Letter to the Editors

Exenatide may aggravate moderate diabetic renal impairment: a case report

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We write in response to a recently published paper in this journal [1] in which mainly nondiabetic patients with renal impairment, without polypharmacy, were evaluated using exenatide. The study concluded that subjects with mild to moderate renal impairment were able to tolerate the drug. However, whether this is the case for patients with Type 2 diabetes remains uncertain, and we present a case that highlights potential problems.

Exenatide 5 µg b.i.d. was given to one male patient (66 years, body mass index 35.1 kg m⁻²) with Type 2 diabetes since 1992, who in 1995 was diagnosed with microalbuminuria. By 1998 he had developed macroalbuminuria, in 2000 his creatinine levels exceeded upper limits of normal and in 2004 he had developed renal impairment-related anaemia and metabolic bone disease. Other complications were proliferative retinopathy (diagnosed 1995), peripheral sensory neuropathy (since 1996) and gout (since 2007).

Concomitant medications were losartan potassium 25 mg q.d., furosemide 40 mg b.i.d., spirinolactone 50 mg q.d., alfacalcidol 0.25 µg 3 days week⁻¹, darbepoetin alfa 20 µg month⁻¹, allopurinol 100 mg q.d., biphasic insulin aspart 30 b.i.d. [40–42 units (U) breakfast, 60–66 U dinner] and insulin aspart q.d. (10 U lunch).

Due to non-optimal glycaemic control the patient was given exenatide (February 2008) after careful explanation that this was considered off-label use, since he was taking insulin. In the following 4 weeks the patient's creatinine levels rose (192 to 244 µmol l⁻¹) and, correspondingly, the Cockcroft–Gault [2] creatinine clearance (CrCL) was reduced (53.1 to 41.8 mg min⁻¹, Figure 1). Reductions were also seen in HbA_{1c}, fasting plasma glucose (respectively 7.6 to 6.8% and 7.2 to 5.1 mmol l⁻¹) and total daily insulin dosages (by 40%). The worsening of renal impairment was not related to urinary tract infection, obstruction or dehydration, although he experienced some nausea and diarrhoea. Hence, exenatide was stopped, and within the next 2 weeks his kidney function parameters returned to pretreatment levels (creatinine 196 µmol l⁻¹, CrCL 52.1 mg min⁻¹).

In contrast with the previous report [1], we suggest that exenatide might not be well tolerated in patients with Type 2 diabetes with mild to moderate renal impairment, although it apparently seems safe in subjects without diabetes.

One explanation could be that patients with Type 2 diabetes, compared with subjects without, at similar elevated creatinine levels metabolically tolerate the renal impairment poorer, hence should cautiously receive substances with primary renal elimination. This has been underscored, for example, in a study reporting level of renal function at the initiation of dialysis [3], where patients with end-stage renal disease (ESRD) caused by diabetes required this earlier than patients with ESRD due to other causes.

Another possibility is that the polypharmacy associated with Type 2 diabetes, added to the above, could lead to unexpected drug–drug interactions further impairing renal function, perhaps particularly relevant for compounds affecting the renin–angiotensin system.

A third, perhaps less likely explanation is that the combination of exenatide with insulin may aggravate the kidney function. Although this combination currently is not approved [4], such a combination is in fact being used in clinical practice, e.g. as reported in one retrospective analysis reporting weight loss and reductions in HbA_{1c} [5]. Interestingly, exenatide has even been reported being used in patients with Type 1 diabetes [6].

We suggest that it is imperative to explore further the impact of exenatide in patients with Type 2 diabetes and renal impairment. Until proven safe, exenatide should be used cautiously in this patient group, especially with polypharmacy.

Competing interests

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Figure 1

Serum creatinine levels and estimated CrCL the first year before treatment, during the 4 weeks' treatment period and the 2-week period following after exenatide 5 μg b.i.d. was discontinued (medium dashed arrow). Right y-axis indicates creatinine levels (solid curve) and the right axis the CrCL (dotted curve). CrCL, creatinine clearance

Takeda and Astra Zeneca, and was an employee of Novo Nordisk in 2006/2007.

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