Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20163202

Review Article

Empagliflozin: a wonder drug in preventing diabetic nephropathy and cardiovascular effects

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Received: 09 August 2016
Accepted: 10 September 2016

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ABSTRACT

Diabetes, a terrible disease, with highest incidence in world produces many complications which will end up in dreadful situations. Diabetes nephropathy is one of the complications which lead to dialysis, renal replacement. empagliflozin, sodium glucose cotransporter 2 inhibitors decreases plasma blood glucose level, HbA1C and weight by excreting glucose in urine. It by decreasing HbA1C results in decrease in complications of diabetes due to high blood sugar and fluctuating blood sugars. It decreases the blood pressure, arterial stiffness and vascular resistance. It decreases the risk factors of diabetic nephropathy like hyperglycemia and high blood pressure. It also decreases the diabetes-related glomerular hypertrophy, markers of renal inflammation, as well as mesangial matrix expansion and thus ameliorates the early signs of diabetic nephropathy. The efficacy in decreasing blood glucose levels was confirmed in four randomized placebo controlled studies. The safety concern was seen in studies were urinary and genital tract infections. It thus proves to be an efficient option for diabetes in preventing diabetes nephropathy and cardiovascular effects.

Keywords: Empagliflozin, Diabetic nephropathy, Diabetes, SGLT2

INTRODUCTION

Diabetes is one of the most dreadful diseases affecting mankind of all ages. According to a recent World Health Organization (WHO) report, India, with 32 million diabetic individuals in 2000, currently has the highest incidence of diabetes worldwide; these numbers are predicted to increase to 80 million by the year 2030.[1] Diabetic nephropathy (DN), which carries a heavy clinical and economic burden, is present in up to 40% of patients with type 2 diabetes mellitus.[2] Diabetic nephropathy, which is a progressive kidney disease caused by damage of capillaries in the glomeruli of kidney and characterized by nephrotic syndrome and diffuse scarring of glomeruli, is a prime reason for dialysis and renal replacement therapy in many developed countries.[3,5] Hyperglycemia and increased blood pressure levels are the main risk factors for the development of diabetic nephropathy which increases the risk of death due to cardiovascular causes.[4] Empagliflozin is one of the sodium glucose cotransporter 2 inhibitors and has shown a magnificent effect on lowering blood glucose level by excretion of glucose in urine and helps in decreasing blood pressure.[6,7] We have reviewed the literature on empagliflozin bringing to focus the mechanism of action, efficacy, safety and pharmacokinetics of this molecule.

Mechanism of action

Kidney mainly contributes to maintenance of blood glucose levels by reabsorption of glucose from glomerular filtrate to blood. All filtered glucose is reabsorbed into the blood by sodium - glucose cotransporters (SGLTs) along with facilitative glucose transporters (GLUTs) in the proximal tubule of nephron. As the plasma concentration of glucose exceeds 180 - 200 mg/dl these transporters cannot reabsorb glucose, glucose starts appearing in urine. This reabsorbed glucose in diabetes contributes to increased plasma sugar levels.

In diabetes there is increased expression of SGLT2 in the proximal convoluted tubular cells which leads to increased absorption of glucose raising the blood glucose levels.[9]

Table 1: Summary of findings in placebo controlled studies on Empagliflozin.

Study	Sample Size	Period of study	Study groups	Adjusted mean changes for HbA1C	Adverse effects	% of Adverse effects reported	% of urinary tract infections reported	% of genital tract infections reported
Hans-Ulrich Häring et al[11]	666	24 weeks	Empagliflozin 10 mg (n = 225),	-0.82% (p<0.001)	Urinary tract infections and genital infections	62.7%	10.3%	0.9%
			Empagliflozin 25 mg (n = 216) and	-0.77% (p<0.001)		67.9%	8.3%	2.7%
			Placebo (n = 225)	-0.17%		64.1%	8%	2.3%
Hans- Ulrich Haring et al[12]	637	24 weeks	Empagliflozin 10 mg (n = 217)	-0.70% (p<0.001)	Urinary tract infections and genital infections	49.5% – 57.1%	5.1%	4.7%
			Empagliflozin 25 mg (n = 213) or	-0.77% (p<0.001)			5.6%	3.7%
			Placebo (n = 207)	-0.13%		58.7%	4.9%	0%
Michael Roden et al[13]	899	24 weeks	Placebo (n = 228)	-	Urinary trials and genital infections	61%	Not Accessed	AN
			Empagliflozin 10 mg (n = 224)	-0.74% (p<0.0001)		55%	NA	NA
			Empagliflozin 25 mg (n = 224) or	-0.85% (p<0.0001)		60%	NA	NA
			Sitagliptin 100 mg (n = 223)	-0.73% (p<0.0001)		53%	NA	NA
E. Ferrannini[14]	408	12 weeks	Empagliflozin 5 mg,	-0.4% (p<0.0001)	Urinary tract infections, genital tract infections, pollakiuri, thirst, nasopharyngitis	29.1%	1.6%	2%
			Empagliflozin 10 mg	-0.5% (p<0.0001)				
			Empagliflozin 25 mg	-0.6% (p<0.0001)				
			Placebo/open-label metformin	+0.09%		32.9%	1.2%	0%

Empagliflozin is an SGLT2 inhibitor and inhibits reabsorption of glucose from filtrate into blood through SGLT2. This leads to excretion of glucose, decreasing plasma glucose concentration. It decreases average glucose levels in the blood leading to decrease in HbA1C levels with improving glycaemic control. Besides inhibiting glucose reabsorption, it also blocks sodium reabsorption from the proximal tubule of nephron to blood. It increases plasma renin angiotensin aldosterone system (RAAS) mediators resulting in diuresis leading to decrease in blood pressure both systolic and diastolic blood pressure.[10] It decreases arterial stiffness and vascular resistance by phleomorphic effects of SGLT2 inhibition.[11] The energy deficit resulting from excretion of calories into urine induces weight loss or has a weight-neutral effect. Its action does not depend on presence of insulin or insulin resistance or impairment of pancreatic β-cell function. It doesn't stimulate insulin release.

By decreasing blood glucose levels and blood pressure, the risks of developing diabetic nephropathy have been decreased resulting in prevention of diabetic nephropathy. It decreases the diabetes-related glomerular hypertrophy, markers of renal inflammation, as well as mesangial matrix expansion and thus ameliorates the early signs of diabetic nephropathy. It has been reported

to decrease the onset of renal disease and prolong the progression of severity of renal disease.

Efficacy

The efficacy of Empagliflozin was tested in four randomized placebo controlled clinical trials in diabetic individuals. (Table 1) the first three studies were conducted for 24 weeks whereas the last study for 12 weeks. All the above studies affirmed the significant decrease HbA1C levels by using empagliflozin when compared to placebo. The adverse effects reported in placebo group were more or less similar to empagliflozin groups. In the study of Han Ulrich et al reported significant decrease in mean daily glucose, weight and systolic pressure.[11] E. Ferrannini reported the decrease in body weight in empagliflozin group when compared to placebo groups.[14] All the above studies had shown the higher incidence of urinary tract infections and genital tract infections in empagliflozin group than that in Placebo group. One of the above studies had declared the occurrence of frequent hypoglycemic episodes in some individuals in empagliflozin study group due to excretion of glucose in urine frequently. All the above studies had positive insight towards usage of empagliflozin as add on therapy or as monotherapy for treating type II diabetes. The mechanism of action of empagliflozin also suggests that it has the potential to be used in combination with other oral antidiabetic agents as well as insulin to exert additive or synergic effects on lowering glucose levels in type 2 diabetes.

Safety

The drug empagliflozin had no devastating side effects reported in the studies except minor side effects of urinary and genital tract infections. Headache was also reported as a frequent side effect. These neither decrease the efficacy of drug nor create miserable conditions. These can be treated symptomatically. Sometimes hypoglycemic episodes are also being reported. As the empagliflozin efficacy is based on Glomerular filtration rate and depends on the kidney function, it is ideal to monitor the renal function frequently.

Pharmacokinetics

Empagliflozin has an excellent oral bioavailability. It has no interaction with food. Median time to reach maximum plasma concentration ranged from 1.5 to 2.1 hours.[24] It has a longer half-life (t½) of 13.1 hours allowing once daily administration.[24] There are no active metabolites. Renal clearance (CLR) over 72 hours ranged from 32.1 to 51.3 mL/min, and the cumulative fraction of empagliflozin excreted in urine (fe) over 72 hours ranged from 11.0 to 18.7%.[24] No drug-drug interactions were reported till date. Empagliflozin is co-administered with other medications commonly used in patients with type 2 diabetes mellitus. It is co-administered with other oral glucose-lowering agents (metformin, sitagliptin, linagliptin and glimepiride) in combination therapy of diabetes management.[16-19] It is also administered with cardiovascular/ antihypertensive compounds (diuretics, verapamil, ramipril and digoxin) and cholesterol lowering agent (simvastatin) in cases of diabetes with hypertension and diabetes with hyperlipidemia.[21,22] It can be administered with an anticoagulant (warfarin) and an oral contraceptive (ethinylestradiol/ levonorgestrel).[20,23] There is no effect of empagliflozin on the pharmacokinetics of the above drug and vice versa.

Current status and future directions

Currently empagliflozin is in use as a hypoglycemic agent for many patients suffering from diabetes mellitus. but there is a need to clear the efficacy of this drug in chronic renal failure as glomerular filtration rates decrease in it.

CONCLUSION

Empagliflozin, an SGLT2 inhibitor decreases blood glucose level thus reducing HbA1c. It also reduces arterial stiffness, vascular resistance and blood pressure. Excretion of glucose results in decrease in calories and weight loss. It has good safety profile with mild headache, urinary and genital tract infection. It has excellent oral bioavailability, longer $t^{1/2}$ allowing once daily administration with little or no drug-drug interactions. Nevertheless it is a wonder drug in preventing the complications of diabetes mellitus mainly diabetic nephropathy and cardiovascular side effects.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Mohan V, Deepa M, Deepa R, Shanthirani CS, Farooq S, Ganesan A, et al. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban South India - the Chennai Urban Rural Epidemiology Study CURES-17. Diabetologia. 2006;49:1175-8.
2. Parving HH, Mauer M, Ritz E. Diabetic nephropathy. In: Brenner BM (ed.) Brenner and rector's the kidney. 7th ed. Philadelphia, PA: WB Saunders; 2004:1777-818.
3. Diabetes nephropathy, 2016. Available at https://en.wikipedia.org/wiki/Diabetic_nephropathy. Accessed on 23 July 2016.
4. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care. 2005;28(1):164-76.
5. Mogensen CE, Christensen K, Vittinghus E. The stages in diabetic renal disease: with emphasis on the stage of incipient diabetic nephropathy. Diabetes 1983;32(Supplement 2):64-78.

6. Zinman B, Wanner C, Lachin JM, Fitchett D. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117-28.
7. Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes, Obesity and Metabolism. 2013;15(12):1154-60.
8. Fujita Y, Inagaki N. Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: clinical data and mechanism of action. Journal of Diabetes Investigation. 2014;5(3):265-75.
9. Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with noninsulin-dependent diabetes. Diabetes. 2005;54:3427-34.
10. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovascular Diabetology. 2014;13:28.
11. Häring HU, Merker L, Becker ES, Weimer M. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes. Diabetes Care. 2013;36(11):3396-404.
12. Häring HU, Merker L, Becker ES, Weimer M, Meinicke T, Broedl UC, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24- week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37(6):1650-9.
13. Roden M, Weng J, Eilbracht J. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Diabetes and Endocrinology. 2013;1(3): 208-19.
14. Ferrannini E, Seman L, Seewaldt-Becker E, Hantel S. A phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism 2013;15(8):721-8.
15. Cherney DZ, Perkins BA. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol. 2014;13(28):1475-2840.
16. Macha S, Dieterich S, Mattheus M, Seman LJ, Broedl UC, Woerle HJ. Pharmacokinetics of empagliflozin, a sodium glucose cotransporter-2 (SGLT2) inhibitor, and metformin following co-administration in healthy volunteers. Int J Clin Pharmacol Ther. 2013;51:132-40.
17. Brand T, Macha S, Mattheus M, et al. Pharmacokinetics of empagliflozin, a sodium glucose cotransporter-2 (SGLT-2) inhibitor, coadministered with sitagliptin in healthy volunteers. Adv Ther.2012;29:889–899.
18. Friedrich C, Metzmann K, Rose P, Mattheus M, Pinnetti S, Woerle HJ. A randomized, open-label, crossover study to evaluate the pharmacokinetics of empagliflozin and linagliptin after coadministration in healthy male volunteers. Clin Ther. 2013;35:A33-42.
19. Macha S, Mattheus M, Pinnetti S, Seman L, Woerle HJ. Pharmacokinetics of empagliflozin, a sodium glucose cotransporter 2 inhibitor, and glimepiride following co-administration in healthy volunteers: a randomised, open-label, crossover study. Diabetes Res Clin Metab. 2012;1:1-7.
20. Macha S, Rose P, Mattheus M, Pinnetti S, Woerle HJ. Lack of drug-drug interaction between empagliflozin, a sodium glucose cotransporter 2 inhibitor, and warfarin in healthy volunteers. Diabetes Obes Metab. 2013;15:316-23.
21. Macha S, Sennewald R, Rose P, Schoene K, Pinnetti S, Woerle HJ, et al. Lack of clinically relevant drug-drug interaction between empagliflozin, a sodium glucose cotransporter 2 inhibitor, and verapamil, ramipril, or digoxin in healthy volunteers. Clin Ther. 2013;35:226-35.
22. Macha S, Lang B, Pinnetti S. Lack of pharmacokinetic interaction between the sodium glucose cotransporter-2 (SGLT-2) inhibitor empagliflozin and simvastatin in healthy volunteers. J Diabetes Investig. 2012;3:228.
23. Macha S, Mattheus M, Pinnetti S. Effect of empagliflozin on the steady-state pharmacokinetics of ethinylestradiol and levonorgestrel in healthy female volunteers. Clin Drug Investig. 2013;33:351-7.

Cite this article as: Naveena T. Empagliflozin: a wonder drug in preventing diabetic nephropathy and cardiovascular effects. Int J Basic Clin Pharmacol 2016;5:1704-7.