CASE REPORT

Hallucinations associated with miglitol use in a patient with chronic kidney disease and hypothyroidism

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Accepted 20 January 2015

SUMMARY

A 71-year-old woman with type 2 diabetes mellitus, chronic kidney disease stage IV, primary hypothyroidism and osteoarthritis, whose prescribed treatment included miglitol 50 mg thrice daily with the first bite of meals, reported that she suffered visual hallucinations while taking miglitol, which resolved within a few days of stopping the drug. When she resumed miglitol, hallucinations recurred within a few days and again resolved within a few days of stopping the drug. To our knowledge, this is the first reported case of hallucinations associated with the use of an α -glucosidase inhibitor and highlights a previously unappreciated risk associated with the use of this generally quite benign drug class.

BACKGROUND

The rising incidence of type 2 diabetes mellitus (T2DM), a disease that often coexists with end-organ dysfunction and other metabolic diseases, is of public health concern.¹ The treatment of T2DM often warrants the use of multiple medications to achieve good glycaemic control including the α -glucosidase inhibitors, like miglitol. The documented side effects of this class of medication are only of the nuisance variety, for example, abdominal pains, bloating and diarrhoea.² Hallucination as a side effect of α -glucosidase inhibitors is not widely appreciated and is not a reported adverse effect in the package inserts. This case report could help in prevention or timely diagnosis of a potentially dangerous treatment side effect.

CASE PRESENTATION

Our patient is a 71-year-old African-American woman with T2DM, associated chronic kidney disease stage IV (CKD IV) and primary hypothyroidism. For the T2DM, her medications included: insulin glargine 24 units at bedtime, sitagliptin 50 mg (renal dose), and glipizide XL 10 mg daily. She was also taking miglitol (Glyset), 50 mg thrice daily with the first bite of meals. Subsequently, she noticed visual hallucinations in the awake state. The hallucinations were very brief in duration, lasting 'no longer than two eye blinks'. They were all well formed and in colour, consisting of sumo wrestlers, emergency room ceiling gap open with wires hanging out, and her street being blocked by a large lorry. These resolved within 3–4 days of stopping the drug and recurred within 3–4 days of resuming miglitol ingestion. She had never experienced similar episodes in

the past. At no point were the hallucinations associated with proximal weakness, myalgia or symptoms of hypoglycaemia, nor did she report low finger stick whole blood glucose readings in association with these episodes when questioned, rather corresponding blood glucose levels were always either euglycaemic or hyperglycaemic. There was no relationship with mealtimes. Significantly, there is no history of psychiatric illness or use of psychoactive medications or hallucinogens. Her glycaemic control was suboptimal with glycated haemoglobin (HbA1c) of 11.2%, as was the control of her hypothyroid condition with serum thyroid-stimulating hormone of 67.7 mIU/mL. Her calculated glomerular filtration rate was 28 mL/min/m² using the MDRD (Modification of Diet in Renal Disease) equation (creatinine=2.06). The liver function tests were normal except for occasional minimal increases of serum alkaline phosphatase, consistent with expected secondary hyperparathyroidism due to CKD.

INVESTIGATIONS

HbA1c was determined by immunoturbidimetry. Serum thyroid-stimulating hormone was determined by immunoassay. Serum creatinine was determined by spectrophotometry.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included central nervous system (CNS) changes associated with advanced CKD and or hypothyroidism (myxoedema madness), hypoglycaemia, and transient ischaemic attacks, which could readily occur in a patient with so many risk factors for cerebrovascular disease.

OUTCOME AND FOLLOW-UP

On discontinuation of miglitol, her visual hallucinations ceased. She is currently being managed with insulin and renal replacement therapy, and hypothyroidism is being controlled with l-thyroxine replacement.

DISCUSSION

Miglitol is an oral hypoglycaemic agent, an iminodisaccharide.³ It is a piperidine derivative that acts by a reversible, competitive inhibition of intestinal α -glucosidase enzyme. This enzyme, located in the small intestinal brush borders, hydrolyses oligosaccharides and disaccharides to glucose and other monosaccharides. Consequently, there is delayed absorption of glucose leading to less postprandial hyperglycaemia.

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To cite: Ezeji GC, Inoue T, Bahtiyar G, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207345

The α -glucosidase inhibitors, acarbose and miglitol, have proven to be useful adjuncts in the treatment of postprandial hyperglycaemia in patients with T2DM.⁴ In addition to this US Food and Drug Administration—approved indication, these agents have modest utility in the management of postprandial hyperglycaemia in T1DM,⁵ and are very effective in the management of functional reactive hypoglycaemia,⁶ as well as post-gastrectomy reactive hypoglycaemia.⁷ The resulting delay in postmeal glucose absorption is also useful in preventing hypoglycaemia when the next meal is delayed or as a result of vigorous exercise between meals.

The common side effects include abdominal pains, bloating and diarrhoea, chiefly in patients unaccustomed to high-fibre diets. These side effects have limited their use in the USA despite the impressive data from the STOP-NIDDM Trial, showing their efficacy in the prevention of coronary artery disease events.⁸

Generally miglitol is minimally absorbed (2–3%) via the oral route; it is mostly cleared unchanged via the renal route.⁹ Therefore, it might accumulate in the setting of renal failure¹⁰ and this could be exacerbated by hypothyroidism,¹¹ which further reversibly lowers the glomerular filtration rate. Following its absorption, miglitol is able to cross the blood/brain barrier⁹ and potentially inhibit the α -glucosidase enzymes of the CNS, for example, isomaltase, resulting in CNS glycogen accumulation mimicking genetic glycogen storage diseases, for example, Pompe's disease—which may also present with hallucinations. Deficiency of α -glucosidase enzyme activity in the CNS has been reported to be associated with hallucinations.¹² Furthermore, aneurysm formation of cerebral arteries with accompanying neurological signs has been reported in patients with late onset Pompe's disease.^{12–15} Although one series has reported a 2% incidence of hallucinations in patients taking the related drug acarbose, the risk is not widely appreciated and it is not a reported adverse effect in the package insert of either medication (<http://www.ehealthme.com/ds/acarbose/hallucination>). The other differential diagnoses listed above are less likely for several reasons:

- ▶ CKD is unlikely to cause hallucinations until such point as the patient is frankly uraemic (uraemic encephalopathy) and then would be unlikely to improve until renal replacement therapy was under way.¹⁶
- ▶ Hallucinations associated solely with hypothyroidism are very rare and would not be expected to resolve when miglitol was discontinued and reappear when the patient restarted miglitol.¹⁷
- ▶ Our patient, who was very perspicacious, had already excluded hypoglycaemia by self-monitoring during these episodes. In addition, she did not experience any other hypoglycaemic symptoms accompanying the hallucinations to suggest pseudohypoglycaemia. While miglitol does not cause hypoglycaemia, it may prolong it if starches or sucrose, rather than glucose, are used to reverse it.
- ▶ Transient ischaemic attacks would not be expected to persist over several days and resolve with the discontinuation of miglitol and then reappear within a few days of resuming miglitol.¹⁸

Our report is limited by the fact that this hallucinogenic effect was observed in only one patient and that we have no anatomic/histopathological documentation in this patient of either CNS glycogen accumulation or aneurysm formation.

Learning points

- ▶ Although extremely rare, the use of α -glucosidase inhibitors may be associated with central nervous system (CNS) complications suggestive of an iatrogenic glycogen storage disease.
- ▶ Patients with renal failure and hypothyroidism may be particularly susceptible to adverse CNS effects of this generally safe class of oral antihyperglycaemic agents.
- ▶ A high index of suspicion is required in patients with diabetes with background renal impairment cum hypothyroidism undergoing α -glucosidase inhibitor therapy for early identification and optimal management of a consequent visual hallucination.

Acknowledgements The authors are grateful to the following colleagues who helped in literature search and abstract preparation: Dhruv Chaudhary and Chaudhari S Abhay, MD and T Hlaing, MD.

Contributors AS and GB participated in patient care, literature review, manuscript review and its production. While GCE and TI were involved in literature search, and manuscript writing.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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