EJA
European Journal of Acne and Related Diseases
Volume 1, n. 1, 2010

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Amiodarone-induced rosacea


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SUMMARY

Amiodarone is an anti-arrhythmic agent. Its most common cutaneous side effects are photosensitivity and hyperpigmentation. Furthermore, amiodarone rarely causes allergic rash, exfoliative dermatitis, toxic epidermal necrolysis, leucocytoclastic vasculitis, pseudoporphyria, linear IgA bullous dermatosis, vegetating iododerma and myxoedema. An increased susceptibility to the development of basal cell carcinomas was also reported. Only one case of rosacea due to amiodarone was reported so far. We describe a case of papulo-pustular rosacea which appeared four months after the beginning of the therapy with amiodarone. The disease did not improve despite several topical and oral therapies. However, it improved within six weeks after amiodarone discontinuation and completely cleared up within three months. Follow-up at one year was negative.

Key words: Amiodarone, rosacea.

Introduction

Amiodarone hydrochloride is a benzofuran derivative used for the treatment of severe arrhythmias[1]. It was originally marketed as antianginal agent for its potent vasodilatatory effect. Subsequently, it was employed in the treatment of atrial and ventricular arrhythmias. Amiodarone is widely used for cardioversion of atrial fibrillation and maintenance of normal sinus rhythm.

Amiodarone distributes extensively in several tissues, because of its high protein- and lipid-bond. A prolonged, although variable, period of administration with a loading dose (600 mg-1 g/day) is necessary before the adipose storage is saturated. Subsequently, lower dosages (200-400 mg/day) are usually sufficient. Extensive accumulation of amiodarone, especially in adipose tissue, explains its prolonged elimination, which ranges from 13 to 103 days.

Side effects of amiodarone involved cardiovascular system, lungs, thyroid, eyes, nervous system, liver and gastrointestinal tract[1, 2]. Incidence and characteristics of side effects are reported in Table 1.

Side effects may be idiosyncratic or dose-related (dependent on the daily dosage, the duration of the therapy or the total cumulative dosage).

Side effects can appear months or years after the beginning of therapy. Furthermore, side effects can last weeks or months after amiodarone discontinuation. We report a case of rosacea induced by amiodarone.

Case report

A 59-year-old man was admitted to our Institute because of a typical papulo-pustular rosacea. The patient stated that he was affected by essential hypertension and ventricular arrhythmia, for which he was under therapy with amiodarone (400 mg/day since six months). The patient also stated that the dermatitis had appeared two months before.

Dermatological examination showed no signs of photosensitivity as well as hyperpigmentation. General physical examination did not reveal anything pathological, except for the known mild essential hypertension. Laboratory examinations were within normal ranges or negative.

Bacteriological examinations of three pustules were negative; the search for *Demodex folliculorum* was also negative.

Table 1. Systemic side effects of amiodarone[1, 2]

TOXICITY	INCIDENCE	SIDE EFFECTS	FEATURES	TREATMENT
Cardiovascular	~28%	Hypotension	During i.v. administration	Dosage reduction
	2-3%	Heart failure		Dosage reduction
	<1%	Torsade de pointes	Idiosyncratic reaction, especially when a concomitant hypokalemia is present or in association with other antiarrhythmic agents (quinidine)	Beta-blockers and/or cardioversion
	<0.3%	Worsening of arrhythmia		Discontinuation
Pulmonary	2-17%	Eosinophilic alveolitis	Usually before one year of therapy	Discontinuation and systemic corticosteroids
Thyroid	~2%	Hyperthyroidism		
	2-10%	Hypothyroidism		
Ocular	70-100%	Corneal maculae	Caused by intracytoplasmatic deposits of amiodarone, especially during long-term therapy	Complete resolution in 3 to 7 months after amiodarone discontinuation
	50-60%	Lens opacities	Caused by intracytoplasmatic deposits of amiodarone, especially during long-term therapy	Complete resolution in 3 to 7 months after amiodarone withdrawal
	<2%	Retinopathy (macular degeneration), optic neuritis, optic neuropathy	Decreased or blurred vision. Rare progression to permanent blindness	Discontinuation
Neurological	20-40%	Tremor, ataxia, sleep abnormalities, dizziness, fatigue, headache, peripheral neuropathy	Dose-related, usually during the first weeks of therapy	Dosage reduction
Gastrointestinal	~25%	Nausea, loss of appetite, taste abnormalities, abdominal pain, vomiting	During the first weeks of therapy, probably dose-related	Dosage reduction and/or drug intake with meals
Hepatic	4-25%	Abnormalities in liver function tests (increased aminotransferase and alkaline phosphatase levels, hyperammonemia, hyperbilirubinemia, hypoalbuminemia)	Asymptomatic	Dosage reduction

The patient was treated with 15% azelaic acid gel (two applications/day) and oral azithromycin (500 mg/day for three consecutive days/week) for eight weeks. Two months later, the patient was examined; however, his rosacea had worsened.

Topical 0.75% metronidazole (two applications/day) and oral doxycycline (100 mg/day) were therefore prescribed for two months. Two months later, the clinical picture was unchanged. A biopsy was performed. Histopathological examination

confirmed the clinical diagnosis of rosacea. At the same time, the patient began to complain of blurred vision.
Because of the well-known ocular toxicity of amiodarone, the latter was stopped. Approximately six weeks after discontinuation of amiodarone, rosacea spontaneously improved; within three months, complete remission of the dermatitis, without specific treatment, was observed. A one year follow-up was negative.

Discussion

The most common side effect of amiodarone on the skin is photosensitivity. Its incidence ranges from 5 to 20% of patients; however, in some studies higher percentages (30 to 75%) were reported[3]. Photosensitivity occurs after exposure to both UVA[4] and UVB[5] and is not related to the skin phototype. It is possible that this photosensitivity is dependent by the total cumulative dosage of the drug (approximately 40 g: this amount can be reached in approximately four months of therapy). Photosensitivity gradually disappears in 4 to 12 months after amiodarone discontinuation. A histopathological study of sun-exposed skin confirmed a higher concentration of amiodarone complexes when compared with non-sun-exposed skin[3]. By means of electron microscopy, an accumulation of intracytoplasmic inclusions of phospholipids combined with amiodarone or its metabolites was demonstrated. Other authors suggested that these inclusions could be lipofuscins[6]. Sunscreens are useful, but the avoidance of sun exposure is the main way to prevent or minimize photosensitivity.
The second most common cutaneous side effect by amiodarone is hyperpigmentation. It occurs in almost 8% of patients, consists in a blue-grey or purplish discoloration and is more visible in sun-exposed areas, especially the face[7, 8].
This pigmentation is more common in patients with a previous history of photosensitivity, but a true correlation with sun sensitivity was not demonstrated. Among the patients with hyperpigmentation, a predominance of skin phototype was observed. This pigmentation seems to be related to the daily dosage and duration of amiodarone[9]. It appears after 12 to 24 months of therapy, which is approximately the time needed to reach a cumulative dose of 160 g. The pathogenesis of this pigmentation is unknown[5, 6, 10].
Pigmentation usually improves within 12 months after amiodarone withdrawal[11, 12], although a persisting (more than two years) pigmentation was also reported. In the latter case, Q-switched ruby laser represents an effective treatment[13].
An increased susceptibility to the development of basal cell carcinomas was also suspected[14-16].
Leucocytoclastic vasculitis is another rare side effect of amiodarone[17].
It is dose-dependent and improves spontaneously with a reduction of the dosage. Furthermore, amiodarone was responsible for isolated cases of vegetating iododerma[18], which appears after approximately two years of therapy and can be successfully treated with cyclosporine[19], pseudoporphyria[20], linear IgA bullous dermatosis[21], toxic epidermal necrolysis[22], exfoliative dermatitis[23] and facial myxedema[7].
To our knowledge, only one case of amiodarone-induced rosacea was reported so far[24]. Rosacea occurred in a 68-year-old man who was treated with amiodarone for two years. The disease was characterized by teleangectasias, rhinophyma, and multiple, large, confluent chalazia.
We believe that, also in our patient, amiodarone played a pathogenetic role in the development of rosacea for several reasons:

a) the appearance of rosacea four months after the beginning of the therapy with amiodarone;
b) the resistance of the disease to multiple topical and oral treatments;
c) the marked improvement of rosacea six weeks after amiodarone discontinuation;
d) the complete remission of the dermatitis three months later, and
e) the lack of relapses one year later.

These factors are highly suggestive for the existence of a correlation between amiodarone and the appearance of rosacea.
However, as *Reifler et al.*[24], we are not able to suggest pathogenetic hypotheses.

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