Acute pancreatitis associated with saxagliptin treatment presented by metabolic acidosis

The DPP-4 inhibitor, saxagliptin, was approved in the US and Europe both as monotherapy and in combination with metformin, sulphonylurea, thiazolidinedione or insulin. An increased risk of acute pancreatitis has been identified for all approved DPP-4 inhibitors. Patients treated with DPP-4 inhibitors should be informed of the characteristic symptoms of acute pancreatitis. A causative relationship between DPP-4 inhibitors and pancreatitis has not been established. Diabetes itself is a risk factor for pancreatitis. Other risk factors such as hypercholesterolaemia, hypertriglyceridaemia and obesity were also present in 51% of US cases.

We present the case of a type 2 diabetes (T2DM) patient who developed acute pancreatitis which was initially thought to be diabetic ketoacidosis (DKA) after Kombiglyze XR (saxagliptin combined with metformin slow release) therapy that reversed to normal after stopping the drug.

Case history
A 33-year-old man had a known case of T2DM for about five years, along with mild dyslipidaemia and hypertension. He was on regular treatment with metformin 500mg thrice daily, amlodipine + valsartan 5/160 once daily (od), and fenofibrate 300mg od; he drinks alcohol occasionally. Saxagliptin (Onglyza) 5mg od was added in February 2014; the patient was seen in the outpatient clinic a few months later. Subsequently, the treatment was changed to glimepiride and Kombiglyze XR (saxagliptin/metformin slow release). On October 2015, the patient was admitted to hospital with a history of breathlessness, dizziness, vomiting and palpitations. His investigations revealed: high blood glucose 538mg/dL, mildly elevated urea 9.4mmol/L and creatinine 141μmol/L, in addition to elevated CRP 99mg/L. Arterial blood gases showed pH 7.10, HCO₃⁻ 4.0, and high ketones in the urine. His last triglycerides checked were 5.54mmol/L and he was re-started on fenofibrate (having stopped the medication for a period of time).

The patient was treated as a case of DKA. However, reviewing the history, the patient admitted he had a history of abdominal pain and vomiting, thinking he had food poisoning prior to hospitalisation. This led to the consideration of acute pancreatitis: he had T2DM and so DKA would be unlikely in his case. Therefore, an abdominal ultrasound scan was done and showed irregular turbid fluid located around the pancreas, raising the possibility of acute pancreatitis. Serum amylase was done on the third day of admission and it was normal (96u/L). Further, his abdominal CT scan with contrast was done and showed signs of acute pancreatitis with evidence of necrotic changes in the tail of the pancreas, with excessive surrounding oedema and fluid extending from the retroperitoneal region around the tail of the pancreas to the anterior intraperitoneal region above the level of the transverse colon.

Islet-cell antibodies and glutamate decarboxylase antibodies were negative. Later, he was discharged home in a stable condition on metformin XR 750 twice a day and premixed insulin (NovoMix 30) 18 units am, 16 units pm.

Discussion
Pancreatitis is now included in the product information for all DPP-4 inhibitors as a possible adverse reaction. The reporting rate of pancreatitis appears to be low (ranging between 1/1000 and 1/100 patients receiving the drug), but the precise frequency is unknown as few cases have been reported in clinical trials. In most cases, pancreatitis resolved after discontinuation of treatment.

In 21% of the 88 reported cases in the US, pancreatitis occurred within 30 days of starting sitagliptin or metformin + sitagliptin. Hospitalisation was required in 66% of the patients. Upon discontinuation of sitagliptin, 55% of the 88 cases resolved.

The SAVOR-TIMI 53 trial examined the cardiovascular efficacy and safety of saxagliptin vs placebo in patients with or at risk for cardiovascular disease. The investigators reported 35 events of pancreatitis in each treatment arm in 63 patients (33 [0.40%] in the saxagliptin arm and 30 [0.37%] in the control arm), with a hazard ratio (HR) of 1.09 (95% CI 0.66–1.79; p=0.80). Adjudication confirmed pancreatitis in 24 patients (26 events) in the saxagliptin arm (0.29%) and in 21 patients (25 events) in the placebo arm (0.26%), with an HR of 1.13 (0.63–2.06; p=0.77). So, the risk for pancreatitis in T2DM patients treated with saxagliptin was low and apparently similar to placebo. However, the trial did not completely resolve the issue.

Conclusion
This case shows one needs to be vigilant in the use of DPP-4 inhibitors in high-risk patients who already have a high risk of pancreatitis. Acute pancreatitis should be in differential diagnosis in patients on DPP-4 inhibitors admitted with metabolic acidosis, hyperglycaemia and abdominal pain; even if criteria of diagnosis of DKA are met, consider other causes of metabolic acidosis such as pancreatitis in patients on DPP-4 inhibitors. Further studies are needed to completely resolve the pancreatic safety issues with incretin-based therapy.

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Declaration of interests
There are no conflicts of interest declared.

References
References are available in Practical Diabetes online at www.practicaldiabetes.com.
Diabetes vignette

Acute pancreatitis

References