1.1. Alpha-1 blocking agents and liver disorders

Introduction

Selective post-synaptic α_1-blockers are indicated for treatment of the functional symptoms associated with benign prostatic hyperplasia (BPH). Alfuzosin (Xatral®) is registered in the Netherlands since 1990, tamsulosin (Omnic®) since 1995 and terazosin (Hytrin®) since 1991 [1-3].
The effect of α-blockers in BPH is based on antagonism of α_1 receptors in the bladder and in the smooth muscle of the bladder neck and the prostate. Despite their high degree of uroselectivity, α-blockers also block α_1-receptors in the vasculature which can lead to vasodilatation and a decrease of blood pressure. Therefore, orthostatic hypotension and related symptoms like dizziness, tachycardia and syncope are commonly occurring adverse drug reactions (ADRs). Hepatic ADRs are not mentioned in the SmPCs of alfuzosin, tamsulosin and terazosin. Severe hepatic insufficiency is mentioned as a contra-indication for alfuzosin and tamsulosin [1,2].

Reports

On November 24th 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of liver disorders associated with the use of alfuzosin (Table 1)* and four with tamsulosin (Table 2). No hepatic ADRs were reported for terazosin.

Table 1. Reports of liver disorders associated with the use of alfuzosin.
(Most prominent lab values are shown in bold format)

Patient, Number, Sex, Age, Medical history Reporter	**Suspect drug Daily dose Indication for use**	**Concomitant medication (underlined = possible cause of hepatic ADRs)**	**Suspected adverse drug reaction Lab tests**	**Time to onset, Action with drug, Outcome**
A 13580 M, 84 CARA, AP Internist	alfuzosin 2 dd 2.5mg	ipratropium, omeprazole, isosorbide mononitrate, budesonide, <u>diltiazem</u>, ranitidine	cholestatic hepatitis, icterus **Bili 180, dir 145** umol/l; **AF 461**, **GGT 95**, ASAT 46; ALAT 43u/l ERCP: no obstructions Serologic tests for hepatitis A, B, C, Epstein-Barr and cytomegalovirus negative CT: normal Liver biopsy: isolated cholestasis, matching drug-induced hepatitis	9 months alfuzosin discontinued, (diltiazem continued) recovered
B 20549 = 23018 M, 74 Malaria,	alfuzosin 2 dd 2.5mg	none	intrahepatic cholestasis, icterus **Bili 124, dir 112**, **AF 213**, ASAT 23, ALAT	5 months discontinued slowly recovering

* The Lareb Quarterly Report send to the Medicines Evaluation Board contained a duplicate report. This is corrected in the current version.

episodes of jaundice Internist / MAH			38, LD 241, GGT 34, amylase 161 CT: normal Liver biopsy: cholestatic hepatitis, probably drug induced Echography, CT scan, serology, virology: no abnormalities other causes were excluded	
C 21830 M, 64 Internist	alfuzosin 3 dd 2.5mg hyperplasia of prostate	none	cholestatic hepatitis	4 months discontinued not yet recovered
D 37077 = 37391 M, 65 Mild hepatic cirrhosis GP / MAH	alfuzosin 1 dd 10mg hyperplasia of prostate	terbinafine, omeprazole, paracetamol, famotidine, cetirizine, vitamin B	hepatic cirrhosis aggravated, death	3 weeks discontinued fatal

The time to onset varied from three weeks to nine months. In three cases cholestatic injury was diagnosed. (Partial) recovery after discontinuation of alfuzosin was reported in two cases: A and B. Patient A also used diltiazem – with hepatitis being a possible, rare ADR - over the last three months prior to his hepatic problems. But despite the continued use of diltiazem this patient recovered upon discontinuation of alfuzosin only. Patient B had episodes of jaundice 50 years ago, possibly related to the malaria he had at that time. Fatal outcome was reported for patient D. Patient D had pre-existent mild liver cirrhosis for ten years with hardly any enzyme deviations. The initial cause of this cirrhosis was not reported. Alfuzosin was discontinued after four weeks of treatment. The patient died 2.5 month later, cause of death was not reported.
Other causes for the hepatic injury (alcohol, viral or auto-immune) were not reported.

Table 2. Reports of liver disorders associated with the use of tamsulosin.

Patient, Number, Sex, Age Medical history Source	**Suspect drug Daily dose Indication for use**	**Concomitant Medication**	**Suspected adverse drug reaction, Lab tests**	**Time to onset, Action with drug outcome**
A 35611 M, 69 Parkinson's disease MAH	tamsulosin 0.4mg lansoprazole 30mg riluzole 50mg simvastatin 20mg	omeprazole, pantoprazole, tolbutamide, metformin, glibenclamide, glibornuride, insulin, losartan, atenolol, ascal	icterus, hepatitis **bili 231, dir 134** umol/l, **LD 754, ASAT 765, ALAT 1207 u/l** Liver biopsy: signs of inflammation, drug-induced hepatitis	unknown tamsulosin: withdrawn / recovery after discontinuation of simvastatin
B 55514 = 55620 M, 38 No hepatic medical history Pharm / GP	tamsulosin 0.4mg hyperplasia of prostate	paracetamol rabeprazole	hepatic function abnormal, elevated liver enzymes bili 5, GGT 29, **ASAT139, ALAT 285 u/l**, AF 80 Virus/ faeces neg.	20 days discontinued recovered: liver values normalized
C 62198	tamsulosin 0.4mg	not reported	liver function disorder	6 months

M, 82 Pharm			**bili 81, dir 51**, **GGT 243, ASAT 869, ALAT 1798 u/l**; AF 112 amylase 62	discontinued recovered
D 73574 M, 78 Internist	tamsulosin 0.4mg prostatic hypertrophy	macrogol laxative, prednisolone, salmeterol/ fluticasone, tiotropium, risedronate, calcium	cholestatic icterus **bili >400**, Echography and ERCP: no abnormalities	3 months discontinued recovered

The latency time varied from 20 days to 6 months. In three cases hepatocellular injury was most likely. Tamsulosin was withdrawn in all four cases; all patients recovered. Patient A discontinued the use of tamsulosin, lansoprazole and riluzole but his symptoms did not improve. It was not until simvastatin was discontinued, several weeks later, that the patient recovered. Therefore, a contribution of simvastatin to the hepatic symptoms was likely.
Other possible causes for the liver-injury (alcohol, viral or auto-immune) were not reported for either of these patients.

Other sources of information

Literature

Drug-induced liver injury is described in a recently published review [4]. However, the association with α-blockers is not mentioned in this review. The association between alfuzosin and liver disorders was described in three case reports [5-7], the association between tamsulosin and liver disorders in one case report [8].

Other databases

The database of the World Health Organisation for adverse drug reactions contained 9,496 reports of ADRs in association with the α-blockers, 206 of which refer to hepatic disorders (2.2%). Table 3 shows the different kind of hepatic ADRs that were reported for each of the α blockers. Due to the different MedDRA terms that were used for these hepatic ADRs, an overall ROR could not be calculated.

Table 3. Hepatic ADRs associated with α blockers in the WHO database.

Hepatic ADR	alfuzosin	tamsulosin	terazosin	Total
Bilirubinaemia	1	3	9	13
Cholangitis		2		2
Cholecystitis			2	2
Gallbladder disorder			2	2
GGT increased	3	8		11
Hepatic cirrhosis	2		4	6
Hepatic enzymes increased		9	3	12
Hepatic function abnormal	3	9	28	40
Hepatitis	9		3	12
Hepatitis cholestatic	10	6	6	22
Hepatitis viral	1			1
Hepatocellular damage	4	3		7
Hepatomegaly		1		1
Hepatosplenomegaly	1	1		2
Jaundice	10	13		23
ASAT increased	4	8	14	26
ALAT increased		11	13	24
Total number of hepatic ADRs	48	74	84	206

On December 8th, 2008, the Eudravigilance database contained 16 reports of hepatitis, cholestatic hepatitis or hepatocellular liver injury occurring in patients using alfuzosin, tamsulosin or terazosin. Specified ages ranged from 56 to 88 years. In all but one case seriousness was specified, all other reports were serious. Hospitalisation was reported in 15 cases.

Prescription data
The number of patients using α-blockers in the Netherlands is shown in Table 4. The relatively low number of users of terazosin may explain the lack of hepatic reports on this drug in the Netherlands.

Table 4. Number of users of α blockers in the Netherlands 2003-2007
(Source: Drug Information System of the Dutch Health Care Insurance Board (GIP)

	2003	2004	2005	2006	2007
G04CA01 Alfuzosin (Xatral®)	47,988	57,792	58,100	66,797	63,301
G04CA02 Tamsulosin (Omnic®)	82,032	99,771	105,730	131,800	145,080
G04CA03 Terazosin (Hytrin®)	3,530	3,198	2,810	2,836	2,513

Mechanism

Drug-induced liver disorders may range from mild biochemical abnormalities to acute liver failure. About 15% of all acute liver failure cases are attributed to idiosyncratic drug reactions. Drugs can cause hepatocellular, cholestatic or mixed liver injury. Drug withdrawal may lead to recovery, which may be delayed up to 1 year in cases of cholestatic injury. However, in 6% of the cases chronic disease may occur [4]. Various different drugs have been associated with liver disorders, antibiotics and NSAIDs being the most common cause. Alpha blockers were only associated with liver disorders in few case reports so far. Alpha blockers are extensively (>90%) metabolized by the liver.) Although the mechanism of α-blocker induced hepatotoxicity has not been identified yet, an idiosyncratic reaction seems most plausible [5-7].

Conclusion

Lareb received four reports of liver disorders associated with the use of alfuzosin and four associated with the use of tamsulosin. In five cases liver injury was confirmed by lab tests. Positive dechallenge was reported in five cases.

References

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4. Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: an overview. Expert Opin Drug Saf 2007;6(6):673-84.
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7. Zabala S, Thomson C, Valdearcos S, Gascon A, Pina MA. Alfuzosin-induced hepatotoxicity. J Clin Pharm Ther 2000;25(1):73-4.
8. Fremond L, Diebold MD, Thiefin G. [Acute pseudoangiocholitic hepatitis probably induced by tamsulosin]. Gastroenterol Clin Biol 2006;30(10):1224-5.

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).