

Topical Treatment of Psoriatic Skin with Methotrexate Cream: A Clinical, Pharmacokinetic, and Histological Study

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Bjerring P, Beck H-I, Zachariae H, and Søgaaard H. Topical treatment of psoriatic skin with methotrexate cream: a clinical, pharmacokinetic, and histological study. *Acta Derm Venereol (Stockh)* 1986; 66: 515-519.

Five patients were treated with either 0.25% methotrexate cream or placebo in a double blind trial. The evaluation showed no clinical or histological effect although the drug was absorbed from the skin. Methotrexate (MTX) accumulated in locally treated psoriasis plaques as well as in untreated plaques. The psoriatic skin concentrations were increased by a factor of 119 and 4, respectively. This observation is discussed in relation to the possible role of action of methotrexate in psoriasis. We suggest that methotrexate inhibits the chemotaxis of neutrophil leukocytes systemically and not primarily in the skin, thereby preventing development of the early stages in the psoriatic lesions. (Received February 22, 1986.)

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Topical treatment of psoriasis with methotrexate (MTX) has been tested clinically before. Previous investigators have used either topical application of MTX creams or prolonged intralesional infusions with MTX solutions (1-5).

Fry et al. examined 9 patients with areas of localized psoriasis, which were treated for 2 weeks with 0.2% MTX cream topically under occlusion for 24 hours. All lesions improved but the study did not include a control group (5). Comaish et al. studied 20 patients, treated with MTX cream (0.1-10%) under occlusion. This controlled trial, however, showed no clinical effect (1).

Stewart et al. (4) increased the study period from 2 to 3 weeks. They investigated 9 patients in a controlled trial. MTX cream was applied under occlusion. No clinical effect was detected, and no MTX was found in skin or plasma. It was concluded, that lack of cutaneous penetration by physical and chemical properties, i.e. molecular size, ionisation at physiologic pH, and unfavorable lipid/water partition coefficient might explain the ineffectiveness of topical MTX.

As Fry et al. (5) previously obtained good responses in their early clinical study, and because Newbold et al. reported that 3% of ³H-MTX penetrated human skin of 4 patients (6), we decided to perform a double blind study with a MTX cream and placebo, in which a new cream base might favour penetration of MTX into the skin.

MATERIAL AND METHODS

Patients and materials

Five adult patients (26-69 years) with en plaque psoriasis and 5-40% total body surface affected were included. Prior to the trial, all treatment with local steroids was stopped for at least one week. None of the patients had been treated with MTX systemically. Only moisturizing cream was allowed as supplementary treatment. Each patient was treated on symmetrically located psoriatic lesions at each side of the body either at the abdomen or on the upper extremities.

The area for each treatment was about 25 cm². After randomizing, one area was treated with placebo and the other with MTX cream. The MTX was applied in a new cream base, containing 12%

carbamide, 12% sodium chloride, and 0.25% MTX. This composition was chosen because an increase of the hydrational status of the skin might be able to increase the permeability of the drug. The placebo cream also contained 12% sodium chloride and 12% carbamide and was coloured yellow by an approved food dye to the same colour as the MTX cream. Both creams were used within 7 days after preparation. The creams were applied once daily for 21 days without occlusion. No other areas of psoriasis present were treated during the trial. Systematically administered MTX was not allowed during the trial.

Laboratory tests

The amount of cream applied by each patient was measured by weighing the tubes before treatment, after 7, 14 and 21 days. At the same intervals we examined the MTX concentration in serum. At day seven a blood sample was drawn for examination one hour after MTX application. At day 14 two hours passed before blood was drawn for examination and at day 21 three hours passed. Hemoglobin, leucocytes and differential counts, platelets, serum creatinine, ASAT, LDH, alkaline phosphates, serum bilirubin, and urine protein & glucose were examined. Urine was collected during 24 hours for determinations of MTX at day 7 and 14. At day 7 and 21 skin punch biopsies were taken from MTX- and placebo treated area in order to determine the MTX content and for histological examination. A suction blister was raised on untreated abdominal skin day 7 in order to determine MTX in the intercellular fluid of unaffected skin (7).

The clinical effect was assessed by a visual score system after 7, 14 and 21 days of treatment. The score system used was: 0-3 for redness, infiltration and scaling. Besides noting the change of the lesions treated, the overall results were scored: -1 (worse), 0 (unchanged), +1 (better) and +2 (complete disappearance of lesion). The clinical assessment was supported by clinical photos after 7, 14 and 21 days. All determinations of MTX in skin biopsies, intercellular fluid, serum, and urine were made by a RIA method (International CIS), (18).

The following 6 histological parameters were evaluated: papillomatosis, parakeratosis, thickness of epidermis, Monroe's abscesses, number of capillaries, and degree of lymphocytic infiltration. Evaluation was performed on basis of the following scale: 0 = normal skin, 1 = slight or doubtful psoriatic alterations, 2 = moderate psoriasis, 3 = severe psoriasis.

RESULTS

There was no clinical effect of local MTX application compared with placebo. This was confirmed by blind examination of all clinical photographs taken during the trial.

The score system for redness, infiltration and scaling showed no difference for the two test areas. Examination of the weight of the tubes showed a good patient compliance with only a slight difference between the consumption of the MTX containing cream compared with placebo cream (Table I).

The MTX concentration was 407 ng/l (310-500 ng/l) in serum. The values were independent of the time between MTX application and blood sampling (1-3 h). Also, MTX serum concentration was independent of the amount of MTX applied on the skin (0.25-2.25 mg/day) and body weight (50-97 kg). The concentration of MTX in the skin was increased 119 times in the MTX-treated psoriatic plaques (48.5 ng/g), and 4 times in the placebo treated plaques (1.7 ng/g) compared to serum levels.

The MTX concentration in intercellular fluid of unaffected, non-treated skin was 9.3 ng/ml which was 5.2 times lower than the concentration in the MTX-treated plaques, but 23 times higher than in serum (Table I).

Laboratory screening of the bone marrow-, kidney-, and liver-function showed no abnormalities.

The blinded histological examination of the skin biopsies showed no differences between MTX- and placebo treated psoriatic plaques.

DISCUSSION

The present investigation was not able to confirm any clinical or histological effect on psoriasis by application of topical MTX as reported by Fry *et al.* (5).

Table I. Determination of Methotrexate (MTX) in serum, urine, suction blister fluid, and skin (psoriatic plaques) after topical application of MTX

N.D. = no data

Patient number	MTX (ng/l) serum	MTX (ng/24 h) urine	Excretion in % of applied MTX	MTX (ng/l) intercellular fluid	MTX (ng/g)	
					MTX skin	Placebo skin
1	310	—	—	—	—	—
	—	951	0.1	7 600	34.2	1.3
	340	1 278	0.09	—	—	—
	460	—	—	—	34.3	2.1
2	310	—	—	—	—	—
	350	1 068	0.05	—	27.0	1.7
	310	1 033	0.08	—	—	—
	—	—	—	—	100.0	4.7
3	500	—	—	—	—	—
	—	1 177	0.47	640	5.5	0.57
	460	721	0.29	—	—	—
	440	—	—	—	7.6	0.59
4	500	—	—	—	—	—
	420	—	—	20 000	230.0	ND
	460	—	—	—	44.0	3.4
	460	2 706	1.10	—	21.0	0.39
5	310	—	—	—	—	—
	450	1 958	0.21	8 800	9.8	0.37
	400	986	0.19	—	—	—
	350	—	—	—	20.7	1.5
Mean	407 ng/l	1 320 ng/24 h	0.3 %	—	48.5	1.7

The investigation showed an absorption rate of MTX from skin of 0.3%/24 hours. This was determined by urinary excretion. MTX is significantly bound to plasma proteins and in low concentrations it is virtually not metabolized but excreted unaltered through the kidneys. The MTX serum concentrations were considered in a steady state during the trial, and the excreted amount of MTX/day was therefore taken as a measure of the absorption from the skin. The result is in accordance with the study of Comaish et al. (1) who found that less than 0.55% of MTX applied with occlusion was excreted in the urine for a period of 72 hours.

Even though the absorption rate of MTX was only 0.3%/24 h we found a steady state mean serum concentration of MTX of 407 ng/l. A very interesting point is that MTX was absorbed from the treated areas, and cleared from the serum into the placebo treated psoriatic lesions to a concentration 4 times that of serum. This might be due to both an increased filtration rate of free and plasma protein bound MTX and an increased blood flow in the psoriatic capillaries (8, 9). The concentration of MTX in placebo treated psoriatic skin was 1.7 ng/g while the concentration in treated plaques was 48.5 ng/g. The concentration in intercellular suction blister fluid from untreated, unaffected skin was 9.3 ng/ml (0.60–20.0 ng/ml). Studies on the distribution of systemically administered MTX have shown peak skin concentrations of approximately 60 ng/g after 5 mg MTX *i/v*, and 460–850 ng/g after a 50 mg *i/v* dose (10–11).

This indicates that the MTX concentration in psoriatic lesions in our investigation was of almost the same level as can be found in the skin following a systemic dose of MTX normally used for treatment of psoriasis. However, it was not sufficient for a clinical or

histological effect on psoriasis. The reason for the present, low cutaneous concentrations of MTX may be a too slow absorption from the skin surface combined with increased blood flow and capillary filtration rate in the psoriatic plaque, or a too low concentration of MTX in the cream. Recently, it has been shown that the most favorable environment for MTX is a pH between 4 and 5 where the concentration of unionized MTX would be optimal (12). Our cream had a pH of 5–5.5 but was composed as an oil-in-water emulsion. This may explain a lower concentration of unionized MTX and thus a lower absorption.

Although we found no clinical effect of topical MTX, we demonstrated that MTX is accumulated in placebo treated, psoriatic plaques and in intercellular fluid of untreated, unaffected skin. This might suggest a skin affinity for MTX. Previous investigators have focused on a metabolic inhibition of metabolism (13) and a specific inhibition of the enzyme dihydrofolate reductase (14–15). However, inconsistent results with combined MTX-leucovorin therapy of psoriasis and possibly also the demonstrated ineffectiveness of topical application of MTX indicate that other targets may be involved in the action of MTX in psoriasis (14–16). A recent investigation has shown increased neutrophilic chemotaxis in serum from untreated psoriasis patients (17). The mode of action of systemically administered MTX might be mediated by an inhibition of this chemotaxis. A possible explanation for lack of clinical effect of topical MTX might thus be a too low systemic MTX concentration for sufficient inhibition of chemotaxis to prevent the initial events in the psoriasis plaque information. This, however, will not be elucidated before a topical application has been developed, which results in MTX concentrations in the skin comparable to the concentrations found after effective systemic MTX administration.

ACKNOWLEDGEMENT

The authors wish to thank N. Alexander, cand. pharm., Pharmacia, Denmark for supplying the methotrexate and for valuable assistance with MTX determinations.

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