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Fumaric acid therapy for psoriasis: A randomized, double-blind, placebo-controlled study

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During the past few years, fumaric acid therapy for psoriasis has gained interest among Dutch and German patients. This treatment was empirically devised by the German chemist Schweckendiek[1] and further developed by the German physician Schäfer.[2] Fumaric acid therapy is based on the following principles: (1) oral treatment with monoethyl and dimethyl esters of fumaric acid, (2) topical treatment with monoethylfumarate, and (3) a diet that forbids the consumption of nuts, spices, wines, and distilled products of wine. Because controlled studies have not been reported, we decided to investigate the clinical efficacy and side effects of fumaric acid therapy.

Patients and methods. Thirty-nine psoriasis patients (12 women and 27 men), ranging in age from 20 to 73 years (mean 44 years), entered the study. The patients had to fulfill the following criteria: (1) involvement of at least 10% of the body surface, (2) stable disease, (3) normal kidney and liver function, (4) no cardiac or gastrointestinal problems, and (5) no current pregnancy. The patients were randomly assigned to three groups. Group 1 was treated orally with enteric-coated tablets containing 120 mg dimethylfumarate, 87 mg calcium monoethylfumarate, 5 mg magnesium monoethylfumarate, and 3 mg zinc monoethylfumarate. Group 2 was treated orally with enteric-coated tablets containing 284 mg octyl hydrogen fumarate, 5 mg magnesium monoethylfumarate, and 3 mg zinc monoethylfumarate. Group 3 was given orally administered placebo tablets. All tablets (provided by Fumapharm AG, Muri, Switzerland) had the same appearance, size, and color. The double-blind treatment lasted 16 weeks for each patient. The dosage schedule called for a gradual increase from one to six tablets daily. All patients received topical treatment with 5% salicylic acid in white petrolatum. From 2 weeks before treatment until the end of the study, no other antipsoriatic therapy was allowed. All patients were asked to follow strictly the dietary guidelines associated with fumaric acid therapy (avoidance of nuts, spices, wines, and distilled products of wine). Extent and activity of skin disease were assessed by estimating the percentage of body surface affected with psoriasis and by scoring the degree of infiltration and scaling of the plaques (from 0, no infiltration or scaling; to 8, very severe infiltration or scaling). The following laboratory investigations were performed: erythrocyte sedimentation rate; leukocyte differential count; and determination of levels of hemoglobin, hematocrit, urea, creatinine, AST (SGOT), ALT (SGPT), lactate dehydrogenase, alkaline phosphatase, gamma glutamyltransferase, total bilirubin, glucose, and protein. Urinalysis for levels of glucose and protein and 24-hour creatinine clearance rate were also performed. Statistical analysis was performed with the Kruskal-Wallis test,[3] a nonparametric analysis of variance.

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Results. At baseline no significant differences were found among the three groups with regard to sex ratio, age, type and duration of psoriasis, extent and severity of the skin lesions, and preceding antipsoriatic therapy. Of 39 patients, 34 completed the study. In the patients treated with the combination of monoethyl fumarate and dimethylfumarate (group 1, $n = 12$), the mean percentage of the body surface affected with psoriasis was reduced from 21% (at baseline) to 6.7% after 16 weeks. This effect was significantly different from the results obtained in patients of groups 2 ($n = 10$) and 3 ($n = 12$) ($p < 0.01$). After 16 weeks of treatment, the mean scores for infiltration and scaling were significantly lower in patients in group 1 than those in groups 2 and 3 ($p < 0.01$). In group 1, six patients showed complete clearance and three showed improvement. In group 2 no such results were observed, and in group 3 only one patient showed improvement.

The main side effects of the treatment in group 1 were flushing (12 patients), diarrhea (13), fatigue (7), and nausea (6). One patient became ill as a result of renal insufficiency. In group 2 diarrhea was the main side effect (12 patients). Laboratory investigations showed a transient rise in liver function tests in group 1 (eight patients) and in group 2 (four). The patient in group 1 in whom a reversible renal insufficiency developed showed a rise of serum creatinine up to 238 μmol/L and a 51% reduction in the 24-hour creatinine clearance rate. Other abnormalities observed in group 1 were transient eosinophilia (five patients) and lymphopenia (four).

Discussion. The results of this study show that oral treatment with tablets containing a combination of dimethyl fumarate and monoethylfumarate may be effective in the treatment of psoriasis. This treatment may provide a new alternative for patients with severe psoriasis. The drawback of fumaric acid therapy may be its side effects. Carefully administered, low-dose regimens, however, may overcome this problem. Further studies with regard to the treatment's long-term therapeutic effects, toxicity, and mode of action are needed.

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Pimozide in delusions of parasitosis

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Delusions of parasitosis is a type of monosymptomatic hypochondriac psychosis (MHP). In MHP the patient's sole complaint focuses on a single delusion. For some, the delusion may be their belief in the abnormal shape of their face; for others it may take the form of a fantasized odor emitted from their body. Dermatologists frequently deal with patients who bring a jar full of debris and claim that these are creatures that infest their scalp, limbs, or orifices (Fig. 1). What seems to set these patients apart is that beyond their delusion they are normal, or at least within acceptable bounds.

Case report. A 71-year-old white woman had an 8-month history of burning and itching of the scalp. She had been treated without success with antibiotics and shampoos. Physical examination revealed keratotic papules and a few areas of patchy alopecia. Results of laboratory studies revealed no significant abnormality. Prurigo nodularis was diagnosed and the patient was treated with oral doxepin, 25 mg, taken at bedtime.

Shortly thereafter, she reported "something crawling under my scalp" and was convinced that some bugs were either "dead" or "moving around" on her scalp. The doxepin was discontinued and she was treated with oral pimozide, 1 mg, twice a day. In one month the patient was much improved although she still had a burning sensation of the scalp. The dosage of pimozide was increased to 2 mg twice a day and the complaints subsided. She discontinued her medication at 6 months and the delusions returned. Pimozide, 2 mg, twice a day was given again and the patient's symptoms were under control for an additional year.

Discussion. Pimozide is approved for the treatment of chronic schizophrenia and Gilles de la Tourette syndrome but has also been found effective in the treatment of MHP.[1-6] In addition, Duke[5] found that patients who had postherpetic neuralgia with neurotic excoriations, symptoms of delusions of parasitosis, or both also benefited from pimozide. Only patients with severe pain and no other complaint did not benefit from the drug.[4] However, Hamann[7] observed pimozide to be effective in a case of onychotillomania.

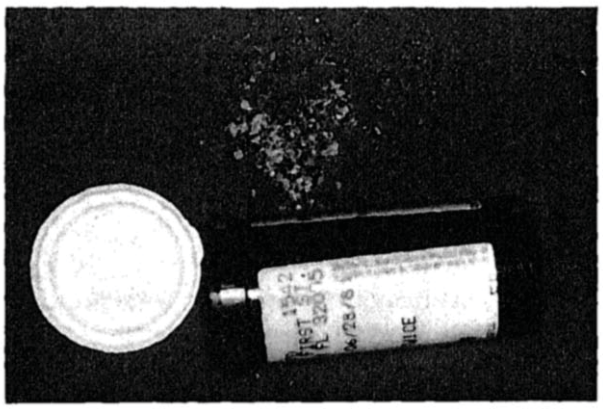

Fig. 1. Patients with delusions of parasitosis may bring in assorted scale and debris to "prove that they are infested."

Contraindications to pimozide include vascular insufficiency of the central nervous system, blood dyscrasias, Parkinson's disease, prolonged congenital QT syndrome, cardiac dysrhythmias, or drugs that prolong the QT interval. Pimozide also reduces the convulsive threshold and should be used with caution in persons with epilepsy. Its safety has not been established in children or pregnant women.

Acute and transient adverse effects include extrapyramidal reactions (restlessness, dystonia, parkinsonism). Tardive dyskinesia is a serious reaction; elderly patients receiving high-dose therapy are at greatest risk. This may be irreversible after long-term use of the drug. However, fine vermicular movements of the tongue may be an early sign of tardive dyskinesia; if the medication is stopped at that time, the syndrome may disappear. Electrocardiographic changes have been reported with prolongation of QT interval, T-wave changes, and the appearance of U waves. Sudden unexpected deaths and grand mal seizures have occurred at doses greater than 20 mg/day.

Dosage, after a baseline electrocardiogram, should be begun at 1 to 2 mg/day in divided doses. Dosage may be increased every other day; however, doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended. In no case should the dose exceed 0.3 mg/kg/day or 20 mg/day.[8]

Gould and Gragg[9] recommended that, in a patient who has delusions of parasitosis, the role of the dermatologist should be to rule out other causes of pruritus that may contribute in some way to the delusion. Any attempt at referral to a psychiatrist will be often resisted. In fact, it may even alienate a patient who has already chosen the type of treatment he or she wants or will accept.

Munro[2] recommends that all patients with diagnoses

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