

The reaction index and positivity ratio revisited

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Background and Objectives: Assessing the quality of patch test preparations continues to be a challenge. 2 parameters, the reaction index (RI) and positivity ratio (PR), have been proposed as quality indicators by the Information Network of Departments of Dermatology (IVDK). The value of these statistics has not been examined by others.

Methods: We calculated the RI and PR for the 24 TRUE[®] test allergens in 7635 patients with consecutive eczema tested at the Department of Dermatology, Odense University Hospital over a 15-year period, and data for 7 selected standard allergens were compared with corresponding data from the original IVDK papers.

Results and Conclusions: At our patch test laboratory, RI's are lower, even negative, and the PR's are considerably lower than the IVDK results. The most likely explanation is a difference in reading/scoring tradition between the different departments of the IVDK and our department. Calculation of RI's and PR's for patch test allergens is of limited value as a measure of quality of the patch test materials, because it predominantly reflects differences in scoring and reading of patch test reactions. Further, questionable reactions (+?) may be clinically relevant and very important for the individual patient. Focus on standardization of patch test materials, patch test technique, and reading of patch test reactions is mandatory.

Key words: patch testing; patch test materials; positivity ratio; quality control; reaction index; standardization; TRUE[®] test. © Blackwell Munksgaard, 2008.

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The reaction index (RI) was suggested as a parameter to assess the quality of patch test preparations (1, 2). The RI is defined as the ratio of positive patch test reactions minus questionable and irritant reactions divided by the total sum of these reactions. A RI clearly larger than 0 is suggested as a characteristic of an appropriate patch test preparation, and a negative RI should indicate that the patch test material gives rise to more doubtful and irritant reactions compared with the number of positive reactions. In a later publication, an additional parameter, the positivity ratio (PR), was developed to be used in combination with the RI to identify problematic allergens (3). The PR is defined as the frequency of + reactions among the total number of positive patch test reactions (+ to +++).

The value of these statistics as possible indicators for the quality of patch test preparations is not documented. This report describes the RI and PR for TRUE[®] test panels 1 and 2 (Mekos A/S,

Hillerød, Denmark) based on the Allergen database from Department of Dermatology, Odense University Hospital.

Materials and Methods

From 1992 to 2007, consecutive contact dermatitis patients have been tested with TRUE test panels 1 and 2.

The routine procedure includes test application on the upper back for 2 days and reading twice on D3 and D5–D7. A positive reaction is scored according to standard procedure as + to ++++. Patch test reactions scored as irritant are rarely seen with the standard allergens, as they cannot be differentiated from doubtful reactions (+?) that are readings frequently used and defined as erythema only (not palpable). In few cases, positive reactions are scored as a follicular/papular reactions not fully compatible with the International Contact Dermatitis Research Group (ICDRG)

reading scale for + reactions, because of lack of homogenous infiltration (4). These follicular/papular reactions are considered as positive in the following calculations. In other cases, an allergen is omitted from the test procedure because the patient has previously been documented allergic to the compound in question, and they are also considered as positive. The results from our database are compared with published data from the Information Network of Departments of Dermatology (IVDK).

Results

A total of 7635 patients were tested, and the calculated RI and PR for the 24 TRUE test allergens are shown in Table 1, and in Table 2 results for 7 selected standard allergens are shown in comparison with published IVDK data.

Discussion

There is a considerable difference between the RI's and PR's reported by IVDK and the TRUE test data from our department. In our hands, the RI's with the TRUE test are much lower and often negative compared with the IVDK results, and our PR's are considerably lower compared with the IVDK results. A plausible interpretation is a difference in reading/scoring tradition between the compiled IVDK data and the patch test scor-

ing at our department. As routine procedure in Odense, all patch tests throughout the years are scored by the same 3–4 experienced nurses, and the dermatologists determine the relevance of the test reaction. Many reactions are scored as doubtful (+?), and few are scored as irritant reactions (IR) when it concerns standard allergens. In IVDK there may be other criteria for the definition of a + positive reaction explaining the shift in RI and PR of selected standard allergens between Odense and IVDK. The variation between readers from many departments in IVDK is not reported.

An inherent challenge in diagnostic patch testing is that reading is subjective, based on inspection and palpation of the test area. Even scoring systems vary. Among 5 experienced Swedish dermatologists, there was complete agreement in reading 327/400 (82%) patch test reactions. However, when the presence of morphological features erythema, infiltration, papules, vesicles, and bullae were recorded, the total concordance for positive and negative test reactions was only 36% and 46%, respectively (5). This unique experiment included 40 volunteer dermatitis patients with previously documented contact allergy to 1 of 4 selected standard allergens tested with liquid dilution series of the allergen in question and by use of Finn Chambers dosed with 15 µl solution.

In a recent study, 5 dermatologists scored 55 photographic images of office patch test reactions

Table 1. RI and PR for TRUE[®] test allergens in panels 1 and 2 based on patch test results from 7635 patients with consecutive eczema tested at Department of Dermatology, Odense University Hospital from 1992 to 2007

Allergen	Pos. – IR – +?	Pos. + IR + +?	RI	No +	No + to +++	PR (%)
Nickel sulfate	727	2261	0.32	289	1206	24
Wool alcohols	–85	243	–0.35	53	71	75
Neomycin sulfate	20	328	0.06	79	149	53
Potassium dichromate	–400	954	–0.42	121	219	55
Caine mix	–114	294	–0.39	41	81	51
Fragrance mix	–177	961	–0.18	197	353	56
Colophony	184	554	0.33	152	332	46
Epoxy resin	–99	489	–0.20	68	168	40
Quinoline mix	–29	213	–0.14	46	81	57
Balsam of Peru	–49	277	–0.18	52	97	54
Ethylenediamine dihydrochloride	–217	333	–0.65	17	47	36
Cobalt dichloride	–316	974	–0.32	141	279	51
<i>p</i> -tert-Butylphenol formaldehyde resin	–269	483	–0.56	42	87	48
Paraben mix	–154	236	–0.65	20	30	67
Carba mix	–221	819	–0.27	172	274	63
Black rubber mix	–189	361	–0.52	31	71	44
Cl+Me–isothiazolinone	75	395	0.19	85	220	39
Quaternium 15	27	329	0.08	80	156	51
Mercaptobenzothiazole	–71	165	–0.43	17	43	40
<i>p</i> -Phenylenediamine	22	312	0.07	56	147	38
Formaldehyde	75	343	0.22	91	184	49
Mercapto mix	–86	198	–0.43	22	52	42
Thimerosal	21	629	0.03	134	304	44
Thiuram mix	45	473	0.10	128	234	55

Pos., positive patch test; PR, positivity ratio; RI, reaction index.

Table 2. Comparison of RIs and PRs obtained in Odense and at IVDK

	TRUE test RI Odense	Hermal RI IVDK ^a	TRUE test PR Odense (%)	Hermal PR IVDK ^a (%)
Nickel sulfate	0.32	0.8	24	48
p-Phenylenediamine	0.07	0.5	38	57
Thiuram mix	0.10	0.6	55	57
Fragrance mix	−0.18	0.5	56	67
Potassium dichromate	−0.42	0.5	55	68
Balsam of Peru	−0.18	0.5	54	72
Formaldehyde	0.22	0.3	49	81

IVDK, Information Network of Departments of Dermatology; PR, positivity ratio; RI, reaction index.

^aData taken from Geier et al. (3).

from 16 slides (between 1 and 11 test sites per slide) in an office environment, and using the ICDRG scoring scale, they scored very differently. When the scoring system was simplified to a tripartite scoring scale, the agreement was good (6).

In routine testing, dosing of test material is less accurate, and petrolatum based preparations are used. This implies a possibility for a certain variation in the amount of petrolatum preparation applied at patch testing. Another recent Swedish study investigated this variation between 3 technicians in 1 department. They reported a significant inter-individual variation in the order of magnitude of a factor up to 2 (7). These sources of variation are most likely more pronounced in the beginning of the patch test scoring scale (between +? and +) compared with the difference between + and ++ to +++ reactions. Bruze et al. (5) found that the main discrepancies in reading were found in reactions with papules and vesicles where optimal illumination and tactile sense are decisive. The difference between +? and + scoring has a decisive impact on a statistic like the RI making it a statistic of doubtful value. The additional parameter, the PR, has to be used simultaneously, because a downward shift in RI concurrent with a fall in PR indicates a variation in reading – more than a shift in patch test material quality. Further, the doubtful patch test responses scored as +? may be relevant and important for the patient. Hannuksela and Salo (8) in their substantial paper from 1986 reported that there was a good concordance between a clearly positive (+ or ++) patch test reaction and a positive repeated open application tests (ROAT), but also that 44% of their patients with questionable (+?) patch test results had positive ROAT with the allergen in question. This finding has recently been confirmed in

an American study. Among 3082 test reactions graded as macular erythema, 2430 (78.8%) were graded as clinically relevant. Reactions with macular erythema are questionable reactions according to the grading scale; however, they may be deemed positive in some cases. Despite this inconsistency in the scoring system, the study confirms that questionable reactions may indeed be relevant (9). Further, in 2 clinical experimental studies using isoeugenol and methyl dibromoglutaronitrile (MDBGN) doubtful patch test reactions were also associated with positive ROAT's with the allergen in question (isoeugenol: 2/9) (MDBGN: 3/51) (10, 11).

In a congress presentation from IVDK, Schnuch et al. (12) reported that 61% of dermatitis patients with a + reaction to the fragrance mix 8% in petrolatum had negative reactions to its 8 single compounds. This may be a high frequency of negative tests to the single compounds when the patients have + reaction to the fragrance mix. If this finding is the result of variation in reading, patch test technique, or patch test preparation is not known.

In summary, diagnostic patch testing with subjective reading and test evaluation is continuously a challenge for the dermatologists. Standardization and training continues to be decisive for the value of this indispensable diagnostic test. You cannot standardize patients, their backs, and the dermatologists. However, you can train dermatologists and improve standardization of patch test materials and patch test technique.

References

1. Brasch J, Henseler T. The reaction index: a parameter to assess the quality of patch test preparations. *Contact Dermatitis* 1992; 37: 203–204.
2. Brasch J, Geier J, Henseler T. Evaluation of patch test results by use of the reaction index. An analysis of data recorded by the Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis* 1995; 33: 375–380.
3. Geier J, Uter W, Lessmann H, Schnuch A. The positivity ratio – another parameter to assess the diagnostic quality of a patch test preparation. *Contact Dermatitis* 2003; 48: 280–282.
4. Fregert S. *Manual of Contact Dermatitis*, 2nd edition. Copenhagen, Munksgaard, 1981.
5. Bruze M, Isaksson M, Edman B, Björkner B, Fregert S, Möller H. A study on expert reading of patch test reactions: inter-individual accordance. *Contact Dermatitis* 1995; 32: 331–337.
6. Ivens U, Serup J, O'goshi K. Allergy patch test reading from photographic images: disagreement on ICDRG grading but agreement on simplified tripartite reading. *Skin Res Technol* 2007; 13: 110–113.
7. Bruze M, Frick-Engfeldt M, Gruvberger B, Isaksson M. Variation in the amount of petrolatum preparation applied at patch testing. *Contact Dermatitis* 2007; 56: 38–42.

8. Hannuksela M, Salo H. The repeated open application test (ROAT). *Contact Dermatitis* 1986; 14: 221–227.
9. Davis M D P, Yannias J A. Should macular erythema reactions be counted as positive allergic patch-test reactions? *Dermatitis* 2005; 17: 12–14.
10. Johansen J D, Andersen K E, Menne T. Quantitative aspects of isoeugenol contact allergy assessed by use and patch tests. *Contact Dermatitis* 1996; 34: 414–418.
11. Gruvberger B, Andersen K E, Brandao F M et al. Repeated open application test with methyldibromo glutaronitrile, a multicentre study within the EEC DRG. *Contact Dermatitis* 2005; 52: 19–23.
12. Schnuch A, Geier J, Uter W, Frosch P J. Another look on allergies to fragrances: frequencies of sensitization to the

fragrance mix and its constituents. *Contact Dermatitis* 2002; 46 (Suppl. 2): 10.

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