

In conclusion, we present a pruritic maculopapular rash due to DHR to ioversol with positive PT and cross-reactivity with iohexol.

AUTHOR CONTRIBUTIONS

Alejandro Raúl Gratacós Gómez: Conceptualization; methodology. **Juana Bautista Joyanes Romo:** Investigation. **Jaime Vinicio Meneses Sotomayor:** Writing – original draft. **M. Aranzazu Martín Iglesias:** Investigation. **Alberto Palacios Cañas:** Resources. **Elisa Gómez Torrijos:** Writing – review and editing; supervision.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Gómez Gratacos AR, Joyanes Romo JB, Meneses Sotomayor JV, Martín Iglesias MA, Palacios Cañas A, Gómez Torrijos E. Maculopapular rash due to delayed-type hypersensitivity from ioversol with positive patch tests. *Contact Dermatitis.* 2022;87(4):379-381. doi:10.1111/cod.14171

Delayed-type hypersensitivity reaction to St. John's wort extract confirmed by patch testing

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KEY WORDS: case report, delayed-type hypersensitivity, drug patch testing, St. John's wort

St. John's wort (*Hypericum perforatum*) is a wild flowering plant and its extracts have been used for centuries to treat mental health problems including low mood, depression and anxiety.¹ Side effects and drug interactions are commonly seen, as it is well-known to induce the liver enzyme CYP3A4.² True allergic or hypersensitivity reactions to St. John's wort, are less well-described and rarely reported.^{3,4} Here, we report a novel case of delayed-type hypersensitivity to St. John's wort extract tablets, confirmed by patch testing.

CASE REPORT

A 54-year-old female was referred to the allergy clinic for a suspected adverse drug reaction. She had no history of atopy or other medical

histories. She developed a maculopapular exanthem 24 h after taking oral aspirin and 10 days after commencing St. John's wort extract tablets (334 mg daily). There was no evidence of mucosal involvement or other severe cutaneous adverse reaction features. No other medications were implicated. Blood tests and a skin biopsy were not performed. She immediately stopped both aspirin and St. John's wort following the skin eruption and was treated with oral prednisolone which led to full rash resolution over 4 weeks (with subsequent skin peeling). There was no prior history of dermatitis and no chemical or contact triggers on enquiry. Delayed-type hypersensitivity to either aspirin or St. John's wort extract tablets was suspected given the clinical presentation. Informed consent was obtained from the patient for publication.

In the allergy clinic 4 months later, patch tests were performed using IQ Ultra chambers (Chemotechnique Diagnostics) with St. John's



FIGURE 1 Day 4 patch test results with strong positive (++) reaction to St. John's wort extract (30% pet.)

wort extract tablets (30% in pet.) and aspirin (30% pet.). The patch tests were read on Day 2 (D2) and D4 in accordance with the International Contact Dermatitis Research Group criteria. Patch testing to aspirin was unequivocally negative, however, there was a strong positive reaction (++) to St. John's wort extract tablets observed at D4 readings (Figure 1), with a clear crescendo effect from D2 reading. To exclude false positivity (irritancy) we also conducted healthy control subject patch testing ($\times 6$ subjects) on St. John's wort extract tablets which were all entirely negative. A subsequent oral aspirin challenge (300 mg, single dose) was also negative and fully tolerated.

The patient was diagnosed with delayed-type hypersensitivity to the St. John's wort extract tablet, given the clear clinical presentation, chronology of events and the confirmatory patch testing. Completion avoidance of St. John's wort extract was advised (in all forms).

DISCUSSION

Here, we describe a novel case of St. John's wort extracts tablet-induced delayed-type hypersensitivity confirmed by patch testing. The occurrence of a maculopapular exanthem and positive patch testing, strongly suggests that a T-cell mediated (Type IV) hypersensitivity mechanism is responsible.

It is important to highlight that the confirmed delayed-type hypersensitivity was to the St. John's wort extract tablet, and not to the plant directly. Each tablet contained 334 mg of extract from St John's wort aerial parts, and the tablet core excipients included: dicalcium phosphate, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate and stearic acid. The tablet coating was removed before patch test preparation. We were unable to test the excipients separately. It is, therefore, possible that a

tablet core excipient could be responsible for the observed hypersensitivity reaction, however, we deem this to be very unlikely, given that the other ingredients have very low allergenic potential. St. John's wort extract is therefore the likely cause of the adverse cutaneous reaction.

In the literature, a reported case of extensive contact dermatitis in a trapper from Australia was suspected to be caused by St John's wort, and patch testing was positive with a strong blister-like reaction.⁵ In a large drug monitoring study on St. John's wort, skin rash and pruritus have been reported as adverse events (with no further details), although they were attributed to the photosensitizing properties of St. John's wort.⁶ In our case, there was no significant photo-exposure reported by the patient.

Only one other similar case report to ours has been formally described in a 44-year-old male, with an erythroderma cutaneous eruption developing 4 days after commencing St. John's wort extract capsules.³ In contrast to our report, no confirmatory allergy testing (patch testing or drug provocation test) was undertaken, and the St. John's wort was the presumed cause based on the temporal relationship and lack of other viable culprits.³

In conclusion, St. John's wort extract should be regarded as a potential relevant allergen, capable of inducing delayed-type hypersensitivity reactions on systemic (oral) exposure. Patch testing has clear utility in establishing the diagnosis and probable mechanism. We hope this report contributes further to the understanding of cutaneous adverse reactions to this widely available non-prescription herbal medicinal product.

AUTHOR CONTRIBUTIONS

Thomas O'Hagan: Conceptualization; writing – original draft; writing – review and editing. **Ilaria Bisconti:** Investigation; writing – review and editing; methodology. **Claire Leck:** Methodology; writing – review and editing; investigation. **Thippeswamy Billahalli:** Investigation; writing – review and editing; methodology. **Sheena Barnett:** Writing – review and editing. **Karalasingam Rajakulasingam:** Writing – review and editing. **Timothy J. Watts:** Writing – review and editing; conceptualization; investigation; writing – original draft; methodology; validation; visualization.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: O'Hagan T, Bisconti I, Leck C, et al. Delayed-type hypersensitivity reaction to St. John's wort extract confirmed by patch testing. *Contact Dermatitis*. 2022; 87(4):381-383. doi:10.1111/cod.14172

Hand dermatitis aggravated by contact allergy to methylisothiazolinone in protective nitrile gloves

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Funding information

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KEYWORDS: case report, contact dermatitis, hand dermatitis, methylisothiazolinone, nitrile gloves, protective gloves

Methylisothiazolinone (MI) is a frequent sensitizer in cosmetics, household detergents and industrial products.¹ In the occupational setting, the use of protective (nitrile) gloves is often recommended to limit exposure to this preservative, and to prevent allergic contact dermatitis. We here describe a case of hand dermatitis aggravated by MI sensitization, and we discuss different exposure sources.

CASE REPORT

A 57-year-old non atopic man, working as a plumber, suffered from hand eczema since 10 years, which improved when being off work. Although he used protective nitrile gloves (ActivArm Hycron 27-805; ANSELL), he described worsening of his hand dermatitis 3 days after resuming work. Patch tests were performed with the European baseline series, preservatives and a piece of his (used) gloves (semi-open test). Patch test materials were mounted on IQ Ultra patch test chambers (Chemotechnique Diagnostics) occluded for 2 days, and read on Day 2 (D2) and D4. We observed extremely positive (+++) reactions to MI 0.2% aq., but no reactions to methylchlorisothiazolinone/MI 0.01%, benzisothiazolinone (BIT) 0.1% pet. nor to octylisothiazolinone (OIT) 0.1% pet. The test with the (used) glove showed + and ++ reactions on D2 and D4, respectively.

Chemical analysis of a series of used and new gloves were performed in the Official Food and Veterinary Control Authority (Table 1). Briefly, 0.5 g of nitrile was dissolved in 5 ml of methanol, sonicated during 15 min, and centrifuged during 10 min at 3500 RCF. After filtration, the extract was analysed by high pressure liquid chromatography coupled to a diode array detector following a previously published procedure.²

Significant concentrations of MI were identified in the patient's used nitrile glove (26.4 ppm). Interestingly, we also observed traces of MI in a new (unused) nitrile glove (4.9 ppm), and BIT in both new and used gloves (7.8 ppm and 6.9 ppm, respectively). OIT was present only in a new glove, again at only a low level (4.6 ppm). Details of protocol are explained in Appendix S1.

DISCUSSION

Results pertaining to the new gloves, containing MI, as well as BIT and OIT, were interpreted as being likely due to the industrial manufacturing process of the gloves. Allergic contact dermatitis due to a high BIT content (>20 ppm) in (reusable) polyvinyl chloride gloves has previously been described.³ In our case, however, neither BIT nor OIT showed any reactions on patch testing. Our case is interesting