CASE REPORT

Hypoglycaemia due to interaction of glimepiride with isoniazid in a patient with type 2 diabetes mellitus

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SUMMARY

Hypoglycaemia is a well-recognised untoward effect of sulfonylureas. We report a case of severe hypoglycaemia after isoniazid initiation in a type 2 diabetic patient. An oral glucose tolerance test revealed high serum insulin and C peptide, suggesting hyperinsulinaemia, and it was used to ascertain the relationship between insulin, glucose and C peptide levels. Insulin and C peptide elevation was attributed to the interaction between the two drugs. As a cytochrome inhibitor, isoniazid increased serum glimepiride concentration, resulting in hyperinsulinaemia. The diagnosis of occult insulinoma or nesidioblastosis was ruled out by CT and MRI, as we could not perform more sensitive, still invasive, diagnostic procedures. After isoniazid withdrawal, hypoglycaemia regressed and glimepiride was reinitiated. In conclusion, this case illustrates the need of caution when prescribing isoniazid in patients with type 2 diabetes mellitus receiving glimepiride to avoid hypoglycaemia.

BACKGROUND

Hypoglycaemia is attributable to increased levels of either exogenous or endogenous insulin. In participants with diabetes, hypoglycaemia is a usual untoward effect of secretagogue oral agents, mainly sulfonylureas (glimepiride, glipizide, glibenclamide, etc) and insulin therapy.¹ Alternatively, it may be attributed to pancreatic lesions, notably insulinoma or diffuse islet cell hyperplasia.¹

The most common cause of hypoglycaemia is the administration of certain medications or the interaction between them (ie, common cytochrome metabolism) that can increase this risk. We describe a rare case of hypoglycaemia observed after the initiation of isoniazid owing to latent tuberculosis in a 76-year-old diabetic patient receiving glimepiride.

CASE PRESENTATION

A 76-year-old woman was admitted to our hospital owing to exacerbation of chronic obstructive pulmonary disease (COPD). Her medical history included angina, COPD with respiratory failure under long-term oxygen treatment at home and a well-controlled type 2 diabetes mellitus (T2DM; HbA1c<7%) treated for a period of 8 years with 4 mg glimepiride. The patient did not refer previous episodes of severe hypoglycaemia, or a history of alcohol abuse. The family relatives provided excellent home healthcare services ensuring an optimal

level of well being to the patient. Three days before her admission, the patient reported gradually deteriorating dyspnoea on exertion, non-productive cough and fever. Chest x-ray showed atelectasis of the right lower lung lobe with smooth pleural thickening on both the left and the right upper lobes, and fibrous elements on the left upper lobe.

This finding along with a positive tuberculin skin test (30 mm) set the diagnosis of latent tuberculosis. Sputum specimen was negative on fast stain and cultures were negative for mycobacteria. A therapy regimen for latent tuberculosis was started with isoniazid for 9 months.²

One month after initiation of isoniazid, the patient was admitted because of hypoglycaemia, expressed with cold sweating, palpitations and lethargy. Her biochemical values included: serum glucose 1.4 mmol/l (reference values 3.9–5.9 mmol/l), insulin 37.17 µIU/ml (reference values 4–16 µIU/ml), C peptide 10.59 ng/ml (reference values 0.48–3.3 ng/ml) while liver and renal function were normal, as depicted by the corresponding biochemical values (aspartate transaminase 22 U/l, alanine transaminase 18 U/l, γ-glutamyl transferase 43 U/l, alkaline phosphatase 84 U/l, urea 49 mg/dl and creatinine 1.2 mg/dl). Accordingly, hyperinsulinaemic hypoglycaemia was diagnosed. Thus, glucose was promptly administered intravenously (3 amp of dextrose 35% followed by infusion of 1000 ml dextrose 10% with flow rate 50 ml/min), restoring serum glucose to 5.6 mmol/l. However, a new hypoglycaemic event occurred on the next day, and the following values were obtained in a non-fasting state: serum glucose 1.5 mmol/l (reference values 3.9–7.8 mmol/l), insulin 20.72 µIU/ml (reference values 4–16 µIU/ml) and C peptide 6.83 ng/ml (reference values 0.48–3.3 ng/ml). Taking into consideration that isoniazid had been previously associated with hypoglycaemia,³ it was discontinued. After 24 h, symptoms were relieved and serum glucose levels returned to normal (5.4 mmol/l).

INVESTIGATIONS

Capillary blood glucose concentrations were monitored every 2 h to study the pattern of hypoglycaemia. A 24 h blood glucose profile revealed postabsorptive hypoglycaemia, abolishing the need for prolonged fasting. Both insulin and C peptide concentrations obtained during hypoglycaemia were elevated (table 1). A 5 h oral glucose tolerance test was also performed: after a 75 g glucose load,

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Table 1 A 24 h blood glucose profile

Time	Glucose (mmol/l)	Insulin (μ U/ml)	C peptide (ng/ml)
6:00	3.8	46.25	32.22
12:00	2.6	40.50	26.36
18:00	1.5	37.17	21.70
24:00	5	30.10	10.59

Insulin reference values 4–16 μ U/ml, C peptide reference values 0.48–3.3 ng/ml.

insulin level was markedly increased at 30 min, and declined thereafter, remaining in a borderline level above baseline until 5 h; similarly, C peptide level was raised at 30 min, beginning slightly to decline, remaining elevated after 5 h (table 2). Serum cortisol was 15.90 μ g/dl (439 nmol/l) at 8:00, and rose to 20.50 μ g/dl (566 nmol/l) after a low-dose adrenocorticotropin stimulation test, excluding adrenal insufficiency. Rest of the imaging studies, including abdominal CT and MRI, were normal.

OUTCOME AND FOLLOW-UP

Four days after isoniazid withdrawal, glimepiride was reinitiated. The patient was discharged on this sulfonylurea, and a combination of pyrazinamide with ethambutol was also prescribed for 6 months. She visited the diabetes clinic at 2, 4 and 6 months, and remained free from hypoglycaemia.

DISCUSSION

Sulfonylureas including glimepiride are efficacious, generally well-tolerated and cost-effective oral agents for the management of T2DM.^{4–7} Their action involves enhanced insulin secretion from the pancreatic β -cell.^{4–6} Glimepiride, in particular, has emerged as equally efficacious but safer in terms of untoward effects than the earlier agent glibenclamide.⁷

However, severe hypoglycaemia may occur as a serious, potentially life-threatening untoward effect of sulfonylureas, frequently seen in the elderly and those with chronic renal failure and/or concurrent acute illness.^{8–9} Drug interactions may also increase the risk of sulfonylurea-induced hypoglycaemia. Of relevance, glimepiride is metabolised primarily in the liver, first to its active metabolite via the cytochrome P450 isoenzyme CYP2C9 and then to its dehydrogenated inactive metabolite.^{10–11} Cytochrome inhibitions can, therefore, lead to accumulation of glimepiride and its active metabolite, promoting hypoglycaemia. Isoniazid is a potent inhibitor of CYP2C9 and other cytochrome P450 isozymes (CYP2C19 and CYP2E1),² and so its administration in patients receiving glimepiride could increase concentration of the latter.

In our patient, occurrence of hypoglycaemia after isoniazid initiation and regression after isoniazid withdrawal point to an interaction between the two agents. This explanation is rendered more convincing by the fact that no hypoglycaemia

developed after reinitiation of glimepiride and the administration of pyrazinamide/ethambutol combination. In line with this, elevated insulin and C peptide levels were seen, despite declining glucose concentration. Such levels were suggestive of augmented endogenous insulin secretion, which, in turn, could be ascribed to accumulation of glimepiride and its active metabolite owing to reduced hepatic catabolism.

Two alternative diagnoses could be pancreatic lesions (insulinoma or nesidioblastosis) and insulin autoimmune syndrome (IAS). The former could be excluded by the absence of hypoglycaemia with glimepiride treatment after isoniazid withdrawal and by the negative imaging studies. Admittedly, negative CT and MRI results do not completely exclude the possibility of occult islet cell tumour or nesidioblastosis. However, we were not able to perform in our hospital more sensitive diagnostic tests owing to their invasiveness. IAS, which has been described in very rare cases after isoniazid treatment,^{3–12} is excluded in our patient because of high C peptide levels. Indeed, patients with IAS usually exhibit very high insulin levels (sometimes $>1.000 \mu$ U/ml) because of the high capacity of insulin-binding autoantibodies.^{3–12} This contrasts with normal C peptide levels, suggesting the absence of genuine endogenous excess insulin secretion.^{3–12} Conversely, both insulin and C peptide levels were elevated in our patient.

The limitation of this report is that we did not measure serum concentrations of glimepiride and its metabolites. Accordingly, we cannot firmly document cytochrome inhibition with resultant accumulation of glimepiride metabolites in the patient presented. Nonetheless, the absence of hypoglycaemias prior to isoniazid administration, as well as their prompt cessation after withdrawal of this agent point to an interaction between the two drugs.

In conclusion, this case illustrates the need of caution when prescribing isoniazid in patients with T2DM receiving glimepiride. The exact prevalence of the clinically meaningful interaction between these two agents is unknown, still the risk of hypoglycaemia has important implications in everyday practice. To the best of our knowledge, this is the first case report on hypoglycaemia owing to glimepiride and isoniazid interaction in a patient with T2DM.

Learning points

- ▶ The clinician should be aware of interactions between antidiabetic drugs and other agents.
- ▶ Concurrent acute illnesses may increase the risk of sulfonylurea-associated hypoglycaemias.
- ▶ Administration of isoniazid to patients receiving glimepiride may increase the risk of hypoglycaemia.

Competing interests None.

Patient consent Obtained.

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Table 2 A 5 h oral glucose tolerance test

OGTT (time)	Insulin (μ U/ml)	C peptide (ng/ml)
30 min	250	185
1 h	235	170
2 h	200	145
3 h	140	110
4 h	80	73
5 h	30	47

Insulin reference values 4–16 μ U/ml, C peptide reference values 0.48–3.3 ng/ml.

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