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Phototoxicity of Doxycycline: A Systematic Review on Clinical Manifestations, Frequency, Cofactors, and Prevention

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Abstract
Background: One of the most important dermatologic side effects of doxycycline is photosensitivity. As doxycycline is important for malaria prophylaxis and malaria is mainly spread in countries with high sun radiation, special attention should be paid to this adverse effect. While there are many publications on the phototoxicity of tetracyclines in general, only a few exist focusing on doxycycline. The objective of this systematic review was to summarize all available reports on clinical manifestations, influencing factors like UV dose or dose of medication, and the possibilities of prevention by sun protection. ***Methods:*** This review is based on a systematic search in PubMed for articles in English and German and a manual search between 1990 and 2015. ***Results:*** The number of publications is low. Clinical symptoms vary from light sunburn-like sensation (burning, erythema) to large-area photodermatitis. Also, onycholysis is possible. The triggering UV spectrum seems to consist mainly of UVA1 (340–400 nm), so UV-protective products should be used that cover this range. Travelers to tropical countries taking doxycycline for malaria prophylaxis need thorough medical counseling to avoid possibly severe phototoxic reactions. ***Conclusion:*** Evidence base must be improved for giving advice on appropriate prevention measures to travelers taking doxycycline and having a risk of significant sun exposure.

Introduction

Malaria is a tropical infectious disease with potentially severe or lethal outcomes. According to the actual WHO guidelines for the treatment of malaria, doxycycline may be used for prophylaxis and partially also therapy [1]. The main dermatologic side effect of this compound, which is a tetracycline, is photosensitivity. While this is a well-documented adverse reaction of tetracyclines in general, only few publications exist focusing on doxycycline. Therefore, and with regard to its important role in malaria prophylaxis, the aim of this systematic review was to survey all available publications about its phototoxic adverse effects. Our interest was centered on clinical manifestation, frequency of side effects, influencing factors, and sun protection measures to avoid doxycycline phototoxicity.

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Literature Search

This review is based on a PubMed database search (an additional search in Embase did not show additional results) using the query "doxycycline AND (phototoxicity OR photosensitivity)." The search was limited to "English" and "German" language articles, "human" subjects, and publications from 1 January 1990 to 31 December 2015, documenting adequate information on the phototoxicity of doxycycline. Eligibility of the studies was assessed by one reviewer.

A total of 51 articles were identified from the initial search in PubMed. After reviewing all full-text articles and excluding reviews, papers about other diseases, and articles without reporting on phototoxicity of doxycycline, a total of 21 papers remained for analysis. These articles consist mostly of case reports, while there are only few studies. For each paper included, a summary of author/study year, study design, number of patients, clinical manifestation, and results is given in Table 1.

Clinical Manifestation

Within 24 h following exposure to relatively intense sunshine, the typical initial skin symptom of a phototoxic reaction to doxycycline is a sunburn-like sensation (burning, erythema) in sun-exposed areas like the nose, upper cheeks, lips, and dorsal aspects of the forearms, hands, and fingers, partially resembling pseudoporphyria (but without scarring, milia, or hirsutism as observed in true porphyria). After that, slightly palpable erythematous plaques appear in the mentioned areas adjacent to which may be small papules [2, 3]. Patients complain of moderate to intense pain or itching. In severe cases, up to 80% of the body may be affected [4]. The symptoms resolve within 10–14 days after discontinuing doxycycline therapy [2]. Another possible symptom of a phototoxic reaction to doxycycline is photo-onycholysis [5]. There are also a few reports of children with a particularly serious manifestation at all 20 nails [6, 7]. A case reporting a lag time of 2 weeks between discontinuing of doxycycline and the beginning of onycholysis shows that symptoms may start with a considerable delay after sun exposure [8]. The phototoxic reaction may also lead to a lichenoid eruption with pink polygonal papules, with some confluence into plaques [9] or to actinic granulomata after months [10].

Frequency of Phototoxic Side Effects and Dependence on Dose and Wavelength

In a phase II study over 6 months, Baxter et al. [11] found that 3 of 36 patients (8.3%) treated with doxycycline (orally, 100 mg twice per day) suffered heavy phototoxic reactions and 22 patients (30.8%) mild ones. In another study comparing cefuroxime axetil and doxycycline (3 × 100 mg doxycycline per day) in the treatment of patients with early Lyme disease associated with erythema migrans, 6% of the patients developed phototoxic reactions [12]. In a therapeutic study, Layton and Cunliffe [2] treated 106 acne patients with doxycycline (150 or 200 mg per day) over 2 years. Six of 30 patients (20%) treated with 150 mg doxycycline per day and 32 of 76 subjects (42%) taking 200 mg per day developed a phototoxic reaction. The authors came to the conclusion that the frequency of reaction is dose related. In countries with high solar radiation phototoxic reactions to doxycycline are more frequent even at lower doses. In a United Nations peacekeeping deployment to East Timor, a group of islands within the Malaysian archipelago, 22 of 135 (16%) Australian troops exhibited phototoxic reactions to doxycycline 100 mg daily [13]. However, in children, even very low doses of doxycycline may cause phototoxicity. That is shown by the case of a child having reacted to 20 mg per day doxycycline with onycholysis [6]. It is not known whether there is a minimal dose of doxycycline which causes a phototoxic reaction in either case.

The main spectrum of wavelength causing phototoxic reactions seems to be UVA1 (340–400 nm) [13, 14] while the minimal dose of UV light, being able to provoke a significant increase of erythema reaction compared to placebo, seems to be around 50 J/cm^2 (investigated doses were 25, 50, 75, and 100 J/cm^2, whereas no significant increase of erythema reaction was found at 25 J/cm^2) as detected by Bjellerup and Ljunggren [14] using a UVA system emitting mainly between 345 and 445 nm, with a peak at 370 nm. Nevertheless, doxycycline may also lead to a reduction of the minimal erythema dose in the spectrum of UVB [4].

It seems that there is no relation between severity of phototoxic reaction and sex, age, duration of therapy, or duration of illness [2, 15], but it is suggested that patients with skin types 1 and 2 according to the Fitzpatrick scale could be more susceptible to doxycycline photosensitivity than patients with darker skin pigmentation [7]. A lower antioxidant status, as seen in cystic fibrosis patients, for example, may be another possible, probably genetic, reason for explaining an increased phototoxicity to doxycycline [7].

Table 1. Summary of the included studies and case reports

Author, year	Study type (level of evidence[a])	Patients, *n*	Dose of doxycycline	Clinical manifestation	Results
Baxter et al. [11], 2002	prospective (phase II) multicenter study (3)	36	2 × 100 mg/day		cutaneous photosensitivity reactions (8.3%); easily managed episodes of photosensitivity (22.2%)
Bjellerup et al. [14], 1994	double-blind cross-over study (2)	15	2 × 100 mg/day		doxycycline showed a substantial increase in erythema compared with placebo, which was highly significant
Habif [3], 2006	case report (5)	1	2 × 100 mg/day	erythema on the cheeks, nose, and upper lip; impetiginazation of the lower lip	
Hafiji et al. [22], 2010	case report (5)	1		burning tingling rash on the left side of the face	
Kus et al. [23], 2005	randomized investigator-blinded study (2)	26 in the doxy-cycline group	2 × 100 mg/day		photosensitivity in 2 patients in the doxycycline group
Kuznetsov et al. [4], 2011	case report (5)	1	2 × 100 mg/day	erythema and itching of the skin on the trunk, upper, and lower limbs; relatively sharply demarked palpable erythemata, which were accentuated in previously untanned skin areas	
Layton et al. [2], 1993	prospective study (3)	106	150 mg/day (30 patients) 200 mg/day (76 patients)	sunburn-like sensation on the nose, upper cheeks, and dorsal aspect of the hands and fingers	light sensitive rash: 150 mg/day: 6 patients (20%) 200 mg/day: 32 patients (42%)
Lim et al. [13], 2003	retrospective study (4)	135	100 mg/day	exaggerated sunburn with diffuse erythematous plaques more pronounced on sun-exposed areas such as the face, neck and dorsum of hands	phototoxic reactions in 22 patients (16%)
Lim et al. [10], 2003	case report (5)	2	100 mg/day		actinic granuloma after phototoxic reaction caused by doxycycline
Luger et al. [12], 1995	randomized, multicenter, investigator-blinded clinical trial (2)	232	3 × 100 mg/day		phototoxic side effects in 6%
Nowakowski et al. [15], 1995	2-part retrospective study (4)	38	2–3 × 100 mg/day		phototoxic reaction in 4 patients (10.5%), no difference between 14- or 20-day therapy
Ogrinc et al. [20], 2006	prospective trial (3)	46	2 × 100 mg/day		phototoxic reactions in 7 patients (15.2%)
Passier et al. [5], 2004	case report (5)	5	200 mg/day	photo-onycholysis	
Pazzaglia et al. [6], 2014	case report (5)	1	20 mg/day	13-year-old boy with photo-onycholysis	
Rabar et al. [8], 2004	case report (5)	1	100 mg/day	photo-onycholysis	
Schuhwerk et al. [24], 1998	case report (5)	1		phototoxic dermatitis	
Strle et al. [21], 1996	retrospective study (4)	42	2 × 100 mg/day		phototoxic reaction in 5 patients (11.9%)
Susong et al. [9], 2014	case report (5)	1		pink polygonal papules with some confluence into plaques, nose, knees, and lower legs	lichenoid aspect of phototoxic reaction
Tanaka et al. [19], 1997	case report (5)	1	2 × 100 mg/day	scaly erythema and vesicles on the face, neck, arms, and dorsal aspect of the hands and feet	
Thalmann et al. [25], 2009	case report (5)	1	200 mg/day	palmoplantar erythema with papules and bullous reaction	
Yong et al. [7], 2000	case report (5)	1	2 × 100 mg/day	14-year-old girl with photo-onycholysis of all 20 nails	

[a] Level of evidence based on the 2011 Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence.

Sun Protection

Lim and Murphy [13] report that all of the soldiers in East Timor (see above) used a sunscreen and nevertheless suffered from doxycycline-related phototoxic reactions. The sunscreen preparation used consisted of octyl methoxycinnamate 7.5%, octyl salicylate 4%, and oxybenzone 3% and had a UVB sun protection factor of 15. Oxybenzone is found in many broad-spectrum sunscreens and absorbs UVA radiation up to 340–360 nm [16, 17]. As the phototoxicity of tetracyclines is mediated in the long wavelength of the UVA spectrum, sunscreens containing oxybenzone as the primary UVA absorber are ineffective for preventing sunburn reactions [13]. Therefore, sunscreens filtering the whole UVA spectrum (340–400 nm) should be used to avoid phototoxic reactions to doxycycline. Nevertheless, besides sunscreens, behavioral, environmental, as well as clothing photoprotection are important tool to prevent phototoxicity [18].

Discussion

Only few publications exist about the phototoxicity of doxycycline, resulting in a low number of included papers. The information gathered is derived mainly from case reports, while there are only few studies. The quality of evidence differs in that there are double-blind crossover studies [14] as well as case reports with rechallenge [19] and mere case reports [3], as shown in Table 1. The low number of reports on doxycycline phototoxicity may be interpreted in 2 ways: either a true low incidence of events or serious underreporting. The fact that the only field study available [13] reported an incidence of 16% of phototoxic reactions in soldiers taking doxycycline for malaria prophylaxis points to the latter.

The clinical manifestation of phototoxic reactions to doxycycline is characterized by the typical symptoms of a phototoxic reaction (sunburn-like sensation in sun-exposed areas, slightly palpable erythematous plaques, small papules, moderate to intense pain or itching, as well as blisters) [2, 3]. Also, photo-onycholysis is possible [5–8]. Lichenoid reaction and actinic granuloma were reported in only 1 case each [9, 10].

To determine the frequency or risk of phototoxic reactions in the course of a therapy with doxycycline is difficult because it depends on the geographical location of the country in which the patient stays, the patient's behavior referring to sun exposure, and also the sunscreen preparation used, if at all [10, 13]. Moreover, the term "phototoxic reaction" is not consistently used in publications and varies from sunburn-like sensation with light erythema to heavy manifestation with large-area erythematous plaques. With these shortcomings in mind, rates of phototoxic reactions to doxycycline vary from 6 to 42% [2, 11–13, 15, 20, 21].

As the exposure area to malaria infections is mainly close to the equator with high levels of solar radiation, special attention should be paid to sun protection throughout a prophylaxis with doxycycline, which is preferred by many travelers due to its much lower price compared to other preventive antimalarials [13]. As far as possible, sun exposure should be prevented by sun avoidance or protective textiles. Sunscreens should cover the whole UVA1 spectrum (340–400 nm) and have factor 50+ [13].

As a conclusion, travelers to tropical countries taking doxycycline for malaria prophylaxis need thorough medical counseling to avoid possibly severe phototoxic reactions. In addition, studies are needed to prove the efficacy of sunscreen products in the prevention of doxycycline phototoxicity in order to enable evidence-based advice.

Disclosure Statement

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