Patch test results with caine mix III and its three constituents in consecutive patients of the IVDK

Wolfgang Uter1 | Margitta Worm2 | Richard Brans3,4 | Nicola Wagner5 | Andrea Bauer6 | Johannes Geier7 for the Information Network of Departments of Dermatology (IVDK)

1Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen/Nürnberg, Erlangen, Germany
2Division of Allergy and Immunology, Department of Dermatology, Venerology and Allergy, Charité - Universitätsmedizin Berlin, Berlin, Germany
3Department of Dermatology, Environmental Medicine and Health Theory, University of Osnabrück, Osnabrück, Germany
4Institute for Interdisciplinary Dermatological Prevention and Rehabilitation (iDerm) at the University of Osnabrück, Osnabrück, Germany
5Department of Dermatology, University Hospital Erlangen, Medical Faculty Friedrich-Alexander University, Erlangen/Nürnberg, Germany
6Institute for Interdisciplinary Dermatological Prevention and Rehabilitation (iDerm) at the University of Osnabrück, Osnabrück, Germany
7Information Network of Departments of Dermatology (IVDK), Institute at the University Medical Center Göttingen, Göttingen, Germany

Correspondence
Dr. Wolfgang Uter, Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Waldstr. 6, D-91054 Erlangen, Germany.
Email: wolfgang.uter@fau.de

KEYWORDS: baseline series, benzocaine, caine mix III, cinchocaine (dibucaine), clinical epidemiology, contact allergy, RRID:SCR_001905, tetracaine

In the 2019 version of the European Baseline Series (EBS), benzocaine 5% pet. had been replaced by caine mix III 10% pet., which contains 5% benzocaine, 2.5% tetracaine-hydrochloride (HCl), and 2.5% cinchocaine-(syn, dibucaine)-HCl.1 Although it is assumed, and supported by previous reports, that caine mix III will detect more cases of contact allergy to local anaesthetics (LA),2–4 the actual performance of the mix against its single constituents has not been assessed recently.

METHODS

The Information Network of Departments of Dermatology (IVDK: www.ivdk.org) is a clinical network dedicated to the surveillance of contact allergy. Patch testing follows international5 and national6,7 guidelines. For a further description, see Schnuch et al.8 Briefly, patch test results along with core information from the patient’s history are recorded in local departments of dermatology in Germany, Switzerland, and Austria and transmitted twice yearly in a pseudonymous fashion to the data centre in Göttingen. There, after a quality check,9 they are pooled and analyzed. For the present analysis, results with the so-called “monitor series”, a temporary addition to the national baseline series to be tested along with this, ie, in consecutive patients, used by 18 departments in the present period, were considered. Caine mix III 10% pet. was obtained from Chemotechnique Diagnostics (Vellinge, Sweden) and the single ingredients from SmartPractice Europe (Barsbüttel, Germany). While the test concentration of benzocaine was 5% pet., as in the mix, the concentration of cinchocaine-HCl (5% pet.) and tetracaine-HCl (1% pet.) differed. Exposure time was 1 day in five departments contributing 25% of the patients and 2 days in the remainder. For the final reading, the result at day (D) 3 was considered or, if no D3 reading was available, the result at D4. For data management and analysis
the R software (RRID:SCR_001905, www.r-project.org; version 4.0. x) was used.

RESULTS

Between July 2018 and March 2020, 3563 patients were tested with all four allergen preparations in the context of the “monitor series”, ie, consecutively. These were 36.6% males, 27.2% with occupational dermatitis, 32.1% with atop dermatitis, 41.5% with hand, 5.4% leg, and 14.2% with face dermatitis. The mean age was 49.9 years, and 72.5% of the patients were age ≥40 years. Patch test results are shown in Table 1.

Irritant or doubtful reactions to the mix and the single constituents were (much) more common than clear-cut positive reactions (Table 1). The sensitivity of caine mix III against reactivity to its single constituents, ie, the share of patients with positive reaction to any one single constituent who are picked up by the mix, was 52.1% (95% exact confidence interval [CI]: 37.2%–66.7%). Sensitivity regarding detection of positive patch test reactions to the single constituents and 100-Sensitivity (% false-negative) are shown in Table 1; sensitivity to caine mix III vs. the three substances did not differ significantly (P = .28, Fisher’s exact test).

Specificity, that is, the share of patients who reacted negative to each of the three constituents and were also negative to caine mix III, was 99.6% (95% CI: 99.3%–99.8%). In view of the use of caine mix III as screening agent in the context of the European baseline series (EBS), the predictive values are of interest. The positive predictive value (PPV), ie, the share of patients with a positive reaction to the screening mix who are positive to any one (or more) of the single constituents, was 62.5% (95% CI: 45.8–77.3%). The negative predictive value (NPV) was 99.3% (95% CI: 99–99.6%). Coupled reactivity among the three single constituents was limited to positive reactions to both benzocaine and tetracaine-HCl in three patients (Table S1).

DISCUSSION

Ideally, a screening test, such as the use of a mix of ingredients as commonly employed in the EBS (fragrance mixes, paraben mix, thiuram mix, mercapto mix, textile dye mix, sesquiterpene lactone mix and, recently, caine mix III), should validly indicate sensitization to one, or perhaps more, of its single constituents. That is, if the mix is positive, at least one of the constituents should also be positive (ideal PPV: 100%); and if the mix is negative, none of the single constituents should be positive (ideal NPV: 100%); these ideal properties would go along with a sensitivity and specificity of 100%. In reality, such ideal properties are never observed, and caine mix III is not an exception to this rule; sensitivity can only be called moderate, and the PPV is not satisfactory. In practice, this would mean that single constituents should be tested (i) because the mix may not uncommonly fail to detect sensitization and (ii) a positive result to the mix may not necessarily imply contact allergy to one of the constituents. Conversely, specificity and the NPV are very high. In practice, this would imply that in a screening situation with a low a priori likelihood of specific contact allergy, almost all negative results are indeed true negatives. This notwithstanding, the share of false-negatives can be regarded as being possibly too high.

If agreement between mix and single constituents is examined, it appears that just regarding benzocaine a reasonable sensitivity is seen (Table 1), which is in a range to that seen for example with mercapto mix 1% pet. and mercaptobenzothiazole 2% pet. concerning the single benzothiazoles. A study of the North American Contact Dermatitis Group involving 10 061 consecutive patients between 2001–2004 examined reactivity to single LA ingredients, the ranking of which was similar to that observed in the present study, albeit on a much higher level: 1.7% positive to benzocaine 5% pet. with very limited overlap to other LAs, 0.95% positive to dibucaine (syn. cinchocaine) 2.5% pet., and 0.38% positive to tetracaine 1% pet.3,11 A study from Coimbra, Portugal, analyzed 2736 patients consecutively patch tested between 2000–2010 with caine mix III 10% pet., yielding 4.0% positive reactions. Eighty-six patients, including 84 positive to the mix, were tested with seven LAs including the mix’s single constituents, albeit at twice the concentration for cinchocaine and tetracaine than in the mix, ie 5% pet. each, and benzocaine 5% pet. Despite this, 39% of the mix-positive patients tested negative to the single LAs.4 In other words, the PPV was 61% and thus very similar to the present estimate. However, as only a small fraction of consecutive patients had also been tested with all single constituents, the study results are difficult to compare directly; in part, varying the test concentrations of cinchocaine and tetracaine add to these difficulties.

A mix of allergens used for screening in any baseline series requires a reasonable sensitivity, to trigger break-down testing of mix ingredients and, at any rate, further investigation. While caine mix III may be regarded as a satisfactory replacement for benzocaine itself, sensitivity towards the two other LAs is rather poor. Therefore, the mix should not be relied on, neither if positive nor if

| Allergen               | n ?+/IR | n + | n ++/+++ | Positive, % (95% CI) | Sensitivity % | False-negative (100-Sens.) % |
|------------------------|---------|-----|----------|----------------------|--------------|-----------------------------|
| Caine mix III 10%      | 99      | 28  | 12       | 1.12 (0.8–1.53)      | –            | –                           |
| Benzocaine 5%          | 28      | 12  | 9        | 0.59 (0.37–0.9)      | 71.4 (47.8–88.7) | 28.6 (11.3–52.2)          |
| Cinchocaine-HCl 5%     | 61      | 18  | 3        | 0.59 (0.37–0.9)      | 38.1 (18.1–61.6) | 61.9 (38.4–81.9)         |
| Tetracaine-HCl 1%      | 20      | 9   | 0        | 0.25 (0.12–0.48)     | 44.4 (13.7–78.8) | 55.6 (21.2–86.3)        |

Abbreviations: CI, confidence interval; HCl, hydrochloride; Sens., sensitivity.
negative. In conclusion, other strategies for testing LAs are required and should be developed and evaluated following the present analysis, but also against a robust construct of clinical relevance and/or repeated open application testing for verification of positive reactions, which, as a limitation, is not included in the present routine surveillance data.

ACKNOWLEDGEMENT
Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTERESTS
W.U. has accepted travel reimbursement and research funds from the International Fragrance Association and has received a lecture fee from dermatology-related sponsors for an educational lecture on contact allergy. The IVDK, maintained by the IVDK e.V., of which J. Geier is an employee, is sponsored by the cosmetic and fragrance industry (associations) as well as by public funds. The other authors have no conflicts of interests to declare.

AUTHOR CONTRIBUTIONS
Wolfgang Uter: Conceptualization; formal analysis; methodology; project administration; software; visualization; writing-original draft; writing-review and editing. Margitta Worm: Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. Richard Brans: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. Nicola Wagner: Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. Andrea Bauer: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. Johannes Geier: Conceptualization; formal analysis; funding acquisition; methodology; project administration; resources; software; validation; visualization; writing-review and editing.

ORCID
Wolfgang Uter https://orcid.org/0000-0002-4498-3710
Richard Brans https://orcid.org/0000-0002-1245-024X
Andrea Bauer https://orcid.org/0000-0002-4411-3088
Johannes Geier https://orcid.org/0000-0002-5047-8948

REFERENCES
1. Wilkinson M, Gonçalo M, Aerts O, et al. The European baseline series and recommended additions: 2019. Contact Dermatitis. 2019;80(1):1-4.
2. Sidhu SK, Shaw S, Wilkinson JD. A 10-year retrospective study on benzocaine allergy in the United Kingdom. Am J Contact Dermatitis. 1999;10(2):57-61.
3. Warshaw EM, Schram SE, Belisio DV, et al. Patch-test reactions to topical anesthetics: retrospective analysis of cross-sectional data, 2001 to 2004. Dermatitis. 2008;19(2):81-85.
4. Brinca A, Cabral R, Gonçalo M. Contact allergy to local anaesthetics - value of patch testing with a canine mix in the baseline series. Contact Dermatitis. 2013;68(3):156-162.
5. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. Contact Dermatitis. 2015;73(4):195-221.
6. Mahler V, Nast A, Bauer A, et al. S3 guidelines: epicutaneous patch testing with contact allergens and drugs - short version, part 1. J Dtsch Dermatol Ges. 2019;17(10):1076-1093.
7. Mahler V, Nast A, Bauer A, et al. S3 guidelines: epicutaneous patch testing with contact allergens and drugs - short version, part 2. J Dtsch Dermatol Ges. 2019;17(11):1187-1207.
8. Schnuch A, Geier J, Lessmann H, Arnold R, Uter W. Surveillance of contact allergies: methods and results of the information network of departments of dermatology (IVDK). Allergy. 2012;67(7):847-857.
9. Uter W, Mackiewicz M, Schnuch A, Geier J. Internale Qualitätssicherung von Epikutantest-Daten des multizentrischen Projektes “Informationsverbund Dermatologischer Kliniken” (IVDK). Dermatol Beruf Umwelt. 2005;53(7):107-114.
10. Geier J, Uter W, Schnuch A, Brasch J, German Contact Dermatitis Research Group (DKG), Information Network of Departments of Dermatology (IVDK). Diagnostic screening for contact allergy to mercaptobenzothiazole derivatives. Am J Contact Dermatitis. 2002;13(2):66-70.
11. Warshaw EM, Belisio DV, DeLeo VA, et al. North American contact dermatitis group patch-test results, 2003-2004 study period. Dermatitis. 2008;19(3):129-136.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Uter W, Worm M, Brans R, et al. Patch test results with caine mix III and its three constituents in consecutive patients of the IVDK. Contact Dermatitis. 2021; 84:481–483. https://doi.org/10.1111/cod.13778