin 25 mg QD for 8 days with a single dose of digoxin 0.5 mg on day 5 (treatment B). Subjects were randomly allocated to 1 of 2 treatment sequences (AB or BA) with a washout period of ≥14 days between doses of digoxin. Subjects were screened before inclusion into the treatment phase and attended an end-of-treatment examination ≤14 days after the last pharmacokinetic sampling of the trial.

Safety Assessments

Adverse events (AEs) were monitored throughout the studies and coded by using the Medical Dictionary for Drug Regulatory Activities (version 13.1 [verapamil study] and version 14.0 [digoxin and ramipril studies]). The safety evaluation was based on the frequency of AEs, vital signs (BP and pulse rate), 12-lead ECGs, physical examinations, clinical laboratory tests, and an overall assessment of tolerability made by the investigator ("good," "satisfactory," "not satisfactory," or "bad") after every treatment period.

Verapamil Study

For treatment A, vital signs were measured at screening; for treatment B, they were measured on day 1 (2 hours pre-empagliflozin dose); at 0, 1, 4, and 24 hours post-empagliflozin dose; and at the end-of-study examination. Laboratory tests and ECGs were measured at screening and at the end-of-study examination.

Ramipril Study

Vital signs and ECGs were measured at screening and at the end-of-treatment examination. For treatments B and C, vital signs were also measured on day 1 (1 hour pre-dose and 2, 4, and 23.45 hours post-dose), day 2 (2 and 4 hours post-dose), days 3 and 4 (5 minutes pre-dose), and day 5 (15 minutes pre-dose and 12 hours post-dose); ECGs were also recorded on day 1 (1 hour pre-dose and 4 and 23.45 hours post-dose) and day 2 (4 hours post-dose). Laboratory tests were measured at screening and at the end-of-treatment examination.

Digoxin Study

Vital signs were measured at screening and at the end-of-treatment examination, 1.5 hours pre-dose, and 23.5 hours post-digoxin dose in treatment A, and on days 5 (1.5 hours pre-coadministered dose) and 6 (23.5 hours post-digoxin dose or 30 minutes pre-empagliflozin dose) in treatment B. ECG recordings were made at screening and at the end-of-treatment examination, at 1.5 hours predose, and 2, 4, 6, 10, and 23.5 hours post-digoxin dose in treatments A and B. Clinical laboratory tests were conducted at screening and at the end-of-treatment examination.

Sample Collection and Analysis

Verapamil Study

For both treatments A and B, empagliflozin plasma concentrations were measured pre-dose and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 72

hours post-dose. For treatment B, verapamil plasma concentrations were measured pre-dose and at 25, 49, and 73 hours post-dose.

Ramipril Study

Empagliflozin plasma concentrations were measured pre-dose and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours post-dose on the final day of dosing with treatments A and C. Ramipril and ramiprilat plasma concentrations were measured pre-dose and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours post-dose on the final day of dosing with treatments B and C. In addition, pre-dose concentrations of empagliflozin, ramipril, and ramiprilat were collected on days 1 to 4 of the respective treatments to evaluate attainment of steady state.

Digoxin Study

For both treatments A and B, digoxin plasma concentrations were measured pre-dose and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours post-dose. For treatment B, pre-dose plasma concentrations of empagliflozin were measured on day 1 and days 3 through 8.

Approximately 120 mL (verapamil study), 250 mL (ramipril study), and 116 mL (digoxin study) of blood was taken from each subject for pharmacokinetic analysis and laboratory tests. For quantification of empagliflozin, verapamil, ramipril, and ramiprilat plasma concentrations, 2.7 mL of blood was drawn into a tripotassium EDTA-coated blood-drawing tube. For quantification of digoxin plasma concentration, 2.7 mL of blood was drawn into a heparinized blood-drawing tube. Samples were centrifuged at 2000 to 4000 g and 4°C to 8°C for 10 minutes within 60 minutes of collection. Empagliflozin, digoxin, and verapamil plasma aliquots were stored at –20°C and ramipril/ramiprilat plasma aliquots at –70°C or lower until analysis.

Plasma concentrations of all analytes were determined by using a validated HPLC-MS/MS assay. The lower limit of quantification for empagliflozin in plasma was 1.11 nmol/L with linearity to 1110 nmol/L. The lower limits of quantification of verapamil, ramipril, ramiprilat, and digoxin were 1.0 mg/mL with linearity to 1000 ng/mL (verapamil), 0.05 ng/mL with linearity to 50 ng/mL (ramipril and ramiprilat), and 0.1 mg/mL with linearity to 50 ng/mL (digoxin). Results were calculated by using peak area ratios, and calibration curves were created by using weighted ($1/x^2$) quadratic regression.

Pharmacokinetic Assessments

The primary end points of the verapamil study were $AUC_{0-\infty}$ and C_{max} of empagliflozin. The primary end points of the ramipril study were AUC at steady state over a uniform dosing interval τ ($AUC_{\tau,ss}$) and C_{max} at steady state over a uniform dosing interval τ ($C_{max,ss}$) of empagliflozin, ramipril, and ramiprilat. The primary end points of the digoxin study were $AUC_{0-\infty}$ and C_{max} of digoxin. AUC_{0-tz} was used to estimate $AUC_{0-\infty}$. Other endpoints investigated were: T_{max} and terminal $t_{1/2}$ of verapamil, ramipril, ramiprilat, digoxin, and empagliflozin and the fraction of the digoxin dose excreted in urine over 96 hours (fe_{0-96}) and renal clearance over 24 hours ($CL_{R,0-24}$). Trough plasma concen-

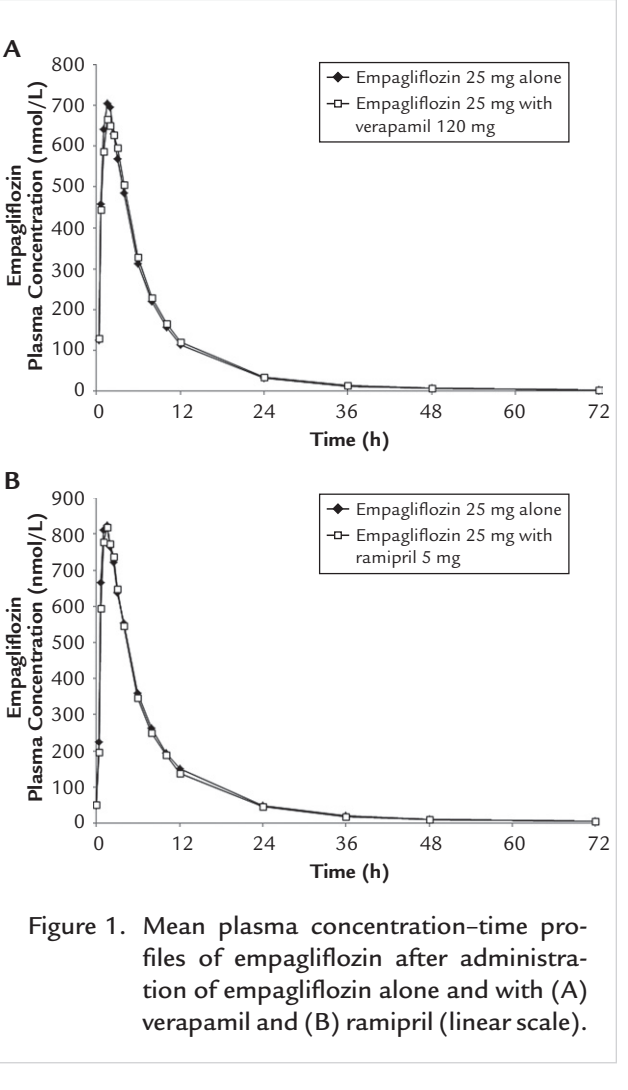

Figure 1. Mean plasma concentration–time profiles of empagliflozin after administration of empagliflozin alone and with (A) verapamil and (B) ramipril (linear scale).

trations of empagliflozin were investigated in the digoxin study.

Relative bioavailabilities were estimated on the basis of the geometric mean ratios (GMRs) and 90% CIs of the test (combination treatment) to reference (single administration) AUC and C_{max}. The linear trapezoidal rule for ascending concentrations and the log-trapezoid rule for descending concentrations were used to calculate AUC_{0-tz} (digoxin and verapamil studies), and $AUC_{0-\infty}$ values were estimated as the sum of AUC to the last measured concentration, with the extrapolated area given by the quotient of the predicted last measurable concentration and λz. Plasma concentration–time profiles of each subject were used to determine C_{max} and T_{max}. Non-compartmental pharmacokinetic analyses of the plasma concentration–time data were con-

Table I. Mean (%CV) pharmacokinetic parameters of empagliflozin, digoxin, ramipril, and ramiprilat.

Parameter	Treatment	
Empagliflozin	Empagliflozin alone	Empagliflozin + verapamil*
$AUC_{0-\infty}$, nmol · h/L	5330 (22.7)	5500 (25.4)
C_{max}, nmol/L	818 (27.7)	752 (27.2)
T_{max}, h†	1.50 (1.00–2.50)	1.75 (0.68–3.00)
$t_{1/2}$, h	12.5 (27.9)	13.6 (28.1)
	Empagliflozin alone	Empagliflozin + ramipril‡
$AUC_{0-\infty}$, nmol · h/L	5930 (16.8)	5750 (15.5)
C_{max}, nmol/L	899 (23.1)	929 (20.0)
T_{max}, h†	1.02 (0.67–3.00)	1.50 (1.00–4.00)
$t_{1/2}$, h	13.6 (40.2)	15.0 (43.2)
Digoxin	Digoxin alone	Digoxin + empagliflozin§
$AUC_{0-\infty}$, ng · h/mL	38.7 (23.7)	41.2 (25.9)
C_{max}, ng/mL	2.14 (40.3)	2.36 (31.7)
T_{max}, h†	1.00 (0.67–1.50)	1.00 (0.67–1.50)
$t_{1/2}$, h	68.7 (47.3)	55.4 (27.3)
fe_{0-96}, %	40.6 (24.7)	40.1 (22.3)
$CL_{R,0-24}$, mL/min	153 (14.5)	139 (18.8)
Ramipril	Ramipril alone	Ramipril + empagliflozin‡
$AUC_{\tau,ss}$, nmol · h/L	6.98 (32.8)	7.73 (35.4)
$C_{max,ss}$, nmol/L	9.18 (41.3)	10.0 (46.0)
$T_{max,ss}$, h†	0.33 (0.33–1.00)	0.33 (0.33–1.00)
$t_{1/2,ss}$, h	3.58 (72.1)	3.37 (85.1)
Ramiprilat	Ramipril alone	Ramipril + empagliflozin‡
$AUC_{\tau,ss}$, ng · h/mL	88.2 (15.4)	86.7 (20.2)
$C_{max,ss}$, ng/mL	11.9 (38.0)	11.6 (45.7)
$T_{max,ss}$, h†	2.00 (1.48–4.02)	2.00 (1.50–4.00)
$t_{1/2,ss}$, h	75.2 (24.6)	80.0 (34.2)

ss = steady state; fe_{0-96} = dose excreted in urine over 96 hours; $CL_{R,0-24}$ = renal clearance over 24 hours; $AUC_{\tau,ss}$ = AUC over a uniform dosing interval τ at steady state.
*Single dose of empagliflozin 25 mg with single dose of verapamil 120 mg.
†Median (range).
‡Multiple doses of empagliflozin 25 mg with multiple doses of ramipril 5 mg (2.5 mg on day 1); values at steady state.
§Multiple doses of empagliflozin 25 mg with a single dose of digoxin 0.5 mg.

ducted using WinNonlin software version 5.01 or 5.2 (Pharsight Corporation, Mountain View, California).

Statistical Analysis

The primary analyses were based on the pharmacokinetic analysis set (ie, all subjects who provided ≥1 observation for ≥1 primary pharmacokinetic end point, with no relevant protocol violations). Safety analyses were performed on the treated set (ie, all subjects who received ≥1 dose of study medication). A subject's data were excluded if the pre-dose concentration was >5% of the respective C_{max} in that subject. An ANOVA was used in all studies to determine log-transformed (ln) AUC and C_{max}. The ANOVA included "subjects within sequences" as a random effect and "sequence," "period," and "treatment" as fixed effects. Relative bioavailabilities were investigated by application of the average bioequivalence method to the ratio between AUC and C_{max} for each treatment. The difference between the expected means for log(test)–log(reference) was estimated by the difference in the corresponding least square means (point estimate). Two-sided 90% CIs based on the t distribution were calculated. These quantities were then back-transformed to the original scale to give the point estimator (GMR) and interval estimates for the median (verapamil study) and geometric mean (digoxin and ramipril studies) intrasubject ratio between response under test and reference conditions. Pharmacokinetic results are provided as mean or median values for each treatment period (not differences between treatments).

RESULTS

Study Population

Verapamil Study

Sixteen healthy volunteers (8 men and 8 women) were enrolled, treated, and completed the study. All subjects were white. Median (range) age, weight, and body mass index (BMI) were 31 (20–50) years, 71 (55–94) kg, and 23.75 (21.4–28.4) kg/m^2, respectively.

Ramipril Study

Twenty-three healthy volunteers (8 men and 15 women) were enrolled, and 22 subjects completed all 3 treatment periods. One subject discontinued the study after the first treatment period due to a knee ligament rupture. All subjects were white. Median (range) age, weight, and BMI were 43 (21–52) years, 69 (57–97) kg, and 24.6 (19.7–29.7) kg/m^2, respectively.

Digoxin Study

Twenty healthy volunteers (11 men and 9 women) were enrolled, treated, and completed the study. One subject was excluded from the pharmacokinetic analysis set (but included in safety analyses) because the predose plasma concentration of digoxin after treatment B in this subject was >5% of C_{max}. All subjects were white. Median (range) age, weight, and BMI were 35.5 (20–50) years, 76 (55–99) kg, and 23.9 (20.2–29.4) kg/m^2, respectively.

Pharmacokinetics of Empagliflozin

Mean plasma concentration–time profiles of empagliflozin were similar when administered alone and in

Table II. Pharmacokinetics of empagliflozin given alone and in combination with verapamil or ramipril.

				90% CI for GMR	
Parameter	Test	Reference	GMR (%)	Lower Limit (%)	Upper Limit (%)
Empagliflozin + verapamil study					
$AUC_{0-\infty}$	Empagliflozin + verapamil*	Empagliflozin	102.95	98.87	107.20
C_{max}	Empagliflozin + verapamil*	Empagliflozin	92.39	85.38	99.97
Empagliflozin + ramipril study					
$AUC_{\tau,ss}$	Empagliflozin + ramipril†	Empagliflozin	96.55	93.05	100.18
$C_{max,ss}$	Empagliflozin + ramipril†	Empagliflozin	104.47	97.65	111.77

GMR = geometric mean ratio; ss = steady state; $AUC_{\tau,ss}$ = AUC over a uniform dosing interval τ at steady state.
*Single dose of empagliflozin 25 mg with single dose of verapamil 120 mg.
†Multiple doses of empagliflozin 25 mg with multiple doses of ramipril 5 mg (2.5 mg on day 1).

combination with verapamil or ramipril (Figures 1A and 1B, respectively). Empagliflozin was rapidly absorbed, and after reaching peak levels, plasma concentrations declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. Pharmacokinetics of empagliflozin were similar when empagliflozin was administered alone or with verapamil or ramipril (Table I). Based on standard bioequivalence boundaries of 80% to 125%, the pharmacokinetics of empagliflozin were not affected by coadministration with verapamil or ramipril (Table II). In the ramipril and digoxin studies, trough levels of empagliflozin indicated that steady state was achieved by day 5 (data not shown).

Pharmacokinetics of Ramipril and Ramiprilat

Mean plasma concentration–time profiles of ramipril and ramiprilat were comparable when ramipril was given alone or with empagliflozin (Figures 2A and 2B). Mean (%CV) ramipril and ramiprilat $AUC_{\tau,ss}$, $C_{max,ss}$, $T_{max,ss}$, and $t_{1/2}$ were similar when ramipril was administered alone or with empagliflozin (Table I). Based on standard bioequivalence boundaries of 80% to 125%, the pharmacokinetics of ramipril and ramiprilat were not affected by coadministration with empagliflozin (Table III).

Pharmacokinetics of Digoxin

The mean plasma concentration–time profiles of digoxin were similar when administered alone or with empagliflozin (Figure 3). Based on standard bioequivalence boundaries of 80% to 125%, coadministration with empagliflozin had no relevant effect on the $AUC_{0-\infty}$ of digoxin (Tables I and III). Coadministration with empagliflozin resulted in a slight increase in digoxin C_{max} that was not considered clinically relevant. Digoxin T_{max} and $t_{1/2}$ were similar whether administered alone or with empagliflozin (Table I). Mean $CL_{R,0-24}$ of digoxin was similar with and without coadministration of empagliflozin (139 and 153 mL/min, respectively), as was mean fe_{0-96} (40.1% and 40.6%, respectively).

Safety and Tolerability

Verapamil Study

At least 1 AE was reported by 8 subjects (50.0%) with treatment A (single dose of empagliflozin 25 mg) and 9 subjects (56.3%) with treatment B (single dose of verapamil 120 mg with empagliflozin 25 mg). All AEs were of mild or moderate intensity. The most frequent AEs were headache (in 3 subjects with treatment A and 4 subjects with treatment B) and oral herpes (in 2 subjects with treatment B). Three AEs (dizziness, nausea, and constipation) reported with treatment B were considered by the investigator to be related to study drug. There were no discontinuations due to AEs, no serious AEs, and no clinically relevant changes in laboratory parameters, ECG, or vital signs. The overall tolerability assessment by the investigator was good for all subjects with treatment A and for 14 subjects with treatment B; 1 subject was assessed as 'satisfactory' and 1 as 'not satisfactory' with treatment B.

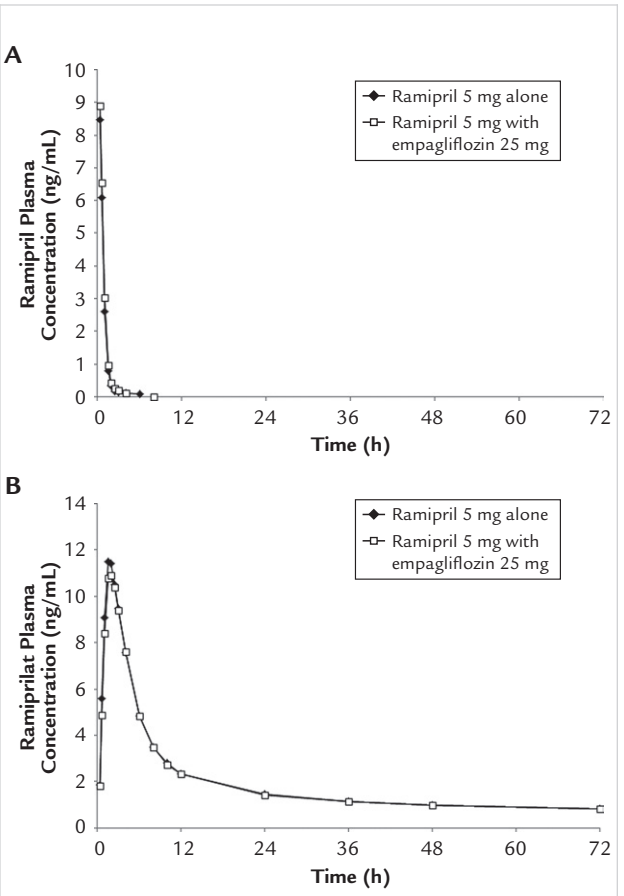

Figure 2. Mean plasma concentration–time profiles of (A) ramipril and (B) ramiprilat after administration of ramipril alone and with empagliflozin (linear scale).

Ramipril Study

At least 1 AE was reported by 3 subjects (13.6%) with treatment A (empagliflozin 25 mg QD for 5 days), 6 subjects (27.3%) with treatment B (ramipril 2.5 mg

Table III. Pharmacokinetics of digoxin, ramipril, and ramiprilat after administration of digoxin or ramipril alone and in combination with empagliflozin.

Parameter	Test	Reference	GMR (%)	90% CI for GMR	
				Lower Limit (%)	Upper Limit (%)
Digoxin					
$AUC_{0-\infty}$	Empagliflozin + digoxin*	Digoxin	106.11	96.71	116.41
C_{max}	Empagliflozin + digoxin*	Digoxin	113.94	99.33	130.70
Ramipril					
$AUC_{\tau,ss}$	Empagliflozin + ramipril†	Ramipril	108.14	100.51	116.35
$C_{max,ss}$	Empagliflozin + ramipril†	Ramipril	103.61	89.73	119.64
Ramiprilat					
$AUC_{\tau,ss}$	Empagliflozin + ramipril†	Ramipril	98.67	96.00	101.42
$C_{max,ss}$	Empagliflozin + ramipril†	Ramipril	98.29	92.67	104.25

GMR = geometric mean ratio; ss = steady state; $AUC_{\tau,ss}$ = AUC over a uniform dosing interval τ at steady state.
*Multiple doses of empagliflozin 25 mg with a single dose of digoxin 0.5 mg.
†Multiple doses of empagliflozin 25 mg with multiple doses of ramipril 5 mg (2.5 mg on day 1).

on day 1 and 5 mg QD on days 2–5), and 5 subjects (21.7%) with treatment C (empagliflozin 25 mg QD with ramipril for 5 days). The most common AEs were headache (in 3 subjects with treatment B and 1 subject with treatment A) and nausea (in 2 subjects with treatment C). One report of fatigue and 1 report of upper abdominal pain with treatment A, and both reports of nausea with treatment C, were considered by the investigator to be study drug related. All AEs were of mild or moderate intensity, except for 1 severe AE (hyperventilation) with treatment B. There were no serious AEs or discontinuations due to AEs, and no clinically relevant changes in laboratory parameters or ECG recordings. Treatment with ramipril and empagliflozin reduced systolic and diastolic BP by a mean (SD) of 10.7 (7.6) and 4.8 (5.4) mm Hg after 28 hours without signs or reports of hypotension. The overall tolerability assessment by the investigator was 'good' in all subjects after every treatment period.

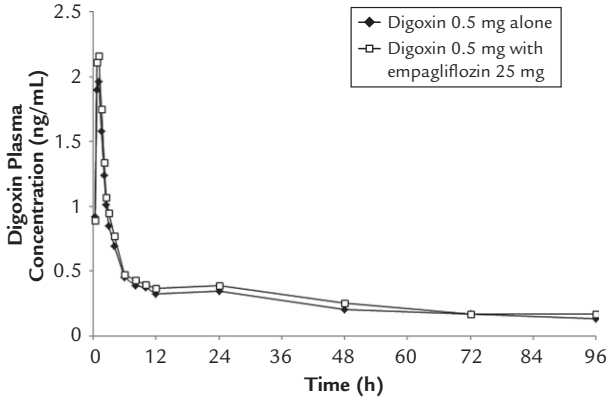

Figure 3. Mean plasma concentration–time profiles of digoxin after administration of digoxin alone and with empagliflozin (linear scale).

Digoxin Study

Three subjects (15.0%) reported ≥1 AE, all with treatment A (single-dose digoxin 0.5 mg). One subject reported mild headache and moderate fatigue, 1 subject reported moderate fatigue, and 1 subject reported a severe influenza-like illness. The reports of headache and fatigue were considered by the investigator to be study drug related. There were no serious AEs or AEs leading to discontinuation. There were no clinically significant changes in clinical laboratory values, ECG, or vital signs. The overall tolerability assessment by the investigator at the end of each treatment period was 'good' in all subjects.

DISCUSSION

The objective of the 3 studies presented here was to investigate any potential drug–drug interactions between empagliflozin and 3 commonly prescribed CV drugs, verapamil, ramipril, and digoxin.

Coadministration of verapamil did not affect the pharmacokinetics of empagliflozin. Because empagliflozin has been shown to be a P-gp substrate in vitro (data on file, Boehringer Ingelheim) and verapamil is a known P-gp inhibitor, the lack of drug–drug interaction between empagliflozin and verapamil indicates that there is no relevant effect of P-gp inhibition on the pharmacokinetics of empagliflozin. Coadministration of empagliflozin with ramipril had no relevant effect on the pharmacokinetics of either agent or ramiprilat, the active metabolite of ramipril. Coadministration with empagliflozin had no relevant effect on the $AUC_{0-\infty}$ of digoxin, yet resulted in a small increase in digoxin C_{max} that was not considered clinically relevant. Digoxin is a P-gp substrate that can be considered a probe to investigate the effects of P-gp inhibition,[32] as coadministration of digoxin with P-gp modulators results in marked changes in the renal elimination of digoxin.[33] The lack of clinically meaningful drug–drug interaction between empagliflozin and digoxin indicates that empagliflozin has no relevant effect on the pharmacokinetics of drugs that are P-gp substrates.

Coadministration of empagliflozin with verapamil, ramipril, or digoxin was well tolerated in all 3 drug–drug interaction studies.

CONCLUSIONS

No relevant drug–drug interactions were observed between empagliflozin and the commonly prescribed CV drugs, verapamil, ramipril, and digoxin. Based on standard bioequivalence boundaries, no dose adjustment of digoxin or ramipril is required when coadministered with empagliflozin, and no dose adjustment of empagliflozin is required when coadministered with verapamil or ramipril.

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CONFLICTS OF INTEREST

All authors are employees of Boehringer Ingelheim. These studies were funded by Boehringer Ingelheim.

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