1.1. Tamsulosin and depressive reactions

Introduction

Tamsulosin (Omnic®) is an adrenergic alpha1-receptor (alpha1-AR) blocker. It is registered for *the treatment of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH)* [1]. In the Netherlands, tamsulosin is the most used alpha1-AR blocker for the treatment of LUTS and BPH. The number of tamsulosin users in the Netherlands is shown in Table 1 [2].

Table 1. Number of tamsulosin users in the Netherlands between 2006 and 2010 [2].

	2006	2007	2008	2009	2010
G04CA02 tamsulosin (Omnic-ocas ®)	131,810	146,670	162,100	172,910	187,420

The mechanism of action of tamsulosin is based on the inhibition of postsynaptic alpha1-ARs, mainly alpha1a and alpha1d. Inhibition of these receptors results in relaxation of the smooth muscles in the prostate and the urethra. It improves the flow of urine through the urethra and it decreases disorders such as frequent urination [1]. The most common adverse drug reaction associated with oral tamsulosin use is dizziness. Others are: headache, palpitations, orthostatic hypotension and constipation [1].

Lareb received nine reports of depression and depressed mood with the use of tamsulosin. According to the DSM-IV criteria depressive disorders can be specified as ‘major depressive disorder’, ‘dysthymic disorder’ and ‘depressive disorder not otherwise specified’. The essential feature of a major depressive episode is a period of at least two weeks, during which there is either depressed mood or a loss of interest/pleasure in nearly all activities. The individual must also experience at least four of the following symptoms: changes in appetite, weight, sleep, psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty with thinking, concentrating, making decisions; recurrent thoughts of death, suicidal ideation, plans or attempts [3].

At the Pharmacovigilance Centre Lareb, adverse drug reactions are coded the way it is reported by the reporter. It is therefore likely that the use of the term ‘depression’ on the reporting form not always reflects a true depression, according to the DSM-IV criteria, but a ‘depressed mood’.

Depression and depressive mood are not mentioned in the Dutch SPC of tamsulosin [1]. Here, the reports received by the Netherlands Pharmacovigilance Centre Lareb concerning the MedDRA terms ‘depression’ or ‘depressed mood’ with the use of tamsulosin will be discussed. Because of the difference in seriousness a differentiation between depression and depressed mood is made.

Reports

On July 14, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained nine reports concerning ‘depression’ or ‘depressed mood’ in association with the use of tamsulosin, see Table 2.

Table 2 Reports of depression or depressed mood associated with the use of tamsulosin.

Patient, Sex, Age,	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome

Patient, Sex, Age,	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 44172 M, 51-60 years General Practitioner	Tamsulosin capsule 0,4 mg Hyperplasia of prostate		depression	not reported discontinued recovered
B 45220 M, 61-70 years Consumer	Tamsulosin capsule 0,4 mg Malignant neoplasm of prostate	chlorthalidone tablet 25mg, valsartan capsule 80mg	depression, hypotension orthostatic	3 hours discontinued recovered
C 48375 M, 51-60 years Pharmacist	Tamsulosin capsule 0,4 mg		drug ineffective, sleeplessness, depressed state	3 day discontinued not recovered
D 52781 M, 51-60 years General Practitioner	Tamsulosin capsule 0,4 mg Prostatic disorder		anxiety, depression	2 day discontinued recovered
E 62706 M, 61-70 years General Practitioner	Tamsulosin capsule 0,4 mg Benign prostatic hyperplasia		suicidal ideation, depression	1 month discontinued recovered
F 102645/103663 M, 51-60 years General Practitioner/ Pharmacist	Tamsulosin capsule 0,4 mg Benign prostatic hyperplasia	glimepiride tablet 2mg, simvastatin tablet 40mg, carbasalate calcium sachet 100mg	depressed mood	2 weeks / 40 days discontinued recovered
G 108178 M, 61-70 years Pharmacist	Tamsulosin capsule 0,4 mg		depression	within a day discontinued recovered
H 117686 M, 51-60 years General Practitioner	Tamsulosin capsule 0,4 mg Prostatism	dutasteride capsule 0,5mg	depressed state	1 week discontinued not yet recovered

Patient, Sex, Age,	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
I 122291 M, 71 years and older Pharmacist	Tamsulosin capsule 0,4 mg Benign prostatic hyperplasia		muscle tone decreased, depressed mood	3 day discontinued recovered

In six patients (patient B, C, D, G, H and I) the depression/depressed mood had a latency of less than a week after start of tamsulosin. In patient G tamsulosin was started on 3 February 2000 and withdrawn on 3 May 2010. The reporter reports a latency of less that one day after start. The accuracy of this latency is doubtful. Case F was reported twice, once by the general practitioner and once by the pharmacist. There is a discrepancy in latency between these two reports (two weeks versus 40 days).

With exception of patient C, all patients had a positive dechallenge. In only one of these patients (patient G) the depression was treated with antidepressants. In patient D, E and H recovery took place two weeks after withdrawal of tamsulosin.

The Netherlands Pharmacovigilance Centre Lareb received the medical history of three patients (patient B, F and G). Patient B is known with prostate carcinoma, in patient F there is a suspicion of a silent myocardial infarction and patient G had an unspecified operation.

In the nine reports no positive rechallenge was reported.

Other sources of information

SPC

The Dutch SPC of tamsulosin does not mention depression or depressed mood[1].

Literature

No supporting analyses/case reports were found in literature. Unlike the cases of the Netherlands Pharmacovigilance Centre Lareb, *Clifford and Farmer, 2002* [4], performed a study which rejects this association. The study was performed in two parts: a cohort analysis (754047 men, of which 6336 with BPH therapy) comparing the incidence of depression for current users of BPH therapy versus that in non-users and comparing the incidence of depression in men with BPH versus those without, and a nested case-control analysis (51608 cases) comparing exposure to BPH therapy in cases of depression versus age-matched controls with adjustment for confounding variables.
Cases of depression were restricted to men who had their first prescription for an antidepressant after 12 months of registration on the General Practice Research Database to ensure the identification of the first antidepressant prescription. *Clifford and Farmer* found that the risk of depression was significantly higher in men with BPH compared with those without. This risk was not significantly different from men exposed to alpha1-AR blockers versus those unexposed when adjusted for the presence of BPH. The crude incidence of depression associated with exposure to a specific therapy for BPH is shown to be confounded by underlying disease.

Database

For the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO, the MedDRA Preferred terms 'depression' and 'depressed mood' in association with tamsulosin were taken into account.

Table 3. Reports of depression and depressed mood associated with tamsulosin in the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Drug	Number of reports	ROR (95% CI)
Tamsulosin and depression	Lareb: 6 WHO: 52	1,27 (0,57-2,85) 0,48 (0,37-0,63)
Tamsulosin and depressed mood	Lareb: 3 WHO: 4	2,4 (0,8-7,5) 0,50 (0,19-1,32)

On August 15, 2011, the Eudravigilance database contained 25 reports of depression or depressed mood associated with the use of tamsulosin, which was reported disproportionally (ROR = 0.5, 95% CI: 0.3 – 0.7). All patients were males and the median age of the patients was 65 years (range 48 – 86 years). A total of eighteen reports were classified as serious, seven were non-serious and in one case the seriousness was not reported. Most of the serious cases were classified as such due to hospitalisation of the patient.

Mechanism

The mechanism by which tamsulosin might induce depressive reactions is unknown. *Stone and Quartermain, 1999* [5], reported that alpha1-AR blockade in the central nerve system induces depressive behaviour in mouse models of depression. Subsequent, *Stone et al., 2003* [6], researched the mouse brain and found new evidence that the alpha1-ARs are essential for behavioural activation in response to either novelty or psychostimulant drugs.
Doze et al, 2009 [7], investigated the effect of alpha1a-AR and alpha1b-AR signalling on depression-related behaviour in mice. They demonstrated that constitutively active mutant adrenergic alpha1a-receptor (CAM alpha1a-AR) expression influences antidepressant-like behaviour in mice. They also found that constitutively CAM alpha1a-AR expression promotes neurogenesis in mice. This neurogenesis was also enhanced by chronically treating wild type mice with the alpha1a-AR agonist, cirazoline.

Discussion

Lareb received nine reports concerning depressive reactions with the use of tamsulosin. In eight reports there was a positive dechallenge. In majority of the reports the depressive reaction started within a short period of time (for six of the eight reports, within a week) and in only one report the depression was treated with antidepressants. In four of the reports a 'depression' was reported. According the DSM-IV criteria, presentation of depressive symptoms within two weeks of tamsulosin cannot be coded as 'depression'.

The association between tamsulosin and depressive reactions is not statistically supported by the database of the Netherlands Pharmacovigilance Centre Lareb or the WHO. In fact, when it comes to the association between tamsulosin and depression, the WHO gives a ROR with upper limit of the 95% CI below one. This might indicate a protective effect.

Cifford and Farmer, 2002, found that the risk of depression was significantly higher in men with BPH compared to those without and that the incidence of depression associated with BPH therapy is shown to be confounding by

underlying disease. They found no significantly higher risk of depression after exposure to alpha1-AR blockers. The difference between this research and the reports of the Netherlands Pharmacovigilance Centre Lareb is the used inclusion criteria. *Clifford and Farmer* included alpha1-AR blocker users after first prescription for an antidepressant. The Netherlands Pharmacovigilance Centre Lareb included all reports of depression or depressed mood with the use of tamsulosin. In only one of these reports the depression was treated with antidepressants.

Although the mechanism by which tamsulosine might induce depressive symptoms is unknown, there are a few studies that associate the alpha1-AR with depressive behaviour. *Doze et al, 2009*, demonstrated antidepressant-like behaviour in mutant alpha1a-AR expression in mice. They also found neurogenesis in wild type mice after chronically treatment with the alpha1a-AR agonist cirazoline. One can imagine that an opposite reaction, by blocking the alpha1a-AR gives depressive-like behaviour.

Conclusion

These cases suggest a signal of depressive reactions associated with the use of tamsulosin. It is not certain if these cases reflect a depression according to the DSM-IV criteria. To extent this signal the PSUR's of tamsulosine should be verified on depressive reactions as listed in MedDRA terminology.

- PSUR of tamsulosin should be verified on depressive reactions

References
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This signal has been raised on November 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).