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DISABLING WORK-RELATED PERSISTENT PHOTOSENSITIVITY FOLLOWING PHOTOALLERGIC CONTACT DERMATITIS FROM CHLORPROMAZINE AND OLAQUINDOX IN A PIG BREEDER

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Abstract: The use of veterinary medicines and medicated feed has a potential for the exposure of agricultural workers to pharmaceuticals with phototoxic and photoallergic side-effects. We present a 67-year-old self-employed farmer and pig breeder with a 22-year history of severe persistent photosensitivity following photoallergic contact dermatitis due to direct occupational dermal and airborne contact to chlorpromazine (sedative) and olaquindox (antibiotic and animal growth promoter, AGP). His first dermatitis symptoms appeared at the age of 45 when the pig breeding was intensified. He showed erythematous, scaly, and pruritic plaques localized symmetrically on the sun-exposed backs of his hands, fingers, and forearms, spreading to his face and other sun-exposed body sites. Without protective measures, he injected the animals with chlorpromazine. Besides, for several years he mixed by hand a powder containing olaquindox into the pigs' dry food. Epicutaneous and photo-patch tests showed positive reactions to promethazine, chlorpromazine, and olaquindox. In spite of the complete avoidance of the identified photoallergens for several years, his life is still extremely disabled due to the persistent photosensitivity. Our case report stresses the observation that olaquindox and chlorpromazine as phototoxic agents and photoallergens are capable of inducing a persistent and severe photosensitivity for many years, even after termination of exposure. Although the use of phenothiazine derivates and APGs for animals has meanwhile been banned in the European Union (EU), AGPs are still widely used in Asia. Physicians, especially occupational physicians, should be still aware of these phototoxic and photoallergic agents to reduce the burden of skin disease at work.

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INTRODUCTION

The use of veterinary medicines and medicated feed has a potential for the exposure of agricultural workers to antimicrobial drugs, tranquilizers, and other chemicals with phototoxic and photoallergic side effects. Phototoxic and photoallergic reactions may occur as a result of such exposure, but occupational skin diseases frequently remain undiagnosed for years. Self-employed farmers are especially affected by this problem because of the lack of periodical health checks and the low awareness of occupational skin diseases among both farmers and their physicians [27, 28]. Reports from dermatologists indicate high rates of occupational contact dermatitis in the personal services industries

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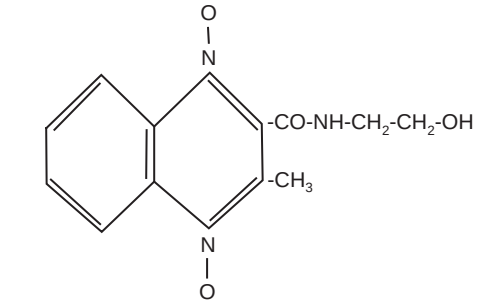
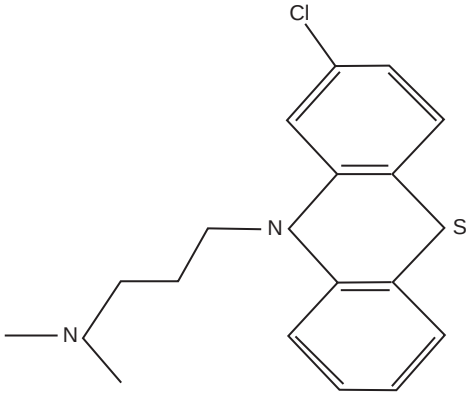


olaquindox



chlorpromazine

Figure 1. Chemical structure of animal growth promoter (AGP) olaquindox, or 2-[N-(2-hydroxyethyl)-carbomoyl]-3-methyl-quinoxaline-1,4-dioxide, has structural similarities with quindoxin, or quindoxaline-1,4-dioxide, which is very sensitive to long wavelength ultraviolet radiation (UVA). The chemical structure of chlorpromazine belongs to the phenothiazine class of neuroloeptic drugs.

(mainly hairdressers and barbers) and in agriculture [15]. In the past, some cases of occupation-induced airborne allergic and photoallergic dermatitis have been described for the antibiotic olaquindox (Fig. 1) in agricultural workers followed by transient or persistent photosensitivity [8, 9, 24, 31]. In addition, persistent and severe chronic actinic dermatitis and photodermatitis in animal husbandry staff as a result of exposure to chlorpromazine are reported [7] (Fig. 1).

Photosensitization may take the form of phototoxicity (photoirritancy) and photoallergy. The underlying photochemical mechanisms of these photoreactions differ completely. In phototoxic reactions, the drug absorbs energy from ultraviolet A (UVA) light and releases it into the skin, causing cellular damage. In photoallergic reactions, light may cause a structural change in a drug so that it acts as a hapten, possibly by binding to proteins in the skin [1]. Phototoxicity is much more common than photoallergy. For example, acute phototoxic reactions can appear as side-effects of a wide range of pharmaceutical agents or their metabolites, such as quinine (including olaquindox), phenothiazine (including chlorpromazine), phenylbutazone, psoralens, porphyrins, coal tar, antibiotics, and nonsteroidal anti-inflammatory agents (NSAIDS). Clinically, the patients show symptoms very similar to exaggerated sunburn reaction (dermatitis solaris) composed of erythema, infiltration or edema followed by hyperpigmentation. Long-term ultraviolet phototoxicity results in chronic sun damage (actinic keratosis) and skin cancer.

Chlorpromazine and several other related phenothiazines are known to cause both phototoxic and photoallergic reactions in the skin and eyes of patients receiving these drugs [5].

Other drugs capable of causing photoallergic reactions include topical antimicrobial agents, fragrances, sunscreens, nonsteroidal anti-inflammatory agents (NSAIDS), plants, and psychiatric medications such as sedatives. The photoallergy response is a delayed hypersensitivity reaction, i.e. immunologically mediated, which is clinically characterized by erythema, infiltration, and papulovesicles erosions or bullae. The action spectrum for photoreactions to exogenous agents usually at least includes the ultraviolet A rays for both phototoxicity and photoallergy. Meanwhile, the use of the tranquilizer chlorpromazine and the animal growth pomoter olaquindox has been forbidden in Europe. However, olaquindox is still widely produced and used in Asia, especially in China [10].

We report a very severe case of a farmer and pig breeder with a disabling chronic actinic dermatitis which stresses the importance of olaquindox and chlorpromazine as allergens and photoallergens capable of inducing a persistent and severe photosensitivity.

CASE DESCRIPTION

A 67-year-old self-employed farmer and pig breeder presented himself with a 22-year history of recurrent erythematous and crusting lesions on sun-exposed areas such as his forehead, the cheeks, the periorbital regions, the sides of his neck, the presternal area, and the backs of both hands and forearms. The submental triangle and the retroauricular area were clear (Fig. 2). Since childhood he had been involved in agricultural work on his parents' farm in Lower-Saxony, Germany. The patient`s medical history revealed no atopic eczema, putative allergy or psoriasis. The members of his family had no history of skin diseases. In 1968, he took over the parents' farm and since 1980 specialized in pig breeding. In 1982 the pig breeding was intensified. The patient worked for many years in direct dermal and airborne contact to various types of dry food. Especially, the antibiotic substance olaquindox was included in a vitamin and mineral complex presented in powder form. The antimicrobial drug is added to the piglets' food to avoid enteritis at the time of weaning. Without the use of protective clothing or gloves, the patient mixed the powder with grain by hand. Furthermore, between 1983-1985 the patient injected the animals with the sedative drug chlorpromazine without wearing gloves. In 1983, the patient noticed the first dermal lesions and reported that erythematous, scaly, and pruritic plaques had appeared symmetrically on the backs of his hands and fingers and on the extensor

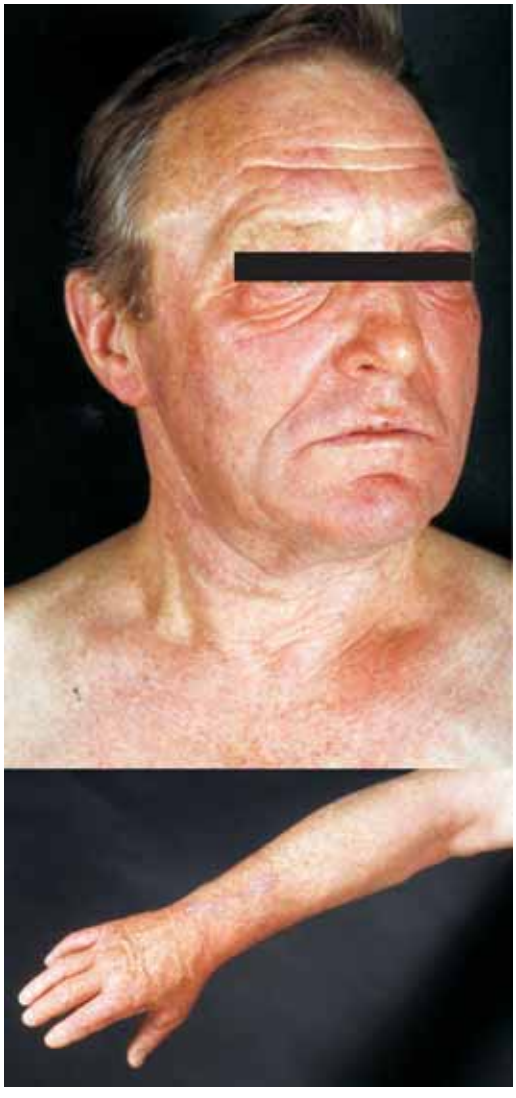
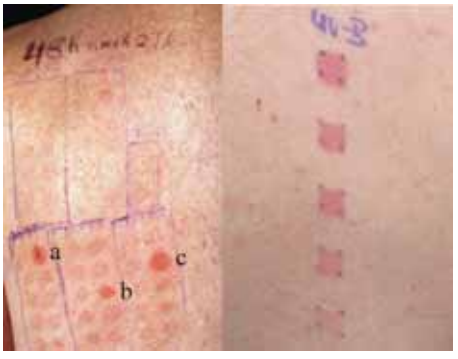


Figure 2. The 67-year old farmer and pig breeder depicted with a 22-year history of recurrent erythematous and crusting lesions on sun-exposed areas: forehead, cheeks, periorbital regions, sides of the neck, presternal area, and backs of both hands and forearms. The submental triangle and the retroauricular area were clear.



	February 2001	February 2005
MED-UVB (mJ/cm^2) [normal value]	15 [≥25]	10 [≥25]
MED-UVA (J/cm^2) [normal value]	6 [≥20]	1.5 [≥20]
MED-UVA1 (J/cm^2) [normal value]	30 [≥30]	20 [≥30]

MED-UVB – minimal erythema dose (MED) to UVB light (280-320 nm),
MED-UVA – minimal erythema dose (MED) to UVA light (320-400 nm),
MED-UVA1 – minimal erythema dose (MED) to UVA1 light (340-400 nm).

Figure 3. The patient exhibited positive photopatch test results (left picture) against the substances promethazine (a), chlorpromazine (b), and olaquindox (c). He showed an abnormal erythema reaction, especially within the ultraviolet light spectrum, UVA and UVB (right picture). From 2001-2005, the threshold dose levels of the minimal erythema dosis (MED) obtained with long (UVA) wavelength ultraviolet light and UVB light were highly abnormal and worsened.

sides of his arms upon contact with chlorpromazine. Later, the dermal lesions spread to the face. During the summer periods dermal lesions affected well-demarcated areas of his light-exposed body sites.

First diagnostic phototesting by a Dermatological Clinic in June 1985 revealed photoallergic contact eczema due to chlorpromazine. Unfortunately, no physician informed the patient about the severe side-effects of olaquindox and chlorpromazine, or notified the German accident insurance agency or the medical authority responsible for labour safety about the suspicion of an occupational photoallergic skin disease. In 1986, the patient decided to quit using the substances by himself, because he noticed aggravation of his skin condition. For the following 10 years he avoided contact with animal feed additives, since several medical reports of increased photosensitivity to olaquindox had been made public [21]. In the mid 1990s a relapse occurred when he accidentally used a low-priced animal feeding mixture containing olaquindox imported from a foreign country. He developed a severe and generalized dermatitis on sunlight-exposed skin. A long-term therapy with potent oral and topical corticosteroids was applied in combination with protective clothing. Lesions temporarily improved after treatment. However, after using physical sunscreens, skin irritation to different sunscreens' ingredients appeared and the skin symptoms worsened. He continued to work on his farm until August 2001. He then retired on account of ill health. In 2001, the patient was seen for the first time in our Department of Dermatology, Georg-August-University of Göttingen. Photopatch testing was performed according to the guidelines of the multicenter photopatch test procedure of the German, Austrian, and Swiss Group (DAPT) [17]. The minimal erythema doses (MEDs) for UVA and UVB to unexposed skin of the lower back were established before photopatch testing. Then, test substances were applied, including olaquindox and chlorpromazine, various occupational substances, and sunscreen products following the German, Austrian, and Swiss photopatch test recommendations [17, 19] and the German Contact Dermatitis Research Group (DKG) recommendations [4] for patch testing (Hermal, Reinbek, Germany). The patient exhibited positive photopatch test results against the substances promethazine, chlorpromazine, and olaquindox (Fig. 3). In addition, he had an abnormal erythema reaction especially within the ultraviolet light spectrum. From 2001-2005 the threshold dose levels of MEDs obtained with both short

(UVB) and long (UVA and UVA1) wavelength ultraviolet light were highly abnormal and worsened (Fig. 3). A persistent photosensitivity with lowered minimal erythema doses due to photoallergies against olaquindox and chlorpromazine was diagnosed. The photocontact dermatitis and the allergies were acknowledged by the German accident insurance agency in 2002 as an occupational and work-related disease affecting the skin. The patient`s quality of life is still dramatically reduced on account of his persistent photosensitivity, and sometimes he suffers from severe depression episodes.

DISCUSSION

Farmers, other animal husbandry staff, and veterinarians face a variety of hazards on a daily basis. Veterinary medicinal products and animal growth promoters (APGs) are only 2 of these hazards. The combination of sunlight with drug medication can lead to photosensitivity responses in susceptible patients [16, 20, 26]. In general, photoallergic contact dermatitis has been regarded as rare but severe. To our knowledge, a severe persistent combined photosensitivity due to photocontact allergies against olaquindox and chlorpromazine has rarely been reported in occupational medicine literature. The photoallergic contact dermatitis may resemble an allergic airborne contact dermatitis, although a photo-induced dermatitis tends to spare the anatomically shadowed portions of the body such as the eyelids, the retro-auricular and submandibular regions, and those covered by hair. Generally, the well- demarcated and mostly symmetrical lesions occur on sun-exposed areas. Photoallergic contact dermatitis is a classic T-cell-mediated or delayed-type hypersensitivity reaction of the skin in response to a photoallergen or photoantigen in a person who has been previously sensitized to the same chemical or one that cross-reacts with it. As with the allergic contact dermatitis, the lesions usually clear when contact with the photoallergen ceases. Occasionally, however, the patient may continue to develop lesions in the presence of sunlight even after removal of the photoallergen, and may present recurrent transient or persistent light reactions (chronic actinic dermatitis). The formation of endogenous photosensitizers might perhaps explain this phenomenon [28].

The major group of antibiotic drugs that caused skin problems in workers exposed during animal production are the quindoxaline-1,4-di-*N*-oxides typified by olaquindox (Fig. 1) [11, 12, 20, 23]. Olaquindox, an oral chemotherapeutic derivative of quinoxaline, is a photosensitizer capable of producing photocontact dermatitis. It has been used extensively as a growth promoter for pigs because of its preventive and therapeutic properties against protozoa, and both aerobic and anaerobic bacteria. Chemically, olaquindox, or 2-[*N*-(2-hydroxyethyl)-carbomoyl]-3-methyl-quinoxaline-1,4-dioxide, has structural similarities with quindoxin, or quindoxaline-1,4-dioxide, which is very sensitive to long wavelength ultraviolet radiation (UVA). These structures form a reactive oxaziridine upon exposure to light [6]. Structurally, olaquindox presents 2 benzene rings with alternating simple and double bounds leading to its photosensitizing properties (Fig. 1). It is soluble in water and, partially, in organic solvents. Olaquindox is genotoxic although it has not been shown to be carcinogenic [30].

Additionally, the patient developed a photoallergic contact dermatitis and photodermatitis as a result of direct dermal exposure to chlorpromazine [7]. This is a member of the phenothiazine class of neuroleptic drugs used in both human and veterinary medicine (Fig. 1). Upon irradiation the phenothiazines are known to elicit a wide variety of phototoxic responses including cross-photoreactions. Cross-photoreactions between chemically related substances have been frequently reported, e.g. chlorproethazine cross-photoreacts with other phenothiazines and can induce persistent light reactions [3]. Phenothiazines are variously metabolized and one of the main metabolites of chlorproethazine is norchlorpromazine, which is also the most phototoxic metabolite of chlorpromazine. While the detailed mechanisms of photosensitization are not known, it is obvious that the first step must be the absorption of light by the drug, its metabolites, or photoproducts, or possibly an induced endogenous chemical. The free-radical photochemistry of phenothiazines is a likely candidate for the phototoxicity [5]. Whereas phenothiazine derivates for animals have been forbidden in the meantime, they are still licensed worldwide as medications for humans. Today, there are also *in vitro* and *in vivo* test systems available that allow for the evaluation of phototoxic and photoallergic potentials of suspected compounds [13, 18].

Chlorpromazine can lead to allergic, photoallergic, and phototoxic skin reactions. Normally, avoidance of the photoallergen leads to the disappearance of the dermatitis symptoms. However, occasionally a chronic actinic dermatitis with severe sun sensitivity may persist, even long after cessation of photoallergen contact [3, 22]. This was the case in our patient. Even after withdrawal of the photoallergens in 1999 and strict avoidance of renewed contact since 2001, the chronic actinic dermatitis with increased UVA- and UVB-sensitivity persisted, and has even worsened until today (Fig. 2 and 3). This may possibly be the result of formation of endogenous photosensitizers that may lead to this phenomenon as described before [28]. There were no indications that the patient had contact with other substances that might contain olaquindox or chlorpromazine (e.g. neuroleptic drugs, etc.). Also, his wife did not perform the disease-causing occupation of pig breeding. In the literature there are reports of hidden, non-occupational sources of an offending substance or connubial sources that can lead to disease relapse [14, 25, 29].

The observation shows that in cases of persistent and prolonged photocontact dermatitis in agricultural workers, the physician should be aware of hidden triggers such as veterinary antibiotics or sedatives. The eczematous lesions may be misleading in their resemblance to other types of

occupational dermatitis, i.e. cement dermatitis. Therefore, we recommend photobiological testing in agricultural workers on a regular basis. Phototesting and photopatch testing are necessary to elucidate the specific subtype of photoallergy, because such patients may have multiple cutaneous allergies and photoallergies. In Germany, olaquindox became a "historic photoallergen" and is no longer available as a phototesting substance, except in our Department of Dermatology. This case also stresses the need of continuous medical and/or occupational health checks and medical education of agricultural workers on the variety of hazards in daily work. The use of AGPs has been banned in the European Union (EU) since 1 September 1999 according to the regulation 2788/98 of the Council Directive [2]. However, APGs are still widely used as feed additives for prevention of bacterial enteritis in pigs and piglets in Australia, South America and Asia, especially in China [10]. Besides, chlorpromazine for animals has been benned since 1997 in the EU, but is still used worldwide as medication for humans. Olaquindox ought to be withdrawn worldwide because of the potential persistent nature of olaquindox contact photoallergy. In spite of the complete avoidance of the identified photoallergens, for the past several years the patients' life has still been extremely disabled. The case report demonstrates the problem of under-recognising occupational skin diseases in farmers by themselves and by the physicians [27]. Physicians, especially occupational physicians, should be still aware of these phototoxic and photoallergic agents to reduce the burden of skin disease at work.

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