

Tamsulosin and hyperglycaemia in patients with diabetes

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ABSTRACT

Three patients developed hyperglycaemia during tamsulosin use. All patients had diabetes and recovered after withdrawal. A pharmacological mechanism for this adverse drug reaction is suggested: stimulation of the α_1 -receptor is one of the insulin-independent pathways for glucose uptake, hence inhibition might increase plasma glucose concentrations. Physicians should be aware of hyperglycaemia as possible adverse drug reaction in patients with diabetes using tamsulosin.

KEYWORDS

Adverse drug reaction, hyperglycaemia, tamsulosin, α_1 -receptor antagonist, diabetes

INTRODUCTION

Achieving glycaemic control is one of the key elements in disease management of patients with type 1 or type 2 diabetes.¹ Maintaining glucose levels has proved to have a positive effect on diabetic complications.^{2,3} Hyperglycaemia is defined as an increased level of plasma glucose. The following cut-off levels for concentrations in venous plasma are used: ≥ 11.1 mmol/l in non-fasting and ≥ 7.0 mmol/l in fasting conditions.⁴

Tamsulosin is an α_1 -receptor antagonist that binds selectively and competitively to α_1 -receptors. It is indicated for the treatment of urinary tract symptoms related to benign prostate hyperplasia.⁵ Common adverse drug reactions are dizziness, headache, palpitations and nausea.⁵ In this paper we present three reports on hyperglycaemia in association with tamsulosin use in patients with type 2 diabetes and discuss a possible pharmacological explanation.

METHODS AND RESULTS

Case reports

The Netherlands Pharmacovigilance Centre Lareb received three reports of hyperglycaemia in association with the use of tamsulosin. The reporters were contacted to obtain clinical information according to the guidelines for publications about adverse drug reactions.⁶ These reports are summarised in *table 1*.

All patients used insulin for diabetes. Patient A was a 61-year-old male with type 2 diabetes, who used oral antidiabetic drugs (metformin and glimepiride) and insulin. He was prescribed tamsulosin for benign prostatic hyperplasia. On the first day of treatment his glucose levels – normal 8 to 9 mmol/l – increased to 18 to 20 mmol/l. After withdrawal his glucose levels returned to normal. The patient was taking metoprolol, quinapril, atorvastatin, acetylsalicylic acid and sildenafil (as needed) as concomitant medication.

What was known on this topic?

- Tamsulosin is an α_1 -receptor antagonist that can act peripherally
- Hyperglycaemia has not been associated with tamsulosin use in patients with diabetes

What does this add?

- Hyperglycaemia was associated with the use of tamsulosin in three patients with diabetes in the Netherlands.
- The adverse drug reaction is pharmacologically plausible by inhibition of an alternative, insulin independent, α_1 -receptor mediated route of glucose uptake.

Table 1. Reports of increase of blood glucose concentration associated with tamsulosin use

Patient, sex, age	Suspect drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to first symptoms, outcome
A (75483) M, 61	Tamsulosin 0.4 mg for benign prostatic hyperplasia	Metformin Glimepiride Insulin Metoprolol Atorvastatin Acupril Acetylsalicylic acid Sildenafil	Blood glucose increased (normal level: 8-9 mmol/l; increased to 18-20 mmol/l)	1 day, recovered after discontinuation of tamsulosin
B (61032) M, 67	Tamsulosin 0.4 mg for miction problems	Metformin Insulin Enalapril Atorvastatin Telmisartan Sildenafil	Blood glucose increase (normal 7.5 mmol/l; increase to 18.8 mmol/l) Drug interaction between insulin and tamsulosin	2 days, recovering after discontinuation of tamsulosin
C (53015) M, 71	Tamsulosin 0.4 mg for benign prostatic hyperplasia Insulin for diabetes	Enalapril Simvastatin	Blood glucose increased Drug interaction between insulin and tamsulosin	1 day, discontinuation of tamsulosin, recovered

Patient B was a 67-year-old male who was diagnosed with type 2 diabetes 11 years prior to the adverse drug reaction. Initially he was treated with oral antidiabetic drugs, and after three years insulin was added. The patient experienced few complications from his diabetes and was adherent. The patient visited his GP with micturition problems. He had normal plasma glucose levels of 7.5 mmol/ml, and the GP initiated tamsulosin treatment. Two days later, his plasma glucose had increased to 17.8 mmol/l. Tamsulosin was withdrawn, and the GP now suspected that a urinary tract infection had caused the micturition problems. The patient was treated with antibiotics: first one day of sulphamethoxazole/trimethoprim (discontinued due to hypersensitivity) and subsequently ciprofloxacin. The patient had no fever or other objective symptoms that supported the diagnosis of the urinary tract infection. Glucose levels returned to normal two to three days after withdrawal of tamsulosin. Concomitant chronic medication consisted of insulin, atorvastatin, metformin, enalapril, telmisartan, and sildenafil (as needed).

Patient C was a 71-year-old male who had been diagnosed with type 2 diabetes eight years ago. His diabetes was well controlled, although the patient had complications. The patient was on enalapril for hypertension and simvastatin for hypercholesterolaemia, as concomitant medication. Insulin had been added five years ago; the patient was not taking oral antidiabetic drugs. Glucose levels increased to 10 to 11 mmol/l at one day after tamsulosin was started to treat benign prostatic hyperplasia compared with normal fasting levels of 3 to 4 mmol/l. Within two weeks after withdrawal of tamsulosin, the glucose levels returned to normal. The reporter mentioned that no other explanations for hyperglycaemia were present.

DISCUSSION

In our cases, all patients were diabetic, and this association might be related to patients in whom insulin-dependent glucose uptake is limited. We suggest a potential mechanism that could explain limited glucose uptake by blockade of the α_1 -receptor that might be relevant if insulin-dependent pathways are impaired. The Lareb database does not contain any other reports of α_1 -receptor antagonists associated with hyperglycaemia.

The major pathway for glucose uptake is insulin-dependent. Glucose is transported into the cell by the GLUT4 glucose transporter.⁷ After binding to the insulin receptor, diverse intracellular signalling pathways result in translocation of the GLUT4 glucose transporter, and glucose uptake is initiated.⁷

However, in diabetic patients non-insulin dependent pathways may also contribute to glucose uptake.⁸ One of these is regulated by the α_1 -receptor.⁸⁻¹⁰ Several studies have demonstrated that α_1 -receptors mediate increase in glucose uptake in rat muscle cells and adipocytes. Stimulation of the α_1 -receptor leads to phospholipase C activation initiating hydrolysis of phosphatidylinositol biphosphonate. This leads to activation of protein kinase C (PKC) by release of intracellular calcium and diacylglycerol.¹¹ Lipids in the phosphatidylinositol biphosphonate pathway can be substrates for phosphatidylinositol 3-kinase (PI3K), which is an important kinase for glucose uptake.⁹ The stimulatory effect of α_1 -antagonist on glucose uptake was inhibited by the α_1 -receptor antagonist prazosin.⁸

The role of the α_1 -receptor in glucose uptake in humans was also shown. In two studies, one in healthy¹² and the other in obese subjects,¹³ interstitial glucose concentrations were measured using microdialysis. Stimulation with

an α_1 -agonist resulted in a decrease of interstitial glucose concentrations.^{12,13} The α_1 -antagonist uradipil was able to inhibit α_1 -agonist induced glucose decrease.¹³ Also, α_1 -receptor stimulation increased glucose intake in human adipose tissue.^{12,13}

The described studies illustrate a potential clinical role for the α_1 -receptor in glucose metabolism, especially in diabetic patients in whom insulin-stimulated glucose uptake is impaired.⁸ These pathways might be more prominent in obese persons who have relatively more adipose tissue.¹³ Inhibition of the α_1 -receptor pathway can result in a decreased glucose uptake, and hence an increased glucose plasma concentration.

In patients with diabetes, several other causes might explain hyperglycaemia, such as intake of glucose/carbohydrates, non-adherence to antidiabetic drugs or (infectious) diseases.¹⁴ In our reports, patient B reported a concomitant urinary tract infection which could have contributed to increased glucose levels. However, no objective support for an infection was found. In the patients we have presented, further alternative causes for hyperglycaemia were reported to be unlikely.

This adverse drug reaction and the proposed mechanism need to be further proven. The mechanism might offer a clue for studies in diabetes management: as inhibition of the α_1 -receptor can result in decreased glucose uptake, stimulation might lead to increased uptake, which might be relevant, for example, for patients who develop insulin resistance.

In conclusion, we present three cases relating hyperglycaemia to the use of tamsulosin, and propose a plausible pharmacological mechanism. Health care professionals should be aware of hyperglycaemia as possible adverse drug reaction in patients with diabetes using tamsulosin.

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