Renal impairment with sitagliptin: is there a need for active monitoring of potential renal toxicity?

Introduction

Sitagliptin is the first oral antidiabetic agent within the recently introduced dipeptidyl peptidase 4 class. This article reports a novel case of severe sitagliptin-associated renal failure in a 71-year-old woman. In view of the limited data supporting the long-term safety of dipeptidyl peptidase 4 inhibitors the authors suggest that active monitoring of renal function should be considered following initiation of sitagliptin.

Discussion

The first dipeptidyl peptidase 4 inhibitor, sitagliptin, received Food and Drug Administration approval in 2006 and is now widely used in the treatment of type 2 diabetes mellitus. To date, limited evidence has suggested that sitagliptin can safely be used in patients with moderate to severe renal insufficiency. Animal studies, however, have demonstrated renal toxicity within this drug class, leading to withdrawal of the agnate compound, vildagliptin, from the US market. Additionally, renal impairment with related compounds, such as exenatide, has been described (Ferrer-Garcia et al, 2010).

Renal impairment with sitagliptin may arise either through direct renotoxic effect, or as a consequence of pre-renal failure secondary to gastrointestinal symptoms and subsequent dehydration. It was not possible to definitively establish whether renal impairment occurred solely as a result of direct renotoxicity in this case. However, given the relatively mild degree of clinically-apparent dehydration compared with the severity of biochemical disturbance at presentation, it is probable that a direct renal insult occurred, which was then exacerbated by uraemia and gastrointestinal upset.

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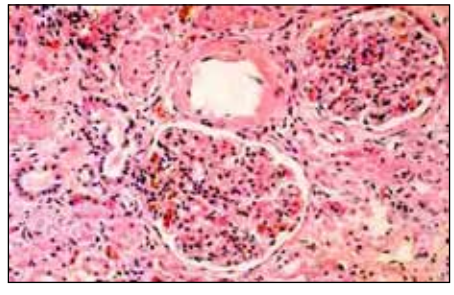
Active renal secretion is the primary means of sitagliptin excretion, and there is currently only limited evidence from open-label single-dose studies to suggest that this agent can safely be used in patients with renal insufficiency (Bergman et al, 2007). Acute renal impairment resulting from rhabdomyolysis in a patient receiving sitagliptin in association with a statin and amiodarone has been described (Kao et al, 2008). Interestingly, this patient also received a stable dose of statin in association with sitagliptin.

The risk of adverse interactions between statins and other drug classes is associated with polymorphisms in the organic anion-transporting polypeptide OATP1B1 gene sequence, which regulates hepatic uptake of statins (Link et al, 2008). As noted by Boucher (2009), investigating the potential predictive value of OATP1B1 polymorphisms in these patients may allow risk stratification in diabetic patients receiving concurrent statins and sitagliptin.

Furthermore, work in rodents has demonstrated direct effects of sitagliptin on the renal vasculature, suggesting that sitagliptin may lead to a potentially detrimental enhancement of renal angiotensin II sensitivity in individuals with metabolic syndrome (Tofovic et al, 2010). Studies examining the long-term effects of dipeptidyl peptidase 4 inhibitors on renal physiology in humans are eagerly awaited.

Renal impairment induced directly by sitagliptin appears to be relatively rare when compared to other adverse events, such as nausea, vomiting, abdominal pain, flu-like symptoms and acute pancreatitis (Chan et al, 2008; Olansky, 2010). Importantly, gastrointestinal upset may precipitate indirect renal toxicity through a pre-renal mechanism in patients who continue to take sitagliptin despite symptoms as occurred in this case. The diabetic population are at particular risk of renal insufficiency, and gastrointestinal symptoms should therefore be considered as a

Figure 1. Renal biopsy demonstrating glomerular sclerosis, tubular atrophy and moderate interstitial cellular infiltrate consistent with persistent renal scarring.



Case Report

A 71-year-old woman presented with a 4-week history of gradual onset nausea, vomiting and general malaise. She had a history of type 2 diabetes mellitus, hypertension, hypothyroidism and hypercholesterolaemia. The patient had received stable doses of aspirin, gliclazide, metformin, levothyroxine, simvastatin, losartan, bendroflumethiazide and omeprazole for 5 years. She had been converted 8 weeks before admission from rosiglitazone to sitagliptin 100 mg daily. There was no history of use of any non-steroidal anti-inflammatory drug or herbal remedy. Renal function at the time of hospital admission had significantly deteriorated (creatinine 667 μmol/litre, estimated glomerular filtration rate 5 ml/min/1.73m^2) from baseline figures obtained over the previous 5 years (creatinine 109 μmol/litre, estimated glomerular filtration rate 43 ml/min/1.73m^2). There was no history of myalgia suggestive of rhabdomyolysis and creatine kinase was not significantly raised (44 u/litre).

Renal function gradually improved following withdrawal of all medications except aspirin, and stabilized after 28 days with a persistent impairment consistent with stage IV chronic kidney disease (creatinine 290 μmol/litre, estimated glomerular filtration rate 16 ml/min/1.73m^2). Once stable, all medications other than sitagliptin were reinstated, with no further deterioration in renal function over the subsequent 6 months. Renal biopsy at 6 months demonstrated marked tubulointerstitial and global glomerular scarring (*Figure 1*).

potential indication for cessation of treatment with sitagliptin. Patients should certainly be counselled that such symptoms necessitate contact with their health-care provider for immediate advice.

Conclusions

In view of the limited data supporting the long-term safety of dipeptidyl peptidase 4 inhibitors in the setting of renal impairment, and the potential for persistent renal impairment highlighted by this case, the authors suggest that deterioration of renal function should be actively monitored following initiation of these agents, and that this should be an explicit aim of post-marketing drug surveillance. **BJHM**

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LEARNING POINTS

- Sitagliptin is a dipeptidyl peptidase 4 licensed for use in type 2 diabetes mellitus. It is most often used as dual therapy with metformin, sulphonylurea or thiazolidinedione, but is also licensed as monotherapy, in triple therapy, and with insulin where adequate glycaemic control is not achieved.
- There is limited evidence to suggest that sitagliptin is safe in moderate to severe renal impairment in diabetic patients.
- The long-term outcomes of dipeptidyl peptidase 4 inhibitors have yet to be established.
- Sitagliptin may precipitate renal insufficiency through a potential direct renotoxic effect as well as indirectly through dehydration secondary to gastrointestinal upset. Monitoring of renal function should be considered in asymptomatic patients starting sitagliptin therapy, particularly in the presence of diabetic nephropathy, and gastrointestinal upset should be considered a potential indication for cessation of treatment given the risk of pre-renal failure.
- Patients with diabetes mellitus are particularly susceptible to renal impairment, and renal function should be closely monitored following the institution of a potentially renotoxic agent.