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Revisión

Contact dermatitis due to gallates

Gallates are antioxidant compounds that are used in the food, cosmetics and drug industries. Even though they behave as powerful antigens in animal models, only a rather limited number of cases of gallate-induced contact dermatitis has been reported in humans. This phenomenon has been attributed to immunologic tolerance through oral exposure, as described in experimental animal models. The most frequent clinical presentation in humans is cheilitis, although eczema in other locations and even generalised dermatitis are also possible. Widely different concentrations and vehicles have been used for the epicutaneous tests in the cases reported. As for the therapeutic management of gallate-induced contact dermatitis, and considering that at present these substances are scarcely relevant in the formulation of drugs, the preventive measures may be restricted to the use of cosmetics and the industrial manipulation of certain foodstuffs.

Key words: Contact dermatitis. Cosmetics. Food. Gallates. Patch tests.

Dermatitis de contacto por galatos

Los galatos son sustancias antioxidantes que se emplean en la industria de alimentos, cosméticos y medicamentos. Pese a que se comportan como antígenos potentes en experimentación animal, se ha descrito sólo un número limitado de dermatitis de contacto por galatos, lo que se ha atribuido a la tolerancia inmunológica de estas sustancias inducida por vía digestiva, tal como ocurre en modelos de experimentación animal. La clínica más habitual es la queilitis, aunque pueden ser causa de eczema en otras localizaciones, incluso de dermatitis generalizada. Se destaca la variabilidad de concentraciones y vehículos para las pruebas epicutáneas en los casos publicados. En cuanto al tratamiento de las dermatitis de contacto por galatos y dado que en la actualidad apenas tienen importancia en la composición de medicamentos, las medidas de prevención se limitarán al uso de cosméticos y a la manipulación de ciertos alimentos en la industria.

Palabras clave: Alimentos. Cosméticos. Dermatitis de contacto. Galatos. Pruebas epicutáneas.

Gallates are a group of antioxidant substances that are used as preservatives in cosmetics, foods and in the pharmaceutical industry (in topical preparations) for preventing the oxidation of fats, vitamins, perfumes and essential oils. They thus prevent those preparations from acquiring a rancid aspect and a disagreeable smell. Chemically, gallates are alkyl esters of the trihydroxybenzoic acid, which differ from each other in their side chains (Fig. 1). The most usually employed variants are propyl gallate (PG), octyl gallate (OG) and dodecyl gallate (DG). These three substances have been coded, accor-

ding to the European Directive on Alimentary Additives (Directive 95/2/CE) as "E-310", "E-311" and "E-312".

The gallate esters have been associated to adverse events such as contact dermatitis and methemoglobinaemia¹.

EUROPEAN LEGISLATION

According to the European Directive on alimentary additives different from colorants and sweeteners (Directive 95/2/CE), the maximum allowed dose for PG (E-310), OG (E-311) and DG (E-312) is 200 mg/kg in fats and oils destined to the professional manufacture of heat-treated alimentary products and in a number of manufactured foods, with the exceptions of dehydrated potatoes (25 mg/kg) and chewing gums and dietary supplements (400 mg/kg).

The concentrations allowed in cosmetics and pharmaceutical products range, according to Martindale¹, from 0.001 to 0.1%.

As regards their presence in drug formulations, an information request to the Drug Surveillance Centre of the Autonomous Community of the Basque Country (CEVI-ME, *Centro de Vigilancia del Medicamento de Euskadi*) has yielded only three registered preparations for topical use, all of them but little used: Hemoderm®, Alphosyl® and Cusigel®.

ANTIGENICITY

Hausen and Beyer², in 1992, sensitised Guinea pigs with eight different gallates and came to the following conclusions: the eight gallates tested were considered to be moderate to strong sensitising agents; the increase in length of the side chain correlates with increasing sensitising capacity; finally, cross-reactivity between these compounds occurs when the chemical difference in their side chains is less than four carbon atoms (Fig. 1).

In human experimentation, the open repeated application test with PG at concentrations below the 1% one allowed in cosmetics did not induce any dermatitis manifestations in 850 subjects. However, this same compound, vehiculised in ethanol, sensitised eight out of ten volunteers³. One case has been reported of active sensitisation after the application of PG at varying concentrations in ethanol/water (25/75)⁴.

Khan et al.³ induced sensitisation in Guinea pigs

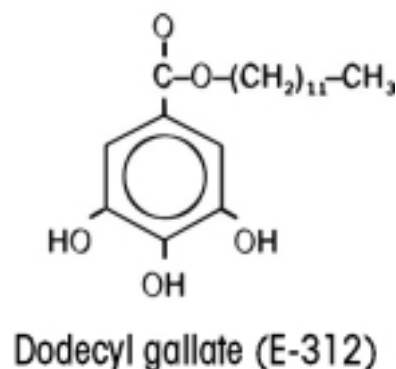
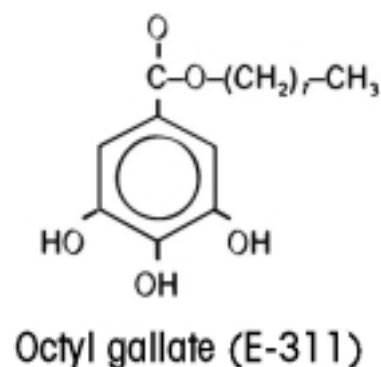
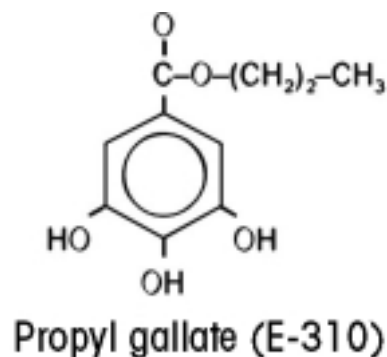


Fig. 1. Chemical structure of gallates.

using the intradermal route. They applied on alternate days three 0.1 ml doses of 5% PG together with Freund's complete adjuvant; ten days after induction, 2%, 0.5% and 0.1% PG patches were applied, with 70% alcohol as the vehicle. Positive reactions occurred after 24 and 48 hours, and the sensitisation persisted when the animals were re-tested three months later. When these authors tried to achieve sensitisation by the epicutaneous route in another

group of Guinea pigs, the concentrations required were higher than those used intradermally.

The same investigators induced PG tolerance³. They exposed Guinea pigs by the digestive route to seven consecutive daily 1.5 ml doses of 10% PG in a 1:10 alcohol solution and in olive oil. The animals were then intradermally immunised with PG and dinitro-chlorobenzene (DNCB); finally, the latter two substances were patch-tested. The results were negative for PG and positive for DNCB.

According to one multicentre study in which various antimicrobial and biocide preservatives were tested⁵, it was demonstrated that the one gallate with the greatest sensitising capacity is OG (1.1%), followed by DG (0.6%) and PG (0.3%). In the literature, however, the cases related to PG predominate, possibly because this is the most widely used gallate⁶⁻¹².

Hemmer et al.⁶, after studying one case, suggested the possibility that the gallates might have cross-reactivity with other compounds (catechol, protocatechuic acid and *p*-tert-butylcatechol), all of them phenols occurring in vegetable pigments and having in common in their chemical composition the presence of two hydroxyl groups in "ortho-" position. These investigators ruled out positivities with other substances with hydroxyl groups in "meta-" or "para-" position.

Finally, Marston⁷ published a series of 13 cases of PG positivity among 245 women studied; 10 out of these 13 had used cosmetics with liposomes that contained this gallate in their composition. He explained this high number of cases through the adjuvant capacity of the liposomes. One of the cases in the series published by Romaguera and Vilaplana was also due to a liposome-containing cosmetic, but in this case the patient was sensitised to PG, OG and DG.

REVIEW OF THE PUBLISHED CASES

This review includes 45 cases, 40 females and 5 males; 44 of them were adults (age range, 19 to 65 years), and the remaining one was a 6-year-old child (Table I).

The clinical presentation was cheilitis in 18 cases, disseminated dermatitis in 10, dermatitis of the hands in 6, facial dermatitis in 3, and other locations in 8 cases.

The causative agents were PG in 32 cases, OG in 13 and DG in 7. In most of the patients the clinical manifestations were associated to one single gallate; all three gallates were involved in three cases, and two of them in a further three.

As for the origin of the manifestations, cosmetics were involved in 35 cases (lipsticks/lip balms in 15, liposome-containing cosmetics in 11, body lotions in 6, and other cosmetics in 3), drugs/medicinal preparations in 7 cases, and foods/foodstuffs in 3 cases.

Cosmetics. The most usual clinical presentation was that of cheilitis, in relation to the use of lipsticks⁸⁻¹⁴; only one of these cases involved a male patient¹¹. The remainder of the clinical manifestations involved the face in 15 cases^{6-8,12-14}, and in 6 cases the distribution was generalised, in relation to a body milk containing 16 components¹⁵.

The gallate involved was PG in most cases; only in the series published by Serra-Baldrich and Puig¹¹ are four cases involving OG and two cases involving DG reported. These results question the possibility of cross-reactivity among the various gallates, even though in one case⁶ there were positive tests with PG, OG and DG and also with gallic acid and with ethyl- and methyl-gallate. On the other hand, in a number of cases only PG was tested^{7,9,15}.

It is noteworthy that in the case reported by Hemmer et al.⁶ the contactants were tested at a 0.3% concentration and in an aqueous vehicle, despite the difficulties in dissolving them in such a vehicle¹.

The cases related to the application of liposome-containing creams^{7,8} bear special mention; the authors speculate that these substances may in these cases have acted as adjuvants.

Foods and foodstuffs. Three of the four cases reported had an occupational origin: preparation of ginger bread, manipulation/sale of cheeses, and preparation of chicken fats¹⁶⁻¹⁸. The fourth case was related to the ingestion of margarine, in a child presenting with labial oedema that remitted after an exclusion diet¹⁹.

Among the clinical manifestations, a particularly striking one was an occupational airborne dermatitis¹⁸ in a female worker in the alimentary industry; this patient's work consisted in mixing powdered OG with heated chicken fat, and she had possibly become sensitised at her previous workplace in the elaboration of margarines. In this particular case a test with 1% OG in alcohol is reported, with an irritative result.

Drugs and medicinal preparations. The male gender predominated in this group, and in all the patients the only contactant reported was PG, in various vehicles and at different concentrations.

The origin of the clinical manifestations was a "natural" lip balm²⁰ containing 24 components, one of which

Table I. Gallate-induced contact dermatitis: review of the literature

Author(s)	No. of cases	Gender (F/M)	Clinical manifestations	Epicutaneous tests		Origin
				Gallate tested	Concentration	
Romaguera and Vilaplana ⁸	5	5 m	4 cheilitis	4 PG	1% vas	Lipstick
		5/0	1 face	1 OG	0,25% vas	Liposome cream
Heine ¹⁵	6	6/0	Disseminated	PG	1% vas	Body lotion
Cronin ⁹	1	1/0	Cheilitis	PG	2% vas	Lipstick
Kanthraj et al ¹⁰	1	1/0	Cheilitis	PG and OG		Cosmetics
Serra-Baldrich and Puig ¹¹	7	6/1	Cheilitis	1PG	1% vas	Lipstick
				4OG	0,25% vas	
				2DG	0,25 vas	
Giordano and Schwange ¹²	1	1/0	Cheilitis	OG	0,3 % vas	Lipstick
Pérez and Rodríguez ¹³	1	1/0	Cheilitis	PG and OG	1 % vas	Lipstick
Nandkishor and Athevale ¹⁴	1	1/0	Cheilitis	PG and OG	1% y 0,25 vas	Lipstick
Hemmer et al ⁶	1	1/0	Face	PG, OG, DG	0,3% aqueous	Cosmetic
Marston ⁷	10	10/0	Face and neck	PG	1% vas	Cosmetics with liposomes
Bojs et al ¹⁶	1	1/0	Disseminated and hands	PG, OG, DG	1 y 0,25 % vas	Flour and hand cream
Raccagni et al ¹⁷	1	1/0	Hands	DG	0,1% vas	Cheese
Lewis et al ¹⁹	1	0/1	Labial oedema	DG	0,2% vas	Margarine
De Groot and Geskemos ¹⁸	1	1/0	Airborne CD	OG	0,1% vas	Chicken fat
Wilson et al ²⁰	1	0/1	Cheilitis	PG	2% vas	"Natural" remedy
Corazza et al ²⁵	1	0/1	Hand and arm	PG	0,5, 1 and 2%	Drug (medicinal preparation)
Pigatto et al ²⁶	1	1/0	Ulceration	PG	0,1% vas	Drug (medicinal preparation)
Hernández et al ²²	1	0/1	Penis	PG?		Drug (medicinal preparation)
Lidén ²³	1	0/1	Disseminated	PG	1% ethanol	Drug (medicinal preparation)
Valsecchi and Cainelli ²¹	2	1/1	Disseminated	PG and product as such	1% vas	Drug (medicinal preparation)

PG = propyl gallate; OG = octyl gallate; DG = dodecyl gallate; vas. = vaseline (petroleum jelly); CD = contact dermatitis.

was PG. Further origins of clinical manifestations in this group were an antibiotic cream^{15,21}, a corticosteroid cream²² and one anti-psoriasis cream, Alphosyl®²³.

Diagnostic tests. The concentrations and vehicles used in the diagnosis of the different cases were quite varied; the most frequently used concentrations were 0.25% for OG and 1% for PG, with vaseline (petroleum jelly) as the vehicle.

De Groot²⁴ recommends testing the gallate esters at 0.1 to 1.0% concentration in vaseline or olive oil.

The availability of these contactants for diagnostic tests, in the Spanish market, is as follows: Laboratorios Aristegui, PG and OG, 1% in vaseline; Chemotecnica Laboratories, OG and DG, 0.25%, and PG, 1%, in vaseline (bakery and cosmetics panels); Laboratorios Leti, OG and DG, 0.3%, and PG, 0.5%, in vaseline (antimicrobial preservative panel); Laboratorios Marti-Tor, PG, 1% in vaseline; Laboratorios Trolab, DG, 0.3% in vaseline (antioxidant panel), OG, 0.3% in vaseline, and PG, 0.5% in vaseline.

REFERENCES

- Martindale. The complete drugs reference, 32nd ed. Londres: Pharmaceutical Press, 1999; 1011.
- Hausen BM, Beyer W. The sensitizing capacity of the antioxidants propyl, octyl, and dodecyl gallate and some related gallic acid esters. *Contact Dermatitis* 1992; 26: 253-258.
- Kahn G, Phanuphak P, Claman HN. Propyl gallate-contact sensitization and orally-induced tolerance. *Arch Dermatol* 1974; 109: 506-509.
- Kraus AL, Stotts J, Altringer LA, Allgood GS. Allergic contact dermatitis from propyl gallate: dose response comparison using various application methods. *Contact Dermatitis* 1990; 22: 132-136.
- Schnuch A, Geier J, Uter W, Frosch TJ. Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicenter study. *Br J Dermatol* 1998; 38: 467-476.
- Hemmer W, Focke M, Wolf-Abdolvahab S, Bracun R, Wantke F, Gotz M, et al. Group allergy to tri- and ortho-diphenols (catechol) in a patient sensitized by propyl gallate. *Contact Dermatitis* 1996; 35: 110-111.
- Marston S. Propyl gallate on liposomes. *Contact Dermatitis* 1992; 27: 74-76.
- Romaguera C, Vilaplana J. Contact dermatitis from gallates. *Am J Contact Dermatitis* 1993; 4: 231-234.

9. Cronin E. Lipstick dermatitis due to propyl gallate. *Contact Dermatitis* 1980; 6: 213-214.
10. Kanthraj GR, Shenoi SD, Srinivas CR. Patch testing in contact cheilitis. *Contact Dermatitis* 1999; 40: 285.
11. Serra-Baldrich E, Puig LL, Giménez Arnau A, Giménez Camarasa J. Lipstick allergic contact dermatitis from gallates. *Contact Dermatitis* 1995; 32: 359-360.
12. Giordano-Labadie F, Schwarze HP, Bazex J. Allergy Contact Dermatitis from octyl gallate in lipstick. *Contact Dermatitis* 2000; 42: 51.
13. Pérez Ferriols A, Rodríguez Serna M, De la Cuadra Oyanguren J. Queilitis alérgicas de contacto y de fotocontacto por lápices labiales. *Actas Dermosifiliogr* 1994; 85: 545-548.
14. Nandkishor V, Athavale, Srinivas CR. Contact cheilitis from propyl gallate lipsticks. *Contact Dermatitis* 1994; 30: 307.
15. Heine A. Contact dermatitis from propyl gallate. *Contact Dermatitis* 1988; 18: 313-314.
16. Bojs G, Nicklasson B, Svensson A. Allergic contact dermatitis to propyl gallate. *Contact Dermatitis* 1987; 17: 294-298.
17. Raccagni AA, Frattagli M, Baldari U, Righini MG. Lauryl gallate hand in a cheese counter assistant. *Contact Dermatitis* 1997; 37: 182.
18. De Groot AC, Gerkens F. Occupational airborne contact dermatitis from octyl gallate. *Contact Dermatitis* 1990; 23: 184-185.
19. Lewis FM, Shah M, Gawkrödger DJ. Contact sensitivity to food additives can cause oral and perioral symptoms. *Contact Dermatitis* 1995; 33: 429-430.
20. Wilson AG, White IR, Kirby JDT. Allergic contact dermatitis from propyl gallate in a lip balm. *Contact Dermatitis* 1989; 20: 145-146.
21. Valsecchi R, Cainelli T. Contact allergy to propyl gallate. *Contact Dermatitis* 1988; 19: 313-314.
22. Hernández N, Assier-Bonnet H, Terki N, Revuz J. Allergic contact dermatitis from propyl gallate in desonide cream (Locapred®). *Contact Dermatitis* 1997; 36: 111.
23. Lidén S. Alphosyl® sensitivity and propyl gallate. *Contact Dermatitis* 1975; 1: 257-258.
24. De Groot AC. Patch testing. Test concentrations and vehicles for 3.700 chemicals, 2^a ed. Amsterdam, Londres, Nueva York, Tokyo: Elsevier Science BV, 1994; 289.
25. Corazza M, Mantovani L, Roveggio C, Virgili A. Allergic contact dermatitis from propyl gallate. *Contact Dermatitis* 1994; 31: 203-204.
26. Pigatto PD, Boneschi V, Riva F, Altomare GF. Allergy to propyl gallate, with unusual clinical and histological features. *Contact Dermatitis* 1984; 11: 43.