

Ter-butylhydroquinone is a marker for sensitivity to *Nigella sativa* oil allergy: 5 new cases.

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Use of complementary and alternative medicine has increased in western industrialized countries (1,2). *Nigella sativa* oil (NSO), used as an herbal medicine for thousands of years, draws interest for its immunoregulatory, antimicrobial, cardiovascular and antitumoral properties (3). Although alternative medicine are supposed to be safe by the patients (4), allergic contact dermatitis (ACD) and bullous dermatitis with NSO, have been reported (5,6). The hypothesis that thymoquinone (TQ), its major component, was the causative substance of allergic reaction to NSO was proposed (7) but thymoquinone is not yet available in France for patch tests. Only NSO patch test can be performed. In one recent case report (8), we reported that due to a close chemical structure between ter-butylhydroquinone (TBHQ) and TQ, positive patch tests with TBHQ, TQ and NSO could be observed, suggesting that TBHQ could be a marker for sensitivity to TQ and so, to NSO. In order to confirm this hypothesis, we report the results obtained in 5 consecutive patients with ACD to NSO also having been tested with TBHQ.

OBSERVATION:

4 patients with topical application and 1 patient with topical and also oral intake of NSO presented NSO ACD. Patch tests with the European baseline, cosmetic series including TBHQ

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at 1% petrolatum (Chemotechnique, Vellinge, Sweden), with the own patient NSO at 5% petrolatum patch test and as is it semi-open test were performed with readings at Day 2 and 4. In all cases, positive patch-test reactions occurred with NSO and TBHQ patch tests (Figure 1, Table 1).

DISCUSSION:

TBHQ (synonym: 2-ter-butylbenzene-1,4-diol), known as non-irritative, is an antioxidant who prevents oxidation of lipid component in cosmetics such as vegetable skin oil (9), lipstick, and hair dye. It has also industrial uses: to stabilize chemicals or to delay polymerization of polyesters (10). A few cases of contact dermatitis from TBHQ have been reported, mainly with hair dyes (10). In our patients, no previous exposure and sensitization to TBHQ was found and NSO was the relevant allergen. TBHQ is not contained in NSO (11) but its chemical structure is very similar to those of TQ (8,12). TBHQ could be a pro-hapten. Through an oxydation process, ter butyl hydroquinone (2-tert-butylbenzene-1,4-diol) could lead to a 1,4-benzoquinone structure, also called para-quinone, with a close chemical structure of those of thymoquinone (2-methyl-5-isopropyl-1, 4-benzoquinone. Thereby, the similar patch tests profile results in our 5 patients support the hypothesis that TBHQ is a good marker for NSO allergy through a TQ sensitization. Unfortunately, we could not obtain TQ to do patch tests with a fresh preparation in these 5 cases. In a previous study we used a pre-diluted solution of TQ prepared by a chemist. This preparation was no longer available. TQ is commercialized for laboratory investigations and not for human use, thus it cannot be used for patch test material in our country. Studies are ongoing on the pharmacological effect of TQ. TQ has anti-cancer activity, inducing apoptosis or activating tumor suppressor genes. Therefore, using TQ in powder and dilute it in petrolatum could not be proposed, due to a potential risk of toxicity in handling this molecule which has anti-oncogenic properties (13).

The clinical and histological presentation of NSO may considerably differ and the diagnosis could be challenging. Indeed, patient #1 was referred for suspicion of symmetrical drug-related intertriginous and flexural exanthema to radiocontrast media, while patient #5 looked like an acute localized exanthematous pustulosis (ALEP). In 4 of 5 cases, patients did not spontaneously mention the use of NSO and information was found only after questioning about the use of essential or vegetable oils or NSO. As previously reported (14), our cases highlight the necessity of questioning patients for their undisclosed use of alternative medicine . In patient #5, referred for a suspicion of an antibiotic-induced ALEP or ACD to antiseptics, the positive

result of the TBHQ patch test straightened the diagnosis by re-questioning the patient that initially did not mentioned the use of NSO.

These 5 cases and the previously published one, sustained the hypothesis that due to chemical similarities with TQ which is supposed to be the responsible for NSO sensitization, TBHQ would be a good marker for NSO allergy. Moreover, in case of positive TBHQ patch test it is necessary to question the patient on his use of NSO and inform him to avoid any further application of this vegetal oil.

- Accepted Article
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Figure 1. Patient #1, NSO 5%, Open NSO as it and TBHQ patch test.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	F	F	F	F	F
Age (y.o)	46	55	47	48	41
Reason for use Nigella sativa oil	Hemorrhoids (TA)	Atopic dermatitis (TA)	Joint pain of hands and feet (Ingestion and TA)	Alopecia (TA on scalp)	Otodynia (TA on the left ear)
Clinical features	Gluteal fold erythema, target- like erythematous papules of the left thigh	Worsening of atopic dermatitis	Papulo-vesicular generalized rash	Oedematous eczema on the scalp, extended to the face	Left ear inflammation and edema extended to the left hemi- face with pustules
Delay of onset after the beginning of NSO application	48h	Several weeks (application 2 to 3 times a week)	1 month	3 months (application twice a week)	72h
Patch tests results	NSO 5% pet ++/++ Open NSO as it +++/+++ TBHQ ++/++ (Fig 1)	NSO 5% pet ++/++ TBHQ +/-	NSO 5% pet ++/++ Open NSO as it +++/+++ TBHQ +/-	NSO 5% pet ++/++ TBHQ ++/++	NSO 5% pet ++/++ Open NSO as it ++/++ TBHQ +/-

Table 1. Clinical features and results of patch tests at Day 2 and 4 in 5 patients with Nigella sativa oil allergy

F: female, NSO: Nigella sativa oil, pet: petrolatum, TA: topical application, TBHQ: t-butylhydroquinone,