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Photodermatitis to topical phenothiazines: a case series

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Conflicts of interest: None to declare.

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SUMMARY

Background:

In Europe, contact photosensitivity to phenothiazines is known particularly in southern countries. Topical phenothiazines are widely used and sold over-the-counter for the treatment of mosquito bites and pruritus in France.

Objective:

To report a series of cases with photodermatitis to topical phenothiazines.

Method:

A retrospective study of cases of contact dermatitis to phenothiazines seen in French photodermatology centres was performed.

Results:

In all, 14 patients with the diagnosis of contact dermatitis to phenothiazines were included. These developed eczema on the application sites, and in 13 the eruption spread to photodistributed sites. Topical products containing isothipendyl were the most common cause of photodermatitis. One patient had photoaggravated eczema due to promethazine cream. All patients stopped using topical phenothiazines and were treated successfully with topical corticosteroids. One patient relapsed and developed persistent light eruption. In all of the 9 cases tested, photopatch testing to the topical phenothiazine used “as is” was positive. Isothipendyl, chlorproethazine and the excipients were not tested. Photopatch tests to chlorpromazine and promethazine were positive in 8/12 and 7/13 tested respectively.

Conclusion:

Use of isothipendyl and promethazine as over-the-counter (or even prescribed) drugs needs to be limited due to severe reactions and sensitization to other phenothiazines that otherwise will have to be avoided.

KEYWORDS

Photoallergic contact dermatitis, eczema, topical phenothiazines, isothipendyl, CAS no. 482-15-5, promethazine, CAS no. 60-87-7, photopatch test

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1. INTRODUCTION

Photosensitivity is a potential adverse effect of systemic phenothiazines used as antipsychotic. Topical phenothiazines that have anti-histamine and muscle relaxant effects are widely prescribed and used as over-the-counter (OTC) antipruritic drugs. In Europe, topical photosensitivity to phenothiazines, notably to promethazine, is known[1] particularly in southern countries.[2-4] Neuriplege ointment responsible for generalized and photoaggravated contact dermatitis due to active ingredient chlorproethazine[5,6] was withdrawn from the French market in 2007. Three topical products containing phenothiazine, isothipendyl (Apaisyl gel, Sedermyl cream) and promethazine (Phenergan cream) are registered, and currently sold OTC for the treatment of mosquito bites and pruritus in France. Isothipendyl and promethazine are also sold in other European countries. The marketing authorization holders for these products are mainly located in Western Europe. The objective of the present study was to address the question of photosensitive dermatitis to topical phenothiazines since 2007.

2. METHODS

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A retrospective study of cases of contact dermatitis to phenothiazines seen in French photodermatology centres from January 1, 2007 to October 31, 2019 was performed. Patients with a clinical diagnosis of contact dermatitis to a topical phenothiazine were included.

All members of the French Society of Photodermatology (SFPD) from 21 different French photodermatology units were contacted to contribute their eligible patients. A standardized questionnaire was sent to the SFPD members. The following information was collected from patient medical records: age, sex, medical history, current medications, clinical features, results of skin tests and photobiological exploration if performed.

3. RESULTS

3.1 Patient characteristics

A total of 14 patients were diagnosed with contact dermatitis to topical phenothiazine between January 2007 and October 2019. There were 6 female and 8 male patients, with a mean age at the time of diagnosis of 62 years (range: 27-88). The clinical characteristics of the patients are shown in Table 1. Case 11 has been previously reported.[7] Of the 14 patients, 3 had a history of photosensitive diseases. Case 3 had solar urticaria and cases 4 and 7 polymorphous light eruption. All developed eczema at the site of application of phenothiazine during sunny seasons. Distant sites were secondarily involved, including photodistributed areas, in 13 of 14 patients. The duration of eczema was longer than 3 months in 9/14, with recurrence in spring and summer (cases 3-5, 7 and 12). Topical product containing isothipendyl were the most common cause of photodermatitis (13/14). One patient used both isothipendyl gel and chlorproethazine ointment. Case 14 had photoaggravated eczema due to promethazine cream. Hospitalization was needed in cases 1, 2, 11 and 12. All patients stopped using topical phenothiazine and were treated successfully with a topical corticosteroid within 1 month. Relapse was observed in case 13 who developed persistent light eruption in the 2 years following contact photosensitization to isothipendyl, and needed to use photoprotective clothes and sunscreens. Other long-term medication was continued in all cases.

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3.2 Photobiological investigations

Phototesting was performed on the back of patients using a solar simulator (Dermolum UM-UW, Müller Elektronik, Moosinning, Germany) equipped with a xenon light and metal halide lamp providing polychromatic irradiation (solar spectrum, 95% UVA/5% UVB) filtered with Schott WG 305 (cases 1, 3-5, 7-14) to evaluate minimal erythema dose (MED) at 24h after exposure. UVA MED and irradiation of patches were performed with UVA source: Waldmann (Reischtett, France) in cases 1, 3-5 and 12 (UV 182), case 6 (UV 801 KL) and cases 7-11 (UVA 700); and Dermolum (UM-UW, Müller Elektronik) with Schott WG 345 filter in cases 13 and 14. Photopatch tests included the SFPD standard series (29 photoallergens: antiseptics, cosmetics, plant products, promethazine, chlorpromazine and 8 UV filters)[6] with an extended list (11 other UV filters, ketoprofen, methylisothiazolinone, decyl glucoside and patients'own products). Patches were applied on the upper back in triplicate. One set was covered for 24 h and then irradiated with 5J/cm^2 UVA and the other with polychromatic light (0.75 of the MED) whereas the third set was left in occlusion for 72h. Final readings were performed at 72h, according to International Contact Dermatitis Research Group guidelines.

Thirteen patients underwent photobiological explorations (Table 2). In all of the 9 cases tested, photopatch testing to the topical phenothiazine used "as is" was positive. Chlorproethazine, isothipendyl and the excipients were not tested because these substances had not been readily available. Photopatch tests to chlorpromazine 0.1% pet. and promethazine 0.1% pet. were positive in 8/12 and 7/13 tested, respectively. In one patient, the patch test to promethazine was positive without photoaggravation. Case 13 had also photosensitization to mequitazine administered for the treatment of eczema. In addition, past or associated relevant contact sensitivity (*Myroxylon pereirae*, fragrance mix, methylisothiazolinone) was found in 6 patients. The MED (polychromatic spectrum and/or UVA) was decreased in 4 cases. Two patients had repeated assessment of their MEDs which was normal 3 months later in case 11. Concerning the patient with persistent light eruption

(case 13), polychromatic MED returned to normal value while UVA MED was still decreased after one year of follow-up.

4. DISCUSSION

In most of our cases, contact photodermatitis was due to the products containing isothipendyl. One patient had no photobiological work-up. Nevertheless, the diagnosis of photocontact dermatitis to phenothiazines was made because eczema started on light-exposed areas following use of isothipendyl gel without relapse after discontinuation of the drug. In the literature, two cases of contact dermatitis to isothypendyl have been previously reported,[7,8] including one of our patients.[7] In France, benefit-risk assessment of isothipendyl products was initiated in 2017. Based on data from the French pharmacovigilance database and isothipendyl marketing authorization holders, 20 cases of severe cutaneous adverse reactions were identified (rash, urticaria, photodermatosis, eczema and purpura). The benefit-risk balance of isothipendyl was considered unfavorable, but this drug is still marketed to date. [9] In our series, 4 patients were hospitalized. We observed one case of persistent light reaction due to isothipendyl as previously reported to chlorproethazine.[5] This patient cross-photoreacted to another phenothiazine (mequitazine). In photoallergic reactions, cross-reactions between molecules belonging to the same chemical class such as phenothiazines may occur.[5,7] In our series, some positive photopatch tests with a + reaction to isothipendyl gel and promethazine may represent just a phototoxic reaction. However, we consider this result as photoallergy owing to prior eczema in the patients. Positive photopatch tests to chlorpromazine and/or promethazine confirmed isothipendyl photoallergy in most of our patients using Apaisyl or Sedermyl. Such cross-sensitivity renders phentothiazines contra-indicated in patients with photocontact dermatitis from isothipendyl, as previously reported in cases with contact sensitization to chlorproethazine (Fig. 1).[5] Moreau et al reported their experience among 20 patients and showed that isothipendyl is potentially phototoxic with UVA exposure, and induces more reactions than promethazine.[10] These results were confirmed by photophysical analysis. The only difference in the chemical structure between isothipendyl and

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promethazine is the presence of nitrogen in isothipendyl, which may explain its higher photosensitizing potential.[7] Contact photoallergy to isothypendyl was probably facilitated by the application of this topical drug on eczematous skin, promoting the penetration of the molecule and allergen presentation to immunocompetent cells. Regarding severe cutaneous drug reactions, 2 cases of toxic epidermal necrolysis after isothipendyl gel application has been reported.[11]

Topical promethazine is known to cause contact dermatitis and photosensitivity.[1-4,12] In our series, one patient had photoaggravated eczema due to promethazine cream as previously published.[13] Goossens et al observed photoallergic reaction in 2 of 14 patients with contact allergy to topical promethazine among 12460 patch tests carried out.[1] In addition to sensitization to promethazine, our patient had concomitant positive photoreaction to *Myroxylon pereirae* (balsam of Peru) and fragrance mix which could be explained by the presence of lavender essential oil as excipient ingredient in Phenergan cream. In our cases of photosensitive eczema to isothipendyl, co-sensitization to *Myroxylon pereirae*, fragrance mix and methylisothiazolinone was not due Apaisyl and Sedermyl in view of the absence of these allergens in isothipendyl products.

The present report confirms the need to keep chlorpromazine and promethazine in the photopatch test baseline series as a diagnostic marker of phenothiazine photoallergy according to the European Society for Contact Dermatitis and the European Society for Photodermatology recommendation.[14] The photobiological explorations showed here that UVA is associated with phenothiazines photosensitivity, as in most drug-induced photosensitization.[15] Some patients also reacted to UVB included in polychromatic spectrum irradiation.

In conclusion, we described a series of cases of contact photodermatitis to phenothiazines. In the most of the patients, eczema was due to products containing isothipendyl. Photocontact allergy to topical phenothiazines may be underestimated and lead to a delay in diagnosis, as in our series. Use of isothipendyl and promethazine needs to be limited due to severe reactions.

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In case of dermatitis on uncovered areas, it is recommended to focus the patient's history on topical products applied, and photopatch testing is recommended.

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TABLES

Table 1. Baseline and clinical characteristics of cases.

Table 2. Patch and phototest results.

FIGURE

Fig. 1. Phenothiazines chemical structures

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Table 1. Baseline and clinical characteristics of cases

Case	Age (y)/ Sex	Past medical history	Long term (over 6 months) concomittant medication	Topical phenothiazine used : Trade name (INN)	Application and period of use	Location of eczema	Symptoms duration before diagnosis
1	68/M	Hypertension, dyslipidemia	Verapamil, irbésartan, hydro-chlorothiazide, atorvastatin	Apaisyl gel (isothipendyl)	Discontinuous, 8 months	Face, neck and upper chest	7 months
2	87/M	Diabetes, dyslipidemia, hypertension	glicazide, simvastatin, benazepril, hydro-chlorothiazide, acétylsalicylate	Apaisyl gel (isothipendyl)	15 days	Face, neck, upper chest, forearms then abdomen and thights	7 days
3	43/F	Solar urticaria	bilastine	Apaisyl gel (isothipendyl)	Discontinuous, 2 years	Face, chest, forearms and dorsum of the hands	2 years
4	27/M	Polymorphous light eruption	Hydroxy-chloroquine	Apaisyl gel (isothipendyl)	Discontinuous 4 years	Face, neck and dorsum of the hands	4 years
5	39/F	Cholecystectomy	None	Apaisyl gel (isothipendyl)	Discontinuous 1 year	Face and upper chest	1 year
6	57/F	Hypothyrodism	Levothyroxine	Apaisyl gel (isothipendyl)	3 days	Neck, shoulders,hand back	3 weeks
7	74/M	Polymorphous light eruption	Hydroxy-chloroquine	Apaisyl gel (isothipendyl)	Discontinuous 3 years	Face, neck, forearms	3 years
8	69/M	Diabetes, dyslipidemia, hypertension,	Metformin, rosuvastatin, perindopril, diltiazem	Apaisyl gel (isothipendyl)	Discontinuous 5 years	Left upper limb	1 month
9	66/M	None	None	Apaisyl gel (isothipendyl), Neuriplege ointment (chlorproethazine)	7 days	Face, neck, foremars, dorsum of the hands	1 month
10	68/M	None	None	Apaisyl gel (isothipendyl)	Discontinuous 3 months	Thumbs, dorsum of the hands, forearms, neck and face then trunk and lower limbs	6 months
11	56/F	Veinous insufficiency of legs	None	Apaisyl gel (isothipendyl)	Discontinuous 4 months	Face neck, forearms, dorsum of the hands then erythroderma	4 months
12	88/F	Dubreuilh melanoma, thyroidectomy	Levothyroxine	Sedermyl cream (isothipendyl)	Discontinuous 13 months	Face, forearms, upper chest	13 months
13	53/F	None	None	Sedermyl cream (isothipendyl)	1 day	Face, dorsum of the hands and feet	4 months
14	72/M	None	None	Phenergan cream (promethazine)	Discontinuous 1 month	Face, neck and back	1 month

Abbreviations. y: years. M: male. F: female. INN: International Non-Proprietary name.

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Table 2. Patch and phototest results

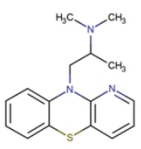
Case	Polychromatic minimal erythema dose (J/cm²)	UVA minimal erythema dose (J/cm²)	Topical phenothiazine used as is NI/UVA/ polychromatic (day 3)	Chlorpromazine 0.1% pet. NI/UVA/ polychromatic (day 3)	Promethazine 0.1% pet. NI/UVA/ polychromatic (day 3)	Other positive patch tests NI/UVA/polychromatic (day 3)
1	Decreased (<0.5, N>1)	ND	Apaisyl - /+++/ND	-/+/ND	-/+++/ND	-/-/-
2†	ND	ND	Apaisyl ND	ND	ND	ND
3	Normal (1.25, N>1)	ND	Apaisyl - /++/ND	-/-/ND	-/+/ND	-/-/-
4	Normal (1.75, N>1)	ND	Apaisyl ND	-/+++/ND	-/-/ND	Methylisothiazolinone 0.2% aq. +++/+++/ND
5	ND	ND	Apaisyl ND	-/-/ND	-/+/ND	*Myroxylon pereirae* 25% pet. +/+/ND
6	ND	ND	Apaisyl -/+++/ND	ND	-/++ /ND	-/-/ND
7	Normal (0.42, N>0.4)	Decreased (<15)	Apaisyl -/+/+	-/-/-	-/-/-	-/-/-
8	Normal (0.7, N>0.4)	Normal (>15)	Apaisyl -/+/+	-/-/-	-/-/-	*Myroxylon pereirae* 25% pet. +/+/+
9	Normal (1.55, N>0.4)	Normal (>15)	Neuriplege and Apaisyl ND	-/+++/++	-/-/-	-/-/-
10	Normal (1.88, N>0.4)	Normal (>15)	Apaisyl -/-/+	-/+++/+++	-/-/-	-/-/-
11	Decreased (0.05, N>0.4)	Decreased (<15)	Apaisyl -/+++/ND	-/+/-	-/-/-	-/-/-
12	Decreased (<0.5, N>1)	ND	Sedermyl ND	-/++/ND	-/++/ND	*Myroxylon pereirae* 25% pet. +/+/ND
13	Decreased (<0.5, N>1)	Decreased (<15)	Sedermyl +/++/++	-/++/-	-/++/++	Mequitazine‡ -/++/++ Fragrance mix 8% pet. -/+/-
14	Normal (1.6, N>1)	Normal (>15)	Phenergan ++/+++/+++	-/++/-	++/++/++	*Myroxylon pereirae* 25% pet. -/+/- Fragrance mix 8% pet. -/+/-

Abbreviations. N: normal value of polychromatic minimal erythema dose depending on center evaluation specified. NI: Non-irradiated. ND: not done. +, ++, +++: positive reaction, -: negative reaction at 72 hours (day 3) according to ICDRG (International Contact Dermatitis Research Group). † Case 2 declined photobiological explorations and did not relapse after 9 months of follow-up. ‡ Mequitazine pet. (contents of Primalan® tablet).

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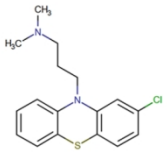
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Isothipendyl:



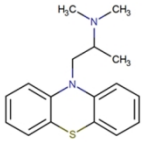
N,N-dimethyl-1-pyrido[3,2-b][1,4]benzothiazin-10-ylpropan-2-amine (CAS no 482-15-5).

Chlorpromazine:



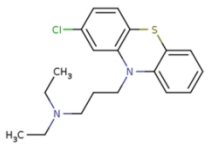
3-(2-chlorophenothiazin-10-yl)-N,N-dimethylpropan-1-amine (CAS no 50-53-3).

Promethazine:



N,N-dimethyl-1-phenothiazin-10-ylpropan-2-amine (CAS no 60-87-7).

Chlorproethazine:



3-(2-chlorophenothiazin-10-yl)-N,N-diethylpropan-1-amine (CAS no 84-01-5).