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## Cutaneous Adverse Reactions of Amiodarone

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Dermatological complications of amiodarone are commonly encountered problems in therapy. The incidence in the population of patients with prolonged use of amiodarone reaches nearly 75% according to various sources. Nevertheless, they are often misdiagnosed or overlooked. The aim of this review is to present the current state of knowledge about skin changes induced by amiodarone, including phototoxic and photoallergic reactions, as well as hyperpigmentation. In most cases, the adverse effects are reversible and disappear after discontinuation of the drug. Although the dermatological complications usually do not influence the outcome of the therapy and rarely cause discontinuation of treatment, they have a great impact on patient quality of life.

**MeSH Keywords:** **Amiodarone • Dermatology • Phototoxic Reactions, Hyperpigmentation**

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## Background

Dermatology and cardiology at a first glance seem to be very distinct medical fields, but the relationship between them is shown by the adverse effects of amiodarone, the key antiarrhythmic drug. Amiodarone has been used by physicians for over 50 years to treat supraventricular and ventricular cardiac arrhythmias, and it often provides the last treatment option due to its high efficacy. However, prolonged amiodarone therapy unfortunately carries an extended risk of adverse effects, mainly involving the thyroid gland, liver, lungs, eyes, and skin [1].

Dermatological complications of amiodarone are commonly encountered. The incidence in the population of patients with prolonged use of this drug reaches nearly 75% according to various sources. The main skin changes induced by amiodarone are phototoxic and photoallergic reactions, as well as hyperpigmentation. In most cases the adverse effects are reversible and disappear after drug withdrawal. Although the dermatological complications usually do not influence the outcome of the therapy and rarely cause the discontinuation of treatment, they have great impact on patient quality of life.

## Phototoxic and Photoallergic Reactions

Phototoxic reactions are the most common dermatological adverse effect of amiodarone therapy, affecting 25–75% of patients on long-term treatment [2]. Photoallergy is considerably less likely to occur, but the risk also increases with prolongation of the therapy.

Amiodarone and its active metabolite, desethylamiodarone, cause decrease of MED (minimal erythema dose) in the range of ultraviolet radiation type A (UV-A 320–400 nm), which can reach up to 50% of the correct values. In individual cases there may also be a reduction of MED for the ultraviolet type B radiation (UV-B 290–320 nm) [3]. The mechanism of the reaction seems to be connected with the creation of active metabolites due to radiation, such as oxygen free radicals, which in turn leads to destruction of DNA particles, cell membranes, and oxygenation of lipids [4,5]. Ferguson et al. demonstrated phototoxic effects of amiodarone and desethylamiodarone by carrying out *in vitro* tests with the use of photohemolysis, DNA synthesis inhibition assay in PHA-stimulated lymphocytes, and the killing of macrophages obtained from mouse peritoneal fluid [6].

Skin changes usually occur after at least 4 months of therapy and with the minimal cumulative dose, which is 40 g [7]. They have the typical erythematous or eczematous appearance with accompanying pruritus in the parts exposed to sunlight, usually on the hands, face, and neck. The eruptions are less prominent

on the chin, lower lip, and behind the ears [8]. The symptoms begin several minutes after exposure to the sunlight, continue up to 24 hours and usually subside by around 48 hours, but in some cases they persist up to 72 hours. Phototoxic and photoallergic reactions might even occur a few months after the withdrawal of amiodarone due to its long elimination time, which on average takes 35–40 days, and in obese patients can take 100 days for complete excretion. In the literature there are also descriptions of prolonged photosensitivity cases (up to 15 years following the discontinuation of therapy) [9]. The extent of the reactions depends mostly on the individual sensitivity of the skin to sunlight, but it is always proportional to the exposure time.

The basis of therapy is withdrawal of the medication and restoration of skin lipid layers. It also includes the use of medium strength topical glucocorticosteroid, oral non-steroidal anti-inflammatory drugs, and intensive sunscreen protection [8].

Prevention of acute reactions caused by sunlight in patients treated with amiodarone should include avoidance of frequent sun exposure on the skin and the proper application of external sun protection products with high protection factors (SPF 50 or 50+), reapplied not less frequently than approximately every 2 hours. Sunscreen should provide the full spectrum of protection, including a UV-A radiation. Particularly effective are creams containing zinc oxide or titanium dioxide [10]. Glass commonly used in windows is permeable to UV-A radiation and does not provide protection to people in buildings and cars.

## Hyperpigmentation

Skin hyperpigmentation is another important adverse effect, affecting 4–9% of patients taking amiodarone [2]. In contrast to the phototoxic reactions, which do not depend on the skin type, hyperpigmentation usually occurs in patients with skin type I phototype [7]. In these patients, long-term therapy with amiodarone leads to characteristic blue-grey discolorations, located mostly on the face, ears, and palms of the hands (Figure 1). The mechanism by which these changes occur is not precisely understood. Histopathological examination of the skin shows yellow-brown deposits of lipofuscin aggregates within macrophages, mast cells, endothelial cells, smooth muscle cells, keratinocytes, and fibroblasts [11]. Pathologically accumulated phospholipids appear under electron microscopy as irregular or oval structures. Some authors report that the hyperpigmentation is likely due to the amiodarone deposits instead of lipofuscin [12,13]. Amiodarone binds to phospholipids and creates insoluble compounds that do not follow the regular degradation pathways, which leads to their accumulation in cellular lysosomes. The discovery of increased amounts of iodine or drug metabolites in granules proves that



**Figure 1.** Amiodarone-induced blue-gray facial pigmentation associated with diffuse erythema in 81-year-old patient treated with amiodarone 200 mg daily for 15 years due to paroxysmal atrial fibrillation. The clinical manifestation is indicative of a phototoxic reaction. The area shaded from the UV-exposure by a hat remained unaffected.

amiodarone or desethylamiodarone are present in the affected skin [12]. In addition to the deposits of lipofuscin, histopathological examination revealed the presence of inflammatory cells around the microvessels [7]. The full explanation of the mechanisms involved in the mentioned processes requires further investigation.

Hyperpigmentation usually occurs 20 months into amiodarone treatment regime and sometimes after longer periods of time [6]. The doses of the drug used are higher in patients with hyperpigmentation (400–800 mg per day) compared to patients with only phototoxic reactions. The minimal cumulative dose is around 160 g [7]. The changes have blue-grey discoloration, but in 10% of patients it takes on yellow-brown pigmentation. Discontinuation of the drug usually causes gradual reduction of the symptoms [14]. Full remission is commonly achieved after a few months to several years, which is the consequence of slow elimination of amiodarone and its metabolites from tissues. Unfortunately, even after drug withdrawal for a few years, some changes may persist. Prophylaxis includes avoidance of direct excessive sunlight exposure to the skin and use of sunscreen products with high protection factors (SPF 50 or higher) against UV-A and UV-B radiation. Switching from amiodarone to another antiarrhythmic drug could also be very beneficial. Targeted treatments usually do not give satisfactory results. There have been individual reports on the efficacy of vitamin B6 at 300 mg per day. Local depigmentation treatment using hydroquinone and monobenzone does not improve the skin condition. In contrast, there are reports of spectacular efficacy of cosmetic laser application, which could possibly be very beneficial in patients with too many cardiovascular complications to allow amiodarone withdrawal [15–17]. There

are accounts of very successful therapy with UV-B rays, leading to higher tolerance to sunlight and prolongation of possible exposure times without adverse effects [18].

## Pseudoporphyria

Amiodarone is considered to be a cause of pseudoporphyria, which is a disease with clinical picture similar to this of porphyria cutanea tarda, but without any identified biochemical changes in the metabolism of porphyrins. Pseudoporphyria is usually manifested by tense bullae, erosions, scars, postinflammatory hyperpigmentation, and increased skin fragility, especially in the sun-exposed regions.

## Linear IgA Bullous Dermatitis

A very rare adverse reaction to amiodarone treatment is linear IgA bullous dermatitis, and it is thought that amiodarone can exacerbate the course of this disease. Characteristic changes include the presence of well-differentiated blisters located either on healthy skin or on erythematous and edematous areas. Location of the changes does not correspond to the sun-exposed parts of the skin.

## Effects of Amiodarone Therapy on Other Cutaneous Diseases

The amiodarone molecule contains a large amount of inorganic iodine, which may exacerbate certain skin diseases, such as dermatitis herpetiformis and psoriasis. Moreover, there have been reports of post-amiodarone pseudo-purulent changes, such as acne or blister-purulent lesions characteristic of iodism [19,20]. This should be considered when choosing the optimal antiarrhythmic therapy.

## Other Adverse Effects

Less common dermatological complications of amiodarone include hives, pruritus, erythema nodosum, purpura, and the most severe variant of erythema multiforme – toxic epidermal necrolysis [21,22]. The acute complication of treatment with intravenous amiodarone administration can take on the form of necrosis of the skin and soft tissue due to venous extravasation. The risk is related to low pH (3.5–4.5) of the solution and the content of solvents, such as benzyl alcohol and polysorbates [23].

There are some reports indicating the possible carcinogenic effects of amiodarone. A few cases of basal cell carcinoma associated with chronic use of this drug have been reported.

Most of the changes were observed on the site of a preexisting acute phototoxic reaction [24,25].

## Conclusions

Complications of chronic amiodarone therapy compel the prescribing physician to inform the patient about all possible adverse reactions, methods of avoiding them, and the need for

specialist advice if symptoms occur. Any doctor approached by a patient with skin lesions secondary to amiodarone must be aware of the risks of stopping treatment, because it can exacerbate the severity of arrhythmias and even lead to sudden cardiac death. Cooperation between cardiologists and dermatologists will undoubtedly facilitate risk stratification and ensure that optimal decisions will be made to provide maximum safety of the patient, while at the same time reducing the adverse effects.

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