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Renal Failure and Rhabdomyolysis Associated With Sitagliptin and Simvastatin Use

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Abstract

Background—Sitagliptin is a new oral glucose lowering medication which acts via the incretin hormone system. The most common side effects are headache and pharyngitis, and few serious adverse events were observed during clinical trials. Dose adjustment is recommended in renal insufficiency, but long-term safety experience is limited.

Case Report—We present a patient with chronic renal insufficiency who developed leg pain, weakness, and tenderness after starting treatment with high dose sitagliptin while on simvastatin. The patient had acute renal failure and rhabdomyolysis which resolved with cessation of sitagliptin, simvastatin, ezetimibe, diuretics and olmesartan. All drugs except sitagliptin and ezetimibe, simvastatin were resumed, and the patient was subsequently started on lovastatin without recurrence of rhabdomyolysis.

Conclusions—High doses of sitagliptin may have worsened this patient's renal failure and precipitated rhabdomyolysis by increasing circulating levels of simvastatin. Given the high likelihood that sitagliptin will be co-administered with statins and renally active medications, further study of long-term safety of sitagliptin in renal sufficiency may be warranted.

Introduction

Sitagliptin, a new oral glucose lowering medication, is already used widely for treatment of type 2 diabetes mellitus. It inhibits the dipeptidyl-peptidase IV enzyme thereby prolonging the post-prandial activity of glucagon-like-peptide-1 (GLP-1). This results in increased insulin secretion and decreased glucagon production. The most common side effects of sitagliptin include headache and pharyngitis, and few serious adverse events were observed during clinical trials, making it an attractive alternative to older oral glucose lowering agents. Animal studies identified the kidney as the primary organ of toxicity, and approval of its nearest competitor, vildagliptin, by the Federal Drug Administration (FDA) has been delayed pending demonstration of safety in renal insufficiency. Single dose studies suggested that sitagliptin may be used in the setting of renal insufficiency, but data regarding its long-term safety is limited. We present a patient with chronic renal insufficiency on statin therapy who developed acute renal failure and rhabdomyolysis after starting treatment with sitagliptin.

History and Examination

A 76 year-old man presented to clinic with 2 weeks of lower extremity pain and weakness. His medical history included type 2 diabetes mellitus, dyslipidaemia, coronary artery

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disease, atrial fibrillation, and chronic kidney disease with a baseline creatinine of 204 μmol/L. His medications included aspirin, clopidogrel, olmesartan, carvedilol, insulin, metolazone, amiodarone, bumetanide, glipizide, levothyroxine, simvastatin, and ezetimibe. Four months prior to presentation, his simvastatin dose had been increased from 40 to 80 mg daily and ezetimibe 10 mg daily was added without incident. He began taking sitagliptin 50 mg daily 6 weeks prior to presentation, increasing his dose 3 weeks later to 100 mg daily. One week after the sitagliptin dose was increased, he noted the onset of pain and tenderness in both thighs. The pain worsened and he became progressively weaker, and he decided to seek medical attention. Examination revealed tenderness and weakness of the proximal muscles in both legs. Laboratory tests revealed urea 43 mmol/L, creatinine 398 μmol/L, and creatine kinase 22,000 IU/L. The patient was admitted to hospital with rhabdomyolysis and acute renal failure, and olmesartan, bumetanide, metolazone, sitagliptin, simvastatin, and ezetimibe were all stopped. His creatine kinase levels fell, his symptoms improved, and his renal function returned to baseline within 7 days. He resumed all medications except simvastatin, ezetimibe, and sitagliptin. He later started lovastatin which was increased to a dose of 10 mg daily without recurrence of rhabdomyolysis.

Discussion

Rhabdomyolysis was not reported in clinical trials with sitagliptin, although it is a well-documented side effect of statins. The reaction is thought to be dose-related, and any factor which increases serum statin levels, including worsening renal function, may also increase the risk of myopathy. At presentation, the patient was taking 100 mg sitagliptin, double the recommended dose given his renal function. (1) High serum concentrations of sitagliptin were achieved following single doses in healthy patients without adverse effects in Phase I and Phase II trials. Drug half-life was observed to decrease and renal clearance of sitagliptin was preserved. (2) However, both the maximum serum concentration and terminal half-life of sitagliptin are increased in renal insufficiency, and the maximum recommended doses are 50 mg and 25 mg daily in moderate and severe renal insufficiency, respectively. (1) Toxicology studies in rats showed renal tubular necrosis as the primary cause of death and loss of renal parenchyma at sub-lethal doses, (3) suggesting that elevated doses of sitagliptin may result in renal injury in humans. We suspect that initiation of sitagliptin and escalation of dose in this patient may have produced prolonged, elevated sitagliptin levels resulting in decreased renal function and precipitating rhabdomyolysis by increasing circulating simvastatin levels.

The association of sitagliptin and renal insufficiency in this case is classified as “possible” using the method of Kramer, et al. (4) There is no published data regarding the safety of chronic administration of sitagliptin with renal insufficiency in humans, but analysis of reports involving sitagliptin submitted through the FDA's Adverse Event Reporting System (AERS) until September, 2007 revealed that 96/2914 reported events (3.2%) specified renal injury. This included 37 hospital admissions, 17 life threatening events and 2 deaths. In 91/96 (95%) cases involving renal injury, sitagliptin was designated as the ‘primary suspected’ drug. Patients' condition improved with discontinuation of sitagliptin in 20 cases and returned on rechallenge in 1 case. In 40/96 (41 %) of cases, and 22/37 (59 %) of hospital admissions, patients also took angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, NSAIDs, or diuretics (5).

A major confounding factor in this case is the number of concurrent medications which could also affect both renal function and serum statin levels. However, doses for most concurrent medications had been stable for months, and the patient had tolerated simvastatin and ezetemibe for at least 4 months prior to the onset of symptoms or worsening of his renal function, suggesting that this event was precipitated by initiation of sitagliptin therapy.

Conclusions

Given the high likelihood that sitagliptin will be co-administered with renally active drugs and statins in many diabetic patients, our findings suggest that additional studies regarding the long-term safety of sitagliptin in renal insufficiency may be warranted.

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