Probable Tamsulosin-Induced Hyperglycemia: A Case Study

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Background

Growing evidence has linked insulin resistance with the development of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS). Hyperinsulinemia is purported to enhance prostate smooth muscle tone and size and alter the transcription of genes involved in sex hormone metabolism (1). α-Adrenergic antagonists remain the cornerstone of care for treating LUTS. Tamsulosin was the first selective α-1a antagonist approved by the U.S. Food and Drug Administration in 1997. It has gained popularity among prescribers because it does not require dose titration and has marginal effects on blood pressure. Although side effects such as headache, dizziness, and abnormal ejaculation are well documented (2), less is known about what, if any, effects tamsulosin has on glucose homeostasis. Here, we present evidence supporting a probable association between tamsulosin and hyperglycemia.

Case Presentation

A 68-year-old Caucasian man with a history of type 2 diabetes (diagnosed >10 years ago), BPH, erectile dysfunction, osteoarthritis of the knee, stage 2 chronic kidney disease, and gout presented to his primary care provider's (PCP's) office. He complained of 2+ nocturia and problems with urinary stream. Uncontrolled diabetes was ruled out after evaluating the patient's A1C (6.7%), fasting plasma glucose (FPG) (111 mg/dL), and home glucose logs (range 97–131 mg/dL). At the time of this visit, the patient was enrolled in a diabetes wellness pilot program and had successfully lost 11 lb (BMI 28.43 kg/m^2) and lowered his A1C from 7.5 to 6.7% in the past 6 months. The PCP suspected LUTS and started tamsulosin 0.4 mg daily; no other medication changes were made. His other medications and doses were stable at the time of the visit and included exenatide extended release (ER) 2 mg weekly, glipizide 10 mg twice daily, empagliflozin 25 mg daily, metformin ER 2,000 mg daily, allopurinol 300 mg daily, aspirin 81 mg daily, atorvastatin 10 mg daily, lisinopril 5 mg daily, and fish oil 1,000 mg daily.

Seven days after initiating tamsulosin, the patient called his diabetes care coach with concerns about his rising blood glucose readings. He noted that his fasting glucose values for the preceding 3 days were all >200 mg/dL, with elevations starting as early as 48 hours after tamsulosin initiation. Upon interview, he denied any signs or symptoms of hyperglycemia, recent illness or infection, or any other medications changes other than tamsulosin. The patient also noted that he continued his nutrition and exercise plans without interruption. In fact, he reported increasing his physical activity from walking 3 days/week to 5 days during that week, which resulted in an additional 2-lb weight loss.

The care coach placed an electronic consultation with the clinical pharmacist for evaluation of this possible adverse effect. After discussing the case, the PCP advised the patient to hold his tamsulosin dose and closely monitor and log his blood glucose levels. Eight days after stopping tamsulosin, the patient reported that his fasting glucose values were back to his normal range of <130 mg/dL.

Questions

1. What is the proposed mechanism of tamsulosin-induced hyperglycemia?
2. Are there data to support this probable adverse reaction?
3. How should this interaction be managed if encountered in clinical practice?

Commentary

A literature search of Medline was conducted through November 2020 using the Medical Subject Headings

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terms type 2 diabetes mellitus, adrenergic α-antagonists, tamsulosin, hyperglycemia, and blood glucose metabolism. The search revealed a case series depicting three reports of hyperglycemia as the result of a possible adverse effect of tamsulosin (3), although the authors did not use the Naranjo probability scale (4). Male patients with comorbid type 2 diabetes were prescribed tamsulosin 0.4 mg daily for management of BPH. Within 1–2 days of initiating tamsulosin, all three patients experienced worsening glycemic control (Table 1). Alternative causes for hyperglycemia were deemed unlikely and subsequently ruled out. In all cases, dysglycemia resolved after the patients discontinued tamsulosin. Notably, all three patients were treated with insulin; however, the type and dose of insulin and duration of its use were not disclosed. The authors asserted that a drug interaction between insulin and tamsulosin was possible in two of the three cases; however, a review of drug information databases and a Medline search did not yield any documentation of such an interaction. To our knowledge, this is the first report linking tamsulosin with hyperglycemia in a noninsulin-treated patient with type 2 diabetes.

In this case, a score of 6 on the Naranjo Adverse Drug Reaction Probability Scale (4) suggested that an adverse effect was probable, and this was mechanistically supported by pharmacodynamic studies that have connected α-adrenergic pathways to glucose homeostasis. Although the dominant pathway for glucose uptake is mediated by insulin via glucose transporter type 4 expression on skeletal muscle and adipose tissue in the periphery, several studies have suggested that an additional noninsulin-dependent pathway may also contribute (5,6). Specifically, agonism of α-1 adrenergic receptors has been shown to increase interstitial glucose uptake in insulin-sensitive tissues, resulting in a decrease in plasma glucose concentrations. The proposed mechanism involves stimulation of phospholipase C, causing downstream hydrolysis of phosphatidylinositol bisphosphonate and protein kinase C activation, which results in the activation of phosphatidylinositol 3-kinase, leading to glucose uptake (6,7). Use of prototypical α-adrenergic agonists, including methoxamine in rats and phenylephrine and norfenefrine in humans, has confirmed this pathway's effect on glucose homeostasis in both healthy and obese subjects. Furthermore, in one human study, administration of the α-1 antagonist urapidil negated the hypoglycemic effect (6).

Specific to α-1a antagonism in subjects with diabetes, data are currently limited to murine studies. In one study, researchers induced diabetes in 18 of 24 male rats through administration of streptozocin (8). Six rats were treated with saline and served as nondiabetic controls. Six diabetic rats were given oral tamsulosin 1 mg/kg daily to assess what, if any, effect tamsulosin had on blood glucose and adrenaline levels. An additional six diabetic rats received glimepiride 4 mg/kg daily. The remaining six rats served as the diabetic control group. Blood glucose levels were recorded at days 0 and 21. After 3 weeks of daily treatment, blood glucose levels increased from 259.33 to 365.66 mg/dL in the tamsulosin-treated rats compared with an increase from 266.33 to 297.5 mg/dL in the diabetic control group ($P < 0.05$). Adrenaline levels were also statistically significantly higher in the diabetic control and diabetic rat groups treated with tamsulosin compared with the nondiabetic controls, suggesting that having diabetes itself is associated with heightened sympathetic activity.

In a later study, researchers evaluated tamsulosin's effects further in both euglycemic ($n = 12$) and alloxan-induced diabetic rats ($n = 24$) (9). A total of six groups, each consisting of six male rats, were used to evaluate changes in blood glucose. Four groups of diabetic rats were given 0.5 mL normal saline, 5 mg/kg glibenclamide, 0.072 mg/kg tamsulosin, or a combination of glibenclamide and tamsulosin, respectively. Blood glucose levels were recorded at baseline, day 3, and day 7. After 1 week, tamsulosin caused a significant increase in

TABLE 1 Published Case Reports of Tamsulosin and Hyperglycemia in Patients With Diabetes (3)

Patient	Duration of Type 2 Diabetes, years	Concomitant Antidiabetic Drugs	Reported Blood Glucose Before Tamsulosin Initiation, mg/dL	Reported Blood Glucose After Tamsulosin Initiation, mg/dL
61-year-old man	Not reported	Metformin, glimepiride, and insulin	144–162	324–360
67-year-old man	11	Metformin and insulin	135	320
71-year-old man	8	Insulin	54–72	180–198

blood glucose in euglycemic rats, but not in the alloxan-induced diabetic rats. Although these results are incongruent with previous findings, it is plausible that the lower dose of tamsulosin along with the choice of alloxan to induce diabetes may have affected the findings. Alloxan generates a greater increase in blood glucose levels after 48 hours ($P < 0.001$) and 72 hours ($P < 0.05$) compared with streptozocin (10) and may be less selective for pancreatic β-cells (11). Also of interest, this study found that tamsulosin delays the hypoglycemic effect of glibenclamide. On day 3, glibenclamide caused a 48% reduction in blood glucose levels compared with an 18% reduction when coadministered with tamsulosin. Because sulfonylurea prescribing trends are still inordinately high in patients with type 2 diabetes (12), the implications of this interaction may have clinical significance and warrant further exploration.

Clinical Pearls

- Current evidence supports a probable association between tamsulosin and hyperglycemia. Although no documented reports exist linking other α-1a antagonists such as silodosin and alfuzosin to hyperglycemia, clinicians should anticipate similar outcomes.
- Predicting which patients will experience tamsulosin-induced hyperglycemia is an impossible task, as it is unknown what percentage contribution α-receptors play in maintaining glucose homeostasis. We hypothesize that this adverse effect may be more common in obese patient populations and/or those with insulin resistance. We further speculate that increased adipose tissue expression, coupled with an inability to maintain glucose homeostasis through insulin-dependent pathways, may lead to compensatory reliance on α-receptors to maintain glycemic control.
- Clinicians should be aware of this potential adverse effect but understand that its clinical significance is unclear.
- At minimum, clinicians should closely monitor patients with diabetes who are co-prescribed α antagonists for hyperglycemia upon initiation and with subsequent dose changes.
- If hyperglycemia develops, clinicians can elect to modify/intensify preexisting antidiabetic therapies or stop the α antagonist altogether, depending on the severity. Fortunately, discontinuation of α antagonists has been shown to result in recovery and a return to euglycemia.

AUTHOR CONTRIBUTIONS

S.C.N. and R.N. researched data and wrote and edited the manuscript. N.B. wrote and edited the manuscript.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported. All authors are guarantors of this work and take responsibility for the integrity of the manuscript.

REFERENCES

1. Breyer BN, Sarma AV. Hyperglycemia and insulin resistance and the risk of BPH/LUTS: an update of recent literature. Curr Urol Rep 2014;15:462

2. Boehringer Ingelheim. Flomax (tamsulosin) [package insert], 2009. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020579s026lbl.pdf. Accessed 18 December 2020

3. Borgsteede S, Bruggeman R, Hoefnagel R, Huiskes M, van Puijenbroek E. Tamsulosin and hyperglycaemia in patients with diabetes. Neth J Med 2010;68:141–143

4. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–245

5. Boschmann M, Krupp G, Luft FC, Klaus S, Jordan J. In vivo response to alpha(1)-adrenoreceptor stimulation in human white adipose tissue. Obes Res 2002;10:555–558

6. Flechtner-Mors M, Jenkinson CP, Alt A, Biesalski HK, Adler G, Ditschuneit HH. Sympathetic regulation of glucose uptake by the alpha1-adrenoceptor in human obesity. Obes Res 2004;12:612–620

7. Cheng JT, Liu IM, Yen ST, Chen PC. Role of alpha1A-adrenoceptor in the regulation of glucose uptake into white adipocyte of rats in vitro. Auton Neurosci 2000;84:140–146

8. Moharir G, Shivaprasad K, Bharatha A, Naikawadi AA, Wali RS. Effect of tamsulosin a selective a_1-anatagonist on glucose homeostasis in rats. International Journal of Pharmacy and Pharmaceutical Science 2014;7:232–234

9. Satpute S, Nerurkar R, Kokne M. Effect of tamsulosin on blood glucose levels in euglycemic and alloxan induced diabetic rats and its interaction with glibenclamide. Int J Basic Clin Pharmacol 2018;7:1599–1605

10. Diab RA, Fares M, Abedi-Valugerdi M, Kumagai-Braesch M, Holgersson J, Hassan M. Immunotoxicological effects of streptozotocin and alloxan: in vitro and in vivo studies. Immunol Lett 2015;163:193–198

11. Hoftiezer V, Carpenter AM. Comparison of streptozotocin and alloxan-induced diabetes in the rat, including volumetric quantitation of the pancreatic islets. Diabetologia 1973;9:178–184

12. Kitten AK, Kamath M, Ryan L, Reveles KR. National ambulatory care non-insulin antidiabetic medication prescribing trends in the United States from 2009 to 2015. PLoS One 2019;14:e0221174