Empagliflozin

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Glucose-lowering agents in the management of type 2 diabetes have targeted various organs including the pancreas, liver, muscle cells, adipose tissue and the gut. The latest addition to the armament of treatment options are the sodium-glucose cotransporter 2 (SGLT2) inhibitors, targeting the kidney, which plays a central role in glucose homeostasis.[1] Empaglifozin has been shown to be effective in reducing haemoglobin A1c (HbA1c), with the additional benefits of weight loss, blood pressure reductions, improved renal outcomes and a reduction in the risk of cardiovascular death.[2]

Indications

Empagliflozin is indicated to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise and is available in South Africa as Jardiance®.[3]

It is also indicated as add-on combination therapy with other glucose-lowering medicines, including metformin, thiazolidinediones, sulphonylureas, DPP4 inhibitors or insulin, when diet, exercise and glucose-lowering medicines do not provide adequate glycaemic control.[3]

Mechanism of action

Empagliflozin is a reversible, selective, inhibitor of SGLT2. SGLT2 is highly expressed in the kidney where it is responsible for reabsorption of 90% of glucose from the glomerular filtrate back into the circulation.[3,4] Patients with T2DM display markedly increased amounts of SGLT2 in the proximal renal tubular cells, leading to an increase in glucose reabsorption and hyperglycaemia.[4]

Empagliflozin reduces renal glucose reabsorption and improves glycaemic control in patients with T2DM. The amount of glucose excreted in the urine is dependent on blood glucose concentration and glomerular filtration rate (GFR). Empaglifozin decreases fasting and post-prandial blood glucose levels with a low risk of hypoglycaemia, since its glucose-lowering effect is independent of beta-cell function and insulin pathways.[3,5] The excess glucose excreted in the urine causes a mild osmotic diuresis that may contribute to a moderate but sustained reduction in blood pressure.

Pharmacokinetics

Empagliflozin is rapidly absorbed, reaching peak concentration levels 1.5 hours following oral administration. Although administration with a high-fat and high-calorie meal reduced absorption, changes were not considered to be clinically significant and empagliflozin may be administered with or without food.[3,5] Following oral administration, red blood cell partitioning was approximately 36,8% and plasma protein binding was 86,2%.

Empagliflozin undergoes minimal metabolism via glucuronidation and 41,2% is excreted (mostly unchanged) in the faeces, while approximately half of the 54,4% dose excreted in the urine, is excreted unchanged. The elimination half-life of empagliflozin is 12.4 hours.[3,5]

Dosing

The efficacy of empagliflozin is dependent on renal function and patients need to be assessed with regards to their hydration status and renal function before initiating treatment with empagliflozin.

The recommended starting dose for empagliflozin is 10 mg daily in the morning and may be increased to a maximum of 25 mg per day in patients who tolerate a 10 mg dose well, but require additional glycaemic control.

Renal insufficiency

No dose adjustment is required for patients with mild renal insufficiency (eGFR ≥ 60 ml/min/1,73 m^2). Empagliflozin is not recommended in patients with moderate to severe renal impairment (CrCl < 60 ml/min).

Hepatic insufficiency

Dose adjustments may be required for patients with severe hepatic impairment.

Elderly patients

No age-related dose adjustments are required. However, patients 75 years and older are at increased risk of volume depletion and therefore empagliflozin should be used with caution in this age group. Therapeutic use in patients older than 85 years of

age is limited and initiation of therapy with empagliflozin is not recommended in this population.

Efficacy

Empagliflozin effectively lowers blood glucose and provides additional clinical benefits including body weight and blood pressure reduction.[6] A meta-analysis that included 10 studies with 6 203 participants showed a reduction of 0.62% in HbA1c with the use of empagliflozin 10 mg daily and a 0.66% reduction with the use of 25 mg daily when compared to placebo.[6] Similar improvements in HbA1c were also observed in empagliflozin add-on therapy trials.[7] Empagliflozin 25 mg daily had hypoglycaemic efficacy similar to metformin or sitagliptin, without increasing the risk for hypoglycaemia.[6]

This meta-analysis also showed a weight reduction of 1.8 kg, a reduction in systolic blood pressure of 3.5 to 4.2 mmHg and a reduction of 1.2 to 1.8 mmHg in diastolic blood pressure.[5] Reductions in blood pressure and body weight were observed with both monotherapy and add-on therapy.[7,8]

A randomised controlled trial of patients with diabetes and established cardiovascular disease (EMPA-REG OUTCOME) has shown a lower risk of cardiovascular death with empagliflozin (3.7% risk) compared to a 5,9% risk seen with placebo.[5] The reduction in risk was present regardless of whether patients had baseline heart failure or not. This study also showed a 39% reduction in the risk of incident or worsening nephropathy with the use of empagliflozin compared to placebo.[5]

Safety

Contraindications

Empagliflozin should not be used for the treatment of Type 1 diabetes mellitus or ketoacidosis. Empagliflozin should not be used in patients with renal impairment (creatinine clearance < 60 ml/min), end-stage renal disease or in patients on dialysis.[3,5] Pregnancy, lactation and a history of hypersensitivity to empagliflozin or any of the excipients are also contraindications for use.

Warnings and special precautions

Increased risk of volume depletion

Empagliflozin can cause an osmotic diuresis due to the excretion of glucose and this can lead to symptomatic hypotension. Volume status should be corrected before starting patients on empagliflozin therapy. Patients at increased risk of hypotension include those who are 75 years and older, patients with low systolic blood pressure, patients with renal impairment and concomitant diuretic use.[5] In conditions that may lead to increased fluid loss such as gastrointestinal illness, careful monitoring of blood pressure and electrolytes is recommended and temporary interruption of empaglifolzin treatment should be considered until the fluid loss is corrected.[3]

Ketoacidosis

Cases of metabolic acidosis including ketoacidosis have been reported, may be serious, life-threatening or fatal and may require hospitalisation.[5] Symptoms of ketoacidosis include nausea, vomiting, anorexia, abdominal pain, malaise, shortness of breath, confusion, unusual fatigue or sleepiness and excessive thirst. Patients presenting with these symptoms should discontinue the use of empagliflozin (even if blood glucose levels are below 11 mmol/l) and the patient should be promptly evaluated for ketoacidosis and managed accordingly.[3] Treatment may require fluids, carbohydrate and insulin.[3]

Patients who are at increased risk of developing ketoacidosis include those with a reduced intake of food and fluids, patients on a very low carbohydrate diet, dose reductions in patients using insulin, patients with any pancreatic disease or disorder, patients with a low beta-cell reserve and patients abusing alcohol. In situations where prolonged fasting is required e.g. prior to surgery or due to illness, it is recommended to temporarily discontinue treatment with empagliflozin. Ketones in the blood and urine should be monitored frequently.[3,5]

Adverse effects

Although lower than with insulin, the most frequently occurring adverse event reported with the use of empaglifozin was hypoglycaemia. The risk of hypoglycaemia is increased when empagliflozin is used with insulin or insulin secretagogues such as the sulphonylureas. It may be necessary to lower the dose of insulin or the insulin secretagogue to reduce the risk of hypoglycaemia.[3]

Two network meta-analyses concluded that SGLT2 inhibitors and mostly empagliflozin increase the risk of non-fatal stroke, volume depletion and genital infection.[9]

Urinary tract infections, vaginal thrush, vulvovaginitis, balanitis and other genital infections, especially mycotic infections in females, have been reported as common adverse events with the use of empagliflozin. Genital infections occurred more frequently in females than in males.

Drug interactions

Empagliflozin does not inhibit, inactivate or induce CYP450 isoforms and no clinically meaningful interactions were observed when it was co-administered with other commonly used medicines. Empagliflozin may enhance the diuretic effect of thiazide and loop diuretics and may increase the risk of hypotension and dehydration.[3]

Important prescribing points

- Side-effects may include increased urination, increased thirst, nausea, upper respiratory infection and arthralgia[5]
- Advise patients to report any symptoms of ketoacidosis, hypotension, urinary tract or genital infections[5]
- Inform patients that urine glucose tests will test positive due to the mechanism of action of empagliflozin[5]

References

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