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Immediate and delayed allergic contact reactions to polyethylene glycol

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The lower molecular weight liquid polyethylene glycols (PEG) varying from 200 to 700 are extensively used as solvent vehicles in topical medicaments. Four patients showed allergic reactions to these liquid polyethylene glycols in topical medications. Two had immediate urticarial reactions to PEG 400. Two other patients had delayed allergic eczematous reactions, one to PEG 200, and one to PEG 300. Cross reactions occurred between PEG 200, 300 and 400, but not between these liquid polyethylenes and the higher molecular weight solid polyethylenes from 1000 to 6000.

Key words: Allergic dermatitis – delayed eczematous – immediate urticarial – liquid polyethylene glycols 200, 300, 400.

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Polyethylene glycol HO $(CH_2CH_2)_xOH$, is a mixture of glycols. The lower molecular weights from 200 to 700 are liquids, while the higher weights 1000 to 6000 are solids. Polyethylene glycols of varying molecular weights are extensively used as vehicles in topical medicaments, suppositories, shampoos, detergents, hair dressings, insect repellents, cosmetics, toothpastes and contraceptives.

In industry the polyethylene glycols are used as solvents for nitrocellulose, as plasticizers for glue and casein, and as wetting agents in epoxy hardeners.

Polyethylene glycol ointment (U.S.P.) is made up of solid polyethylene glycol 4000 (U.S.P.) and liquid polyethylene glycol 300. Carbowax is a solid waxy polyethylene glycol. Carbowax 1500 is a synthetic soft wax, used as a softener and lubricant sizing agent for textiles. Carbowax 4000, a hard translucent solid is a binder for pigments and a lubricant in sizing.

Four patients were recently studied with allergic reactions to polyethylene glycol (PEG) in topical medications. Two were of the immediate, urticarial variety, two were of the delayed, eczematous contact type.

Case Reports

Immediate urticarial reactions to polyethylene glycol (PEG)

The first case report in the literature (Fisher 1977) of an immediate reaction to polyethylene glycol 400 was that of a 50-year-old male who had applied Lotrimin® solution for tinea infection of the toe webs. The sites of application of the medication

became red and pruritic within 15 min. When seen 1 week after application of the medication, an excoriated erythematous dermatitis appeared on the dorsal aspect of the toes. Patch tests with Lotrimin solution were negative.

After the acute dermatitis had subsided, the patient had applied Tinactin® solution. The patient again stated that the sites of application of the medication had become red and pruritic within 15 min in a manner similar to that produced by the Lotrimin solution. When examined 2 days after the application of medication, an excoriated erythematous dermatitis had reappeared on the dorsal aspect of the toes. Patch tests with Tinactin solution were negative.

It was noted that each ml of Lotrimin solution contains 10 mg clotrimazole in a non-aqueous vehicle of polyethylene glycol 400 and that each ml of Tinactin solution contains tolnaftate, 10 mg in a similar vehicle of polyethylene glycol 400.

Although the patch tests were negative to both Tinactin and Lotrimin solutions, the patient felt certain that they were both the cause of the superimposed contact dermatitis and insisted that the reactions occurred soon after the antifungal solutions had been applied. Since patch tests for delayed type of hypersensitivity to both antifungal solutions were negative, it was decided to test for immediate urticarial reactions with these solutions.

Testing for immediate urticarial hypersensitivity to Lotrimin and Tinactin solutions. Lotrimin solution was rubbed into the intact skin of the patient's right forearm with a cotton swab and Tinactin solution was similarly rubbed into the left forearm. An urticarial reaction consisting of a large wheal and flare occurred within 15 min on both forearms. No such reactions occurred in three controls. Since both Lotrimin and Tinactin solutions employ polyethylene glycol 400 as a solvent, it was suspected that this solvent vehicle could be causing the urticarial reaction. Indeed, an immediate urticarial reaction occurred when the polyethylene glycol 400 solvent supplied by the manufacturer of Lotrimin solution was rubbed into the normal skin of the patient, but not in five controls. A patch test with the polyethylene glycol 400 read after 48 h was negative.

Case report due to ear medication. The second patient who exhibited an immediate reaction to PEG 400 was a 35-year-old woman with a pruritic chronic otitis externa of 2 years' duration which had been exacerbated by the use of Americaine Otic® which contains 20 % benzocaine and 0.1 % benzethonium chloride in a water-soluble base of 1 % (w/w) glycerine and polyethylene glycol 300. Patch tests to Americaine Otic, benzocaine and polyethylene 300 were negative. However, an immediate urticarial reaction occurred within 20 min when the ear medication was rubbed into the forearm with a cotton swab. No such reaction occurred in five controls. The same type of urticarial reaction occurred in this patient with polyethylene glycol 300 and not in five controls.

Delayed allergic eczematous contact dermatitis due to PEG

Case report due to Furacin® soluble dressing. A 39-year-old woman applied Furacin soluble dressing (Eaton) to a second degree burn of the leg, 48 h later the burned area began to itch and the surrounding previously normal skin became erythematous and edematous. Furacin soluble dressing contains 0.2 % Furacin (nitrofurazone) in Solubase (a water-soluble base of polyethylene glycols 4000, 1000 and 300). Patch tests with Furacin soluble dressing, PEG 300 and 400, were strongly positive in the patient

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and negative in six controls. Patch tests to PEG 1000 and 4000 were negative.

Case report due to Furacin solution. A 64-year-old man who had received cobalt radiation for carcinoma of the lung had developed a severe second degree burn of the irradiated skin of the chest for which he had been treated with a spray of Furacin Solution® (Eaton). A severe, edematous, vesicular and crusted contact dermatitis became superimposed upon the radiation burn.

Furacin solution contains (w/w) 0.2 % Furacin (nitrofurazone) in Solubase (a water-soluble base of polyethylene glycols 4000, 1000 and 300). Furacin solution is often sprayed on burns. On evaporation of the water, a transparent film of Furacin and polyethylene glycol remains.

Patch tests with Furacin solution, PEG 400 and 300 were strongly positive. Patch tests with PEG 1000 and 4000 were negative.

Discussion

The North American Contact Dermatitis Group noting that over 600 topical agents contain the polyethylene glycols, has recently added PEG 400 to a screening tray. Testing is being performed with PEG 400 as is. It is as yet too early to give any statistics on the incidence of positive patch test reactions to PEG 400. Full strength PEG 400 apparently is not a primary irritant. Dr. W. Jordan, in a personal communication, has stated that he tested many patients with full strength PEG 400 without obtaining any reactions.

Maibach (1975) stressed that the polyethylene glycols of varying molecular weights are extensively used as vehicles in topical medicaments but are not listed as sensitizers in standard reference books. In an experimental study Marzulli & Maibach (1974) performed a human Draize test to screen an experimental bar soap for allergic contact sensitization. The soap was tested at 3 % in water with the challenge concentration reduced to 1 %. One subject (out of 200) had a strong spreading reaction at the final elicitation. This was repeated three times at bi-weekly intervals with similar results. Breakdown testing of the soap components revealed a strong reaction only to 3 % polyethylene glycol 300 in petrolatum. This was repeated with a similar result. Additional challenges with 3 % polyethylene glycol 100, 1000, 4000 and 6000 were all positive. He also reacted to these at 1 % in petrolatum. The subject next received liberal use type applications twice a day for 7 days of 3 % polyethylene glycol in petrolatum to his cheek and forearm. No dermatitis developed. Apparently this patient was not sensitive enough to develop dermatitis in an open use test to 3 % polyethylene glycol 300.

Braun (1969) studied 40 patients who showed a delayed allergic contact sensitivity to a medication containing nitrofural which is a Furacin-like product. In three out of 40 cases, the active ingredient nitrofural was not the cause of the dermatitis but the solvent polyethylene glycol 300 proved to be the culprit. Routine tests in 92 dermatological patients with contact allergies gave 4 % positive reactions with polyethylene glycol 300. Group sensitization in the polyethylene glycol series appeared to occur only with polymers of the same molecular weights. Thus out of 12 subjects sensitized with polyethylene glycol 300, five also reacted to polyethylene glycol 400 and only one of them to polyethylene glycol 1500 and 6000 as well. No group allergy could be demonstrated between propylene glycol and the polyethylene glycol derivatives.

Immediate urticarial vs. delayed eczematous contact allergy to PEG

The sensitization to polyethylene glycol de-

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scribed by Maibach & Marzulli (1974) and Braun (1969) is of the usual delayed allergic eczematous variety, not the immediate contact urticarial type that the patients described in the present report acquired from the use of the antifungal agents Lotrimin and Tinactin solutions containing PEG 400 and the ear medication containing PEG 300.

Medication which produces allergic contact urticaria initially causes pruritus, erythema and edema. The itching is usually so intense that the patient scratches or rubs the affected parts so vigorously that excoriations are produced, resulting in dermatitis closely simulating an allergic eczematous contact dermatitis of the delayed variety. A routine covered patch test will be negative in such cases and the allergic reaction will not be discovered unless the patient is observed for about ½ hour before the site of application of the contactant is covered with the patch.

Odom & Maibach (1976) define contact urticaria as an urticarial or wheal-and-flare response occurring upon external contact of certain agents with intact skin. Usually the urticarial response may be noted or elicited within a few to 30 min of contact with the provocative agent. When a topical agent is suspected of producing a reaction and the usual patch test is negative, open testing with the suspected contactant should be performed to determine whether an immediate urticaria sensitization is present. These investigators suggest that such testing be performed by spreading approximately 0.1 ml of the suspected agent with a glass rod or a cotton-tip applicator on the ventral part of the forearm. The observation period should extend to at least 30 min. A positive reaction consists initially of a macular erythema appearing in a follicular pattern evolving into a wheal or wheal flare response.

Maibach & Johnson (1975) caution that if the patient has previously exhibited anaphylactoid symptoms in response to the contactant to be tested, the re-challenge should be performed in a hospital environment with all necessary resuscitation equipment and personnel available for immediate response to anaphylactoid signs.

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