

Polyethylene glycol as marker for nitrofurazone allergy: 20 years of experience from Turkey

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Summary

Background. Polyethylene glycols (PEGs) and propylene glycol (PG) are used as vehicles in various medicinal and cosmetic products. They are potential contact sensitizers, including low molecular weight PEGs in nitrofurazone preparations that are still widely used in Turkey.

Objectives. To investigate the prevalence of allergic contact dermatitis caused by PEG and PG in a relatively large group of patients in Turkey.

Methods. In this retrospective, cross-sectional, single-centre study, 836 patients patch tested with PEG and PG between 1996 and 2015 were reviewed.

Results. Thirty-five patients (4.2%) showed positive patch test reactions to PEG, and 7 (0.8%) showed positive patch test reactions to PG, partly as late positive reactions with PEG. PEG sensitivity was almost exclusively related to nitrofurazone allergy. Patch test reactions to PG were currently relevant mainly with regard to the use of minoxidil, and antiherpetic or corticosteroid creams. Ten patients (25%) had concomitant contact allergies to various topical drugs containing mainly PEGs.

Conclusions. PEG sensitivity seems to be a marker for contact allergy to topical nitrofurazone in Turkey. Nitrofurazone allergy appears to favour concomitant sensitization to PEG. We would suggest the inclusion of PEG in an extended baseline patch test series in Turkey. Late patch test readings are important to diagnose delayed positive reactions to PEG.

Key words: allergic contact dermatitis; excipient; nitrofurazone; patch test; PEG; polyethylene glycol; propylene glycol; topical drug; vehicle.

Polyethylene glycols (PEGs) and propylene glycol (PG) are used as vehicles in topical and systemic medicaments and cosmetic products, as solvents in industrial products, and also as food additives. PG is an effective humectant, and has antimicrobial properties. PEGs and PG are potential

contact sensitizers, especially low molecular weight PEGs in nitrofurazone-containing soluble preparations, which are still widely used in Turkey. Unfortunately, comprehensive data on allergic contact dermatitis (ACD) caused by these vehicle components in Turkish patients are lacking. We therefore aimed to investigate the prevalence of ACD caused by PEG and PG in a relatively large series of patients in Turkey during a 20-year period.

Materials and Methods

This was a retrospective, cross-sectional, single-centre study based on the analysis of the files of patients consecutively patch tested in the allergy unit of our clinic with suspicion of ACD between June 1996 and December

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2015. Of these, 836 patients who were patch tested with PEG 400 'as is' and PG 5% pet. (between 1996 and 2013) and 30% aq. (since 2014) were enrolled in the study. The reason for patch testing was suspected contact allergy to topical medicaments or cosmetics. Patch testing was performed after written or oral consent of patients, or legal guardians for children, had been obtained. Test allergens were supplied by Brial Allergen (Greven, Germany) and Chemotechnique Diagnostics (Vellinge, Sweden), and in the earlier years by Hal-Brial (Leiden, The Netherlands). They were applied in IQ Chambers® (Chemotechnique Diagnostics) to the upper back for 2 days. Patients' own materials, such as topical drugs or cosmetics, were patch tested 'as is', if necessary. Test sites were evaluated on day (D) D2, D3, and D4, and, in some patients, also on D7, according to the ESCD patch test guideline (1). Positive patch test reactions were evaluated whether being of current relevance, past relevance, or unknown relevance.

Results

Forty of 836 patients showed positive patch test reactions to PEG, PG, or both. Thirty-five patients (4.2%) showed positive patch test reactions to PEG, 7 patients (0.8%) showed positive patch test reactions to PG, and 2 showed positive patch test reactions to both PEG and PG. The characteristic features of patients with positive patch test reactions to PEG and PG are summarized in Table 1. There were no statistically significant differences concerning sex, age and atopic status between patients sensitized to PEG and those sensitized to PG. Atopic background was absent in most of the patients ($n = 28$), but 3 patients had atopic skin diathesis according to criteria defined by Diepgen and Fartasch (2).

Strong (++) or extreme (+++) positive patch test reactions to PEG and to PG were observed in 22 of 35 (62.8%) patients, and in 5 of 7 (71%) patients, respectively. More than one-third of the patients (34.3%, $n = 12$) with PEG sensitivity showed late positive patch test reactions starting on D4 or later. Among 35 patients with contact allergy to PEG, 28 (80%) showed clinical relevance, and also showed positive patch test reactions to nitrofurazone 1% pet. and/or nitrofurazone-containing soluble preparations 'as is' (Fig. 1). Information on the use of nitrofurazone or other PEG-containing products was lacking for 7 patients, so the clinical relevance of positive patch test reactions to PEG was classified as 'unknown' in those cases. The most frequent reasons for nitrofurazone use were infected skin lesions, followed by skin wounds, burns, stasis dermatitis, and surgical procedures.

Six of the seven positive patch test reactions to PG were currently relevant to the use of different spray and cream

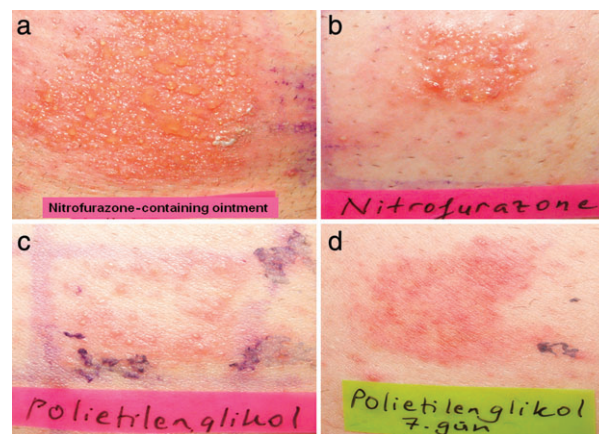


Fig. 1. A +++ positive patch test reaction with nitrofurazone-containing ointment ('as is') on day (D) 3 (a), a +++ positive patch test reaction with its active ingredient nitrofurazone (1% pet.) on D3 (b), a questionable (?+) positive reaction with its vehicle component polyethylene glycol 400 on D3 (c), and a + positive reaction with polyethylene glycol on D7 (d).

preparations (Table 1). In 1 patient, PG contact allergy was found to be of past relevance, resulting from minoxidil use. A total of 10 patients (25%) had contact allergies to various topical drugs/preparations containing PEGs ($n = 7$), PG ($n = 1$), or both ($n = 2$) (Table 2).

Discussion

This study presents the largest dataset on patch test results with PEG and PG from Turkey, and highlights the high prevalence of PEG sensitivity in this country. PEGs (synonym: macrogol) are condensation polymers of ethylene glycol of varying molecular weights. They are generally regarded as weak contact sensitizers in comparison with their widespread presence in various topical preparations such as topical drugs or cosmetics. Oral and parenteral administration of some products containing high molecular weight PEGs may cause immediate-type hypersensitivity reactions (3, 4). Contact sensitization is mainly reported with low molecular weight PEGs, for example PEG 200 to PEG 400 (5–8). Previous studies from the United States, Europe, and India, mainly in the 1970s and 1980s, reported a high prevalence of sensitization to low molecular weight PEGs, both in patients with suspected topical medicament sensitivity, and also during routine patch testing (6, 8–11). Hence, it was decided to include PEG 400 in the baseline or the topical drug patch test series in many countries, such as India (8, 12) and Germany (6, 7). As >600 topical drugs contained PEG in the United States in the 1970s (9), PEG

Table 1. Characteristic features of patients with positive patch test reactions to polyethylene glycol (PEG) and propylene glycol (PG)

Characteristic features	Patients with PEG sensitivity (n = 35)	Patients with PG sensitivity (n = 7)
Sex (female/male)	13:22	3:4
Age (years)	24–79 (median: 48)	25–73 (median: 47)
Atopy	None (n = 27), unknown (n = 5), atopic skin diathesis (n = 3)	None (n = 2), unknown (n = 4), atopic skin diathesis (n = 1)
Suspicion of allergic contact dermatitis caused by:	Topical drugs (n = 30), cosmetics (n = 5)	Topical drugs (n = 6), cosmetic cream (n = 1)
Degree of positive patch test reaction	+ (n = 13), ++ (n = 18), +++ (n = 4)	+ (n = 2), ++ (n = 4), +++ (n = 1)
Late positive patch test reaction	n = 12 On day 4 (n = 8), on day 7 (n = 4)	None
Clinical relevance	Current (n = 26), past (n = 2), *unknown (n = 7)	Current (n = 6), past (n = 1)
Relevant topical preparation (probable source of primary sensitization)	Nitrofurazone soluble dressing (n = 28)	Minoxidil spray (n = 2), acyclovir cream (n = 1), corticosteroid cream (n = 1), lidocaine cream (n = 1), terbinafine cream (n = 1), cosmetic cream (n = 1)
Reason for use of the clinically relevant topical preparation	Infected eczema or other skin lesions (n = 12), traumatic skin wounds (n = 7), burns (n = 4), stasis dermatitis (n = 3), surgical procedures (n = 2)	Alopecia (n = 2), herpes labialis (n = 1), eczema (n = 3), tinea corporis (n = 1)
Duration until the diagnosis of allergic contact dermatitis	3 days to 30 years (median: 35 weeks)	2–52 weeks (median: 3 weeks)
Site of dermatitis	Generalized (n = 16) Localized (n = 13): leg (n = 4), face (n = 3), hand (n = 3), foot (n = 2), arm (n = 1) Local spread (n = 6)	Localized (n = 4): scalp (n = 1), neck (n = 1), hand (n = 1), leg (n = 1) Generalized (n = 2) Local spread (n = 1)
Concomitant positive patch test reactions to PEG/PG	Yes (n = 2): both clinically relevant	Yes (n = 2): both clinically relevant
Sensitivity to a variety of topical drugs containing PEG/PG proven by additional patch testing (n = 10)	Yes (n = 7 + 2 [†]) (Table 2)	Yes (n = 1 + 2 [†]) (Table 2)

*These patients were not asked about nitrofurazone use.

[†]These 2 patients are included in both groups.

was included in the North American Contact Dermatitis Group (NACDG) patch test series as well.

Interestingly, contact allergy to low molecular PEGs was most frequently reported in patients with ACD caused by topical nitrofurazone preparations containing this vehicle (5, 13–17). In one study, 12 of 40 patients (30%) with ACD caused by nitrofurazone-containing topical preparation had positive reactions to PEG, whereas 3 patients reacted only to PEG (14). Nitrofurazone is a strong contact sensitizer (14, 18–20). ACD caused by this drug might be severe, and might require hospitalization or treatment with systemic corticosteroids in a significant number of patients (18). It is well known that PEG in topical nitrofurazone preparations facilitates the skin penetration of nitrofurazone (21). On damaged skin with impaired barrier function, on the other hand, the risk of concomitant sensitization to nitrofurazone and PEG seems to be particularly high.

Nitrofurazone is no longer used as frequently as it was before the 1990s in most countries. Recent reports on contact sensitization to vehicle components or in patients

with chronic leg ulcers or stasis dermatitis from the United States (22) and from Europe did not show a single case of PEG or nitrofurazone allergy (23, 24). Therefore, PEG 400 is no longer included in the NACDG routine test series (22). It is, however, still included in the baseline patch test series in India, together with nitrofurazone 1% pet. (12, 25). Recent reports from India indicate a continuous decline in the prevalence of sensitization to nitrofurazone and PEG 400, from 10.7% to 6%, and from 2.8% to 1%, respectively (25, 26). The discrepancy between the sensitization prevalence of nitrofurazone and PEG in these studies was unexpected. We would assume that late positive reactions to PEG might have been missed in these studies, in which delayed patch test readings beyond D4 were not performed. The occurrence of late positive patch test reactions to PEG was, indeed, one of the important observations of our study. The reactions started on D4 or later in more than one-third of patients (Table 1).

Nitrofurazone is still an important cause of ACD caused by topical drugs in Turkey. Nitrofurazone-containing

Table 2. Characteristics of patients with contact allergies to various topical drugs containing polyethylene glycol (PEG), propylene glycol (PG), or both

Patient no.	Active ingredient of the clinically relevant topical preparation	PEG/PG as the vehicle component
1	Nitrofurazone/sertaconazole/urea-containing emollient	PEG
2	Nitrofurazone/mupirocin	PEG
3	Nitrofurazone/dexpantenol	PEG
4	Nitrofurazone/ <i>Triticum vulgare</i> extract	PEG
5	Nitrofurazone/extractum cepae	PEG
6	Nitrofurazone/ <i>Triticum vulgare</i> extract/extractum cepae	PEG
7	Nitrofurazone/ciclopirox olamine	PEG
8	Mometasone furoate*/clobetasol propionate	PG
9	Nitrofurazone/mupirocin/ <i>Triticum vulgare</i> extract	PEG
	<i>Centella asiatica</i> extract	PG
	Lidocaine	PEG + PG
10	Nitrofurazone/mupirocin	PEG
	Fluticasone propionate/clobetasol propionate	PG

*Mometasone furoate preparation contains PG-monostearate, which might not cross-react with PG.

soluble dressing, which contains 0.2% nitrofurazone and PEGs 300, 1000, and 4000, is still the most frequently prescribed antibacterial topical agent in Turkey, especially by surgical specialists, for the treatment of wounds, burns, or infected skin lesions. Patients with stasis eczema and leg ulcers were known to be particularly prone to develop ACD. In the present study, however, infected skin lesions other than stasis eczema, traumatic skin wounds and burns were the main reasons for nitrofurazone-induced ACD. Recently, we reported that nitrofurazone was the leading causative agent of foot contact dermatitis in Turkish patients (27).

The most striking finding of our study was that PEG sensitization accompanied nitrofurazone allergy almost exclusively. Furthermore, a significant number of patients reacted to various topical drugs containing PEG (Table 2). Skin problems caused by other drugs started after the use of nitrofurazone preparations in these patients. Thus,

nitrofurazone topical preparations seem to be the cause of primary sensitization to PEG.

PG (synonyms: dihydroxypropane; propane-1,2-diol), on the other hand, is generally regarded as a weak contact sensitizer (28). There have been concerns about its irritant effects on the skin, and debates on the optimum patch test concentration and vehicle (28, 29). Today, PG is included in the NACDG series at 30% aq. Many topical products, for example topical corticosteroids, antiherpetic creams, minoxidil solutions, ultrasonic gels and cosmetics, contain PG (28, 30, 31). The reported patch test positivity varies from 2.3% to 7.8% (28, 29, 32–34), and the clinical relevance seems to be high (32, 33, 35). It was recommended to include PG in a minimum patch test series for patients with leg ulcers (22). PG was regarded, together with PEG, among potential contact allergens in emollients in a recent review (36). In the present study, PG showed strong positive patch test reactions in the majority (5/7) of patients. All patients had clinically relevant positive patch test reactions, mainly to topical drugs such as minoxidil solution (Table 1). None of the patients had leg ulcers or stasis dermatitis.

Conclusions

PEG sensitivity seems to be a marker for topical nitrofurazone allergy in Turkey. It appears to be essential to inquire about current or previous nitrofurazone use in every patient with a positive patch test reaction to PEG. We would suggest the inclusion of PEG in the extended baseline patch test series in Turkey, as it fulfils the requirements to be included in a standard patch test series, such as: (i) a high sensitization prevalence, exceeding 0.5–1% in routine patch testing; (ii) a common presence in the topical preparations; (iii) strong positive and reliable patch test results; (iv) a high degree of clinical relevance; and (v) a minimal risk of patch test sensitization (37). Late positive reactions are frequent with PEG, and late readings are important in order not to overlook them. Moreover, nitrofurazone allergy appears to favour concomitant sensitization to PEG, which seems to be an important problem, as PEG is included in various topical preparations as a vehicle or stabilizer.

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