

Tea tree oil attenuates experimental contact dermatitis

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Received: 14 July 2010 / Revised: 8 September 2010 / Accepted: 9 September 2010
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Abstract Herbs and minerals have been used in clinical dermatology for hundreds of years and herbal ingredients are becoming increasingly popular with the public in treatment of various dermatological conditions characterised by inflammation and pruritus. The aim of this study was to compare the efficacy of traditional topical therapeutic agents with a moderate potency topical glucocorticoid on experimental contact dermatitis and contact urticaria. The effects of ichthammol 10% pet, zinc oxide 20% pet, camphor 20% pet, levomenthol 10% pet, tea tree oil 20 or 50% and clobetasone butyrate 0.05% ointment were studied in the following experimental models: elicitation of allergic contact dermatitis to nickel, irritant contact dermatitis to benzalkonium chloride, and in immediate reactions to histamine and benzoic acid (non-immunological contact urticaria) respectively. Delayed reactions were evaluated using a clinical scoring system and immediate reactions were estimated by planimetry. Histamine-induced pruritus was evaluated using VAS. Tea tree oil reduced allergic contact dermatitis by 40.5% ($p = 0.003$), zinc oxide by 17.4% ($p = 0.04$) and clobetasone butyrate by 23.5% ($p = 0.01$). Zinc oxide reduced histamine induced flare by 18.5% ($p = 0.01$), ichthammol by 19.2% ($p = 0.02$) and clobetasone butyrate by 44.1% ($p = 0.02$). Irritant contact dermatitis and non-immunological contact urticaria were not influenced by the pre-treatments. Pruritus induced by histamine also remained unchanged. In conclusion, tea tree oil seems to be a more effective anti-eczematic agent than zinc oxide and clobetasone butyrate, while clobetasone

butyrate is superior to both ichthammol and zinc oxide in topical treatment of urticarial reactions.

Keywords Tea tree oil · Zinc oxide · Ichthammol · Clobetasone butyrate · Contact dermatitis · Contact urticaria

Introduction

Topical corticosteroids have revolutionised dermatological care. However, the public has become increasingly concerned about their safety and turns attention towards medicinal plants and minerals [1].

The purpose of this study was to compare the efficacy of traditional topical therapeutic agents with a moderate potency topical glucocorticoid on experimental contact dermatitis and contact urticaria.

Materials and methods

Provocation of positive patch tests in patients allergic to nickel was chosen as a model for contact dermatitis. Nickel allergy may not be representative for all contact allergens but it is very common which makes it easier to recruit subjects for the experiments.

Weal and flare reactions to histamine were used as a simplified model for allergic contact urticaria as the main mediator is histamine. In contact urticaria also other mast cell derived mediators are released and contribute to more prolonged duration of the reactions. The effect of different traditional topical therapeutic agents on contact dermatitis was compared with clobetasone butyrate which is a moderate potency topical glucocorticoid. The study was

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Fig. 1 a The effect of tea tree oil and menthol on allergic contact dermatitis to nickel (first row), petrolatum used as control (second row) and irritant contact dermatitis to benzalkonium chloride (third row). The sites of patch tests are indicated on the right side by blue pen marks. **b** The effect of tea tree oil, zinc oxide, camphor, ichthammol, menthol and clobetasone butyrate on histamine-induced flare and weal. Petrolatum and physiological saline are used as controls. The sites of histamine prick tests are indicated on the lateral side by blue pen marks

approved by the local ethics committee. A letter was sent to 70 patients with contact allergy to nickel verified by patch test performed within 20 months preceding the study. Twenty-one patients (19 females, 2 males, mean age 48 years, range 25–73 years) with ++ or +++ reactions to nickel agreed to participate, giving a written informed consent.

The tests of delayed hypersensitivity were performed on the dorsal part of the upper arms and the tests of contact urticaria were performed on the ventral part of the lower arms.

On the first day the subjects were tested with nickel 2% in petrolatum (patients with +++ reactions) or 5% (patients with ++ reactions), with benzalkonium chloride 1% in water and with petrolatum alone. Finn chambers, 8 mm in diameter on Scanpore, were used. All tests were applied at nine sites on each upper arm. Approximately 15 mg of nickel sulphate and 15 mg petrolatum and 20 µl of benzalkonium chloride were used. One additional test with nickel sulphate and benzalkonium chloride was used as a control. The subjects returned after 48 h and the tests were removed and evaluated using a scoring system according to the guidelines of the International Contact Dermatitis Research Group [4].

According to this system, palpable erythema is denoted by +, erythema with papules or infiltration by ++, and vesicular or bullous reaction by +++. The test reactions were then covered according to a randomised schedule using Finn chamber 12 mm, containing approximately 50 mg of clobetasone butyrate ointment, ichthammol 10% pet, zinc oxide 20% pet, camphor 20% pet, levomenthol 10% pet and 60 µl tea tree oil 20 or 50% (Fig. 1a). New samples of Australian® bodycare tea tree oil were supplied by Maxmedica AB (info@maxmedica.se) and stored at 5°C. The selection of concentrations was based on the common preparations used for treatment of eczema [3, 13]. The same substances were also placed on the ventral part of the lower arms in 18 mm Finn chambers containing approx 150 mg of the substances in petrolatum and 120 µl tea tree oil according to a randomised schedule. After 24 h the subjects returned, all Finn chambers were removed and the tests on the upper arms were read. On the eight pre-treated sites of the lower arms, 50 mg of benzoic acid 5% pet was applied in 18 mm Finn chambers for 45 min and the tests

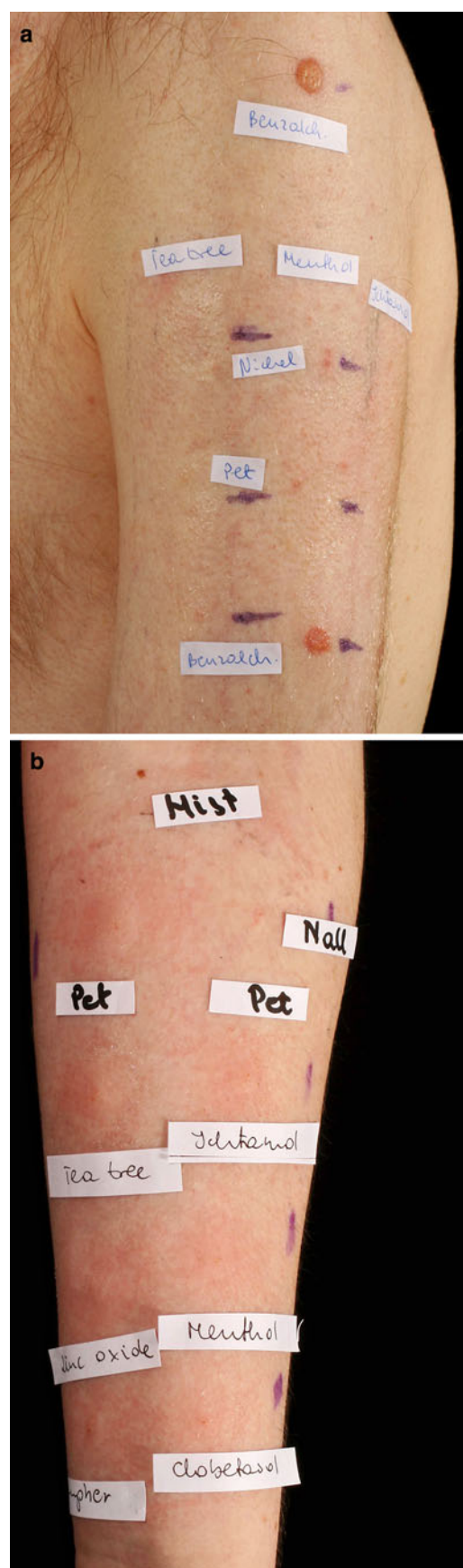


Table 1 Experimental contact dermatitis to nickel sulphate and benzalkonium chloride after different pre-treatments

No.	Nickel sulphate							Benzalkonium chloride						
	Petrolatum	Tea tree oil	Zinc oxide	Camphor	Ichthammol	Menthol	Clobetasone butyrate	Petrolatum	Tea tree	Zinc oxide	Camphor	Ichthammol	Menthol	Clobetasone butyrate
1	++	+	+++	++	+++	+++	+++	+	+++	++	0	++	++	0
2	++	++	++	++	++	++	++	+++	0	+++	+	++	0	0
3	+++	++	++	+++	+++	+++	++	+	+++	0	+++	+++	++	0
4	+++	0	0	+++	+++	+++	++	+++	0	0	+++	+++	+++	++
5	0	0	0	0	0	0	0	++	+++	++	++	++	++	++
6	++	0	0	++	+	++	0	+	++	++	+++	+	0	+
7	++	+	++	0	+	0	+	++(+)	+++	++	+++	+++	+++	+++
8	++	++	+++	+	++	++	+++	+	0	+	+	+++	+++	+
9	+++	++	+++	+++	+++	+++	+++	++	++	+++	+++	+++	+++	+++
10	++	+++	++	++	++	0	0	+	0	+	+++	0	0	+
11	++	0	++	+++	0	+++	0	+++	+++	++	+++	0	+++	0
12	++	++	+	++	++	++	++	+++	++	+++	++	+++	0	+
13	+++	+	++	+(+)	+	++	++	++	0	+++	+	++	+	0
14	++	++	++	+++	+++	0	++	++	+++	++	+	++	+	+
15	+++	+++	+++	+++	+++	+++	+++	0	0	++	(+)	0	0	+++
16	+++	+++	+++	+++	+++	+++	+++	+++	+	++	++(+)	+++	+	++
17	+++	+++	+++	++	+++	+++	++	++	+	+++	+++	0	+	++
18	++	++	+++	+++	++	+++	+++	++	0	0	0	++	0	++
19	++	+	+	0	0	++	0	+++	0	+++	++	+++	+++	+++
20	+++	+++	++	+++	+++	++	++	0	0	0	0	0	0	0
21	++	+	+	+	++	0	++	+	++	+	0	+	+	0

were read 10 min after removing the Finn chambers. Histamine was pricked on the other eight corresponding sites; the itch was evaluated after 5 min and the flare and weal were recorded after 15 min, which is common procedure in reading prick test reactions (Fig. 1b). The area of flare and weal were calculated using planimetry. The volume of the weal was calculated as a product of weal area and depth (skinfold thickness-baseline/2) [11].

Data analysis was performed using Students *t* test for paired parametric data.

Results

In all but one subject nickel elicited positive ++ or +++ patch test reactions, the mean score being 2.3 ± 0.57 . Many nickel containing test chambers may induce an “angry arm” with stronger positive reactions to nickel compared to testing with single patch tests. However, the intensity of the test reactions should not affect the subsequent readings after application of the therapeutic test substances.

Tea tree oil 50% was applied to fifteen patients. As this concentration induced some redness in several patients, a concentration of 20% was administered to the remaining

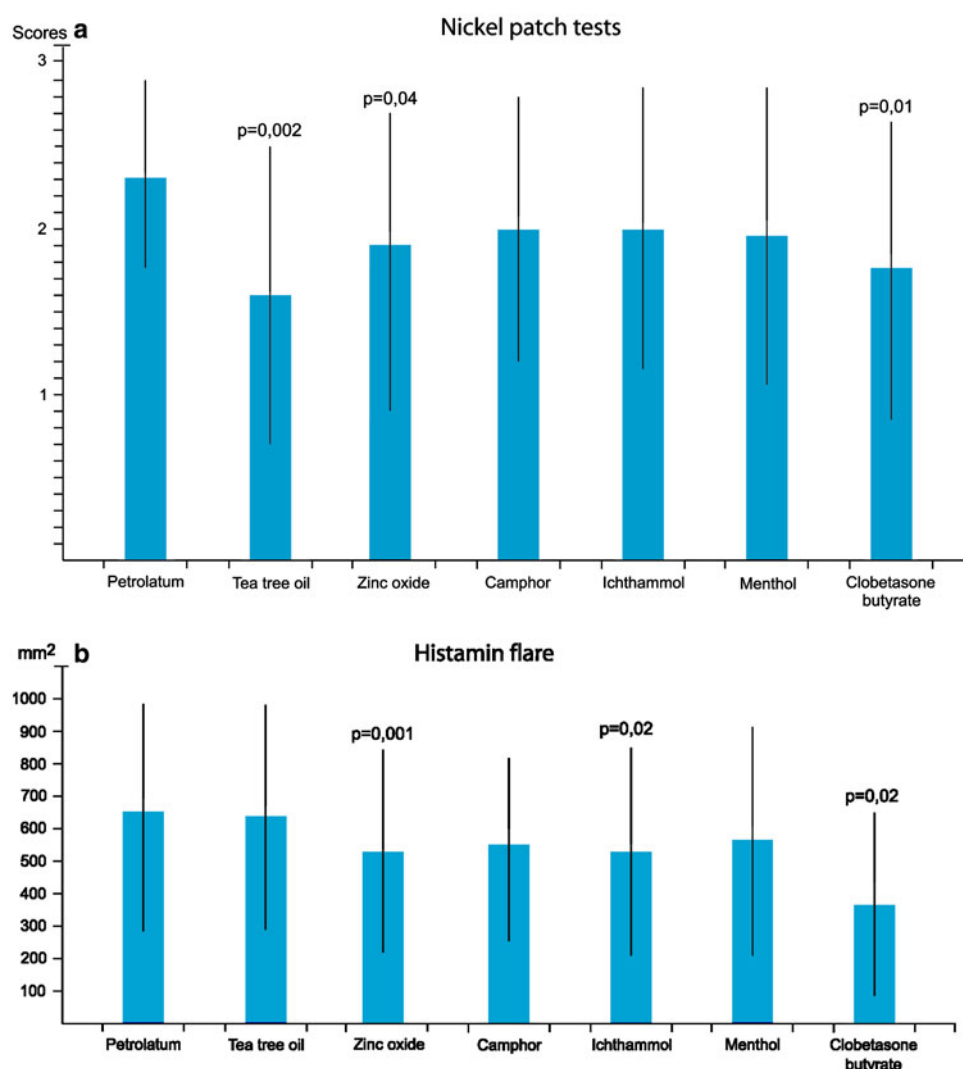
six patients. Tea tree oil reduced patch test reactions to nickel by 40.5% (mean scores 1.6 ± 0.9 , $p = 0.003$). Zinc oxide reduced the reactions by 17.4% (1.9 ± 0.8 , $p = 0.04$) and clobetasone butyrate by 23.5% (1.8 ± 0.9 , $p = 0.01$) (Table 1; Fig. 2a). The other pre-treatments did not significantly reduce reactions to nickel.

All but one subject reacted to benzalkonium chloride, the mean scores being 1.8 ± 0.8 . However, none of the pre-treatments given significantly reduced the reactions, but clobetasone butyrate was most effective (1.3, $p = 0.07$) (Table 1). The patients were asked about pruritus on the sites of all tests, but found it difficult to discriminate itch from patch tests very close to one another (Fig. 1a).

Histamine induced itch in all but one patient (no. 12) who had not interrupted her antihistamine treatment for hay fever and was consequently excluded from the histamine-related experiments. Pruritus was not influenced by any pre-treatment, the values ranging from 44 ± 21 to $50 \pm 29\%$.

Histamine prick tests induced a flare with a mean area of $652.2 \pm 331.2 \text{ mm}^2$ and a weal with mean area of $70.4 \pm 10.7 \text{ mm}^2$ and a volume of $102.9 \pm 37.2 \text{ mm}^3$ (Fig. 2b; Table 2). Two patients, 62 and 58 years old, responded with weal but no flare. The latter of these two patients suffered from long-standing diabetes and reduced

Fig. 2 a The effect of tea tree oil, zinc oxide, camphor, ichthammol, menthol and clobetasone butyrate on histamine-induced flare and weal. Petrolatum and physiological saline are used as controls. The bars indicate mean values $\pm$ SEM. **b** The effect of tea tree oil, zinc oxide, camphor, ichthammol, menthol and clobetasone butyrate on histamine-induced flare. The bars indicate mean values $\pm$ SEM



flare reactions can actually be used to diagnose peripheral neuropathy in patients with diabetes [10]. Zinc oxide reduced the flare reaction by 18.5% ($531.8 \pm 306.0 \text{ mm}^2$, $p = 0.01$), clobetasone butyrate by 44.1% ($364.8 \pm 279.6 \text{ mm}^2$, $p = 0.02$) and ichthammol by 19.2% ($527.5 \pm 313.3 \text{ mm}^2$, $p = 0.02$) (Fig. 2b). Tea tree oil increased the histamine-induced weal by 52.5% ($155.4 \pm 73.0 \text{ mm}^3$, $p = 0.002$) while zinc oxide increased the reaction by 47.4% ($150.3 \pm 85.4 \text{ mm}^3$, $p = 0.02$). The increase of the weal was due to the increased skin depth as the areas of the weal after the pre-treatment with tea tree oil and zinc oxide were almost the same (71.4 ± 16.7 and $69.9 \pm 18.2 \text{ mm}^2$, respectively). The skin depth induced by tea tree oil 50% was greater than the one induced by tea tree oil 20% (2.3 ± 0.7 and $1.5 \pm 0.5 \text{ mm}$ respectively, compared with skin depth after petrolatum $1.4 \pm 0.4 \text{ mm}$).

Benzoic acid induced an infiltration in all but one patient. The mean volume of the infiltration was $214.0 \pm 119.1 \text{ mm}^3$, range 167.5 ± 107.1 – $261.2 \pm 164.1 \text{ mm}^3$ (after clobetasone

butyrate and ichthammol respectively). None of the pre-treatments changed significantly the response to benzoic acid.

Discussion

Zinc oxide has been used for centuries to soothe, lubricate and cool subacute eczemas [13]. In localised forms of eczema, tar was the most popular topical treatment, often in mixture with zinc paste [13]. This study shows that zinc oxide is as effective as moderate potency corticosteroid in suppressing contact dermatitis while tea tree oil is even more effective. This result accords with a previous report using tea tree oil 100% [7]. Tea tree oil was tested here in two concentrations, 50 and 20%. The higher concentration induced erythema in several patients and also increased skin depth (measured when studying histamine reactions), both signs of irritancy [9]. As tea tree oil 20% had similar anti-eczematic effect as 50% solution, the lower

Table 2 Histamine-induced flare and weal after different pre-treatments

No.	Histamine flare (mm ²)							Histamine weal (mm ³)						
	Petrolatum	Tea tree oil	Zinc oxide	Camphor	Ichthammol	Menthol	Clobetasone butyrate	Petrolatum	Tea tree	Zinc oxide	Camphor	Ichthammol	Menthol	Clobetasone butyrate
1	427	422	153	220	348	277	0	105.9	158.9	87.7	82.0	64.2	63.3	20.0
2	203	210	168	500	222	582	200	90.9	56.4	80.1	42.2	56.9	32.8	36.4
3	836	983	506	462	595	919	558	167.2	311.2	293.6	81.7	92.6	139.4	187.9
4	1224	1227	1033	1377	926	766	587	77.5	80.9	98.6	52.4	55.9	80.0	148.0
5	1272	1091	1050	895	1059	779	850	169.6	245.9	135.6	138.9	107.6	112.4	183.9
6	355	163	0	169	204	108	0	48.0	39.3	36.6	55.7	135.7	34.7	36.6
7	857	389	481	506	177	221	767	137.3	102.3	132.2	65.0	29.2	39.1	39.4
8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
9	528	481	487	292	370	263	143	94.3	99.3	122.3	126.9	159.9	138.6	77.2
10	1106	1078	839	459	1043	879	693	86.3	121.2	114.9	84.8	117.3	151.9	83.2
11	566	566	444	578	383	573	128	98.4	222.0	234.9	147.7	135.9	134.2	85.0
13	382	472	486	414	270	212	148	107.4	160.6	121.3	233.2	117.0	127.0	48.7
14	227	272	355	490	302	222	0	83.0	87.8	52.0	36.6	120.9	36.9	113.4
15	641	1100	556	420	531	467	302	155.3	235.9	148.9	92.1	264.6	201.0	130.2
16	–	–	–	–	–	–	–	140.3	174.8	161.3	116.3	104.7	120.5	91.5
17	630	646	457	556	388	688	276	87.2	135.9	118.5	168.0	211.7	178.1	65.9
18	–	–	–	–	–	–	–	51.1	241.5	106.8	115.4	112.9	90.9	169.6
19	600	529	567	563	649	752	512	123.7	112.4	385.6	216.0	103.1	126.5	169.3
20	881	887	1041	941	1074	1442	528	77.9	170.0	209.3	215.7	125.3	91.0	73.7
21	353	365	419	513	427	330	509	54.2	196.9	215.1	248.5	116.8	73.4	91.3

NR not registered

concentration should be recommended for treatment of eczema, keeping in mind that tea tree oil itself may induce allergic contact dermatitis [8]. In this study, tea tree oil had no effect on irritant contact dermatitis to benzalkonium chloride, which accords with a previous study on mice [2].

Flare reaction to histamine was significantly reduced by zinc oxide and ichthammol but not as effectively as when reduced by clobetasone butyrate. Tea tree oil did not affect flare to histamine but increased the weal (Fig. 1b). Possible pathomechanism for the increased weal is increased skin depth which is a sign of irritancy [9]. Our results are in contrast to the results of Khalil et al. [5] who applied tea tree oil 100% 10 and 20 min after histamine injection and found reduction in flare after 30 min and weal after 50 min. A reason for this discrepancy may be different concentrations and times of the application of tea tree oil as well as reading of the reactions [5, 6]. Histamine flare is maximal after 5 min and weal after 15 min. Thereafter the reactions decline spontaneously and the effects of topical agents on these reactions should therefore be measured at early time points.

Scoring of pruritus was difficult to perform as the patients found it difficult to discriminate itch from patch tests very close to one another. Testing on the back would give a better space for patch tests but discrimination of itch

on the back is even harder, probably due to a less dense innervation of the skin in this region [12].

Compositions with zinc, menthol and camphor have been used mainly to relieve itching [13]. Our patients could not report any difference in the perception of itch from histamine after the treatments used. It can however depend on the difficulty of discriminating itch from eight big patches (350–1270 mm²) localised close to each other on each lower arm (Fig. 1b).

In summary, under occlusion, tea tree oil seems to be a more effective anti-eczematic agent than zinc oxide and clobetasol butyrate, which is superior to ichthammol and zinc oxide in topical treatment of urticarial reactions.

Acknowledgments Technical assistance of Elsa Larsson and Inger Nordgren is gratefully acknowledged. The study was supported by The Welanders and Finsen Foundation and The Asthma and Allergy Foundation. The author declares that she has no conflict of interest.

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