

## SHORT REPORTS

### Efficacy and Transdermal Absorption of Permethrin in Scabies Patients

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The clinical efficacy and transdermal absorption of permethrin, a new synthetic insecticide was investigated in ten scabies patients. All patients were successfully treated with one application of a cream, containing 5% permethrin. Apart from mild postscabies dermatitis no side-effects were observed. The mean weight of cream used per patient was 25 g (range 21-32; mean content of permethrin 1250 mg). The degree of permethrin absorption was assessed indirectly by determination of conjugated and unconjugated *cis*- and *trans*-CVA (a metabolite of permethrin) excretion in urine using two dimensional gas chromatography mass spectrometry. It was found that during the first 48 hours the mean estimated absorption was 6 mg (range 3-11), which is approximately 0.5% of the total dose.

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Gamma benzene hexachloride (Lindane) is widely used for the treatment of scabies, because of its demonstrated efficacy, ease of use and acceptability to patients. The safety of this drug, however, is the subject of considerable controversy (1). Several authors have suggested that its use should be abandoned in young children and pregnant women (2, 3). In its place crotamiton, benzylbenzoate or precipitated sulfur have been recommended, but it is questionable whether these drugs are either as effective as, or more safe than Lindane (1). Recently (4) aqueous malathion (0.5% w/v) was described as an effective scabicide compared with benzylbenzoate in the treatment of children with scabies. Data on absorption and on responses of clinical laboratory parameters after whole body application to man were not collected. However, the 39 malathion treated patients showed no sign of clinical toxicity.

Permethrin is a photostable synthetic pyrethroid with broad spectrum insecticidal activity and low mammalian toxicity. It is a racemic mixture of *cis*- and *trans*-isomers in the ratio 25:75. As a 1% solu-

tion in liquid paraffin it was found to be partially effective against scabies, comparing favourably with Lindane (5). In the present study a more cosmetically acceptable formulation, 5% permethrin in a cream base (6), was used to investigate the clinical efficacy and the transdermal absorption in the treatment of scabies patients.

#### MATERIAL AND METHODS

Ten adult patients, 5 male and 5 female, with an age range of 23-42 years, in whom skin scrapings showed mites and/or their eggs, participated in this study. Exclusion criteria were: pregnancy, lactation, severe skin conditions requiring treatment, therapy with corticosteroids, a history of hypersensitivity to pyrethroids, pyrethrins, chrysanthemums or formaldehyde, treatment for scabies within the past 4 weeks and Norwegian scabies.

Patients were treated with 5% permethrin cream under medical supervision at the outpatients department. The cream was applied to the skin of the whole body excluding head and neck, and the weight of the cream used was recorded. Each patient was instructed to have a thorough wash 8 hours after the permethrin treatment. For the first 2 weeks after the treatment only moisturising cream was allowed as supplementary treatment. Thereafter mild corticosteroid cream could also be used.

The clinical effect was assessed by a visual score system prior to and 7, 14 and 28 days after treatment. A scoring system of absent (0), mild (1), moderate (2), and severe (3) was applied to 5 signs and symptoms (burrows, pruritus, excoriation, papules, and nodules) at 6 sites (hands/wrists, axillae, breasts, groin/genitalia, buttocks and feet/ankles). The total maximum score possible for each individual per control was 90. Side-effects were scored according to a similar scoring system.

Sedimentation rate, haemoglobin, leucocytes, differential counts, platelets, serum creatinin and urea, AST, ALT, serum bilirubin, alkaline phosphatase, albumin, cholesterol, triglycerides and glucose, and urine protein and glucose were examined before and 7 days after the treatment.

A reflection of the degree of permethrin absorption was assessed indirectly by determination of conjugated and unconjugated *cis*- and *trans*-CVA (3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid; a metabolite of permethrin) excretion in urine using two dimensional gas chromatography mass spectrometry (M. V. Doig, in preparation). Patients provided 10 ml of urine before the treatment.

Table I. Urinary excretion of *cis*- and *trans*-CVA before and after application of permethrin body creamn.d. = below detection limit, which was 0.02 µg/ml and 0.08 µg/ml for *cis*- and *trans*-CVA, respectively

	No. of patients measurable CVA/ no. examined	Mean ± SD concentration CVA (µg/ml) <sup>a</sup>		Mean total CVA excreted (µg)/collection
		<i>Trans</i>	<i>Cis</i>	
Predose	0/10	n.d.	n.d.	—
Day 1	7/7 <sup>b</sup>	0.5 ± 0.4	0.1 ± 0.07	414
Day 2	7/7 <sup>b</sup>	0.4 ± 0.3	0.1 ± 0.05	439
Day 1 and 2	3/3 <sup>b</sup>	0.6 ± 0.1	0.1 ± 0.02	1 435
Day 7	3/10 <sup>c</sup>	0.2 ± 0.1	0.04 ± 0.02	—
Day 14	1/10 <sup>d</sup>	0.35	0.07	—

<sup>a</sup> Mean of positive results only.<sup>b</sup> Three patients collected the two 24 hours urine in one container.<sup>c</sup> In 7 patients CVA was not detectable.<sup>d</sup> In 9 patients CVA was not detectable.

Ten ml samples were saved from all urine passed during the first and the second 24 hours after application of the cream. The volume of the 24-hours urine collections was recorded. Further 10 ml samples were collected from urine collected during the controls on days 7 and 14. All samples were stored frozen at -24°C.

## RESULTS

The weight of the cream used was 21 to 32 g (mean 25 g). In most cases the interval between application of permethrin cream and washing was greater than the 8 hours advised. This was caused by the circumstance,

that all patients were treated at about 12.00 noon and they postponed the washing until bedtime or the next morning.

All patients showed considerable improvement within 14 days after treatment (see Fig. 1). From days 14 to 28 there was a gradual further improvement. After 4 weeks 6 patients had zero scores for all parameters. The other 4 patients had mild pruritus (4 pats.) and a few papules (2 pats.) or excoriations (1 pat.). They had no burrows or nodules. After the end of the trial there was a clinical follow-up of these 4 patients and it appeared that, in the next 3 weeks, all symptoms disappeared without any additional scabidical therapy.

The only reaction observed was eczema. A total of 7 patients, one of whom was affected prior to treatment, had mild or moderate eczema on a limited part of the body (not on previously healthy skin) at some time. Of these 7, three patients had eczema on one occasion only. No other side-effects were observed. No abnormal laboratory values of clinical significance were observed in 9 patients. Patient 1 had abnormal liver function tests, which already existed before treatment, and which with exception of the bilirubin were slightly lower after treatment. He turned out to be an alcoholic, who drank large quantities of beer. As a result of this he was unable to make a full collection of urine during the first 48 hours, as the 2 litre containers provided for each 24 hour collection were of insufficient capacity.

The excretion of *cis*- and *trans*-CVA is summarized in Table 1. The concentration of *trans*-CVA in urine

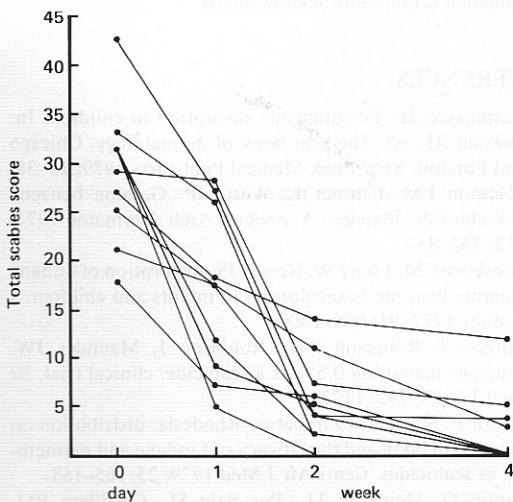


Fig. 1. Individual responses of total scabies scores following permethrin cream application on day 0.

during the first 48 hours varied from 0.11 to 1.07 µg/ml while that of the *cis* isomer varied from 0.02–0.21 µg/ml. CVA was still detectable in urine collected on day 7 in 3 patients. In two of these the levels had dropped markedly, however, in patient 1 both *trans* and *cis* isomer concentrations were similar to those observed during the first 48 hours. The only patient excreting CVA at week 2 was patient 1.

Approximately one third of orally administered permethrin is excreted as CVA in urine (Cridland and Weatherley, personal communication). Assuming 100% absorption following ingestion, it is possible to estimate the amount of permethrin reaching the blood stream by the subsequent excretion of CVA in urine. Thus, in the present study, the mean calculated absorption over the first 48 hours following topical administration of the cream was 6 mg of permethrin (range 3–11), that is approximately 0.5% of the applied dose. The maximum observed was that shown by patient 1 whose CVA excretion in a total of 4 litres of urine suggested an absorption of 11 mg. The actual figure would be greater as some urine was lost.

## DISCUSSION

In the present study it appeared that one application of about 25 g of a cream containing 5% permethrin was successful in the treatment of all ten scabies patients.

After treatment 6 patients showed mild not preexisting eczema at one or more examinations. This so-called postscabies dermatitis is considered to be an irritative contact dermatitis (7, 8) due to antigens of the killed *Sarcoptes scabiei* or due to the applied drug which penetrates better in the lesions than in previously healthy skin. A high percentage of this postscabies dermatitis was also found after treatment with sulfur ointment, lindane and benzylbenzoate. Only in a very few cases did patchtests give a positive reaction to the applied preparation (8, 9).

Although this was not proven by patch-tests, in our case it is also unlikely, that it was an allergic dermatitis, since: 1) patch testing in human volunteers has indicated that the presently used permethrin cream has a very low irritative and allergic potency (Farquhar and Hutchinson, personal communication) and 2) the eczema in our patients was confined to those areas of skin previously affected by scabies. This high percentage of postscabies dermatitis was not reported by Taplin et al. (6). In our study the eczema could be easily controlled with mild cortico-

steroids and it would possibly have been less prominent, if the corticosteroids were given just after the treatment.

Studies in healthy volunteers have indicated that, following whole body application of permethrin 5% cream, the metabolite *cis-trans*-CVA was detected in the urine. These studies also showed that excretion of CVA, which began within the first 7 hours is at a maximum over the first 48 hours but may continue at a low level for at least 14 days. Rough estimates of permethrin absorption, derived from this CVA excretion, suggested that the maximum absorbed by any one individual over the first 48 hours after application of 16 g of cream (800 mg permethrin) was 18 mg and the overall group mean absorption was 10 mg (Farquhar and Hutchinson, personal communication).

The present CVA analysis gave more or less similar results and suggested that the level of permethrin absorption is of the same order of magnitude in scabies patients as in healthy volunteers (see Table I).

The limited data obtained by the present study suggests that one application of permethrin cream is efficacious and clinically acceptable in the treatment of scabies. Since only small amounts are absorbed and the mammalian toxicity is known to be low, it might be a good and safer alternative to Lindane. Further studies on a larger scale are needed to confirm this, however.

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## Ringworm-like Late Syphilides

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**A peculiar form of late, superficial, serpiginous, non-ulcerative syphilides, leaving no visible scars, resembling clinically the ringworm of the glabrous skin, showing the granulomatous histopathological structure and relatively abundant *T. pallidum*, predominantly spread around the blood vessels is described. Key words: *T. pallidum*.**

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Nowadays, late cutaneous syphilis is observed extremely rarely (1), and every misdiagnosed, clinically atypical case is remarkable, as is the one reported below.

### CASE REPORT

A 54-year-old married woman was admitted to our Clinic because of skin lesions of 5 months' duration and slowly enlarging peripherally; they had been misdiagnosed by her dermatologist as ringworm several weeks earlier. Positive serological tests for syphilis (STS) were revealed during a mass serological screening campaign in the Cracow region. The general health of the patient was satisfactory. She had three non-examined adult children. STS of her husband were negative. The patient has never left Poland, i.e. has never travelled to the tropics.

Examination: on the right side of her neck there was a lesion 6×7 cm in diameter, forming an irregular ring composed of densely grouped rose-colored papules covered with delicate whitish scales without tendency to ulceration, and leaving no visible scars (Fig. 1). In the centre of this ring the formation of the second one, also irregular, was seen. The lesion resembled closely the ringworm of the glabrous skin. Analogous but smaller lesions were located on the left preauricular region and on the left arm. The oral mucosa and anogenital region were free of lesions.

Routine laboratory investigations of blood and urine were normal. Darkfield examination for *T. pallidum* of the tissue fluid squeezed from the artificially-eroded margin of the lesion, repeated 5 times, gave negative results, as did mycologi-

cal examinations including culture. Chest X-ray examination as well as internal, ophthalmological, neuropsychiatric and laryngological consultations did not reveal pathological changes.

The serum Wassermann reaction (WR) was strongly positive, VDRL test: positive, 1:16; TPI test: 100% of immobilization, FTA-200 test: positive, 1:4000; FTA-ABS test: positive.

Cerebrospinal fluid: cell count, protein level, Pandy-Nonne test, WR and VDRL test were negative. The TPI test: 55% of immobilization, FTA test: positive, 1:10.

Two biopsies, one from the centre of the syphilide and the second one from its margin were made. In the sections stained with haematoxylin-eosin (HE), granulomatous infiltrates of the tuberculoid type, without necrosis, with epithelioid and giant cells of Langhans' type were observed around the skin vessels and around hair follicles (Fig. 2).

In sections stained with modified Krajan's silver impregnation method (2) the epidermis was free from treponemes.

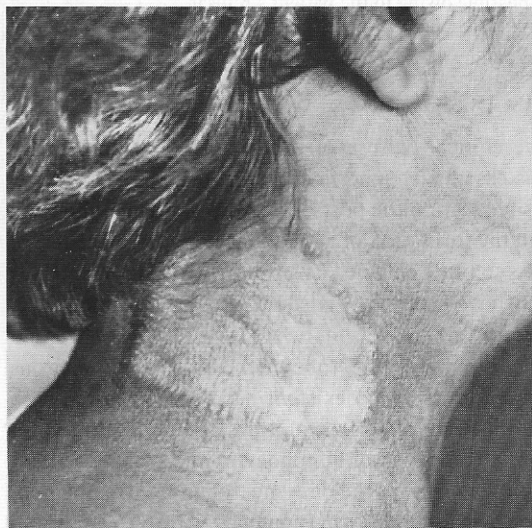


Fig. 1. Ringworm-like syphilide on the neck.