bijwerkingen centrumlareb

Metoprolol and lichenoid eruptions

Introduction

Metoprolol is a cardioselective bèta-1-adrenoreceptorantagonist with effect on bèta-1-adrenoreceptors in cardiac tissue, resulting in reduction of heart rate, cardiac output and blood pressure. Metoprolol is indicated for *the treatment of hypertension, angina pectoris, heart failure, hyperthyroidism and prevention of recurrent myocardial infarction* (1). Metoprolol was granted marketing authorization in the Netherlands in 1980 (2).

Lichen planus is characterized by a papulosquamous eruption of pruritic flat-topped, violaceous papules or plaques. It can affect skin, oral cavity, genitalia, scalp, nails and esophagus. The etiology is not known. An immune-mediated mechanism was postulated, involving activated T-cells directed against basal keratinocytes. Cutaneous lichen planus usually resolves spontaneously within one to two years. Lichen planus of the oral cavity, genitalia, scalp and nails tends to be more chronic. Lichenoid eruptions can be drug-induced. Lesions in lichenoid drug eruptions are less monomorphic compared to lichen planus and can be more eczematous or psoriasiform with marked desquamation. The latency between start date of the culprit drug and occurrence of lichenoid drug eruptions may vary from months to a year or more. The lichenoid drug eruption can resolve in weeks to months after discontinuing the culprit drug, sometimes leaving post-inflammatory hyperpigmentation (3).

In 2012, the Netherlands Pharmacovigilance Centre Lareb published a signal concerning the group of beta-adrenergic blockers in association with lichenoid drug eruption. In this signal four reports concerned metoprolol (4). Lichenoid eruptions are being monitored in the Periodic Safety Update Report (PSUR) of metoprolol. However, Lareb received several additional reports since the signal in 2012 and the next PSUR for metoprolol will only be in 2025 (5). Therefore, the currently received cases of metoprolol in association with lichenoid eruptions are described in this signal.

Reports

From 31 October 1991 to 23 August 2017 the Netherlands Pharmacovigilance Centre Lareb received ten reports of lichenoid eruptions associated with the use of metoprolol. The reports are listed in table 1. In association with metoprolol, there were three reports of lichen planus, two reports of aggravated lichen planus, two reports of oral lichen planus, two reports of lichenoid dermatitis and one report of non-specified lichen. Nine cases involved females, one involved a male. The ages varied between 45 and 68 years, with an average of 59 years. In one case (case J) two other drugs (alendronate and enalapril) were marked suspect. In most cases (seven cases in total) the latency varied between two weeks and six months. In one case (case J) the latency was five years and the latency was unknown in two cases. Metoprolol was withdrawn in six cases. Information regarding treatment of lichenoid eruptions was reported in six cases (cases A, C, E, F, H, J). Treatment included variable topical corticosteroids, corticosteroid mouthwash/gel, lidocaine gel, vaseline and lanette cream. Four patients who were treated recovered or were recovering, three patients did not recover, and in three cases the outcome was unknown. In one case concerning oral lichen planus, a positive rechallenge was described (case C).
In three cases, it was described that the patients consulted a dermatologist (case H, I, J). In one of these cases (case H) lichenoid dermatitis was confirmed by biopsy.

Table 1. Reports of lichenoid eruptions associated with the use of metoprolol in the Lareb database.

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction*	Time to onset, Action with drug, Outcome
A 146690, F, 61-70, pharmacist	Metoprolol succinate MGA 100 mg, 1dd 150 mg, hypertension	Metformin Hydrochlorothiazide Esomeprazole Valsartan	Lichen planus	Unknown Drug withdrawn Unknown
B 228932, F, 61-70, consumer	Metoprolol 100 mg, 1dd1, hypertension		Lichen planus	3 months Dose not changed Not recovered

C 235949, F, 61-70, pharmacist	Metoprolol succinate MGA 25 mg, 2dd1, cardiac arrhythmia	Calcium carbonate Acenocoumarol Esomeprazole Isosorbide dinitrate Sucralfate	Lichen planus	6 months Drug withdrawn Recovered
D 25095, M, 41-50, physician	Metoprolol tartrate 50 mg, 1dd1, acute myocardial infarction	Omeprazole Carbasalate calcium Pravastatin Diltiazem	Lichen planus (aggravated)	Unknown Drug withdrawn Unknown
E 238323, F, 61-70, physician	Metoprolol, 100 mg, 1dd1, blood pressure	Omeprazole Iron supplement Verapamil Diazepam	Lichen planus (aggravated)	3 weeks Dose not changed Recovering
F 122522, F, 41-50, consumer	Metoprolol succinate MGA 50 mg, 1dd1, hypertension		Oral lichen planus	10 weeks Drug withdrawn Recovering
G 164940, F, 51-60, pharmacist	Metoprolol succinate MGA 50 mg, 1dd1, ventricular extrasystoles		Oral lichen planus	2 months Drug withdrawn Not recovered 2 weeks after withdrawal
H 245515, F, 51-60, general practitioner	Metoprolol succinate MGA 50 mg, 1dd1, palpitations	Fusidic acid Hydrocortisone cream Tamoxifen Fluticasone nasal spray Tramadol Oxazepam Levocetirizine Levothyroxine	Dermatitis lichenoid Cutaneous vasculitis	14 days Drug withdrawn Recovering
I 452, F, 41-50, general practitioner	Metoprolol succinate MGA 50 mg, 1dd1, unknown indication	Verapamil	Dermatitis lichenoid	5 Months Unknown Unknown
J 65718, F, 61-70, pharmacist	Metoprolol MGA 100 mg, 1dd1, unknown indication Alendronate 70 mg, 1wk 1, osteoporosis Enalapril 10 mg, 1dd1, hypertension		Lichen	Enalapril, metoprolol: 5 years Alendronate: 2 years Not applicable Not recovered

* Lower Level Terms (LLTs) were reported because of the non-specificity of the associated Preferred Terms (PTs) (the LLT 'lichen' corresponds to PT 'rash papular')

Other sources of information

SmPC

Lichenoid eruptions or related reactions are not mentioned in the Dutch SmPCs of metoprolol. Concerning skin reactions, psoriasis-like dystrophic skin lesions and psoriasis exacerbation or aggravation are labeled adverse drug reactions of metoprolol (1).

Literature

Two case reports of lichenoid drug eruptions likely caused by metoprolol have been published (6;7).
A 71 years and older male patient developed multiple discrete, pruritic, hyperpigmented, lichenoid plaques on the legs and arms eight weeks after metoprolol therapy for palpitations was initiated. Findings of skin biopsy suggested the diagnosis of lichenoid drug eruption. Metoprolol was discontinued and the patient was treated with topical steroids. The patient recovered from the skin reaction and palpitations did not recur (6).
A 71 years and older male patient had been treated with topical tacrolimus for erosive lichen planus on the feet and hands. After starting metoprolol for hypertension six months later, the patient experienced recurrence of erosive lesions within two weeks. Metoprolol was withdrawn and treatment with topical tacrolimus was repeated, resulting in recovery from erosive lesions (7).
Drug induced lichen planus like drug eruptions were described for several other beta-blockers. In 2012 a literature review indicated 29 described cases of lichen planus like drug eruptions associated with beta-blockers (8). Atenolol was the most commonly involved drug. Two cases concerned metoprolol,

including one of the cases described above (6). However, a causal relationship between the beta-blocker and the eruptions could not be established in many cases.
On Dutch dermatologists websites it is described that lichenoid eruptions are frequently caused by drugs, including beta-blockers (9;10).

Databases
The reports of the Preferred Terms (PTs) involving lichenoid eruptions associated with metoprolol in the database are shown in table 2. The PTs of other reported Lower Level Terms (LLTs) were not included because of the non-specificity of the corresponding PT.

Table 2. Reports of the PTs 'lichen planus' and 'oral lichen planus' associated with metoprolol in the Lareb (11), Eudravigilance (12) and WHO database (13).

Database	MedDRA PT	Drug	Number of reports	ROR (95% CI)
Lareb	Lichen planus	Metoprolol	5	10.0 (4.0 – 24.9)
	Oral lichen planus	Metoprolol	2*	
Eudravigilance	Lichen planus	Metoprolol	10	5.0 (2.7 – 9.3)
	Oral lichen planus	Metoprolol	3	7.9 (2.5 – 24.8)
WHO	Lichen planus	Metoprolol	14	3.9 (2.3 – 6.5)
	Oral lichen planus	Metoprolol	4	9.3 (3.4 – 24.9)

* No ROR was calculated because of the small number of reports.

Prescription data

Table 3. Number of patients using metoprolol in the Netherlands between 2012 and 2016 (14).

Drug	2012	2013	2014	2015	2016
Metoprolol	1,013,000	1,009,000	1,010,000	1,009,000	1,019,000

Mechanism

Beta-blockers might lead to the activation of CD8 T-cells, resulting in apoptosis of basal keratinocytes or altered expression of MHC-class-II molecules on keratinocytes by cytokines produced by the activated CD8 T-cells (3;15).
In addition, lichenoid drug eruptions might also be the result of a pharmacological effect of metoprolol. Beta-2-receptors are broadly present in the skin (8). It is known that beta-blockers block cyclic adenosine monophosphate (c-AMP) levels, which is believed to result in increased keratinocyte proliferation, decreased keratinocyte differentiation and increased lymphocyte motility (16).

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received ten cases of lichenoid drug eruptions associated with the use of metoprolol. In one report, it was described that dermatitis lichenoid was confirmed by biopsy. In one case there was positive rechallenge. However, it must be noted that lichenoid eruptions can have various causes. Furthermore, spontaneous regression can occur. Lichenoid eruption is not described in the SmPCs of metoprolol. The Dutch dermatologists websites (9;10) describe that lichenoid eruptions are frequently caused by drugs, including beta-blockers, and a possible class-effect is described in the literature (8). This, combined with the reports received by Lareb, suggests that further attention to this association is warranted.

References

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(2) SmPC Selokeen IV, oplossing voor injectie. (version date: 26-9-2014, access date: 5-12-2017) https://db.cbg-meb.nl/IB-teksten/h08700.pdf .

(3) UptoDate. (version date: 9-12-2016, access date: 1-12-2017) https://www.uptodate.com/contents/lichenoid-drug-eruption-drug-induced-lichen-planus?source=search_result&search=lichenoid%20drug%20eruption&selectedTitle=1~12.
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(11) Lareb Database. (version date 2017, access date: 11-10-2017) www.lareb.nl.
(12) Eudravigilance database. (version date 2017, access date: 1-12-2017) http://bi.eudra.org. (access restricted).
(13) WHO Global Individual Case Safety Reports database (Vigilyze). (version date: 2017, access date: 1-12-2017) http://www.vigiaccess.org/.
(14) GIP database - Drug Information System of the Dutch Health Care Insurance Board. (version date 2017, access date 1-12-2017) https://www.gipdatabank.nl.
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(16) Clayton R, Chaudhry S, Ali I, Cooper S, Hodgson T, Wojnarowska F. Mucosal (oral and vulval) lichen planus in women: are angiotensin-converting enzyme inhibitors protective, and beta-blockers and non-steroidal anti-inflammatory drugs associated with the condition? Clinical and Experimental Dermatology 2017 Apr 23;(35):384-7.

This signal has been raised on March 5, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl