Contact Dermatitis, 2000, 43, 1–3
Printed in Denmark . All rights reserved

CONTACT DERMATITIS
ISSN 0105-1873

Review Article

Use tests: ROAT (repeated open application test)/ PUT (provocative use test): an overview

Tokio Nakada[1], Jurij J. Hostynek[2] and Howard I. Maibach[2]
[1]Department of Dermatology, Showa University School of Medicine 1–5-8, Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan
[2]Department of Dermatology, University of California, School of Medicine, San Francisco, CA 94143–0989 USA

As one step in defining the clinical relevance of exposure to an allergen identified with patch testing, use tests (provocative use test (PUT), and repeated open application test (ROAT)) have been used. In $^1/_2$ of the cases of seemingly reliable patch tests, use tests are negative, suggesting that the patient's biologic threshold of response had not been reached with open application dosing. Dramatic differences exist in regional skin reactivity and percutaneous penetration. Negative results of use tests on normal skin may become positive on diseased skin. To refine this assay further, more controlled observations and analysis of reaction differences between normal and damaged skin, and among regional anatomic sites might be performed. In addition, we require a standardized measurement for the results. Use testing has significant potential in refinement of the evidence-based diagnosis of clinical relevance. However, for general validation, we should fill the deficiencies described above.

Key words: allergic contact dermatitis; use test; provocative use test (PUT); repeated open application test (ROAT); patch testing.

Accepted for publication 6 March 2000

Patch-test results require biologic and clinical interpretation. As one step in defining the clinical relevance of exposure to an allergen identified with patch testing, use tests (1, 2), (provocative use test (PUT) (3, 4), and repeated open application test (ROAT)) (5) have been used. This old technique has recently gained advocates. Although controlled experiments have increased in number, several issues require clarification.

In open use testing, substances are applied 1× or 2× daily for 7–14 days to the flexor forearm, cubital fossa, face or other anatomic sites. A positive reaction to the test usually appears within 4 days and less frequently between 5 and 7 days (5, 6). The size (at least 1 cm in diameter) of the dosed sites does not grossly affect the results (6). Delayed reactions (post 7 days) have only recently been sought.

Table 1 summarizes the literature. As a result of these studies, some consider the technique useful in aiding evaluation of the clinical relevance of positive patch tests; however, use testing requires interpretation. First, in approximately $^1/_2$ of the cases of seemingly reliable patch tests, the use test was negative, suggesting that the patient's biologic threshold of response had not been reached with the use of an open application (7). To clarify this point, more controlled studies must be performed, such as with higher, but still not irritating, concentration.

Dramatic differences exists in regional skin reactivity (8) and percutaneous penetration (9); use testing in the previously clinically involved anatomic site might prove fruitful, but adds the need for more complex non-irritant contrasts.

In addition, negative results of use tests on normal skin may become positive on diseased skin, although there are few documented examples, because visual scoring on damaged skin may be problematic. Studies of reaction differences between normal and damaged skin with use tests are required. Use testing for contact urticaria on

Table 1. Substances tested with ROAT/PUT

Model	Substance	Ref.
man	methylchloroisothiazolinone	(16)
	methylisothiazolinone	(16)
	hexyleneglycol	(17)
	diazolidinyl urea	(18)
	corticosteroid	(19, 20)
	benzalkonium chloride	(21)
	cinnamic aldehyde (cinnamal)	(22)
	isoeugenol	(23)
	calcipotriol	(24, 25)
	formaldehyde	(26)
	olive oil	(27)
	iodopropynyl butylcarbamate	(28)
	antiseptics (chlorhexidine, ethanol, iodine, povidone-iodine)	(29)
	fragrance mix	(12)
	colophony (colophonium)	(15)
guinea pig	cobalt	(30, 31)
	DMSO (dimethylsulfoxide)	(28)
	colophony (colophonium)	(31)

slightly abnormal skin is less difficult, because of the shorter response time (10) and often dramatic morphology.

Few positive use tests reported have had appropriate 'virgin' or negative controls to document that they were not, in fact, irritant in nature. Wahlberg (11) suggested facilitation of interpretation by using 2 coded samples, with and without allergen. If a reaction is seen only to the allergen sample, the initial patch test reaction is more likely to be relevant. If reactions are of the same intensity with and without the allergen, they are regarded as likely irritant in nature (11). Use of coded samples (with and without allergen) are not a substitute for irritant controls in 'virgin' volunteers, as the allergen sample might be more irritant than the vehicle sample.

A difference in the morphological assessment of use test and patch test reactions is also reported (12). We require a standardized measurement of the results of use testing like the ICDRG scoring system for patch testing (13). In positive tests, erythematous papules (some clarify follicular in location) become confluent, and even vesicular, with continued allergen application. Grading can be in intensity (none, mild, moderate, and severe) or with skin bioengineering equipment (14, 15).

In conclusion, in terms of increased refinement of the evidence-based diagnosis of clinical relevance, use testing has significant potential. However, further validation requires filling the data voids delineated above.

References

1. Maibach H I, Bandmann H-J, Calnan C D et al. Triclocarban: evaluation of contact dermatitis potential in man. *Contact Dermatitis* 1978: *4:* 283–288.
2. Ale S, Maibach H I. Clinical relevence in allergic contact dermatitis, An algorithmic approach. *Dermatosen* 1995: *43:* 119–121.
3. Christensen O, Møller H. External and internal exposure to the antigen in the hand eczema of nickel allergy. *Contact Dermatitis* 1975: *1:* 136–141.
4. Wanscher B. Contact dermatitis from propolis. *Br J Dermatol* 1976: *94:* 451–455.
5. Hannuksela M, Salo H. The repeated open application test (ROAT). *Contact Dermatitis* 1986: *14:* 221–227.
6. Hannuksela A, Niinimäki A, Hannuksela M. Size of the test area does not affect the result of the repeated open application test. *Contact Dermatitis* 1993: *28:* 299–300.
7. Marrakchi S, Maibach H I. What is occupational contact dermatitis? An operational definition. *Dermatologic Clinics* 1994: *12:* 477–484.
8. Tur E, Aviram G, Zeltser D, Brenner S, Maibach H I. Regional variations of human skin blood flow response to histamine. In: Surber C, Elsner P, Bircher A (eds): *Exogenous dermatology: advances in skin-related allergology, bioengineering, pharmacology and toxicology*. Basel: Karger, 1995: 59–66.
9. Wester R, Maibach H I. Regional variation in percutaneous absorption. In: Bronaugh R L, Maibach H I (eds): Percutaneous absorption: drugs – cosmetics – mechanisms – methodology. New York: M. Dekker, 1999.
10. Maibach H I. Immediate hypersensitivity in hand dermatitis. Rôle of food contact dermatitis. Arch Derm 1976: *12:* 1289–1291.
11. Wahlberg J. Use tests. In: Rycroft R J G, Menné T, Frosch P J (eds): *Textbook of contact dermatitis*. 2nd edition. Berlin: Springer-Verlag, 1991:
12. Johansen J D, Bruze M, Anderson K E et al. The repeated open application test: suggestions for a scale or evaluation. *Contact Dermatitis* 1998: *40:* 95–96.
13. Schwindt D, Maibach H I. *Cutaneous biometrics*. New York: Plenum Publishing, 2000: in press.
14. Berardesca E, Maibach H I. Bioengineering and the patch test. *Contact Dermatitis* 1988: *18:* 3–9.
15. Farm G. Repeated open application tests (ROAT) in patients allergic to colophony-evaluated visually and with bioengineering techniques. *Acta Dermato-venereologica* 1998: *78:* 130–135.
16. Hannuksela M. Rapid increase in contact allergy to Kathon CG in Finland. *Contact Dermatitis* 1986: *15:* 211–214.
17. Kinnunen T, Hannuksela M. Skin reactions to hexylene glycol. *Contact Dermatitis* 1989: *21:* 154–158.
18. Perret C, Happle R. Contact sensitivity to diazolidinyl urea (Germall II). *Arch Dermatol Res* 1989: *281:* 57–59.
19. Fedler R, Pilz B, Frosch P. Contact allergy to topical glucocorticoids. *Hautarzt* 1993: *44:* 91–95 (in German).
20. Freeman S. Corticosteroid allergy. *Contact Dermatitis* 1995: *33:* 240–242.
21. Fuchs T, Meinert A, Aberer W et al. Benzalkonium chloride – a relevant contact allergen or irritant? Results of a multicenter study of the German Contact Allergy Group. *Hautarzt* 1993: *44:* 699–702 (in German).
22. Johansen J D, Andersen K E, Rastogi S C, Menné T. Threshold responses in cinnamic-aldehyde-sensitive subjects: results and methodological aspects. *Contact Dermatitis* 1996: *34:* 165–171.
23. Johansen J D, Andersen K E, Menné T. Quantitative aspects of isoeugenol contact allergy assessed by use and patch tests. *Contact Dermatitis* 1996: *34:* 414–418.
24. Fullerton A, Avnstorp C, Agner T, Dahl J C, Olsen L O, Serup J. Patch test study with calcipotriol ointment in different patient groups, including psoriatic patients with and without adverse dermatitis. Acta Dermato-venereologica 1996: *76:* 194–202.

25. Frosch P J, Rustemeyer T. Contact allergy to calcipotriol does exist. *Contact Dermatitis* 1999: *40:* 66–71.
26. Flyvholm M-A, Hall B M, Agner T. Threshold for occluded formaldehyde patch test in formaldehyde-sensitive patients. *Contact Dermatitis* 1997: *36:* 26–33.
27. Kranke B, Komericki P, Aberer W. Olive oil – contact sensitizer or irritant? *Contact Dermatitis* 1997: *36:* 156–158.
28. Bryld L E, Agna T, Rastogi S C, Menne T. Iodopropynyl butylcarbamate: a new contact allergen. *Contact Dermatitis* 1997: *36:* 156–158.
29. Tupker R A, Schuur J. Irritancy of antiseptics tested by repeated open exposures on the human skin, evaluated by non-invasive methods. *Contact Dermatitis* 1997: *37:* 213–217.
30. Wahlberg J E, Liden C. Attempts to mimic the repeated open application test in the guinea pig. *Contact Dermatitis* 1994: *30:* 295–298.
31. Wahlberg J E, Farm G, Lidén C. Quantification and specificity of the repeated open application test (ROAT). *Acta Dermato-venereologica* 1997: *77:* 420–424.

Address:

Howard Maibach
University of California
School of Medicine
Department of Dermatology
San Francisco
CA 94143-0989
USA