1.1. Beta-Adrenergic Blockers and lichenoid drug eruption

Introduction

Beta-adrenergic blockers antagonize the effects of sympathetic neurotransmitters by competing for beta-1 and beta-2 receptor binding sites. Beta-1 cardioselective agents, including atenolol, bisoprolol and metoprolol, primarily block receptors located in cardiac tissue. Beta-adrenergic blockers are indicated for *hypertension and angina*. Furthermore beta-blockers are used as an effective treatment for a variety of *ventricular and supraventricular arrhythmias* and following *myocardial infarction for reduction of the risk of re-infarction*. Some beta-blockers are used as for *mild to moderate heart failure, migraine prophylaxis or hyperthyroidy*. Beta-adrenergic blockers are available since the seventies in the last century [1-3].

Common adverse skin reactions with beta-blockers are rash, hypersensitivity, alopecia, psoriasis, aggravation of psoriasis or psoriatiform skin reactions [1-3]. The current observation describes the association between beta-blockers and lichenoid drug eruptions, which are not mentioned in the SmPCs.

Lichen planus (LP) is an inflammatory, pruritic disease of the skin and mucous membranes, which can be either generalized or localized. It is characterized by distinctive purplish, flat-topped papules having a predilection for the trunk and flexor surfaces [4]. On the surface often white stripes (Wickham's striae) might be visible [5]. The lesions may be discrete or coalesce to form plaques. Histologically, there is a "saw-tooth" pattern of epidermal hyperplasia and vacuolar alteration of the basal layer of the epidermis along with an intense upper dermal inflammatory infiltrate composed predominantly of T-cells. The etiology is unknown. It occurs in the general population at a rate of 0.9-1.2 % and oral lesions may be seen in 30-70 % of these patients. It affects men and women almost equally and it is likely to start in middle age [6]. It is diagnosed on clinical symptoms and biopsy can confirm the diagnosis. It is a self-limiting disease, but recovery might be slow an remission occurs in 1-2 years; oral lichen seems to follow a more chronic course, with a mean duration of 4.5 years [5,7].

Drug induced lichenoid eruptions (LDE)* can differ in clinical (and histological) aspects from lichen planus; Next to lichenoid elements, LDE may be accompanied with papular, scaling and eczematous lesions. The predilection sites are rarely involved [8]. On the other hand LDE produces lesions that might be clinically and histologically indistinguishable from idiopathic LP [7]. The two conditions can be differentiated only by the time course of skin or mucous membrane involvement in relation to drug administration and by re-challenging with the suspected agent. Frequently the lichenoid eruptions occur a few months after starting the drug, but the latency may very between days to several years. Clearance of symptoms can occur within a few weeks after withdrawal of the drug; in some reports the healing period stretched from less than a week to many months. In some single case reports, symptoms cleared without discontinuation of the drug, in another study with oral LDE patients did not recover after withdrawal of the drug [7]. Similar as in idiopathic lichen planus LDE results in hyperpigmentation, which regresses slowly or even can be irreversible [7,8]. Histologic differences between LP an LDE are often subtle and not reliable. The dermal infiltrate (as well as peripheral blood) may contain eosinophils and plasma cells ad may sometimes be distinguished from the infiltrate in LP [7].

* A reliable differentiation between lichenoid drug eruption an drug induced lichen planus cannot be made, therefore the term lichenoid drug eruptions (LDE) is used [7].

Reports

On April 3, 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained in total eight reports of lichen planus, aggravated lichen planus, oral lichen planus or lichenoid dermatitis associated with the use of metoprolol, bisoprolol and atenolol. The reports are listed in Table 1. Six cases involved females, two cases involved males, aged between 44 and 66 years. In three cases other drugs (perindopril, enalapril and valsartan/hydrochlorothiazide) were also suspected. The latency varied mostly between four weeks and several months, but was up to five years in case F; in two cases the latency was unknown. In several cases the action with the beta-blocker was unknown or the drug was continued. In two cases (C, H) the beta-blockers was discontinued, but in one the outcome was not reported (C) and one (H) had not recovered after six weeks. Once the dose of the beta-blocker was reduced (E), but symptoms remained at least until the time of reporting, two months later.

Table 1. Reports of lichenoid drug eruptions associated with the use of beta-blockers

Patient, Number, Sex, age, Reporter	**Drug, daily dose Indication for use**	**Concomitant medication**	**Suspected adverse drug reaction**	**Time to onset Action with drug Outcome**
A 452 F, 51 to 60 years general practitioner	metoprolol succinate, 50 mg bid	verapamil	dermatitis lichenoid	5 months unknown not reported
B 13944 F, 44 general practitioner	bisoprolol fumarate, 10mg	estradiol terfenadine diazepam, sumatriptan, nitrofurantoin clorazepate	lichen planus	unknown no change not reported
C 25095 M, 49 to 50 years general practitioner	metoprolol tartrate, 50mg acute myocardial infarction	pravastatin omeprazole, diltiazem carbasalate calcium	lichen planus aggravated	days-weeks discontinued not reported
D 37548 F, 51 to 60 years pharmacist	atenololum, 25mg , perindopril 4mg	psyllium, calcium carbonate mebeverine	(oral)lichen planus-like dermatitis	unknown no change not recovered
E 37594 M, 61 to 70 years pharmacist	atenolol, 100mg primary hypertension	oxazepam carbasalate calcium	lichen planus aggravated	4 weeks dose reduction not recovered after 2 months
F 65718 F, 61 to 70 years pharmacist	enalapril, 10mg hypertension metoprolol succinate, 100mg , alendronate, 70mg osteoporosis		lichen	5 years No change5 years No change 2 years No change not recovered
G 107419 F, 61 to 70 years pharmacist	bisoprolol fumarate, 2,5mg valsartan/hydrochloro-thiazide160/25mg	paracetamol esomeprazole, mometasone nasal bromazepam	(oral)lichen planus, granuloma annulare	months-1 year no change not recovered

Patient, Number, Sex, age, Reporter	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset Action with drug Outcome
H 122522 F, 41 to 50 years patient	metoprolol succinate, 50mg hypertension		oral lichen planus	10 weeks discontinued not recovered after 6 weeks

Below some additional information on the reported cases is given:
In patient A verapamil was started after onset of lichenoid dermatitis. In patient D oral lichen planus was diagnosed by a dermatologist, one year after start of symptoms. Treatment with betamethasone gel was started. In patient E aggravation of lichen planus began one month after dose increase from 50 to 100 mg atenolol. Dose decrease to 50 mg and addition of hydrochlorothiazide did not result in improvement of symptoms within 2 months. Patient F experienced lichen on legs and inflammation of the oral mucosa and tongue with white stripes. A dermatologist was consulted, who prescribed treatment with lidocaine oral gel, hydrocortisone 1% vaseline-lanette cream, miconazole-hydrocortisone cream, vaseline-cetomacrogol cream and ketoconazole 2 % cream. Patient G was diagnosed with granuloma annulare months after start of valsartan/HCT. Lichen planus was diagnosed one year later. It was suspected that lichen might have been worsened by the addition of bisoprolol. Patient H had been treated with metoprolol during a period of 3 months in the past, without complaints.

Other sources of information

SmPC

Lichenoid drug eruptions are not mentioned in the SmPCs of metoprolol, bisoprolol or atenolol. Psoriasis, aggravation of psoriasis or psoriatiform skin reactions are described as very rare to uncommon adverse drug reactions (1: 100-10.000) [1-3].

Literature

Lichenoid drug eruptions as a class effect of beta-blockers have been described in several publications [7-10]. Case reports have been published on metoprolol, nebivolol, levobunolol, labetalol and propranolol.
A 74-year old male developed LDE, eight weeks after initiation of metoprolol for palpitations. LDE was confirmed by biopsy, which showed eosinophils and histopatholical damage to the dermal boundary; also peripheral eosinophilia was present. Four weeks after discontinuation of metoprolol and treatment with topical steroids, symptoms disappeared [11]. Another case on metoprolol was published in a 79 year old male with erosive lichen planus on feet and hands, which reacted well to tropical tacrolimus. Six months later metoprolol was started for hypertension. After two weeks the erosive lichen planus reoccurred. Metoprolol was discontinued and patient was treatment with topical tacrolimus , resulting in resolution within a few weeks [12].
A 62-year old woman presented with erythematous papules on both arms and legs, five weeks after starting treatment with nebivolol. No other medication was used. Treatment with levocetirizine, topical methylprednisolone, a single dose of intravenous dexamethasone or oral prednisone gave no resolution of symptoms. The corticosteroids were discontinued and a biopsy revealed LDE. After withdrawal of nebivolol and subsequent re-administration of topical methylprednisolone and systemic prednisone, the skin lesions resolved within twelve days [13].

A case of LDE after three years use of topical levobunolol for open–angle glaucoma was observed in a 58-year old woman. Papules were present on face, arms, legs and trunk. She also suffered from white striations on her buccal mucosa and pitting and horizontal ridging on her nails. No concomitant medication was used. Biopsy showed blunting of rete ridges and a mixed inflammatory cell infiltrate of the dermis, including eosinophils, suggestive for LDE. Levobunolol was discontinued an oral prednisone was given. Within a couple of weeks itching had resolved and lesions had faded, leaving only a few characteristic hyperpigmented spots after a few months [13].
A 67-year old man with hypertension had been taking labetalol and clonidine for three months. He developed an itchy cutaneous eruption on his penis that spread to his trunk and limbs. After ten weeks a biopsy specimen of the lesion was consistent with LDE. Labetalol and clonidine were replaced with atenolol and amiloride/hydrochlorothiazide and topical steroids were applied to the lesions. Symptoms improved within two days and topical agents were discontinued. One month later only post-inflammatory pigmentation was visible. Labetalol was restarted. After fifteen days lesions on the trunk and penis had reactivated. Labetalol was discontinued again [14].
A 71-year old man with coronary artery disease and diabetes mellitus had a four month history of penile lesions, unresponsive to systemic antibiotics or topical antibiotics and antifungals. He was taking propranolol and dipyridamole. Biopsy specimen from the penile lesions were consistent with LDE. Propranolol was replaced with diltiazem and the lesions improved significantly within ten days [15].

Databases

On April 3, 2012, the database of the Netherlands Pharmacovigilance Centre contained eight reports of lichenoid drug reactions in association with beta-blockers. The corresponding Preferred Terms (PT) consisted of lichen planus (4 cases), oral lichen planus (1 case), lichenoid keratosis (2 cases) and rash papular (1 case) (see table 2). The Reporting Odds Ratio (ROR) for lichen planus was 6.4 (CI 2.3-18.1). For the other preferred terms a reliable ROR could not be calculated because of the low number of cases

Table 2. MedDRA Lower level terms involving lichenoid drug eruptions with corresponding Preferred Terms

MedDRA LLT	**MedDRA PT**
Lichen planus Lichen planus aggravated	Lichen planus
Oral lichen planus	Oral lichen planus
Dermatitis lichenoid Lichen planus like dermatitis	Lichenoid keratosis
Lichenoid changes mouth	Lichenification
Lichen Lichen unspecified	Rash papular

The WHO database of the Uppsala Monitoring Centre contained in total 32 reports of lichen planus in association with selective beta-blockers with a ROR of 5.4 (CI 3.8-7.6). For the individual beta-blockers bisoprolol, atenolol and

metoprolol a statistically significant ROR was observed (Table 3). Oral lichen planus was reported three times in total for metoprolol and atenolol. The combined ROR was 10.4 (CI 3.3-33.3). Lichenoide keratosis was reported 94 times with selective beta-blockers with a ROR of 6.4 (CI 5.2 -7.9). For atenolol, metoprolol, bisoprolol, acebutolol, practolol and nebivolol the ROR was disproportionally present in the database. The WHO database contained only two cases of lichenification- no ROR could be calculated

Table 3. Reports of lichenoid drug eruption of beta-adrenergic blockers in the WHO database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Lichen planus	Bisoprolol	7	13.4 (6.3 - 28.2)
	Atenolol	11	4.6 (2.6 - 8.4)
	Metoprolol	7	3.0 (1.4 - 6.3)
	Celiprolol	2 **	
	Acebutolo	2 **	
	Nevibolol	2**	
	Betaxolol	1**	
Oral lichen planus	Metoprolol	2**	
	Atenolol	1**	
Lichenoid keratosis	Atenolol	41	7.1 (5.2 - 9.6)
	Metoprolol	29	5.1 (3.5 - 7.3)
	Bisoprolol	10	7.8 (4.2 -14.4)
	Acebutolol	6	10.8 (4.9 - 24.1)
	Practolol	4	7.7 (2.9 - 20.6)
	Nebivolol	3	5.2 (1.7 -16.1)
	Betaxolol	1**	
Lichenification	Metoprolol	1**	
	Atenolol	1**	

**numbers too low to calculate a reliable ROR

On April 16 2012, the Eudravigilance database contained seven reports of lichen planus in association with selective beta-blockers, which was reported disproportionally (ROR = 3.1, 95% CI: 1.5 – 6.6). For the individual beta-blockers, a ROR could only be determined for metoprolol (see table 4). Lichenoid keratosis was reported ten times with selective beta-blockers, with a ROR of 3.4 (95%CI: 1.8 – 6.4). For metoprolol this association was disproportionally present in the database. For the other selective beta-blockers, there were not enough reports to calculate a ROR (see table 4). For oral lichen planus and lichenification, no ROR could be calculated due to the low number of reports and the absence of reports respectively.

Table 4. Reports of lichenoid drug eruption of beta-adrenergic blockers in the Eudravigilance database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Lichen planus	Bisoprolol	1**	
	Atenolol	1**	
	Metoprolol	5	4.6 (1.9 – 11.2)
Oral lichen planus	Metoprolol	1**	
Lichenoid keratosis	Atenolol	1**	
	Metoprolol	4	3.1 (1.2 – 8.3)
	Bisoprolol	2**	
	Celiprolol	1**	
	Nebivolol	2**	
Lichenification		No reports	

** Numbers too low to calculate a reliable ROR

Prescription data

The number of patients using selective beta-adrenergic blockers in the Netherlands is shown in table 5 [16].

Table 5. Number of patients using selective beta-adrenergic blockers in the Netherlands between 2007 and 2011

Drug	2007	2008	2009	2010	2011
Selective beta-blockers	1,219,000	1,273,000	1,302,000	1,351,000	1,384,000

Mechanism

The pathogenic mechanism of LDE is not well understood, a type IV allergy is sometimes involved. A dose dependency is suggested [8]. Some drugs change surface antigens, whereas other drugs change enzyme systems. These aberrations may precipitate an immune response, in which cytotoxic CD8+ T cells are activated, which then cause epidermal damage [7,11]. There can also be cross sensitivity to other beta-blockers in compromised patients [10].
Beside hypersensitivity a pharmacological mechanism might be involved in LDE in association with beta blockers [9,10]. A proposed mechanism of action relies on the fact that there are beta-receptors broadly present in the skin. Cyclic adenosine monophosphate (c-AMP) is an intracellular messenger that stimulates proteins and is responsible for keratinocyte differentiation and inhibition of its proliferation. Beta-blockers are known to block c-AMP levels, therefore reduced c-AMP levels results in up- regulation of keratinocyte proliferation, reduced differentiation and increased lymphocyte motility [17].

Discussion

Lareb has received eight reports of lichenoid drug eruption in association with beta-adrenergic blockers. In two patients an ACE–inhibitor was also suspected, in one patient the combined medication valsartan/hydrochlorothiazide was indicated as a possible causative drug. ACE-inhibitors as well as thiazide diuretics have been implied to cause LDE [8]. In one other patient pravastatin was used as concomitant medication, of which an association with LDE has been described in the literature [8]. For none of the patients a positive de-challenge was observed; only in two patients metoprolol was discontinued and in one patient atenolol dosage was reduced, but in all three patients the course of the reaction was only followed until 6-8 weeks hereafter, which might be too short to observe recovery. Because of the continuation of symptoms, with or without discontinuation of the beta-blocker, in a group of middle aged persons, idiopathic

lichen planus cannot be ruled out. No biopsy results in these patients are available to confirm the diagnosis of LDE.
As is described by Ellgehausen it is difficult to distinguish LDE form idiopathic lichen planus, clinically as well as histologically [7]. The time course in relation to drug administration and re-challenging with the suspected agent might be of help, but may also very between days and years. Even the clearance of symptoms in LDE might vary from a week to many months or are irreversible. Nevertheless it is of importance to acknowledge the possible role of beta-blockers in a patient with lichenoid eruption, which might have a major influence on well-being. Discontinuation of these beta-blockers might result in a substantial improvement in symptoms.

Conclusion

Lareb has received eight reports of lichenoid drug eruption in association with beta-adrenergic blockers. Although neither confounding by concomitant medication nor the occurrence of idiopathic Lichen planus could be ruled out in several cases , the association was supported by numerous publications and by the WHO- and Eudravigilance data. For this reason, it is suggested beta-blocking agents might have a causative role in the occurrence of LDE.

- Possible new signal of lichenoid drug eruption in association with the use of beta-adrenergic blockers.
- Attention to this association in Periodic Safety Updates may be warranted

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This signal has been raised on October 2012. 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).