1.1. Fexofenadine and bradycardia

Fexofenadine hydrochloride is a non-sedating H_1 antihistamine. It was registered in the Netherlands in 1997. Fexofenadine is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children aged 12 years or older [1,2]. The past few years, the number of patients using prescribed fexofenadine in the Netherlands has been stable around 150,000 [3]. Fexofenadine is as prescription only drug registered as "Telfast®", but is also available over the counter as "STP-free" [1,2].
The SmPC mentions that patients with a history of or ongoing cardiovascular disease should be warned that antihistamines as a drug class have been associated with tachycardia and palpitations [1,2]. Bradycardia is not mentioned in the SmPC of fexofenadine. However, the Netherlands Pharmacovigilance Centre Lareb received the third serious reports in which the use of fexofenadine was associated with bradycardia. In this report the details on this possible association will be described.

Reports

On June 3, 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports concerning bradycardia during the use of fexofenadine. All three reports were reported as serious.

Patient A (report number 28889) is a 27-year-old male who had been using fexofenadine 120 mg once daily for treatment of allergic rhinitis. He developed an extreme bradycardia for which CPR was needed. No ECG's were made the moment the bradycardia occurred. However, when CPR was started, the QTc interval was within normal range. The patient had a serious post anoxic encephalopathy. This case was reported by a cardiologist.

Patient B (report number 73912) is a 37-year-old female who had been using fexofenadine 120 mg once daily and Sublingual Immunotherapy (SLIT) for the treatment of allergy. She developed peripheral oedema, dyspnoea on exertion, weight increase and bradycardia following administration of both drugs, with an unclear time to onset after start of fexofenadine. The patient was hospitalized and both fexofenadine and SLIT treatment were withdrawn, after which she recovered. The consulting cardiologist confirmed bradycardia. On the ultrasound of abdomen and heart no signs of cardiac failure were found. On a CT scan slight pleural effusion was visible, no signs of pericardial effusion or pulmonary embolism. Cardiac failure was excluded by the consulting cardiologist. This case was reported by an internist/allergist.

Patient C (report number 86460) is a 57-year-old female, who developed bradycardia following administration of fexofenadine 120 mg once daily for allergic rhinitis with a latency of ten days after start. Concomitant medication was not reported. The patient was hospitalized. Fexofenadine was withdrawn. The cardiology report mentioned sinusbradycardia approximately 45-50/min, ECG SR 50/min with an early repolarisation V2-3. The patient gradually recovered within a few days and her heart rate increased to normal values (around 70/min). Although the cardiologist suggested a possible vasovagal reaction, this was considered unlikely by her spouse who, like the patient herself, is a general practitioner and described a slow onset and long duration of the complaints. This is not compatible with a vasovagal reaction.

All three patients had no previous history of cardiac disorders. The absence of a prolonged QTc interval was explicitly mentioned in patients A and C. Possible risk factors for the development of bradycardia were not reported.

Other sources of information

SmPC

The Dutch SmPC of fexofenadine mentions tachycardia and palpitations as possible adverse drug reactions, but does not mention bradycardia. It also states that no significant differences in QTc intervals were observed in seasonal allergic rhinitis patients given fexofenadine hydrochloride up to 240 mg twice daily for two weeks when compared to placebo. Also, no significant change in QTc intervals was observed in healthy subjects given fexofenadine hydrochloride up to 60 mg twice daily for six months, 400 mg twice daily for 6.5 days and 240 mg once daily for one year, when compared to placebo. Fexofenadine at concentrations 32 times greater than the therapeutic concentration in man had no effect on the delayed rectifier K^+ channel cloned from human heart [1,2].

Literature

According to the literature fexofenadine has little cardiotoxicity [4,5]. No case reports of fexofenadine induced bradycardia were found. The safety of fexofenadine in children aged six to 11 years with seasonal allergic rhinitis has been assessed in a large (n=875), double-blind, randomized, placebo-controlled, parallel study. No statistically significant electrocardiographic effects were discovered [6].

Databases

In June 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of bradycardia in association with fexofenadine. The reporting odds ratio (ROR) is statistically disproportional (ROR = 9.5, 95%CI: 3.0-30).

The database of the World Health Organization (WHO) contained eight reports of bradycardia during the use of fexofenadine, two of which are Dutch reports. Four reports concerned male patients, three female and the sex was unspecified in one report. The age of the patients varied from 13 to 62 years (one patient with an unknown age). In two patients an atrioventricular block was reported concomitantly with the bradycardia, as adverse event. In one patient the blood potassium level was decreased to a not specified value.

The WHO database also contained three patients with atrioventricular block, specified as a first degree block in one patient, during the use of fexofenadine. It all concerned male patients with an average age of 32 years [range 26-37].

On the third of June 2009, the Eudravigilance database contained, besides one of the Dutch reports, nine reports of bradycardia associated with the use of fexofenadine (table 2). Striking is that three of these reports originated from doctors who experienced this suspected adverse drug reaction themselves. The proportional reporting ratio (PRR) for fexofenadine and bradycardia in the Eudravigilance database is 2.03 (95% CI 1.10-3.76).

No reports are present under MedDRA Preferred Terms “sinusbradycardia or sinoatrial block” in the Eudravigilance database. However, another four cases of atrioventricular block were reported (table 1).

Please note, patients H, J and M were reported in both the WHO and Eudravigilance database.

Table 1. Reports of fexofenadine and bradycardia in the Eudravigilance database

Patient, Sex, Age Country of origin	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Clinical information
A F, 30.8. 1946 Japan	atorvastatin hyper lipidaemia fexofenadine allergic conjunctivitis		bradycardia QT-prolongation heaviness of head anti-allergic drug interaction	time to onset: four days for fexofenadine, two days for atorvastatin. recovery, first for QT-prolongation, later for bradycardia after withdrawal of both drugs
B F,15 Germany	fexofenadine insect bite		bradycardia extrasystoles unspecified AV block	unspecified AV block, HR 45/min, bradycardia, dizziness, syncope, convulsions. ECG: AV block, extrasystoles, no QT-prolongation
C M,65 India	fexofenadine acute rhinitis	digoxin amiodarone ramipril furosemide/ amiloride	bradycardia syncopal attack	withdrawal of fexofenadine, orcipraenaline treatment, recovery, multiple episodes of syncope after four days use of fexofenadine
D M, 80 Japan	fexofenadine urticaria		bradycardia dizziness nausea vomiting	positive dechallenge (and “intravenous drip”) heart rate 45/minutes. (70-90 normal) on day of use of fexofenadine, doubt whether bradycardia caused dizziness and nausea or vice versa
E M, unspeci fied age, United States	fexofenadine pruritus NOS digoxin	levothyroxine insulin oxymetazoline potassium chloride	bradycardia (30/min) heart block	discontinuation of fexofenadine and all cardiac medication, normalisation to 60-70 bpm, attributed to interaction by reporting physician (patient involved)
F unspeci fied age (13 or 14) and unspecified sex United States	fexofenadine		bradycardia fainting	no information on action taken with drug and outcome of reaction
G F, 30.12. 1971 Brazil	fexofenadine allergic rhinitis		bradycardia mild dyspnoea right branch blocked	reporting physician is patient involved limited additional information

Patient, Sex, Age Country of origin	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Clinical information
H F,43 United States	fexofenadine multiple allergies		bradycardia (40 bpm) heart block first degree	withdrawal recovery
I F,54 Italy	fexofenadine	phenobarbital orphenadrine clothiapine aspirin carbamazepine	bradycardia, hypotension, presyncope	very limited information, first degree AV block?, BAV1
J M, 26 United States	fexofenadine multiple allergies	levothyroxine	first degree AV block chest tightness	withdrawn, recovery, adverse reaction related to fexofenadine 540 mg overdose, clear ECG one month prior and one month after occurrence of reaction
K F, 72 Japan	fexofenadine allergic rhinitis	olopatadine quazepam magnesium oxide odium pciosulfate	third degree AV block	time to onset thirteen days, withdrawal, recovery, pacemaker insertion, apparent need for magnesium suppletion, breast cancer and hepatitis C in medical history
L Age and sexe unspecified United States	fexofenadine	clindamycin	third degree AV block	minimal clinical information provided
M M,34 United States	fexofenadine sinusitis	omeprazole	bradytachyarrhithmia first degree AV block	two weeks, recovery after withdrawal, positive rechallenge
N F, 80 Japan	fexofenadine pollinosis	terbinafine pravastatin senna leaf	third degree AV block	latency twelve hours and ten minutes after ingestion of additional dose of fexofenadine, negative rechallenge

Mechanism

A couple of mechanisms might contribute to the possible cardiotoxicity of fexofenadine. Fexofenadine is the pharmacologically active metabolite of terfenadine. In vitro studies have indicated that terfenadine may have arrhythmogenic effects similar to quinidine [7]. These studies have found that terfenadine is equipotent to quinidine as a blocker of the delayed rectifier potassium current in isolated fenine myocytes. However, fexofenadine did not inhibit this current even at concentrations 30 times higher than the concentration of terfenadine producing a half-maximal effect [7].

It has been reported that fexofenadine can cause a prolonged QTc interval. The exact mechanism is unknown, but the drug might delay repolarization causing a prolonged QTc interval that may induce ventricular arrhythmias, including bradycardia, in susceptible individuals [8]. However, a prolongation of the QTc interval is not reported in any of the Lareb cases and once in the Eudravigilance cases concerning bradycardia.

Another possible mechanism is the theory that fexofenadine is not completely selective for the H_1 receptor, but has also got some affinity for the H_2 receptor. H_2 receptor antagonists can cause bradycardia and even atrioventricular block [9,10].

Discussion and conclusion

Lareb received three recently the third serious reports of bradycardia associated with fexofenadine. All patients were admitted to hospital for adequate treatment, in one patient resuscitation was needed. The association is supported by disproportionality in the Lareb database and Eudravigilance database, but neither by the database of the WHO nor by publications in the literature. However, single reports in the Eudravigilance and WHO database are suggestive for a causal relationship. It is not sure yet which mechanism is responsible for this serious, possible adverse drug reaction of fexofenadine. In seven Eudravigilance cases an AV block was reported, in three of them concomitantly with bradycardia, which might indicate influence of fexofenadine on the AV node. Given the possible consequences of bradycardia and the fact that this product is available as an OTC drug, a clear warning in the SmPC should be stated.

References

1. Dutch SPC Telfast®. (version date: 18-12-2008, access date: 3-6-2009) http://db.cbg-meb.nl/IB-teksten/h21625.pdf.
2. Dutch SPC STP-free®. (version date: 18-12-2008, access date: 3-6-2009) http://db.cbg-meb.nl/IB-teksten/h21624.pdf.
3. College for health insurances. GIP database. (version date: 3-6-2009, access date: 3-06-2009) http://www.gipdatabank.nl/.
4. Eseverri J. [Projection of new antihistamines]. Allergol Immunopathol (Madr) 2000;28(3):143-52.
5. No authors listed. Fexofenadine: new preparation. Terfenadine, without cardiotoxicity. Prescrire Int 1999;8(39):11-3.
6. Graft DF, Bernstein DI, Goldsobel A, Meltzer EO, Portnoy J, Long J. Safety of fexofenadine in children treated for seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2001;87(1):22-6.
7. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. JAMA 1993;269(12):1532-6.
8. Pratt CM, Mason J, Russell T, Reynolds R, Ahlbrandt R. Cardiovascular safety of fexofenadine HCl. Am J Cardiol 1999;83(10):1451-4.
9. Dutch SPC cimetidine (PCH). (version date: 26-4-2000, access date: 3-6-2009) http://db.cbg-meb.nl/IB-teksten/h13898-h13899-h16792.pdf.
10. Dutch SPC Zantac®. (version date: 23-1-2006, access date: 3-6-2009) http://db.cbg-meb.nl/IB-teksten/h09265-h11161-h11485.pdf.

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