Dapagliflozin Induced Pancreatitis

Manish Gutch*1, Annesh Bhattacharya2, Sukriti Kumar1, Rajendra Kumar Pahan4, Rao Somedra Singh4

ABSTRACT
SGLT2 inhibitors are a new class of anti-diabetic drugs recently approved by the FDA which act by a novel beta cell independent mechanism. Acute pancreatitis is a very rare adverse effect of this group of drugs, with only three cases described so far in medical literature. Our case describes the occurrence of diabetic ketoacidosis precipitated by acute pancreatitis in a middle-aged diabetic individual who was recently started on therapy with Dapagliflozin. Timely diagnosis and management lead to complete recovery of the condition with no residual disabilities. This highlights the importance of awareness of this rare adverse effect associated with SGLT2 inhibitors to facilitate prompt detection, management and preventing morbidity.

Key words: Dapagliflozin, Acute pancreatitis, Diabetic ketoacidosis, Type 2 diabetes mellitus, Sodium-glucose co-transporter-2 (SGLT2) inhibitor.

INTRODUCTION
Acute Pancreatitis is an inflammatory condition of the pancreas characterised by pain abdomen along with elevated blood levels of pancreatic enzymes. Common precipitants of acute pancreatitis included gallstones, alcohol, hypertriglyceridemia, hypercalcemia and infections.1 Drugs have also been implicated as causative agents, the common ones being sulphonamides, tetracycline, diuretics and valproic acid.2 Diabetic medications are a rare cause of pancreatitis. Majority of the cases have been described with the use of GLP-1 analogues or DPP-4 inhibitors.3 SGLT-2 inhibitors are a new class of drugs which act by decreasing renal tubular reabsorption of glucose. Pancreatitis as a side effect is extremely rare, and has been described in only 3 cases so far with Canagliflozin. Here we describe a case of diabetic ketoacidosis precipitated by acute pancreatitis caused by Dapagliflozin in a middle-aged diabetic male who was recently started on therapy with this anti diabetic drug.

CASE SUMMARY
A 48 year old man presented to the outpatient department with diffuse pain abdomen, nausea, weakness and multiple episodes of vomiting since the last 4 days. He was a known diabetic who was previously taking metformin (500mg B.D.) and 7 days ago his primary physician added Dapagliflozin (10mg O.D.) in view of uncontrolled blood glucose levels. There was no history of fever, dysuria, cough or any symptoms attributable to any infection. There was no history of any similar episodes in the past. He took vegetarian diet, was physically active with no addiction to alcohol or smoking and was compliant with his medications.

On admission, he was conscious, oriented (Glasgow Coma Scale =15/15), was slight breathless and apprehensive due to pain and had the following vitals: Pulse rate = 120/min, Blood Pressure = 100/60 mm Hg, Temperature = 99°F, Respiratory Rate = 26/min with mild dehydration. We calculated his BMI to be 26.2. He had diffuse abdominal tenderness, mild to moderate in intensity, with no hepatosplenomegaly, palpable lump or any evidence of free fluid. His cardiac, respiratory and nervous system evaluation was within normal limits.

His laboratory investigations including an Arterital Blood Gas analysis revealed the following: Random blood glucose = 430 mg/dl (65-95mg/dl), Haemoglobin = 12 g/dl (13-16 g/dl), Total leucocyte count = 17,800/mm³ (N = 75%), L = 20%) (3,500-9,000/mm³), sodium = 132 mmol/l (135-145mmol/l), potassium = 4.1 mmol/l (3.5-5 mmol/l), chloride = 98 mmol/l (102-109 mmol/l), bicarbonate = 10mmol/l (22-26mmol/l), Creatinine = 1.1 mg/dl (0.6-1.2mg/dl), Urea = 34 mg/dl (7-20 mg/dl), Calcium (total) = 8.8 mg/dl (8.5-10 mg/dl), pH = 7.28 (7.38-7.42), pCO2 = 10 mm Hg (36-44 mm Hg), SpO2 = 97%, PO2 = 90 mm Hg (75-97.5 mm Hg), Lactate = 1 mmol/l (0.5-2.2 mmol/l), Amylase = 300U/L (20-100U/L), Lipase = 110 U/L (3-45U/L), ALT = 40U/L (7-40U/L), AST = 50U/L (10-40U/L), Triglycerides = 180mg/dl (30-200mg/dl), LDL Cholesterol = 100 mg/dl (N <100 mg/dl), HDL Cholesterol = 35 mg/dl (40-60 mg/dl). His urine sample was positive for glucose and 3+ for ketones (normally absent), while his HbA1C was 10.7% (4%-5.6%). β-Hydroxybutyrate levels in plasma were elevated at 300 µmol/L (60-170µmol/L). 12-lead electrocardiogram was within normal limits.

To rule out any source of infection, we ordered urine analysis, chest roentgenogram, blood and urine cultures which were un rewarding. Utrasound study of the abdomen showed the presence of gaseous shadows in the left hypochondrium, while presence of gall-bladder calculi or dilatation of the bile duct was ruled out.
The most common side effects reported with the use of Dapagliflozin by the FDA for therapeutic use in T2DM. They act by a beta cell independent mechanism by inhibiting the numerous second line anti-diabetic drugs available for the physician to choose from, the SGLT2 inhibitors are a new class of drugs recently introduced. Although Metformin has long been considered as the initial drug of choice for the treatment of Type 2 Diabetes Mellitus (T2DM), most patients require add-on therapy to obtain glycemic control. Amongst the numerous second line anti-diabetic drugs available for the physician to choose from, the SGLT2 inhibitors are a new class of drugs recently approved by the FDA (US Food and Drug Administration) for use in T2DM. They act by a beta cell independent mechanism by inhibiting SGLT2 transporters in the proximal renal tubule, thereby decreasing the reabsorption of glucose. Dapagliflozin, a member of this group of drugs, was approved in January 2014 by the FDA for therapeutic use in T2DM. The most common side effects reported with the use of Dapagliflozin are genital infections (commonest) and urinary tract infections while other rare ones include volume depletion, dyslipidaemia, back pain and increase in haematocrit. Some cases of bladder and breast cancer had been reported in the early studies, however the duration of Dapagliflozin use in these patients were too short to be attributed to these cancers. Pancreatitis as a side-effect of SGLT2 inhibitors is very rare. So far, only three case reports describe the occurrence of pancreatitis with the use of Canagliflozin (another SGLT2 inhibitor) and none have been reported with Dapagliflozin till date. The underlying mechanism of pancreatitis is not clear. It is likely to be an idiosyncratic reaction similar to other cases of drug-induced pancreatitis. Such unpredictable reactions are mediated by the immunologic and cytotoxic effects of the drug or its metabolites on the body. SGLT-2 inhibitors may also be associated with ketonuria and ketoadiposis per se without the development of pancreatitis. These drugs reduce the amount of glucose available for utilization by the body for energy utilization. Any precipitating factor like fasting reduced carbohydrate intake, poor gastrointestinal nutrient absorption or increased glucose demands (e.g., pregnancy) may shift the metabolism towards gluconeogenesis and subsequently ketogenesis. Besides SGLT-2 inhibitors also alter the insulin glucagon ratio resulting in relative insulinopenia causing ketosis.

Our patient was on long term metformin therapy following which Dapagliflozin was added due to poor glycaemic control. We ruled out recent infections, alcohol intake, hypertriglyceridaemia, gallstones and other probable causes of pancreatitis. A few case reports have described the probable role of metformin in causing pancreatitis during periods of renal insufficiency, however renal function tests in our patient were normal and this probability can be safely ruled out. There was no recurrence of pancreatitis following discontinuation of Dapagliflozin. Hence it can be concluded that the adverse effect was most likely associated with the use of Dapagliflozin. More research in this aspect is required to make physicians aware of this rare but treatable side effect of SGLT2 inhibitors provided timely intervention is initiated.

**CONCLUSION**

Causation of acute pancreatitis is an extremely rare complication of SGLT2 inhibitors with very few cases reported till date. The treating physician must be vigilant to detect signs and symptoms of acute pancreatitis in any patient who has recently been started on therapy with SGLT2 inhibitors.

**REFERENCES**

3. Cohen D. Reports of pancreatitis are 20–30 times more likely with GLP-1 drugs, analysis finds. BMJ. 2013;346:f2607.

**DISCUSSION**

Although Metformin has long been considered as the initial drug of choice for the treatment of Type 2 Diabetes Mellitus (T2DM), most patients require add-on therapy to obtain glycaemic control. Amongst the numerous second line anti-diabetic drugs available for the physician to choose from, the SGLT2 inhibitors are a new class of drugs recently approved by the FDA (US Food and Drug Administration) for use in T2DM. They act by a beta cell independent mechanism by inhibiting SGLT2 transporters in the proximal renal tubule, thereby decreasing the amount of filtered glucose reabsorbed and resulting in glycosuria. Dapagliflozin, a member of this group of drugs, was approved in January 2014 by the FDA for therapeutic use in T2DM. The most common side effects reported with the use of Dapagliflozin are genital infections (commonest) and urinary tract infections while other rare ones include volume depletion, dyslipidaemia, back pain and increase in haematocrit. Some cases of bladder and breast cancer had been reported in the early studies, however the duration of Dapagliflozin use in these patients were too short to be attributed to these cancers. Pancreatitis as a side-effect of SGLT2 inhibitors is very rare. So far, only three case reports describe the occurrence of pancreatitis with the use of Canagliflozin (another SGLT2 inhibitor) and none have been reported with Dapagliflozin till date. The underlying mechanism of pancreatitis is not clear. It is likely to be an idiosyncratic reaction similar to other cases of drug-induced pancreatitis. Such unpredictable reactions are mediated by the immunologic and cytotoxic effects of the drug or its metabolites on the body. SGLT-2 inhibitors may also be associated with ketonuria and ketoadiposis per se without the development of pancreatitis. These drugs reduce the amount of glucose available for utilization by the body for energy utilization. Any precipitating factor like fasting reduced carbohydrate intake, poor gastrointestinal nutrient absorption or increased glucose demands (e.g., pregnancy) may shift the metabolism towards gluconeogenesis and subsequently ketogenesis. Besides SGLT-2 inhibitors also alter the insulin glucagon ratio resulting in relative insulinopenia causing ketosis. Our patient was on long term metformin therapy following which Dapagliflozin was added due to poor glycaemic control. We ruled out recent infections, alcohol intake, hypertriglyceridaemia, gallstones and other probable causes of pancreatitis. A few case reports have described the probable role of metformin in causing pancreatitis during periods of renal insufficiency, however renal function tests in our patient were normal and this probability can be safely ruled out. There was no recurrence of pancreatitis following discontinuation of Dapagliflozin. Hence it can be concluded that the adverse effect was most likely associated with the use of Dapagliflozin. More research in this aspect is required to make physicians aware of this rare but treatable side effect of SGLT2 inhibitors provided timely intervention is initiated.

**CONCLUSION**

Causation of acute pancreatitis is an extremely rare complication of SGLT2 inhibitors with very few cases reported till date. The treating physician must be vigilant to detect signs and symptoms of acute pancreatitis in any patient who has recently been started on therapy with SGLT2 inhibitors.

**REFERENCES**

3. Cohen D. Reports of pancreatitis are 20–30 times more likely with GLP-1 drugs, analysis finds. BMJ. 2013;346:f2607.


