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Photodermatitis from topical phenothiazines: A case series

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Abstract

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

Objective: To report a series of cases with photodermatitis following use of topical phenothiazines.

Method: A retrospective study of cases of contact dermatitis from phenothiazines seen in French photodermatology centers was performed.

Results: In all, 14 patients with a diagnosis of contact dermatitis from phenothiazines were included. These patients 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 nine 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 of 12 and 7 of 13 tested, respectively.

Conclusion: Use of isothipendyl and promethazine as OTC (or even prescribed) drugs needs to be limited due to severe reactions and sensitization to other phenothiazines that consequently will have to be avoided.

KEYWORDS

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

1 | INTRODUCTION

Photosensitivity is a potential adverse effect of systemic phenothiazines used as antipsychotic. Topical phenothiazines that have antihistamine 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 well-known¹

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responsible for generalized and photoaggravated contact dermatitis due to active ingredient chlorproethazine^{5,6} was withdrawn from the French market in 2007.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

TABLE 1 Baseline and clinical characteristics of cases

Case	Age (y)/sex	Past medical history	Long term (over 6 months) concomitant medication	Topical phenothiazine used: Trade name (INN)	Application and period of use	Location of eczema	Symptom duration before diagnosis
1	68/M	Hypertension, dyslipidemia	Verapamil, irbesartan, hydrochlorothiazide, Atorvastatin	Apaisyl gel (isothipendyl)	Discontinuous, 8 months	Face, neck, and upper chest	7 months
2	87/M	Diabetes, dyslipidemia, hypertension	Glucilazide, simvastatin, benazepril, hydrochlorothiazide, acetylsalicylate	Apaisyl gel (isothipendyl)	15 days	Face, neck, upper chest, and forearms, then abdomen and thighs	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	Hydroxychloroquine	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	Hypothyroidism	Levothyroxine	Apaisyl gel (isothipendyl)	3 days	Neck, shoulders, hand, and back	3 weeks
7	74/M	Polymorphous light eruption	Hydroxychloroquine	Apaisyl gel (isothipendyl)	Discontinuous 3 years	Face, neck, and 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, forearms, and 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	Venous insufficiency of legs	None	Apaisyl gel (isothipendyl)	Discontinuous 4 months	Face neck, forearms, and dorsum of the hands then erythroderma	4 months
12	88/F	Dubreuilh melanoma, thyroidectomy	Levothyroxine	Sedermil cream (isothipendyl)	Discontinuous 13 months	Face, forearms, and upper chest	13 months
13	53/F	None	None	Sedermil 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: F, female; INN, international non-proprietary name; M, male; y, years.

TABLE 2 Patch and phototest results

Case	Polychromatic minimal erythema dose (J/cm ²)	UVA minimal erythema dose (J/cm ²)	Topical phenothiazine used as is		Chlorpromazine 0.1% pet. NI/UVA/polychromatic (day 3)		Promethazine 0.1% pet. NI/UVA/polychromatic		Other positive patch tests NI/UVA/polychromatic	
			NI/UVA/polychromatic		NI/UVA/polychromatic		NI/UVA/polychromatic		NI/UVA/polychromatic	
1	Decreased (<0.5, N > 1)	ND	Apaisyl - /+++ /ND		- /+ /ND		- /+++ /ND		- /- /-	
2 ^a	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	Sedermil ND		- /+++ /ND		- /++ /ND		Myroxylon pereirae 25% pet. +++ /ND	
13	Decreased (<0.5, N > 1)	Decreased (<15)	Sedermil +++ /+++ /++		- /+++ /-		- /+++ /++		Mequitazine ^b - /+++ /++ 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; ND, not done; NI, non-irradiated; +, ++, +++: positive reaction; -, negative reaction at 72 hours (day 3) according to ICDRG (International Contact Dermatitis Research Group).

^aCase 2 declined photobiological explorations and did not relapse after 9 months of follow-up.

^bMequitazine pet. (contents of Primalan tablet).

are also sold in other European countries. The marketing authorization holders for these products are located mainly in Western Europe. The objective of the present study was to address the question of photosensitive dermatitis from topical phenothiazines since 2007.

2 | METHODS

A retrospective study of cases of contact dermatitis from phenothiazines seen in French photodermatology centers from January 1, 2007 to October 31, 2019 was performed. Patients with a clinical diagnosis of contact dermatitis from 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 from topical phenothiazine between January 2007 and October 2019. There were six female and eight 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 reported previously.⁷ Of the 14 patients, three had a history of photosensitive diseases. Case 3 had solar urticaria and cases 4 and 7 had polymorphous light eruption. All developed eczema at the site of application of phenothiazine during sunny seasons. Distant sites were involved secondarily, including photodistributed areas, in 13 of 14 patients. The duration of eczema was longer than 3 months in 9 of 14, with recurrence in spring and summer (cases 3–5, 7, and 12). Topical products containing isothipendyl were the most common cause of

photodermatitis (13/14). One patient used both isothipendyl gel and chlorpromazine 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.

3.2 | Photobiological investigations

Phototesting was performed on the backs 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 24 hours after exposure. UVA MED and irradiation of patches were performed with UVA source: Waldmann (Reischttett, 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 eight 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 hours and then irradiated with 5 J/cm² UVA and the other with polychromatic light (0.75 of the MED), whereas the third set was left in occlusion for 72 hours. Final readings were performed at 72 hours, according to International Contact Dermatitis Research Group guidelines.

Thirteen patients underwent photobiological explorations (Table 2). In all of the nine cases tested, photopatch testing to the topical phenothiazine used "as is" was positive. Chlorpromazine, isothipendyl, and the excipients were not tested because these substances had not been readily available. Photopatch tests to

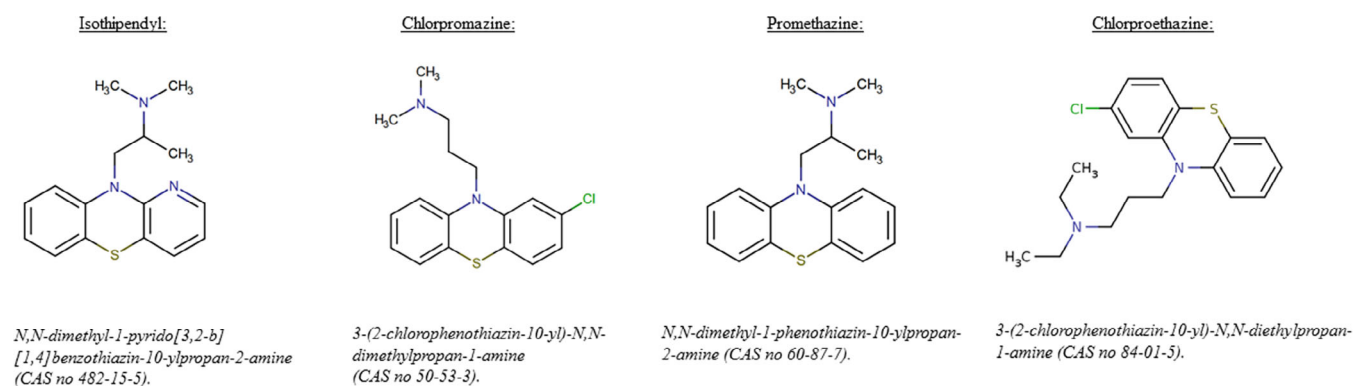


FIGURE 1 Phenothiazine chemical structures

chlorpromazine 0.1% pet. and promethazine 0.1% pet. were positive in 8 of 12 and 7 of 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 six patients. The MED (polychromatic spectrum and/or UVA) was decreased in four 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, whereas UVA MED was still decreased after 1 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 isothipendyl have been reported previously,^{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 unfavourable, but this drug is still marketed to date.⁹ In our series, four patients were hospitalized. We observed one case of persistent light reaction due to isothipendyl as reported previously 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 phenothiazines contraindicated in patients with photocontact dermatitis from isothipendyl, as reported previously in cases with contact sensitization to chlorproethazine (Figure 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 promethazine is the presence of nitrogen in isothipendyl, which may explain its higher photosensitizing potential.⁷ Contact photoallergy to isothipendyl 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, two cases of toxic epidermal necrolysis after isothipendyl gel application have 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 published previously.¹³ Goossens et al observed photoallergic reaction in 2 of 14 patients with contact allergy to topical promethazine among 12 460 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 studies showed here that UVA is associated with phenothiazine 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 from phenothiazines. In 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. In case of dermatitis on uncovered areas, it is recommended to focus the patient's history on the topical products applied, and photopatch testing is recommended.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Goossens A, Linsen G. Contact allergy to antihistamines is not common. *Contact Dermatitis*. 1998;39(1):38-39.
2. de la Cuadra-Oyanguren J, Pérez-Ferriols A, Lecha-Carretero M, et al. Results and assessment of photopatch testing in Spain: towards a new standard set of photoallergens. *Actas Dermosifiliogr*. 2007;98(2):96-101.
3. Katsarou A, Makris M, Zafonitis G, Lagogianni E, Gregoriou S, Kalogeromitros D. Photoallergic contact dermatitis: the 15-year experience of a tertiary reference center in a sunny Mediterranean city. *Int J Immunopathol Pharmacol*. 2008;21(3):725-727.
4. Cardoso JC, Canelas MM, Gonçalves M, Figueiredo A. Photopatch testing with an extended series of photoallergens: a 5-year study. *Contact Dermatitis*. 2009;60(6):325-329.
5. Barbaud A, Collet E, Martin S, et al. Contact sensitization to chlorproethazine can induce persistent light reaction and cross-

- photoreactions to other phenothiazines. *Contact Dermatitis*. 2001;44(6):373-374.
6. Leonard F, Adamski H, Bonneville A, et al. Étude prospective multicentrique 1991-2001 de la batterie standard des photopatch-tests de la Société Française de Photodermatologie. *Ann Dermatol Venerol*. 2005;132(4):313-320.
 7. Bibas N, Sartor V, Bulai Livideanu C, et al. Contact photoallergy to isothipendyl chlorhydrate. *Dermatology*. 2012;224(4):289-291.
 8. Takashima A, Yoshikawa K. Contact allergy to isothipendyl. *Contact Dermatitis*. 1983;9(5):429-430.
 9. ANSM, Agence nationale de sécurité du médicament et des produits de santé. Séance n°5 Commission de suivi du rapport entre les bénéfices et les risques des produits de santé - Compte rendu de la réunion du 3 octobre 2017. https://www.ansm.sante.fr/content/download/115427/1460739/version/1/file/CR_Commission+suivi_031017.pdf. Accessed February 10, 2020.
 10. Moreau A, Domp Martin A, Dubreuil A, Leroy D. Phototoxic and photoprotective effects of topical isothipendyl. *Photodermatol Photoimmunol Photomed*. 1995;11(2):50-54.
 11. Gravante G, Delogu D, Marianetti M, Trombetta M, Esposito G, Montone A. Toxic epidermal necrolysis and Steven Johnson syndrome: 11-years experience and outcome. *Eur Rev Med Pharmacol Sci*. 2007;11(2):119-227.
 12. Cantisani C, Ricci S, Grieco T, et al. Topical promethazine side effects: our experience and review of the literature. *Biomed Res Int*. 2013;2013(151509):1-9.
 13. Arrue I, Rosales B, Ortiz de Frutos FJ, Vanaclocha F. Photoaggravated eczema due to promethazine cream. *Actas Dermosifiliogr*. 2007;98(10):717-718.
 14. Gonçalo M, Ferguson J, Boneville A, et al. Photopatch testing: recommendations for a European photopatch test baseline series. *Contact Dermatitis*. 2013;68(4):239-243.
 15. Khandpur S, Porter RM, Boulton SJ, Anstey A. Drug-induced photosensitivity: new insights into pathomechanisms and clinical variation through basic and applied science. *Br J Dermatol*. 2017;176(4):902-909.

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