Pharmacokinetics of Empagliflozin and Pioglitazone After Coadministration in Healthy Volunteers

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ABSTRACT

Purpose: The aim was to investigate the effects of coadministration of the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin with the thiazolidinedione pioglitazone.

Methods: In study 1, 20 healthy volunteers received 50 mg of empagliflozin alone for 5 days, followed by 50 mg of empagliflozin coadministered with 45 mg of pioglitazone for 7 days and 45 mg of pioglitazone alone for 7 days in 1 of 2 treatment sequences. In study 2, 20 volunteers received 45 mg of pioglitazone alone for 7 days and 10, 25, and 50 mg of empagliflozin for 9 days coadministered with 45 mg of pioglitazone for the first 7 days in 1 of 4 treatment sequences.

Findings: Pioglitazone exposure (C_{max} and AUC) increased when coadministered with empagliflozin versus monotherapy in study 1. The geometric mean ratio (GMR) for pioglitazone C_{max} at steady state ($C_{max,ss}$) and for AUC during the dosing interval at steady state ($AUC_{\tau,ss}$) when coadministered with empagliflozin versus administration alone was 187.89% (95% CI, 166.35%–212.23%) and 157.97% (95% CI, 148.02%–168.58%), respectively. Because an increase in pioglitazone exposure was not expected, based on in vitro data, a second study was conducted with the empagliflozin doses tested in Phase III trials. In study 2, pioglitazone exposure decreased marginally when coadministered with empagliflozin. The GMR for pioglitazone $C_{max,ss}$ when coadministered with empagliflozin versus administration alone was 87.74% (95% CI, 73.88%–104.21%) with empagliflozin 10 mg, 90.23% (95% CI, 66.84%–121.82%) with empagliflozin 25 mg, and 89.85% (95% CI, 71.03%–113.66%) with empagliflozin 50 mg. The GMR for pioglitazone $AUC_{\tau,ss}$ when coadministered with empagliflozin versus administration alone was 90.01% (95% CI, 77.91%–103.99%) with empagliflozin 10 mg, 88.98% (95% CI, 72.69%–108.92%) with empagliflozin 25 mg, and 91.10% (95% CI, 77.40%–107.22%) with empagliflozin 50 mg. The effects of empagliflozin on pioglitazone exposure are not considered to be clinically relevant. Empagliflozin exposure was unaffected by coadministration with pioglitazone. Empagliflozin and pioglitazone were well tolerated when administered alone or in combination. In study 1, adverse events were reported in 1 of 19 participants on empagliflozin 50 mg alone, 4 of 20 on pioglitazone alone, and 5 of 18 on combination treatment. In study 2, adverse events were reported in 8 of 20 participants on pioglitazone alone, 10 of 18 when coadministered with empagliflozin 10 mg, 5 of 17 when coadministered with empagliflozin 25 mg, and 6 of 16 when coadministered with empagliflozin 50 mg.

Implications: These results indicate that pioglitazone and empagliflozin can be coadministered without dose adjustments. EudraCT identifiers: 2008-006087-11 (study 1) and 2009-018089-36 (study 2). (*Clin Ther*. 2015;37:1503–1516)

Key words: diabetes, drug–drug interaction, SGLT2 inhibitor, thiazolidinedione.

INTRODUCTION

The aim of therapy for type 2 diabetes mellitus (T2DM) is long-term glycemic control; however,

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attainment of this goal can be elusive.[1] The continual decline in β-cell function over time means that most patients with T2DM will ultimately require >1 antidiabetic agent to maintain glycemic control.[2]

Empagliflozin is a potent and selective inhibitor of sodium glucose cotransporter 2 (SGLT2)[3] used in the treatment of T2DM. By inhibiting SGLT2, empagliflozin reduces renal glucose reabsorption and thus increases urinary glucose excretion, leading to a reduction in plasma glucose. Because its mechanism of action is independent of insulin, empagliflozin is associated with a low risk of hypoglycemia and can be used in combination with all other classes of antidiabetic agents.[4] Phase III trials have found that empagliflozin is effective at improving glycemic control and at reducing weight and blood pressure in patients with T2DM when used as monotherapy or add-on therapy to other antidiabetic agents.[5–9]

The pharmacokinetic properties of empagliflozin are similar in healthy volunteers and patients with T2DM.[10–12] Empagliflozin is rapidly absorbed, with peak plasma concentrations occurring after a median of ~1.5 hours.[11] Thereafter, plasma concentrations decline with a rapid distribution phase and a relatively slow terminal phase. The single-dose and steady-state pharmacokinetic properties of empagliflozin are similar, suggesting linear pharmacokinetic properties for time; systemic exposure to empagliflozin increases in a dose-proportional manner.[11,12] Empagliflozin undergoes limited metabolism, primarily glucuronidation, and is predominantly excreted unchanged in the urine and feces.[13] Empagliflozin is a substrate of organic anion-transporting polypeptide 1B1/1B3, organic anion transporter 3,[14] and P glycoprotein.[15]

Pioglitazone is an oral antidiabetic agent that selectively stimulates peroxisome proliferator-activated receptor γ, thus increasing the transcription of insulin-sensitive genes involved in the control of glucose and lipid metabolism. As a result, pioglitazone reduces insulin resistance in the liver and peripheral tissues.[16,17] Several studies have found that greater improvements in glycemic control can be achieved when pioglitazone is administered with other agents than with either agent alone.[18–25]

Pioglitazone is rapidly absorbed, reaching maximum plasma concentrations in ~1.5 hours. Plasma levels then decline biphasically with a terminal half-life of ~9 hours.[26,27] Pioglitazone is metabolized in the liver by cytochrome (CYP) 450 enzymes, mainly CYP2C8, which are known mediators of drug–drug interactions.[28] Six metabolites were described, 3 of which, M-II, M-III and M-IV, are pharmacologically active, although M-II concentrations are relatively low and do not contribute substantially to total pharmacologic activity.[27] Formation of the M-IV metabolite is catalyzed predominantly by CYP2C8, whereas M-III is a derivative of M-IV.[28]

No interaction between empagliflozin and pioglitazone was expected, because the metabolic/disposition pathways of empagliflozin and pioglitazone do not overlap,[13–15,28] and given that empagliflozin does not inhibit, inactivate, or induce the major CYP450 isozymes that can cause drug–drug interactions with pioglitazone (data on file). However, given the possibility that empagliflozin and pioglitazone may be administered together in clinical practice, we investigated the effect of empagliflozin on the pharmacokinetic properties of pioglitazone and its metabolites after coadministration in healthy volunteers.

METHODS

A randomized, open-label, crossover study was conducted in healthy volunteers to investigate the effects of coadministration of multiple doses of 50 mg of empagliflozin (the highest dose of empagliflozin investigated in dose-finding studies) and 45 mg of pioglitazone (the maximum recommended dose of pioglitazone) (study 1). Because of unexpected findings in this study, a second randomized, open-label, crossover study was conducted (study 2). In study 2, empagliflozin was administered at the doses under investigation in Phase III trials (10 and 25 mg) in addition to the 50 mg dose administered in study 1.

Participants

Male volunteers aged 18 to 50 years with a body mass index of 18.5 to 29.9 kg/m^2 and in good general health (according to medical history, physical examination, vital signs, 12-lead electrocardiogram [ECG], laboratory tests) were recruited for study 1. Volunteers were excluded if they had evidence or history of a clinically relevant concomitant disease, smoked or abused alcohol or drugs, or had participated in another trial with an investigational drug in the previous 2 months. The inclusion and exclusion criteria for participants in study 2 were the same as those for study 1, except that the upper age limit was 55 years.