1.1. Tamsulosin and hyperglycemia in patients with type 2 diabetes

Introduction

Tamsulosin (Omnic®)is an α_1-receptor antagonist and binds selectively and competitively to α_1-receptors, in particular to the subtype α_{1A}. It has been registered in the Netherlands since 1995 and is indicated for *the treatment of urinary tract symptoms related to benign prostate hyperplasia* [1]. Off-label, tamsulosin is used in patients with urolithiasis [2]. Tamsulosin induces relaxation of the smooth muscle, and this may result in a lower blood pressure. The number of users has strongly increased since 2003 (see Table1), and given the indication the users of tamsulosin are mostly male.

Table 1. Number of patients prescribed tamsulosin in the Netherlands (GIP-database).

Year	Number of patients
2003	82,032
2004	99,771
2005	105,730
2006	131,800
2007	145,080

Hyperglycemia is an increased level of plasma glucose and the following cut-off levels for glucose concentrations in venous plasma, are used to define hyperglycemia: ≥ 11.1 mmol/l in non-fasting, and ≥ 7.0 mmol/l in fasting conditions. [3,4]
The SmPC of tamsulosin (Omnic®) does not mention hyperglycemia or problems with glycemic control as possible adverse drug reaction.
In this report, the association between tamsulosin and hyperglycemia is described.

Reports

On November 28, 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of patients who experienced hyperglycemia during tamsulosin use (see Table 2).

Table2. Reports of increase in blood glucose concentration associated with tamsulosin.

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 75483 M, 61	tamsulosin 0.4 mg benign prostatic hyperplasia	metformin glimepiride insulin metoprolol atorvastatin quinapril acetylsalicylic acid sldenafil	blood glucose increased (increase to 18-20 mmol/l, normal 8-9 mmol/l	1 day, withdrawn recovered
B 61032 M, 67	tamsulosin 0.4 mg miction problems	metformin Insulin enalapril atorvastatin telmisartan sildenafil	blood glucose increased (increase to 17.8 mmol/l, normal 7.5) drug interaction between insulin and tamsulosin suspected	2 days withdrawn recovering

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
C 53015 M, 71	tamsulosin 0.4 mg benign prostatic hyperplasia	insulin (also suspected) enalapril simvastatin	blood glucose increased, drug interaction between insulin and tamsulosin suspected	1 day withdrawn unknown

All patients used insulin for diabetes, with oral antidiabetic drugs (patient A and B), or without concomitant oral antidiabetics (patient C). The changes in blood glucose concentration occurred in all patients on the first or second day of tamsulosin treatment. In patient A and B the outcome was known: these patients were recovering after withdrawal of tamsulosin. In patient B, also a urinary tract infection could have influenced changes in blood glucose. We had no reports of other α_1-receptor antagonists associated with hyperglycemia.

Other sources of information

Literature

To our knowledge, neither tamsulosin nor other α_1-receptor antagonists have been associated with hyperglycemia as adverse drug reaction. An interaction between tamsulosin and insulin has not been described.

Databases

On November 28, the database of the Netherlands Pharmacovigilance Centre Lareb contained three cases of hyperglycemia associated with tamsulosin use on a total of 312 reports on tamsulosin. A case non-case comparison applied on this subset showed that reports of tamsulosin and hyperglycemia were disproportionally present in the database, with a reporting odds ratio (ROR) of 10.5 (CI=3.3-33.5). This association was not disproportional in the database of the World Health Organisation for adverse drug reactions with a total of 15 cases and a ROR of 0.78 (CI=0.47-1.3).
On December 8, 2008, the Eudravigilance database contained 11 reports of increased blood glucose in patients using tamsulosin. Ages of the male patients involved ranged from 68 to 85 year. All reports were rated serious. Hospitalisation was required in seven cases. Decease or life threatening disease did not occur in any of these reports. No information was reported about concomitant use of insulin.

Mechanism

The major pathway for glucose-uptake in non-diabetic persons is insulin-dependent. Glucose is transported into the cell by the GLUT4 glucose transporter, which is inside the cell when there is no insulin binding to the cellular surface. After binding of insulin to the insulin receptor, divers intracellular signaling pathways result in translocation of the GLUT4 glucose transporter from the endoplasmatic reticulum to the cell membrane, and glucose uptake is initiated [5].
However, in diabetic patients non-insulin dependent pathways may also contribute to glucose uptake [6]. One of the insulin independent pathways is mediated by the β_3-receptor, that has been shown to influence glucose-uptake [7]. Another insulin independent pathway is regulated by the α_1-receptor [6,8,9].
Several studies 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 bi-phosphonate. This leads to activation of protein kinase C (PKC) by release of intracellular calcium and diacylglycerol [10]. Lipids in the phosphatidylinositol bi-phosphonate pathway can be substrates for phosphatidylinositol 3-kinase (PI3K), which is an important kinase for glucose uptake [8]. The stimulatory effect of α_1-antagonist on glucose uptake was inhibited by the α_1-receptorantagonist prazosin [6]. In summary, the exact intracellular

mechanism of α_1-receptor mediated glucose uptake has not been revealed, but the effect appears to be related to activation of PKC, PI3K and/or GLUT4 translocation [6,8].
The role of the α_1-receptor in glucose-uptake in humans was also shown. In two sudies, one in healthy [11] and the other in obese subjects [12], interstitial glucose concentrations were measured using microdialysis. These studies showed that stimulation with an α_1-agonist resulted in decrease of interstitial glucose concentrations [11,12]. The α_1-antagonist uradipil was able to inhibit α_1-agonist induced glucose decrease [12]. These studies showed that α_1-receptor stimulation increased glucose intake in human adipose tissue [11,12].
The described studies illustrate a potential clinical role of the α_1-receptor, especially in diabetic patients in whom insulin-stimulated glucose uptake is impaired [6]. These pathways might be even more prominent in obese persons, who have relatively more adipose tissue [12]. Inhibition of the α_1-receptor pathway can result in a decreased glucose uptake, and hence an increased glucose plasma concentration.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb has received three reports of tamsulosin associated with an increase in blood glucose. All patients were diabetics, and this association might be related to patients in whom insulin-dependent glucose uptake is limited. Although in two of the reported cases a dechallenge was present, confounding cannot be excluded.
A pharmacological explanation for hyperglycemia is present: stimulation of α_1-receptors is one of the insulin-independent pathways of glucose uptake, hence inhibition of this route might result in an increase of plasma glucose concentrations. Although no further cases were reported to Lareb, this pharmacological mechanism could also explain hyperglycemia associated with other α_1-receptor antagonists.

References

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This signal has been raised on February 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).