the SUR1 molecule (Fig. 1b) results in a putative stimulatory SUR1 action with an overactive K_{ATP} channel [2]. No mutations within the *INS* or *KCNJ11* genes were found. Analyses of differentially methylated sequences within the transient neonatal diabetes critical region of 6q revealed a normal allelic methylation pattern and normal allele dosage, excluding known genetic causes of 6q transient neonatal diabetes.

The 36-year-old mother (BMI 30.8 kg/m^2) had high glycaemic variability during insulin treatment, with repeated severe hypoglycaemia and overall poor metabolic control. With a normal C-peptide (0.83 nmol/l), negative auto-antibodies against pancreatic islet antigens and the detection of the *ABCC8* mutation, insulin treatment was replaced by glimepiride (starting dose 2 mg daily). With a single dose of 8 mg glimepiride, good glucose control was achieved in the absence of hypoglycaemia, as demonstrated by 6-day continuous glucose monitoring (MiniLink®REAL-time-transmitter, Sof-Sensor®, MiniMed-Paradigm®REAL-time system, Medtronic GmbH, Meerbusch, Germany): mean glucose ± SD 8.5 ± 1.2 mmol/l; area under the curve > 7.7, 17.5%, < 3.8, 0%, minimum–maximum 5.4–12.7 mmol/l. HbA_{1c} decreased from 93 mmol/mol (10.7%) to 70 mmol/mol (8.6%) within 6 weeks (Fig. 1c).

Identification of patients with K_{ATP} channel mutations allows for specific treatment with sulphonylurea compounds to block the stimulatory action of the K_{ATP} channel [1]. As high-dose sulphonylurea therapy is usually necessary to overcome this kind of insulin secretory deficit, non-response to low-dose sulphonylurea does not inevitably indicate failure of sulphonylurea treatment. Until now, patients with diabetes caused by activated K_{ATP} channels were mainly treated with glibenclamide, glicazide, glipizide or tolbutamide. We used glimepiride as another sulphonylurea offering potential clinical advantages, including faster and longer action compared with glibenclamide and single daily application [3]. Lower doses of glimepiride are required to achieve normoglycaemia in Type 2 diabetes, with lower insulin levels generated compared with other sulphonylurea compounds. The reduced potential for hypoglycaemia of glimepiride has been attributed to its lower affinity to the sulphonylurea receptor, while its higher blood glucose-lowering activity has been explained by increase of insulin sensitivity and glucose utilization in peripheral tissues [3]. Sulphonylurea stimulation of insulin secretion occurs via binding to the SUR subunit of the K_{ATP} channel within the cytosolic loops, leading to ATP-independent channel closure. Differential interaction of glibenclamide and glimepiride with the intracellular site of the β-cell sulphonylurea receptor [3] may account for their different pharmacokinetic features. As activated K_{ATP} channels are increasingly diagnosed as distinct causes of permanent diabetes, with the specific opportunity of targeted pharmacological therapy, glimepiride appears to offer a simple and effective treatment option for these patients.

Competing interests

Nothing to declare.

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References

1 Rafiq M, Flanagan S, Patch A, Shields B, Ellard S, Hattersley A *et al.* Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. *Diabetes Care* 2008; **31**: 204–209.

2 de Wet H, Rees MG, Shimomura K, Aittoniemi J, Patch AM, Flanagan S *et al.* Increased ATPase activity produced by mutations at arginine-1380 in nucleotide-binding domain 2 of ABCC8 causes neonatal diabetes. *Proc Natl Acad Sci USA* 2007; **104**: 18988–18992.

3 Müller G. The molecular mechanism of the insulin-mimetic/sensitizing activity of the anti-diabetic sulfonylurea drug Amaryl. *Mol Med* 2000; **6**: 907–933.

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Rhabdomyolysis precipitated by a sitagliptin–atorvastatin drug interaction

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Sitagliptin is a novel pharmacological agent used in the treatment of Type 2 diabetes mellitus, which acts by competitive inhibition of the enzyme dipeptidyl peptidase-4. The advantage of this class of drug compared with existing hypoglycaemic agents is that it has less of a tendency to cause severe symptomatic hypoglycaemia and weight change [1]. We report a case of rhabdomyolysis in a patient taking atorvastatin for several years who had recently started taking sitagliptin. We define rhabdomyolysis as the breakdown of muscle tissue attributable to any cause, which can but does not necessarily predispose to acute kidney injury.

A 75-year-old Caucasian man with Type 2 diabetes mellitus, hypertension and dyslipidaemia was admitted to hospital under the medical team with 3 months of progressive weakness in both his legs. He had been taking atorvastatin for 5 years without any side effects and had been started on sitagliptin 6 months prior to admission to achieve better glycaemic control. Other medications included aspirin, ramipril, gliclazide, metformin and pioglitazone. On examination, he had marked proximal muscle weakness bilaterally [3 out of 5 on the Medical Research Council scale for all movements at the shoulder and hip girdles]

without any sensory impairment. The anterior and posterior muscle compartments of both thighs were tender to palpation. There was no rash or synovitis. The remainder of the physical examination was unremarkable. Serum creatine kinase was 109 710 IU/l (normal range 25–195 IU/l) on admission, with serum urea and creatinine in the normal range. Magnetic resonance imaging of the thighs showed perimuscular oedema consistent with an inflammatory myopathy. Autoimmune screening including anti-nuclear and extractable-nuclear antibodies was negative. Human immunodeficiency virus antibodies were not detected. Thyroid function testing was normal.

Both sitagliptin and atorvastatin were stopped promptly and intravenous crystalloid was administered. Serum creatine kinase fell precipitously within the first 24 h to 11 368 IU/l, and continued to fall exponentially in the following 6 days to 3709 IU/l. Proximal muscle power increased subjectively and objectively (4 out of 5 on the MRC scale) in the same period. The patient was discharged 13 days after admission without sitagliptin or atorvastatin. Long-acting insulin was added in to supplement the existing oral hypoglycaemic agents.

At 4-week follow-up, the patient remained well and objectively the proximal muscle power was 4 + out of 5 on the MRC scale. Serum creatine kinase had reached a plateau at 4000 IU/l. Satisfactory glycaemic control was achieved on the new anti-diabetic drug regimen. The patient will continue to be followed up, initially at 6-week intervals. A muscle biopsy will be conducted if serum creatine kinase remains elevated 3 months after presentation to investigate a synergistic cause of this myopathy.

To date, there have been two reported cases of statin-induced rhabdomyolysis in the presence of sitagliptin [3,4]. Kao *et al.* [3] describe the concomitant use of sitagliptin and simvastatin resulting in acute kidney injury and rhabdomyolysis. The authors suppose that sitagliptin is nephrotoxic (based on data from phase I trials) and that the renal excretion of simvastatin is reduced in its presence. This would theoretically increase its plasma concentration and promote muscle toxicity. DiGregorio and Pisikhova [4] suggest a possible interaction between sitagliptin and lovastatin at the level of the cytochrome P450 enzyme system. Indeed, both drugs are metabolized by the enzyme CYP3A4 [5,6] and, when co-administered, sitagliptin could theoretically increase the plasma concentration of lovastatin by competition for the enzyme. This would increase the likelihood of lovastatin causing muscle toxicity.

Ours is the first report of sitagliptin and atorvastatin interacting to cause rhabdomyolysis. Interestingly, the renal function of our index patient was remarkably normal in the context of such a high level of creatine kinase. This supports the theory that sitagliptin affects the hepatic metabolism of atorvastatin rather than affecting its renal excretion. Indeed, like lovastatin, atorvastatin too is metabolized by CYP3A4. Importantly, none of the other pre-admission medications are metabolized by this enzyme.

In summary, the concomitant use of sitagliptin and statins is not infrequent. This is the third reported case of an interaction between sitagliptin and statin leading to rhabdomyolysis. Patients taking these medications simultaneously should be closely monitored for clinical and biochemical evidence of toxic myopathy. Sitagliptin and atorvastatin should be co-administered with caution.

Competing interests

Nothing to declare.

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References

1 Arechavaleta R, Seck T, Chen Y, Krobot KJ, O'Neill EA, Duran L *et al.* Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2011; **13**: 160–168.
2 Khao DP, Kohrt HE, Kugler J. Renal failure and rhabdomyolysis associated with sitagliptin and simvastatin use. *Diabet Med* 2008; **25**: 1229–1230.
3 DiGregorio RV, Pasikhova Y. Rhabdomyolysis caused by a potential sitagliptin–lovastatin interaction. *Pharmacotherapy* 2010; **29**: 352–356.
4 Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. *Circulation* 2004; **109**: III50–III57.
5 Vincent SH, Reed JR, Bergman AJ, Elmore CS, Zhu B, Xu S *et al.* Metabolism and excretion of the dipeptidyl peptidase 4 inhibitor [14C] sitagliptin in humans. *Drug Metab Dispos* 2007; **35**: 533–538.