

The Relationship of Vehicle and Concentration of Imidazolidinylurea, with Attention to Formaldehyde Allergy Status

To the Editor:

For more than 10 years, the North American Contact Dermatitis Group has patch-tested with imidazolidinylurea at a 2% concentration in both aqueous and petrolatum vehicles.¹⁻⁴ The reactivity has been approximately equal, but each vehicle formulation missed about half of the cases that the other vehicle formulation detected. This led to a continuation of the practice of testing with both forms. However, a more critical analysis of the most recent data since 2000 shows a trend for the petrolatum vehicle to diagnose more cases (Table 1). In our most recent data collection period (2002 to 2004), a sharper difference was observed. In our preliminary analysis, imidazolidinylurea in petrolatum showed a trend for detecting nearly twice as many cases of allergy when compared with the aqueous vehicle. Of patients tested, 94 of 3,492 were positive with petrolatum and 48 with the aqueous form, with 27 positive to both. There were 21 cases missed by petrolatum and 65 cases missed by the aqueous material. In our final data from this study period, we found 147 patients positive with petrolatum and 78 positive with the aqueous material. We wondered why this change in reactivity might have occurred. The data from 1992 to 2002 were compared with those from the 2002–2004 period, and the results showed a statistically significant decrease in the frequency of reactions to imidazolidinylurea in aqueous form ($p < .0001$). A patient tested in the last 2 years was three-fifths as likely to react to the aqueous test as in the past (relative risk, 0.64; 95% confidence interval, 0.50–0.81; $p < .0001$). There was no significant difference in the frequency of positive reactions to imidazolidinylurea in petrolatum between these two periods ($p < .2136$).

One explanation considered was a difference in concentration between the two vehicles. While both were labeled as being 2%, a manufacturing error or a stability problem might explain the difference. A syringe of each form of imidazolidinylurea was provided to Prof. Magnus Bruze of the

University of Lund for analysis. High-performance liquid chromatography (HPLC) analysis of the two confirmed that there was a difference: the petrolatum was found to contain 3.1% imidazolidinylurea, and the aqueous form, 2.0%. The analytic methodology has previously been described.⁵ However, as imidazolidinylurea can also release formaldehyde, we considered the formaldehyde status of the patients tested to be another possible explanation for the observed difference. However, if this were the case, it seems likely that the problem would have been detected in our prior studies. Chromotropic acid evaluation showed no release of formaldehyde from the imidazolidinylurea in petrolatum; however, free formaldehyde was detected in the aqueous formulation. This was confirmed with HPLC and suggested that formaldehyde status should be a consideration.

There were 147 patients who were allergic to imidazolidinylurea in petrolatum, and 100 of these (68%) were also allergic to formaldehyde. There were 78 patients who were allergic to imidazolidinylurea in aqueous form, and 51 of these (65%) were also allergic to formaldehyde. Of the patients who reacted to the aqueous form but not the petrolatum form of imidazolidinylurea, 22 of 36 (61%) were also formaldehyde sensitive. Of the patients who were reactive to the petrolatum form but not the aqueous form of imidazolidinylurea, 71 of 105 (68%) were also formaldehyde sensitive. There was no statistically significant difference in formaldehyde sensitivity between patients who reacted to the aqueous and petrolatum forms of imidazolidinylurea ($p = .668$).

These observations do not support the conclusion that formaldehyde release from the aqueous patch test or formaldehyde allergy status is an adequate explanation for the observed higher prevalence of imidazolidinylurea allergy detected by our “2%” imidazolidinylurea petrolatum patch test. Rather, the data support a conclusion that a 3% test concentration is more sensitive than a 2% concentration. Over the period of time noted in Table 1, there has been no change in the test technique nor in the amount of imidazolidinylurea or in the volumes applied. It appears that about two-thirds of the individuals identified by either aqueous or petrolatum forms of imidazolidinylurea are formaldehyde sensitive. As formaldehyde and imidazolidinylurea are very different chemical structures, it seems inappropriate to consider this a cross-reaction. Since this preservative is used in aqueous products where formaldehyde

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Table 1. Number of Patients Patch-Testing Positive to Imidazolidinyurea, by Study Period

Year	Aq+ Patients	Pet+ Patients	Total Patients Tested
1992–1994	67 (1.9%)	90 (2.5%)	3,523
1994–1996	81 (2.6%)	95 (3.0%)	3,101
1996–1998	102 (2.5%)	131 (3.2%)	4,094
1998–2000	116 (2.0%)	145 (2.5%)	5,784
2001–2002	88 (1.8%)	147 (3.0%)	4,897
2002–2004	78 (1.3%)	147 (2.5%)	5,784

Aq+ = positive to aqueous formulation; Pet+ = positive to petrolatum formulation.

is released, cosensitization could occur, and based on our data, the frequency with which that happens is in the range of 60 to 68% of the time.

A recent study of diphenylmethane diisocyanate found that the stated concentration of this material as used for diagnostic patch testing seldom matched the concentration actually present in the patch-test material. The actual concentration was no more than 12% of the stated amount, as based on analyses from 12 different departments of dermatology.⁶ Our results with imidazolidinyurea raise the same concern about the accuracy of the patch-test materials we rely on to diagnose contact dermatitis. These findings raise the question, What concentrations have we actually been testing with from 1992 to the present? The answer has to be that we are not sure. It is also unclear as to why the aqueous test formulation identified significantly fewer patients than in years past, but without quantitative analysis of the previous patch-test material, it would be difficult to determine if the concentration provides a full answer.

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References

1. Marks JG, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group standard tray patch test results 1992 through 1994. *Am J Contact Dermat* 1995;6:160–5.
2. Marks JG Jr, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998;38:911–8.
3. Marks JG Jr, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 1998 to 2000. *Am J Contact Dermat* 2003;14:59–68.
4. Pratt MD, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 2001–2002 study period. *Dermatitis* 2004;15:176–83.
5. Gruvberger B, Bruze M, Tammela M. Preservatives in moisturizers on the Swedish market. *Acta Derm Venereol* 1998;78:52–6.
6. Frick M, Zimerson E, Karlsson D, et al. Poor correlation between stated and found concentrations of diphenylmethane-4,4'-diisocyanate (4,4'-MDI) in petrolatum patch-test preparations. *Contact Dermatitis* 2004;51:73–8.