This item is the archived peer-reviewed author-version of:

A bad cough : delayed cutaneous hypersensitivity caused by pholcodine

Reference:

Van Acker Julie, Ebo Didier, Faber Margaretha, Sabato Vito, Suys Erw in, Coghe Marjan, Aerts Olivier.- A bad cough : delayed cutaneous hypersensitivity caused by pholcodine

The journal of allergy and clinical immunology. In practice - ISSN 2213-2198 - Amsterdam, Elsevier, 8:4(2020), p. 1449-1451

Full text (Publisher's DOI): <https://doi.org/10.1016/J.JAIP.2019.10.036>

To cite this reference: <https://hdl.handle.net/10067/1654920151162165141>

Journal Pre-proof

A bad cough: delayed cutaneous hypersensitivity caused by pholcodine.

Van Acker Julie, MD, Ebo Didier, MD PhD, Faber Margriet, MD, PhD, Sabato Vito, MD PhD, Suys Erwin, MD, Coghe Marjan, MD, Aerts Olivier, MD PhD.

PII: S2213-2198(19)30928-6

DOI: <https://doi.org/10.1016/j.jaip.2019.10.036>

Reference: JAIP 2532

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 15 August 2019

Revised Date: 10 October 2019

Accepted Date: 28 October 2019

Please cite this article as: Julie VA, Didier E, Margriet F, Vito S, Erwin S, Marjan C, Olivier A, A bad cough: delayed cutaneous hypersensitivity caused by pholcodine., *The Journal of Allergy and Clinical Immunology: In Practice* (2019), doi: <https://doi.org/10.1016/j.jaip.2019.10.036>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

A bad cough: delayed cutaneous hypersensitivity caused by pholcodine.

Van Acker Julie¹, MD, Ebo Didier², MD PhD, Faber Margriet², MD, PhD, Sabato Vito², MD PhD, Suys Erwin³, MD, Coghe Marjan⁴, MD, Aerts Olivier¹, MD PhD.

Affiliations:

¹Department of Dermatology, University Hospital Antwerp and University of Antwerp, B-2650 Antwerp, Belgium.

²Department of Immunology, Allergology, Rheumatology, University Hospital Antwerp and University of Antwerp, B-2650 Antwerp, Belgium. Infla-Med Centre of Excellence, Antwerp University.

³Private Dermatologist, Handelskaai 1/G, B-8500 Kortrijk, Belgium.

⁴Private Dermatologist, Masteneikstraat 61/1, 8870 Izegem, Belgium.

Key words: antitussive, codeine, cough syrup, cross-reactivity, delayed hypersensitivity, drug eruption, erythroderma, morphine, opiates, pholcodine.

Funding: The authors declare no funding.

Conflicts of interest: The authors declare no conflicts of interest.

Correspondence:

Olivier Aerts, MD PhD, Department of Dermatology, University Hospital Antwerp (UZA) and University of Antwerp; Tel: +3238214272 / Email: olivier.aerts@uza.be

Word count (manuscript): 1261

Word count (clinical implications box): 38

Tables: 0

Figures: 2

References: 11

Clinical implications box

Delayed type hypersensitivity caused by pholcodine is rarely reported and poorly documented. Patch tests may be valuable in the work-up, also to identify safer, even chemically related, opiate alternatives, which should not be automatically denied to these patients.

To the Editor,

Cough syrups based on pholcodine (PHO), an opiate related to morphine and codeine, are widely used in the treatment of dry cough (1). They are available in Europe but not marketed in the United States. PHO may cause, besides non-immunologic urticaria, also immediate, IgE-mediated hypersensitivity, including anaphylaxis (2). Here we describe the diagnostic approach of a patient with a delayed type hypersensitivity, presenting as a severe, generalized dermatitis, following the intake of a PHO-containing antitussive syrup.

A 47-year-old female, known with atopic dermatitis and pollinosis, presented with an erythematous, papular and itchy dermatitis accompanied by general malaise and fever ($>38.5^{\circ}\text{C}$). The skin eruption had first started on the legs (**Figure 1**), but rapidly generalized to an erythroderma requiring hospitalization. History revealed that she had used a PHO-containing antitussive (Pholcomeripine[®], Novum Pharma, Sint-Martens-Latem, Belgium) in the last 24-36h, because of a viral respiratory tract infection accompanied by a dry cough, and she claimed to have used this antitussive in the past without any adverse events. No other medication had been started. A skin biopsy showed a vesicular dermatitis with abundant eosinophilia, compatible with a drug eruption. Laboratory results showed a mild leucocytosis of $11650/\text{mm}^3$ ($4000\text{-}10.000/\text{mm}^3$), an elevated C-reactive protein (CRP) of 99 mg/L ($<5\text{ mg/L}$), a mild neutrophilia of $9459/\text{mm}^3$ ($1600\text{-}8300/\text{mm}^3$) and an elevated absolute, but transient, eosinophil count of $722/\text{mm}^3$ ($<400/\text{mm}^3$). Beside empirical treatment with amoxicillin and clavulanic acid, which had been started at the Emergency department, eventually topical betamethasone dipropionate (0.05%) and systemic glucocorticosteroids (methylprednisolone 40 mg once daily, in decreasing doses) led to resolution of the skin eruption and associated symptoms within one week.

Patch tests (Chemotechnique[®], Vellinge, Sweden) were performed, 6 months following the resolution of the dermatitis, including with the antitussive (“as is”) and its active ingredient PHO, the latter provided by the manufacturer and diluted at 10% in petrolatum (pet.). All patch test preparations were mounted on Allergeaze[®] patch test chambers (SmartPractice, Calgary, Canada), applied on the upper back and occluded for 2 days with Fixomull[®] stretch (BSN Medical, Hamburg, Germany). Readings were performed on day (D) 2 and D4, according to published guidelines (3). Strong positive patch test reactions were observed to the cough syrup (++) and to PHO (+++) on D2 and D4 (**Figure 2**). Twenty control individuals showed no reactions to PHO 10% pet.

Although controversial, and not always well substantiated, it has been claimed that patients with a proven and clinically relevant IgE-dependent sensitization to PHO (e.g. presenting with urticaria), which appears to be rare, might be at risk of developing cross-sensitization to other opiates and to neuromuscular blocking agents (NMBAs)(2, 4-5). We wondered whether a similar assumption holds true in the context of delayed type hypersensitivity to PHO.

Additional patch tests were thus performed with codeine (1% and 10% pet.), morphine (1% and 10% pet.) and tramadol (1% and 10% pet.), as well as with rocuroniumbromide, suxamethonium and cis-atracurium, the latter three patch-tested “as is”. Readings on D2 and D4 were negative. Although the time course, the morphology of the skin lesions, the skin biopsy and the positive patch tests did not suggest an immediate type hypersensitivity, a brief screening to verify any concomitant, immediate sensitization to PHO, morphine, codeine and NMBAs was performed. Total IgE was within normal limits (68 kU/L; < 114 kU/L), and specific IgE measurements for PHO, morphine, codeine, rocuronium and suxamethonium (FEIA ImmunoCAP Phadia Thermo Fisher Upsalla, Sweden) were negative. Skin prick tests (SPTs) with rocuroniumbromide 10 mg/mL (1/10 and undiluted), cis-atracurium 2 mg/mL (1/10 and undiluted), and suxamethonium 50 mg/mL (1/5 and 1/10), were performed, as well

as intradermal tests (IDTs; 0.02 mL) with the same concentrations (rocuroniumbromide diluted at 1/1000 and 1/200, cis-atracurium diluted at 1/1000 and 1/100, and suxamethonium diluted at 1/1000 and 1/500) (6). All these tests were negative after 15 min, as well as after 1 and 2 days. SPT and IDT with PHO, morphine and codeine were not performed, as false-positive reactions may occur (7). A basophil activation test (BAT) was not feasible, as the patient was a non-responder, i.e. no responses were observed to the positive control (anti-IgE). Similar to observations that patients with anaphylaxis to PHO might still tolerate strongly related opiates (2), we ultimately wanted to verify whether the negative patch test to morphine also implies potential tolerance to the latter. As PHO can be easily avoided, and codeine has little additional value in pain management, we opted for a graded, oral challenge test with morphine sulphate (MS; MS Direct[®], Bard Pharmaceuticals Ltd., Cambridge, UK). The patient was advised to take a single dose of 0.1 mg MS, and, if negative, 1 week later 1 mg, and, if again negative, another week later the final dose of 10 mg. This was well tolerated with no signs of relapse during or after the procedure. Our patient was thus advised to avoid PHO in whatever form available (cough syrups, suppositories), but no restrictions were given with regard to the future use of morphine.

Delayed type hypersensitivity, including severe cutaneous adverse reactions (SCAR) to PHO, have only rarely been reported and poorly documented. Two case reports describe an acute generalized exanthematous pustulosis (AGEP)(8-9), and in these cases patch tests, although feasible, were not performed. The related opiates codeine and morphine may also cause delayed type hypersensitivity, such as generalized dermatitis and AGEP, and patch tests may also be valuable in these cases (10-11). Here we present a patient with a SCAR to PHO in whom the diagnosis was, for the first time, confirmed with patch tests, and who had a thorough exploration for concomitant sensitization to other opiates and NMBAs. As the patient initially suffered from a mild upper respiratory infection, it might not be excluded that

her signs and symptoms, as well as laboratory findings, originated from the infection. However, arguments in favour of a delayed type hypersensitivity to PHO are: (i) the increased, transient blood eosinophilia, (ii) the results of the skin biopsy, (iii) the time course of the onset and resolution of the skin eruption, and (iv) the positive patch test reaction to PHO. The time delay between the intake of the antitussive and the occurrence of the dermatitis also suggests previous sensitization, which might have occurred during previous treatments.

In conclusion, we here present the first case of a patch-test documented, delayed type of hypersensitivity (SCAR) caused by PHO and we highlight that in such a patient a structurally related opiate, such as morphine, might still be tolerated.

References

1. Blanchard E, Tunon de Lara M. [New insights into the role of pholcodine in the treatment of cough in 2013?]. *Therapie*. 2013;68(2):85-91.
2. Leysen J, De Witte L, Sabato V, Faber M, Hagendorens M, Bridts C, et al. IgE-mediated allergy to pholcodine and cross-reactivity to neuromuscular blocking agents: Lessons from flow cytometry. *Cytometry Part B, Clinical cytometry*. 2013;84(2):65-70.
3. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis*. 2015 Oct;73(4):195-221.
4. Brusch AM, Clarke RC, Platt PR, Phillips EJ. Exploring the link between pholcodine exposure and neuromuscular blocking agent anaphylaxis. *British journal of clinical pharmacology*. 2014;78(1):14-23.

5. Uyttebroek A, Leysen J, Bridts C, Ebo D. Letter to the authors concerning the accepted manuscript: exploring the link between pholcodine and neuromuscular anaphylaxis by Brush et al. *British journal of clinical pharmacology*. 2014;78(4):929-30.
6. Leysen J, Bridts CH, De Clerck LS, Vercauteren M, Lambert J, Weyler JJ et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy*. 2011 Aug;66(8):1014-9.
7. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy*. 2001 Jul;31(7):1014-20.
8. Lee S, Artemi P, Holt D. Acute generalized exanthematous pustulosis. *The Australasian journal of dermatology*. 1995;36(1):25-7.
9. Kline A, Fischer G. Acute generalised exanthematous pustulosis and other severe drug eruptions from over the counter medications: A case report and review of the literature. *The Australasian journal of dermatology*. 2016;57(2):92-6.
10. Rodríguez A, Barranco R, Latasa M, de Urbina JJ, Estrada JL. Generalized dermatitis due to codeine. Cross-sensitization among opium alkaloids. *Contact Dermatitis*. 2005 Oct;53(4):240.
11. Kardaun SH, de Monchy JG. Acute generalized exanthematous pustulosis caused by morphine, confirmed by positive patch test and lymphocyte transformation test. *J Am Acad Dermatol*. 2006 Aug;55(2 Suppl):S21-3.

Figure legends

Figure 1: Erythematous, papular dermatitis on the legs, 1 day following the use of a pholcodine-containing cough syrup.

Figure 2: Strong positive patch test reactions to the cough syrup “as is” (++; upper patch) and to its active ingredient pholcodine 10% in petrolatum (+++; lower patch).

Journal Pre-proof

Journal Pre-proof