ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Online - 2455-3891
Print - 0974-2441

Vol 10, Issue 7, 2017

Review Article

REVIEW ON PHARMACOKINETICS OF EMPAGLIFLOZIN, AN INHIBITOR OF THE SODIUM-GLUCOSE COTRANSPORTER-2

NERMEEN ASHOUSH[1,2]

[1]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, The British University in Egypt, El-Sherouk, Cairo, Egypt. [2]Head of Health Economics Unit, Center for Drug Research and Development, Faculty of Pharmacy, The British University in Egypt, El-Sherouk, Cairo, Egypt. Email: nermeen.ashoush@bue.edu.eg

Received: 21 February 2017, Revised and Accepted: 22 February 2017

ABSTRACT

Empagliflozin is an inhibitor of the sodium-glucose cotransporter-2 (SGLT-2), which is found almost exclusively in the proximal tubules of nephrotic components in the kidneys. SGLT-2 accounts for about 90% of glucose reabsorption into the blood. Blocking SGLT-2 reduces blood glucose by blocking glucose reabsorption in the kidney and thereby excreting glucose (i.e., blood sugar) via the urine. SGLT-2 inhibitors are an optional second-line therapy after metformin; they are generally well tolerated with low risk of hypoglycemia. The various compounds differ with respect to their pharmacokinetic properties; however, their clinical efficacy appears to be similar. The clinical differences between the various compounds stem from effects other than hypoglycemic effects, their safety and side effects profile. The aim of this review was to investigate the different pharmacokinetic studies of empagliflozin in a concise way in the form of tables.

Keywords: Empagliflozin, sodium glucose co-transporter-2 inhibitor, pharmacokinetics

 DOI: http://dx.doi.org/10.22159/ajpcr.2017.v10i9.18067

LITERATURE REVIEW

The type 2 diabetes is a chronic metabolic disorder triggered by insulin insensitivity and reduced level of insulin secretion. Insulin is a hormone that plays a key role in the transport of glucose to organs like the liver. Deficit production of insulin enhances the level of glucose in blood [1]. In addition to hyperglycemia, it leads to many other complications such as hyperlipidemia, hypertension, arthrosclerosis etc. It is estimated that there are 171 million people in the world with diabetes in year 2000 and this is likely to increase up to 366 million by 2030 [2].

The subject of this review is empagliflozin (BI 10773; 1-chloro-4-(β-d-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yl-oxy)-benzyl]-benzene; C23H27ClO7; molecular weight 450.9), an orally active, potent and selective inhibitor of SGLT2 being studied for the treatment of patients with T2DM [3], developed by Boehringer Ingelheim and Eli Lilly and Company. Phase III trials of empagliflozin given as monotherapy or in combination with oral antidiabetes drugs or insulin reported statistically significant and clinically relevant improvements in glycaemic control, body weight and systolic blood pressure when compared with placebo and active comparators [4]. Adverse events with SGLT2 inhibitors include increased rates of genital infection and urinary tract infection, which are attributed to elevated urinary glucose levels. More patients on empagliflozin than on placebo reported events consistent with genital infection; however, events consistent with urinary tract infection were comparable in both groups [5]. Empagliflozin is currently progressing through phase III clinical trials, while regulatory decisions are awaited for marketing applications recently submitted in the USA and Europe.

This review examines the pharmacokinetic characteristics of empagliflozin in healthy individuals, and in patients with T2DM treated with empagliflozin monotherapy (Table 1). An electronic literature

Table 1: Study design and major outcomes of different studies

Study design	Major outcomes
This study was undertaken to compare the steady state pharmacokinetic and pharmacodynamic properties of empagliflozin 5 mg twice daily (BID) and 10 mg once daily (QD) in healthy subjects. In an open-label, 2-way crossover study, subjects (n=16) received empagliflozin 5 mg BID for 5 days and empagliflozin 10 mg QD for 5 days in a randomized order, with a washout period of≥6 days between each treatment	There were no clinically relevant differences in pharmacokinetic or pharmacodynamic properties between BID and QD dose regimens of empagliflozin in healthy subjects. Both dose regimens were well tolerated [6]
The aim was to investigate the effects of coadministration of the SGLT2 inhibitor empagliflozin with the thiazolidinedione pioglitazone. 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	These results indicate that pioglitazone and empagliflozin can be coadministered without dose adjustments [7]
In a double-blind, placebo-controlled, parallel-group study, Chinese patients with T2DM were randomly assigned to receive a single dose of empagliflozin 10 or 25 mg or placebo on day 1 and once daily on days 3-9	Results with single and multiple doses of empagliflozin 10 and 25 mg suggest linear pharmacokinetic properties in Chinese patients with T2DM, with a safety profile similar to that of placebo. Empagliflozin treatment was associated with increases in UGE and reductions in FPG compared with placebo [8]

(*Contd...*)

Table 1: (Continued...)

Study design	Major outcomes
This was an open-label, crossover study. Patients with type 2 diabetes mellitus were randomized to receive empagliflozin 25 mg once daily for 5 days and either and HCTZ 25 mg once daily for 4 days followed by HCTZ 25 mg once daily plus empagliflozin 25 mg once daily for 5 days or TOR 5 mg once daily for 4 days followed by TOR 5 mg once daily plus empagliflozin once daily for 5 days in 1 of 4 sequences, with at least a 7-day washout period between treatments. Pharmacokinetic parameters of empagliflozin, HCTZ, and TOR were assessed, and standard bioequivalence criteria (80-125%) were applied. Tolerability assessments included the frequency of adverse events and an investigator assessment of global tolerability	No pharmacokinetic drug-drug interaction was observed between empagliflozin and HCTZ or TOR [9]
In an open-label, parallel group study, 32 Japanese patients with T2DM and different degrees of renal function (n=8 per renal function category: Normal renal function, estimated glomerular filtration rate [eGFR; Japanese equation] ≥90 mL/minutes/1.73 m^2; mild renal impairment, eGFR of 60-90 mL/minutes/1.73 m^2; moderate renal impairment, eGFR of 30-<60 mL/minutes/1.73 m^2; and severe renal impairment, eGFR of 15-<30 mL/minutes/1.73 m^2) received a single 25 mg dose of empagliflozin	Pharmacokinetic data suggest that no dose adjustment of empagliflozin is necessary in Japanese patients with T2DM and renal impairment because increases in exposure were<2-fold. Urinary glucose excretion decreased with increasing renal impairment [10]
In this open-label study, the effect of renal impairment on the pharmacokinetics, pharmacodynamics and safety of a 50-mg dose of empagliflozin was investigated in 40 subjects, grouped according to eGFR	Renal insufficiency resulted in decreased CL_R of empagliflozin, moderately increased systemic exposure and decreased UGE. A single 50 mg dose of empagliflozin was well tolerated in subjects with normal renal function and any degree of renal impairment. The pharmacokinetic results of this study indicate that no dose adjustment of empagliflozin is required in patients with renal impairment [11]
Two open-labels, 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 3rd 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 2nd day in 1 of 6 randomized treatment sequences	Increases in empagliflozin exposure were<2-fold, indicating that the inhibition of the OATP1B1/1B3, OAT3 transporter, and uridine diphosphate glucuronosyltransferases did not has a clinically relevant effect on empagliflozin exposure. No dose adjustments of empagliflozin were necessary when it was coadministered with gemfibrozil, rifampicin, or probenecid [12]
A total of 78 patients were assigned to empagliflozin 10 mg (n=16), 25 mg (n=16) or 100 mg (n=30), or placebo (n=16) for 28 days. Assessments included AEs and pharmacokinetic and pharmacodynamic endpoints	Oral administration of empagliflozin at doses of 10, 25, or 100 mg once daily over 28 days resulted in significant increases in UGE and reductions in blood glucose compared with placebo and were well tolerated in patients with type 2 diabetes [13]
This randomized, placebo-controlled within dose groups, double-blind, single rising dose study investigated the safety, tolerability, pharmacokinetics and pharmacodynamics of 1 mg to 100 mg doses of empagliflozin in 48 healthy Japanese male subjects	In conclusion, 1 mg to 100 mg doses of empagliflozin had a good safety and tolerability profile in healthy Japanese male subjects. Exposure to empagliflozin was dose proportional. The amount and rate of urinary glucose excretion were higher with empagliflozin than with the placebo and increased with empagliflozin dose [14]
A total of 16 healthy male volunteers received three treatments (A, B, and C) in one of two treatment sequences (AB then C, or C then AB). In treatment AB, 50 mg empagliflozin was administered once daily (q.d.) for 5 days (treatment A), immediately followed by coadministration of 50 mg empagliflozin q.d. and 100 mg sitagliptin q.d. over 5 days (treatment B). In treatment C, 100 mg sitagliptin was administered q.d. for 5 days. A washout period of≥7 days separated treatments AB and C	These results indicate that empagliflozin and sitagliptin can be coadministered without dose adjustments [15]

SGLT-2: Sodium-glucose cotransporter 2, HCTZ: Hydrochlorothiazide, TOR: Torasemide, eGFR: Estimated glomerular filtration rate, UGE: Urinary glucose excretion, and AEs: Adverse events

Table 2: Summary of the pharmacokinetic parameters

AUCτ, ss	Cmax, ss	fe	t½, ss,	Clearance	T maxx, ss	R*
Empagliflozin 5 mg BID Morning dose: Mean (% CV) - 1010 (15.1) nmol. h/L* Evening dose: Mean (% CV) - 867 (18.6) nmol. hour/L* Empagliflozin 10 mg QD: Mean (% CV) - 1900 (20.6) nmol. hour/L*	Empagliflozin 5 mg BID Morning dose: Mean (% CV) - 193 (16.5) Evening dose: Mean (% CV) - 120 (21.0) nmol/L Empagliflozin 10 mg QD: Mean (% CV) - 330 (25.3) nmol/L	ND	Empagliflozin 5 mg BID Morning dose: Mean (% CV) - hour† Evening dose: Mean (% CV) - 14.0 (55.4) hour Empagliflozin 10 mg QD mean (% CV) 13.6 (43.0) hour	ND	Empagliflozin 5 mg BID Morning dose: Median (range) - 1.0 (0.7-2.0) hour Evening dose: Median (range) - 2.0 (1.0-4.0) hour Empagliflozin 10 mg QD: Median (range) - (0.7-2.0) hour	[6]
Empagliflozin (n=18) Mean (% CV) - 8990 (12.4) nmol·hour/mL Empagliflozin + pioglitazone (n=17) Mean (% CV) - 8980 (10.5) nmol· h/mL	Empagliflozin (n=18) Mean (% CV) - 1370 (18.8) nmol/L Empagliflozin+pioglitazone (n=17) Mean (% CV) – 1280 (15.3) nmol/L	ND	Empagliflozin (n=18) Mean (% CV) - 8.6 (15.5) hour Empagliflozin+pioglitazone (n=17) Mean (% CV) - 11.7 (36.9) hour	ND	Empagliflozin (n=18) Median (range) - 1.7 (1.0-3.0) hour Empagliflozin+pioglitazone (n=17) Median (range) - 2.0 (1.5-3.0) hour	[7]
Single-dose period Empagliflozin 10 mg (n=9) AUC0-∞: Mean (% CV) - 2580 (12.4) nmol. h/L Empagliflozin 25 mg (n=9) AUC0-∞: Mean (% CV) - 7450 (26.3) nmol. h/L Multiple dose period Empagliflozin 10 mg (n=9) AUC t, ss: Mean (% CV) - 2680 (16.1) nmol. hour/L Empagliflozin 25 mg (n=9) AUC t, ss: Mean (% CV) - 7670 (21.7) nmol. h/L	Single-dose period Empagliflozin 10 mg (n=9) Cmax: Mean (% CV) - 439 (14.0) nmol/L Empagliflozin 25 mg (n=9) Cmax: Mean (% CV) - 1130 (28.2) nmol/L Multiple dose period Empagliflozin 10 mg (n=9) Cmax, ss: Mean (% CV) - 505 (25.0) nmol/L Empagliflozin 25 mg (n=9) Cmax, ss: Mean (% CV) - 1310 (36.1) nmol/L	Single-dose period Empagliflozin 10 mg (n=9) fe0-24: Mean (% CV) - 18.5 (17.6) Empagliflozin 25 mg (n=9) fe0-24: Mean (% CV) - 18.4 (23.8) Multiple dose period Empagliflozin 10 mg (n=9) fe0-24, ss: Mean (% CV) - 20.1 (14.8) Empagliflozin 25 mg (n=9) fe0-24, ss: Mean (% CV) - 21.4 (24.0)	Single-dose period Empagliflozin 10 mg (n=9) T1/2: Mean (% CV) - 9.62 (29.7) hour Empagliflozin 25 mg (n=9) T1/2: Mean (% CV) - 10.7 (21.6) hour Multiple dose period Empagliflozin 10 mg (n=9) T1/2, ss: Mean (% CV) - 13.9 (52.9) hour Empagliflozin 25 mg (n=9) T1/2, ss: Mean (% CV) - 12.1 (24.1) hour	Single-dose period Empagliflozin 10 mg (n=9) CLR, 0-48: Mean (% CV) - 29.5 (21.6) ml/minutes Empagliflozin 25 mg (n=9) T1/2: Mean (% CV) - 26.7 (31.5) ml/minutes Multiple dose period Empagliflozin 10 mg (n=9) T1/2, ss: Mean (% CV) - 28.1 (15.4) ml/minutes Empagliflozin 25 mg (n=9) T1/2, ss: Mean (% CV) - 27.2 (34.1) ml/minutes	Single-dose period Empagliflozin 10 mg (n=9) tmax: Median (range) - 1.0 (0.7–2.0) hour Empagliflozin 25 mg (n=9) tmax: Median (range) - 1.5 (1.0-3.0) hour Multiple dose period Empagliflozin 10 mg (n=9) tmax, ss: Median (range) - 1.0 (0.7-2.0) hour Empagliflozin 25 mg (n=9) tmax, ss: Median (range) - 1.5 (1.0-2.5) hour	[8]
Empagliflozin 25 mg (n=21)** Mean (% CV) - 5090 (21.8) nmol. h/L Empagliflozin 25 mg+HCTZ 25 mg (n=10) †† Mean (% CV) - 5720 (24.1) nmol. h/L Empagliflozin 25 mg+TOR 5 mg (n=10) Mean (% CV) - 5340 (18.9) nmol. h/L	Empagliflozin 25 mg (n=21) ** Mean (% CV) 961 (23.1) nmol/L Empagliflozin 25 mg+HCTZ 25 mg (n=10) †† Mean (% CV) - 1070 (29.0) nmol/L Empagliflozin 25 mg+TOR 5 mg (n=10) Mean (% CV) - 969 (21.0) nmol/L	Empagliflozin 25 mg (n=21) ** Mean (% CV) - 19.4 (21.1) Empagliflozin 25 mg+HCTZ 25 mg (n=10) †† Mean (% CV) - 17.7 (30.0) Empagliflozin 25 mg+TOR 5 mg (n=10) Mean (% CV) - 18.0 (14.2)	Empagliflozin 25 mg (n=21) ** Mean (% CV) - 15.3 (47.4) hour Empagliflozin 25 mg+HCTZ 25 mg (n=10) †† Mean (% CV) - 14.8 (18.1) hour Empagliflozin 25 mg+TOR 5 mg (n=10) Mean (% CV) -16.1 (14.4) hour	Empagliflozin 25 mg (n=21) ** Mean (% CV) - 36.7 (31.4) mL/minutes Empagliflozin 25 mg+HCTZ 25 mg (n=10) †† Mean (% CV) - 30.2 (36.0) mL/minutes Empagliflozin 25 mg+TOR 5 mg (n=10) Mean (% CV) - 32.5 (31.4) mL/minutes	Empagliflozin 25 mg (n=21) ** Median (range) - 1.5 (1.0-2.0) hour Empagliflozin 25 mg+HCTZ 25 mg (n=10) †† Median (range) - 1.5 (1.0-1.5) hour Empagliflozin 25 mg+TOR 5 mg (n=10) Median (range) - 1.0 (1.0-1.5) hour	[9]

(*Contd...*)

Table 2: (*Continued*)

AUCτ, ss	Cmax, ss	fe	t½, ss,	Clearance	T maxx, ss	R*
Normal renal function (n=8) AUC0-∞: Mean (% CV) -7560 (14.9) nmol. h/L Mild renal impairment (n=8) AUC0-∞: Mean (% CV) - 9730 (14.7) nmol. h/L Moderate renal impairment (n=8) AUC0-∞: Mean (% CV) - 10,800 (9.18) nmol. h/L Severe (n=8) renal impairment AUC0-∞: Mean (% CV) -12,200 (40.1) nmol. h/L	Normal renal function (n=8) Mean (% CV) - 1070 (18.1) nmol/L Mild renal impairment (n=8) Mean (% CV) - 1030 (34.4) nmol/L Moderate renal impairment (n=8) Mean (% CV) - 1000 (26.4) nmol/L Severe (n=8) renal impairment Mean (% CV) - 1070 (42.3) nmol/L	Normal renal function (n=8) fe0–96: Mean (% CV) - 19.1 (16.5)† †† Mild renal impairment (n=8) fe0-96: Mean (% CV) - 16.8 (19.7)† †† Moderate renal impairment (n=8) fe0-96: Mean (% CV) -14.6 (27.7) Severe (n=8) renal impairment fe0–96: Mean (% CV) -5.41 (45.3)‡	Normal renal function (n=8) t½: Mean (% CV) - 19.1 (56.7) hour Mild renal impairment (n=8) t½: Mean (% CV) - 18.4 (33.7) hour Moderate renal impairment (n=8) t½: Mean (% CV) - 24.3 (39.2) hour Severe (n=8) renal impairment t½: Mean (% CV) - 19.4 (44.7) hour	Normal renal function (n=8) CLR, 0-96: Mean (% CV) - 24.1 (25.3)† †† ml/ minutes Mild renal impairment (n=8) CLR, 0-96: Mean (% CV) - 16.4 (23.8) † †† ml/ minutes Moderate renal impairment (n=8) CLR, 0-96: Mean (% CV) - 13.2 (33.3) ml/ minutes Severe (n=8) renal impairment CLR, 0-96: Mean (% CV) - 4.45 (47.4) ‡ ml/ minutes	Normal renal function (n=8) Median (range) - 2.50 (1.00–2.50) hour Mild renal impairment (n=8) Median (range) - 2.50 (1.00-4.00) hour Moderate renal impairment (n=8) Median (range) - 2.50 (0.667-6.00) hour Severe (n=8) renal impairment Median (range) - 3.25 (1.00-6.00) hour	[10]
Normal renal function (eGFR>90 ml/ minutes/1.73 m²) Mean (% CV) - 10 600 (16.4) nmol. h/L Mild renal impairment (eGFR 60-89 ml/minutes/1.73 m²) Mean (% CV) - 12 700 (20.8) nmol. h/L Moderate renal impairment (eGFR 30-59 ml/minutes/1.73 m²) Mean (% CV) - 13 000 (25.1) nmol. hour/L Severe renal impairment (eGFR<30 ml/ minutes/1.73 m²) Mean (% CV) -17 700 (17.8) nmol. h/L Renal failure/ ESRD (requiring dialysis) Mean (% CV) - 16 600 (38.7) nmol. hour/L	Normal renal function (eGFR>90 ml /minutes/1.73 m²) Mean (% CV) - 1240 (23.5) nmol/l Mild renal impairment (eGFR 60-89 ml/minutes/1.73 m²) Mean (% CV) - 1500 (29.4) nmol/l Moderate renal impairment (eGFR 30-59 ml/minutes/1.73 m²) Mean (% CV) - 1290 (37.9) nmol/l Severe renal impairment (eGFR<30 ml/minutes/1.73 m²) Mean (% CV) - 1520 (31.6) nmol/l Renal failure/ESRD (requiring dialysis) Mean (% CV) - 1290 (27.5) nmol/l	Normal renal function (eGFR>90 ml/ minutes/1.73 m²) fe0-96: Mean (% CV) - 16.1 (26.7) Mild renal impairment (eGFR 60-89 ml/minutes/1.73 m²) fe0-96: Mean (% CV) - 11.7 (36.4) Moderate renal impairment (eGFR 30-59 ml/minutes/1.73 m²) fe0-96: Mean (% CV) - 7.7 (70.1) Severe renal impairment (eGFR<30 ml/ minutes/1.73 m²) fe0-96: Mean (% CV) - 3.6 (36.1) Renal failure/ ESRD (requiring dialysis) fe0-96: Mean (% CV) - 0.3 (56.4)	Normal renal function (eGFR>90 ml/ minutes/1.73 m²) Mean (% CV) - 19.9 (58.8) hour Mild renal impairment (eGFR 60-89 ml/minutes/1.73 m²) Mean (% CV) - 24.6 (84.5) hour Moderate renal impairment (eGFR 30-59 ml/minutes/1.73 m²) Mean (% CV) - 23.8 (87.9) hour Severe renal impairment (eGFR<30 ml/ minutes/1.73 m²) Mean (% CV) - 27.9 (76.8) hour Renal failure/ ESRD (requiring dialysis) Mean (% CV) - 22.0 (74.3) hour	Normal renal function (eGFR>90 ml/ minutes/1.73 m²) CLR, 0-96: Mean (% CV) - 28.5 (20.5) ml/ minutes Mild renal impairment (eGFR 60-89 ml/ minutes/1.73 m²) CLR, 0-96: Mean (% CV) - 18.6 (46.9) ml/ minutes Moderate renal impairment (eGFR 30-59 ml/minutes/1.73 m²) CLR, 0-96: Mean (% CV) - 11.8 (69.6) ml/minutes Severe renal impairment (eGFR<30 ml/ minutes/1.73 m²) CLR,0-96: Mean (% CV) - 4.0 (30.6) ml/minutes Renal failure/ ESRD (requiring dialysis) CLR, 0-96: Mean (% CV) -0.5 (59.1) ml/minutes	Normal renal function (eGFR>90 ml/minutes/1.73 m²) Median (range) - 1.0 (1.0-3.0) hour Mild renal impairment (eGFR 60-89 ml/minutes/1.73 m²) Median (range) - 2.5 (2.0-4.0) hour Moderate renal impairment (eGFR 30-59 ml/minutes/1.73 m²) Median (range) - 2.0 (1.5-3.0) hour Severe renal impairment (eGFR<30 ml/minutes/1.73 m²) Median (range) 2.0 (0.7-4.0) hour Renal failure/ESRD (requiring dialysis) Median (range) - 2.5 (1.5-3.0) hour	[11]

(*Contd...*)

Table 2: (*Continued*)

AUCτ, ss	Cmax, ss	fe	t½, ss,	Clearance	T maxx, ss	R*
Empagliflozin alone AUC0-∞: Mean (% CV) - 2330 (31.4) nmol. hour/L Empagliflozin and rifampicin AUC0-∞: Mean (% CV) - 3150 (32.9) nmol. hour/L Empagliflozin and probenecid AUC0-∞: Mean (% CV) - 3540 (33.1) nmol. h/L	Empagliflozin alone Cmax: Mean (% CV) - 313 (27.7) nmol/l Empagliflozin and rifampicin Cmax: Mean (% CV) - 546 (29.0) nmol/l Empagliflozin and probenecid Cmax: Mean (% CV) - 389 (29.6) nmol/l	Empagliflozin alone fe0-72: Mean (% CV) - 19.7 (21.2) % of dose Empagliflozin and rifampicin fe0-72: Mean (% CV) - Not determined % of dose Empagliflozin and probenecid fe0-72: Mean (% CV) - 13.8 (25.7) % of dose	Empagliflozin alone t1/2: Mean (% CV) - 11.8 (34.2) hour Empagliflozin and rifampicin t1/2: Mean (% CV) - 7.53 (21.4) hour Empagliflozin and probenecid t1/2: Mean (% CV) - 13.0 (23.1) hour	Empagliflozin alone CLR,0-72: Mean (% CV) - 32.7 (18.7) ml/ minutes Empagliflozin and rifampicin CLR,0-72: Mean (%CV) - Not determined ml/minutes Empagliflozin and probenecid CLR,0-72: Mean (% CV) -15.2 (25.8) ml/ minutes	Empagliflozin alone tmax: Median (range) - 1.50 (1.00-3.00) hour Empagliflozin and rifampicin tmax: Median (range) - 1.00 (0.67-1.50) hour Empagliflozin and probenecid tmax: Median (range) - 1.50 (1.00-3.00) hour	[12]
Day 1 (single dose) Empagliflozin, 10 mg AUC0-24: Mean (% CV) - 1550 (16.2) nmol. hour/L Empagliflozin, 25 mg AUC0-24: Mean (% CV) - 3930 (22.9) nmol. hour/L Empagliflozin, 100 mg AUC0-24: Mean (% CV) - 15 900 (21.2) nmol. hour/L Day 28 (steady state) Empagliflozin, 10 mg AUCτ, ss: Mean (% CV) - 1870 (15.9) nmol. hour/L Empagliflozin, 25 mg AUCτ, ss: Mean (% CV) - 4740 (21.2) nmol. hour/L Empagliflozin, 100 mg AUCτ, ss: Mean (% CV) - 18 700 (25.2) nmol. hour/L	Day 1 (single dose) Empagliflozin, 10 mg Cmax: Mean (% CV) - 309 (45.2) nmol/L Empagliflozin, 25 mg Cmax: Mean (% CV) - 722 (20.0) nmol/L Empagliflozin, 100 mg Cmax: Mean (% CV) - 2630 (25.8) nmol/L Day 28 (steady state) Empagliflozin, 10 mg Cmax, ss: Mean (% CV) - 259 (24.8) nmol/L Empagliflozin, 25 mg Cmax, ss: Mean (% CV) - 687 (18.4) nmol/L Empagliflozin, 100 mg Cmax, ss: Mean (% CV) - 2390 (28.1) nmol/L	Day 1 (single dose) Empagliflozin, 10 mg fe0-24: Mean (% CV) - 12.5 (24.0) % Empagliflozin, 25 mg fe0-24: Mean (% CV) - 13.3 (24.5) Empagliflozin, 100 mg fe0-24: Mean (% CV) - 13.7 (34.1) Day 28 (steady state) Empagliflozin, 10 mg fe0-24, ss: Mean (% CV) - 18.3 (25.0) Empagliflozin, 25 mg fe0–24, ss: Mean (% CV) - 17.8 (17.8) Empagliflozin, 100 mg fe0–24, ss: Mean (% CV) - 17.5 (28.3)	Day 1 (single dose) Empagliflozin, 10 mg t1/2: Mean (% CV) - 8.8 (13.0) hour Empagliflozin, 25 mg t1/2: Mean (% CV) - 8.2 (14.9) hour Empagliflozin, 100 mg t1/2: Mean (% CV) - 8.7 (18.7) hour Day 28 (steady state) Empagliflozin, 10 mg t1/2, ss: Mean (% CV) - 13.2 (44.7) h Empagliflozin, 25 mg t1/2, ss: Mean (% CV) - 13.3 (32.6) hour Empagliflozin, 100 mg t1/2, ss: Mean (% CV) - 16.5 (47.9) hour	Day 1 (single dose) Empagliflozin, 10 mg CLR,0-24: Mean (% CV) - 30.1 (25.1) ml/ minutes Empagliflozin, 25 mg CLR,0-24: Mean (% CV) - 32.4 (28.1) ml/ minutes Empagliflozin, 100 mg CLR, 0-24: Mean (% CV) - 33.0 (39.3) ml/ minutes Day 28 (steady state) Empagliflozin, 10 mg CLR(τ-ss): Mean (% CV) - 37.0 (31.1) ml/ minutes Empagliflozin, 25 mg CLR(τ-ss): Mean (% CV) - 36.2 (26.3) ml/ minutes Empagliflozin, 100 mg CLR(τ-ss): Mean (% CV) - 36.5 (35.2) ml/ minutes	Day 1 (single dose) Empagliflozin, 10 mg tmax: Median (range) - 1.5 (1.0-2.5) hour Empagliflozin, 25 mg tmax: Median (range) - 1.5 (0.8-2.0) hour Empagliflozin, 100 mg tmax: Median (range) - 1.5 (0.8–3.0) hour Day 28 (steady state) Empagliflozin, 10 mg tmax, ss: Median (range) - 1.5 (1.0-4.0) hour Empagliflozin, 25 mg tmax, ss: Median (range) - 1.5 (0.8-3.0) hour Empagliflozin, 100 mg tmax, ss: Median (range) -1.5 (0.8-6.0) hour	[13]

(*Contd...*)

Table 2: (*Continued*)

AUCτ, ss	Cmax, ss	fe	t½, ss,	Clearance	T maxx, ss	R*
Empagliflozin 1 mg (n=6) AUC0-∞: Mean (% CV) - 266 (23.1) nmol. hour/L Empagliflozin 5 mg (n=6) AUC0-∞: Mean (% CV) - 1,140 (10.2) nmol. hour/L Empagliflozin 10 mg (n=6) AUC0-∞: Mean (% CV) - 2,670 (10.6) nmol. hour/L Empagliflozin 25 mg (n=6) AUC0-∞: Mean (% CV) - 6.180 (13.4) nmol. hour/L Empagliflozin 100 mg (n=6) AUC0-∞: Mean (% CV) - 22,800 (25.5) nmol. hour/L Empagliflozin 10 mg+OGTT (n=6) AUC0-∞: Mean (% CV) - 3000 (14.1) nmol. hour/L	Empagliflozin 1 mg (n=6) Cmax: Mean (% CV) - 36.6 (23.9) nmol/L Empagliflozin 5 mg (n=6) Cmax: Mean (% CV) - 166 (26.6) nmol/L Empagliflozin 10 mg (n=6) Cmax: Mean (% CV) - 379 (19.4) nmol/L Empagliflozin 25 mg (n=6) Cmax: Mean (% CV) - 661 (10.4) nmol/L Empagliflozin 100 mg (n=6) Cmax: Mean (% CV) - 2,980 (31.2) nmol/L Empagliflozin 10 mg+OGTT (n=6) Cmax: Mean (% CV) - 449 (28.9) nmol/L	Empagliflozin 1 mg (n=5) fe0–72: Mean (% CV) - 23.3 (13.0) Empagliflozin 5 mg (n=6) fe0-72: Mean (% CV) - 22.4 (9.97) Empagliflozin 10 mg (n=6) fe0-72: Mean (% CV) - 21.3 (14.7) Empagliflozin 25 mg (n=6) fe0-72: Mean (% CV) - 22.9 (16.7) Empagliflozin 100 mg (n=6) fe0-72: Mean (% CV) - 22.9 (17.7) Empagliflozin 10 mg+OGTT (n=5) fe0-72: Mean (% CV) - 29.4 (4.48)	Empagliflozin 1 mg (n=6) t1/2: Mean (% CV) - 7.76 (13.9) hour Empagliflozin 5 mg (n=6) t1/2: Mean (% CV) - 9.60 (19.9) hour Empagliflozin 10 mg (n=6) t1/2: Mean (% CV) - 9.88 (29.7) hour Empagliflozin 25 mg (n=6) t1/2: Mean (% CV) - 11.7 (30.1) hour Empagliflozin 100 mg (n=6) t1/2: Mean (% CV) - 11.6 (31.9) nmol/L Empagliflozin 10 mg+OGTT (n=6) t1/2: Mean (% CV) - 7.78 (12.7) hour	Empagliflozin 1 mg (n=5) CLR, 0-72: Mean (% CV) - 32.4 (20.2) ml/ minutes Empagliflozin 5 mg (n=6) CLR, 0-72: Mean (% CV) - 36.5 (9.57) ml/ minutes Empagliflozin 10 mg (n=6) CLR,0-72: Mean (% CV) - 29.9 (16.2) ml/ minutes Empagliflozin 25 mg (n=6) CLR,0-72: Mean (% CV) - 34.8 (16.8) ml/ minutes Empagliflozin 100 mg (n=6) CLR, 0-72: Mean (% CV) - 38.7 (19.0) ml/ minutes Empagliflozin 10 mg+OGTT (n=6) CLR, 0-72: Mean (% CV) - 35.3 (10.2) ml/ minutes	Empagliflozin 1 mg (n=6) tmax: Median (range) - 1.25 (1.00-2.00) hour Empagliflozin 5 mg (n=6) tmax: Median (range) - 2.00 (0.75-2.00) hour Empagliflozin 10 mg (n=6) tmax: Median (range) - 1.50 (1.00-3.00) hour Empagliflozin 25 mg (n=6) tmax: Median (range) - 2.00 (1.00-4.00) hour Empagliflozin 100 mg (n=6) tmax: Median (range) - 2.50 (0.75-4.00) nmol/L Empagliflozin 10 mg+OGTT (n=6) tmax: Median (range) - 1.75 (0.75-4.00) hour	[14]
50 mg empagliflozin q.d. administered alone AUCτ, ss: Mean (% CV) - 8.430 (20.9) nmol. hour/L 50 mg empagliflozin q.d. coadministered with 100 mg sitagliptin q.d. AUCτ, ss: Mean (% CV) - 9.280 (19.3) nmol. hour/L	50 mg empagliflozin q.d. administered alone Cmax, ss: Mean (% CV) - 1,180 (23.8) nmol/L 50 mg empagliflozin q.d. coadministered with 100 mg sitagliptin q.d. Cmax, ss: Mean (% CV) - 19.3 (16.8)	50 mg empagliflozin q.d. administered alone fe0-72: Mean (% CV) - 17.1 (18.0) 50 mg empagliflozin q.d. coadministered with 100 mg sitagliptin q.d. t1/2, ss: Mean (% CV) - 10.7 (26.8) hour	50 mg empagliflozin q.d. administered alone t1/2, ss: Mean (% CV) - 8.5 (19.0) hour 50 mg empagliflozin q.d. coadministered with 100 mg sitagliptin q.d. t1/2, ss: Mean (% CV) - 10.7 (26.8) hour	ND	50 mg empagliflozin q.d. administered alone tmax: Median (range) - 2.5 (1.0-4.0) hour 50 mg empagliflozin q.d. coadministered with 100 mg sitagliptin q.d. Cmax, ss: Mean (% CV) - 2.2 (0.7-4.0) hour	[15]

ND: Not determined. *5 mg BID: $AUC_{0-12, ss}$, 10 mg QD: $AUC_{0-24, ss}$, †Duration of sampling was not sufficient to estimate t½ after the morning dose. †††n ¼ 7, ‡n ¼ 6, SS: Steady state. $AUC_{\tau, ss}$: AUC during a dosing interval (τ) at steady state, C_{max}, ss: Cmax during a dosing interval at steady state, $t_{max, ss}$: Time to $C_{max, ss}$, and $t_{½, ss}$: Terminal elimination half-life at steady state. $AUC_{0-\infty}$: Area under the plasma concentration-time curve from time 0 extrapolated to infinity, CV: Coefficient of variation, fe_{0-24}: Fraction of empagliflozin excreted unchanged in the urine over 24 hours, $CL_{R,0-48}$: Renal clearance of empagliflozin over 48 hours after oral administration, and $C_{LR, ss}$: Renal clearance of empagliflozin at steady state. C_{max}: Maximum plasma concentration, t_{max}: Time from dosing to C_{max}, $t_{½}$: Terminal half-life, fe_{0-96}: Fraction of empagliflozin excreted unchanged in the urine over 96 hours, $CL_{R,0-96}$: Renal clearance of empagliflozin over 96 hours, f_{e0-72}: Fraction of the dose excreted in the urine over the time interval from 0 to the time of the last quantifiable data point (72 hours), $AU_{C0-24 (\tau, ss)}$, area under the concentration-time curve over 24 hours (at steady state), and $CL_{R, 0-24 (\tau, ss)}$, renal clearance over 24 hours (at steady state). AUC_{0-tz}, area under concentration-time curve of analyte in plasma over time interval from 0 to last quantifiable data point. fe_{0-72}: Fraction of empagliflozin excreted unchanged in the urine over 72 hours

search was performed on Scopus to identify relevant studies using the generic name 'empagliflozin', without date limits, published as English-language articles. All publications reporting pharmacokinetic and/or pharmacodynamic data on empagliflozinin humans were considered for this review (Table 2).

CONCLUSION

The type 2 diabetes is a chronic metabolic disorder triggered by insulin insensitivity and reduced level of insulin secretion. Insulin is a hormone that plays a key role in the transport of glucose to organs like the liver. Deficit production of insulin enhances the level of glucose in blood [1]. In addition to hyperglycemia, it leads to many other complications such as hyperlipidemia, hypertension, and atherosclerosis. It is estimated that there are 171 million people in the world with diabetes in year 2000 and this is likely to increase up to 366 million by 2030 [2].

After the literature review, empagliflozin was generally well tolerated. Renal impairment, hepatic impairment, heart failure, the other investigated drugs, and BMI had no meaningful effect on its pharmacokinetics, suggesting that dose adjustment is not required. Inspite of the available pharmacokinetic data in literature [3-12] and many analytical methods for determination of empagliflozin in tablets either alone or in combination with linagliptin or metformin [13-20], there are no methods available with full details regarding plasma extraction and analysis of empagliflozin in plasma samples to evaluate the pharmacokinetic parameters. The author will work on a future study dealing with the pharmacokinetic evaluation of empagliflozin accompanied with the detailed analytical procedure in collaboration with the Center for Drug Research and Development.

REFERENCES

1. Pandey N, Pathak R, Sharma N. Comparison of commercially available drugs for Type 2 diabetes with natural molecule from *Tinospora*. Int J Pharm Pharm Sci 2016;8(7):173-5.
2. Saini S, Sharma S. Antidiabetic effect of *Helianthus annuus* L., Seeds ethanolic extract in streptozotocin-nicotinamide induced Type 2 diabetes mellitus. Int J Pharm Pharm Sci 2013;5(2):382-7.
3. Powell DR, Smith M, Greer J, Harris A, Zhao S, DaCosta C, et al. LX4211 increases serum glucagon-like peptide 1 and peptide YY levels by reducing sodium/glucose cotransporter 1 (SGLT1)-mediated absorption of intestinal glucose. J Pharmacol Exp Ther 2013;345:250-9.
4. Rosenstock J, Jelaska A, Wang F, Kim G, Broedl U, Woerle H, *et al*. Empagliflozin as add-on to basal insulin for 78 weeks improves glycemic control with weight loss in insulin-treated (T2DM) [abstract no. 1102-P]. Diabetes 2013;62 Suppl 1:A285.
5. Kim G, Gerich JE, Salsali A, Hach T, Hantel S, Woerle HJ, *et al*. Empagliflozin (EMPA) increases genital infections but not urinary tract infections (UTIs) in pooled data from four pivotal phase III trials [abstract no. 74-LB]. Diabetes 2013;62 Suppl 1:LB21.
6. Macha S, Brand T, Meinicke T, Link J, Broedl UC. Pharmacokinetics and pharmacodynamics of twice daily and once daily regimens of empagliflozin in healthy subjects. Clin Ther 2015;37(8):1789-96.
7. Macha S, Mattheus M, Pinnetti S, Broedl UC, Woerle HJ. Pharmacokinetics of empagliflozin and pioglitazone after coadministration in healthy volunteers. Clin Ther 2015;37:1503-16.
8. Zhao X, Cui Y, Zhao S, Lang B, Broedl UC, Salsali A, *et al.* Pharmacokinetic and pharmacodynamic properties and tolerability of single-and multiple-dose once-daily empagliflozin, a sodium glucose cotransporter 2 inhibitor, in Chinese patients with Type 2 diabetes mellitus. Clin Ther 2015;37(7):1493-502.
9. Heise T, Mattheus M, Woerle HJ, Broedl UC, Macha, S. Assessing pharmacokinetic interactions between the sodium glucose cotransporter 2 inhibitor empagliflozin and hydrochlorothiazide or torasemide in patients with Type 2 diabetes mellitus: A randomized, open-label, cross- over study. Clin Ther 2015;37:793-803.
10. Sarashina A, Ueki K, Sasaki T, Tanaka Y, Koiwai K, Sakamoto W, *et al.* Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of empagliflozin, a sodium glucose cotransporter 2 inhibitor, in Japanese patients with Type 2 diabetes mellitus. Clin Ther 2014;36(11):1606-15.
11. Macha S, Mattheus M, Halabi A, Pinnetti S, Woerle HJ, Broedl UC. Pharmacokinetics, pharmacodynamics and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in subjects with renal impairment. Diabetes Obes Metab 2014;16(3):215-22.
12. Macha S, Koenen R, Sennewald R, Schöne K, Hummel N, Riedmaier S, *et al.* Effect of gemfibrozil, rifampicin, or probenecid on the pharmacokinetics of the SGLT2 inhibitor empagliflozin in healthy volunteers. Clin Ther 2014;36(2):280-90.e1.
13. Heise T, Seewaldt-Becker E, Macha S, Hantel S, Pinnetti S, Seman L, *et al.* Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with Type 2 diabetes. Diabetes Obes Metab 2013;15(7):613-21.
14. Sarashina A, Koiwai K, Seman LJ, Yamamura N, Taniguchi A, Negishi T, *et al.* Safety, tolerability, pharmacokinetics and pharmacodynamics of single doses of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in healthy Japanese subjects. Drug Metab Pharmacokinet 2013;28(3):213-9.
15. Brand T, Macha S, Mattheus M, Pinnetti S, Woerle HJ. Pharmacokinetics of empagliflozin, a sodium glucose cotransporter-2 (SGLT-2) inhibitor, coadministered with sitagliptin in healthy volunteers. Adv Ther 2012;29(10):889-99.
16. Ayoub BM. UPLC simultaneous determination of empagliflozin, linagliptin and metformin. RSC Adv 2015;5:95703-9.
17. Shyamala K, Nirmala K, Mounika J, Nandini B. Validated stability-indicating RP-HPLC method for determination of empagliflozin. Pharm Lett 2016;8:457-64.
18. Ayoub BM. Development and validation of simple spectrophotometric and chemometric methods for simultaneous determination of empagliflozin and metformin: Applied to recently approved pharmaceutical formulation. Der Pharma Chemica 2016;8:23-9.
19. Abdel-Ghany MF, Abdel-Aziz O, Ayad MF, Tadros MM. Comparative study between multivariate and univariate analysis of two antidiabetic combinations. J AOAC Int 2017
20. Ayoub BM. Development and validation of simple spectrophotometric and chemometric methods for simultaneous determination of empagliflozin and metformin: Applied to recently approved pharmaceutical formulation. Spectrochim Acta A Mol Biomol Spectrosc 2016;168:118-22.