

Managing diabetes in a patient at risk of fractures

Prescriber's Corner describes situations encountered by pharmacist prescribers and invites you to consider clinical decisions about the patient. In this case, you are reviewing a patient with osteoporosis who is taking oral hypoglycaemic drugs for type II diabetes.

You are an independent pharmacist prescriber working in a GP practice reviewing patients with diabetes.

The case

Mrs PG is a 74-year-old patient with a complex medical history. She was diagnosed with type II diabetes mellitus eight years ago. She underwent a total nephrectomy of the right kidney in 1988 following the development of a staghorn calculus and has been on the chronic kidney disease register at stage III for the past three years. Her renal function is currently stable.

Mrs PG was diagnosed with atrial fibrillation eight years ago

and hypertension three years ago. A risk analysis has shown her 10-year cardiovascular disease risk to be >20%. Mrs PG has also developed chronic obstructive pulmonary disease, possibly as a result of passive smoking (her husband has smoked for many years). She has recently been diagnosed with depression.

Mrs PG has never smoked and does not drink alcohol. She does not exercise and her current body mass index is 30.4kg/m².

Mrs PG presented at the accident and emergency department 18 months ago following a minor fall and was diagnosed with a fragility fracture of the tibia. She was referred to the orthopaedic department, underwent DEXA (dual energy X-ray absorptiometry) scanning and was diagnosed as having osteoporosis.

Drug history

Mrs PG's current medicines and date initiated are listed in Figure 1.

Mrs PG's diabetes was initially controlled with metformin and rosiglitazone was introduced as the condition progressed. The rosiglitazone was changed to pioglitazone following a drug safety update from the Medicines and Healthcare Products Regulatory Agency in October 2007 and resultant change in local prescribing practice for thiazolidinediones (glitazones). This safety update highlighted an increased risk of cardiac ischaemia in patients taking rosiglitazone. At this time further evidence was published which suggested that the risk of cardiac ischaemia and the related sequelae was not uniform within the therapeutic group.



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Pioglitazone was not shown to demonstrate any risk of cardiac ischaemia but was shown to increase the risk of heart failure in line with the glitazones as a therapeutic class.

The consultation

Mrs PG was called for review in your clinic following an audit of patients taking glitazones who were also receiving treatment for osteoporosis or osteopenia. This audit followed the publication of a meta-analysis in January 2009, which demonstrated an increased risk of fracture in women taking glitazones. The MHRA drug safety update mentioned this risk but, at the time of publication, definitive evidence of the association was lacking. When Mrs PG was diagnosed with osteoporosis, the association with her glitazone therapy was highlighted but it was felt that insufficient evidence existed to alter her therapy.

Mrs PG's recent renal function results and HbA1c levels are shown in Figure 2 (p184).

Medicine	Date initiated
Aspirin 75mg OD (dispersible)	04/09/2006
Simvastatin 40mg ON	06/02/2006
Amlodipine 5mg OM	05/05/2006
Furosemide 40mg OM	17/09/2007
Digoxin 125µg OM (previously 250µg OD)	04/08/2008 (05/03/2001)
Irbesartan 150mg ON	17/09/2007
Metformin 850mg TDS (previously 500mg TDS)	20/10/2003 (02/07/2002)
Pioglitazone 30mg OD (previously rosiglitazone 8mg OD)	23/01/2008 (13/5/2005)
Alendronic acid 70mg once weekly	04/08/2008
Calceos tablets BD	06/03/2009
Co-codamol 2 tablets QDS PRN	02/01/2004
Salbutamol inhaler 2 puffs PRN	04/11/2005
Seretide 125 inhaler 2 puffs BD	10/01/2007
Citalopram 20mg OD	17/04/2009

Figure 1: Mrs PG's medicines

Clinical decision

Why is Mrs PG at such a high risk of fractures?

Does her oral diabetes therapy need changing?

What other treatment options could you consider?

Discussion

Why is Mrs PG at such a high risk of fractures? Before being diagnosed with osteoporosis, Mrs PG had been taking glitazones for four years. Glitazones are now known to increase fracture risk in women. Diabetes itself also increases the risk of fracture in older women. Mrs PG's high dose inhaled corticosteroid therapy (Seretide) and gradually deteriorating renal function also increase her fracture risk.

What action should you take now? The MHRA and the National Institute for Health and Clinical Excellence recommend that glitazones should not be continued in patients at higher risk of fractures including those with osteoporosis and osteopenia. Evidence from a meta-analysis has demonstrated that the fracture risk in patients with type II diabetes increases with age. Among a cohort of patients with a mean age of 72 years, the number needed to harm over a period of one year was 21 (i.e. of 21 patients treated with a glitazone for one year, one extra woman would develop a fracture who would not have done so without taking the glitazone). This evidence suggests that Mrs PG's glitazone treatment should be substituted for an alternative oral hypoglycaemic drug which does not further exacerbate her fracture risk.

Since Mrs PG's eGFR is now 40ml/min/1.73m², her renal function will need to be monitored closely. If it remains at this level or deteriorates further, consideration should be given to reducing the dose of metformin due to the increased risk of

lactic acidosis with this level of renal impairment. Current guidance suggests that metformin should be prescribed with caution in patients with an eGFR of <45 ml/min/1.73m² and that it should be stopped if the eGFR deteriorates to <30ml/min/1.73m².

The complexity of Mrs PG's treatment regimen should not be underestimated. It is important that Mrs PG is fully involved in the discussions about her treatment, including the risks involved, so that she can make an informed decision. It is likely that she is accustomed to alterations in her treatment, but it is important that she understands the risks and benefits of using a glitazone.

What other treatment options could you consider? NICE guidance for type II diabetes recommends a sulphonylurea as the second line option after metformin monotherapy. The most appropriate sulphonylurea for a patient with renal impairment is gliclazide because it is shorter-acting and is predominately metabolised in the liver. Gliclazide should be used with caution in elderly patients with renal impairment due to the risk of hypoglycaemia. It should be started at a low dose (e.g. 40mg in the morning) and, if tolerated, gradually titrated upwards.

Sitagliptin, a dipeptidyl peptidase 4 inhibitor, which is a third line option in the latest NICE guideline (see p167), is not an option for Mrs PG because of her renal impairment (sitagliptin is not recommended in patients whose creatinine clearance is <50ml/min).

If Mrs PG cannot tolerate gliclazide, you could consider adding in acarbose. Acarbose is a competitive inhibitor of intestinal alpha-glucosidase and it delays the digestion and absorption of carbohydrate. It is particularly useful if a patient with diabetes suffers from post-prandial hyperglycaemia. A dose adjustment is not required in patients with moderate renal impairment but acarbose is not recommended in severe renal

impairment (creatinine clearance <25ml/min). It should be initiated at a low dose (50mg once or twice daily) and gradually titrated upwards. It should be taken with the first mouthful of food to minimise gastrointestinal side effects.

If Mrs PG cannot tolerate the sulphonylurea or acarbose, the next option would be to consider either exenatide or insulin.

Exenatide is an incretin mimetic which acts in a similar way to glucagon-like-peptide-1 (GLP-1), increasing insulin release from the pancreatic beta cells. It is licensed in combination with metformin and/or sulphonylureas, so the patient should remain on the oral agent. In elderly patients and in patients with renal impairment, it should be initiated at a low dose and increased cautiously.

One of the advantages of exenatide is that it can lead to significant weight loss. New NICE guidance (see p167) recommends that continuation of exenatide should be considered if there is a reduction in HbA1c of ≥1% after six months or weight loss of ≥3%. An MHRA drug safety update in March this year warned of an increased risk of pancreatitis with exenatide, including cases of haemorrhagic and necrotising pancreatitis (two of which have been fatal), and increased risk of renal failure. Exenatide is a relatively newly licensed medicine (black triangle) and any suspected adverse drug reactions must be reported to the MHRA.

Insulin is also an option for Mrs PG, ideally starting with a twice daily regimen of human NPH insulin or, if multiple insulin injections are not acceptable for the patient, a long-acting analogue such as insulin glargine.

It should be remembered that some patients may be concerned about moving from oral to injectable therapy. As well as concerns about needles, patients might have negative perceptions about injectable therapy being a sign of disease progression. Patient education and reassurance is essential when considering these products.

Prescriber's Corner is provided by the University of Sunderland School of Pharmacy. Written by Andrew Husband, principal lecturer, pharmacy practice and Anne-Marie Bailey, prescribing advisor, South of Tyne & Wear Medicines Management Team.

	1/2/2008	8/5/2008	7/10/2008	8/5/2009
Creatinine (50–100µmol/l)	96	97	95	116
Urea (2.7–7.5mmol/l)	7.7	8.1	8.2	11.3
eGFR (ml/min/1.73m ²)	49	49	50	40
HbA1c (%)	7.3	6.6	6.8	7.2

Figure 2: Mrs PG's renal function and HbA1c results