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Biology of sweat glands and their disorders. I. Normal sweat gland function

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Systemic therapy with fumaric acid derivates: New possibilities in the treatment of psoriasis

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For the past two decades fumaric acid (FA) therapy has become an increasingly popular treatment in Western Europe for psoriasis. FA therapy originally was developed by Schweckendiek and subsequently standardized by Schäfer. Schäfer's fumaric acid compound therapy (FACT) consists of the oral intake of dimethylfumaric acid ester (DMFAE) and several salts of monoethylfumaric acid ester (MEFAE) in combination with topical fumaric acid therapy (1% to 3% MEFAE in an ointment or FA in bathing oils) and a diet. Schäfer claimed excellent results in a large number of patients. Preliminary studies by German dermatologists, however, revealed contradictory therapeutic results and serious side effects, and FA treatment was soon abandoned by dermatologists. To assess the value of FA therapy we conducted an open pilot study of 36 patients in which FACT therapy appeared to be rather effective. Thereafter, several controlled studies with MEFAE sodium in two different dosages versus placebo, and DMFAE versus placebo, were done. The results indicated that MEFAE sodium in dosages up to 240 mg daily was ineffective, whereas daily dosages of 720 mg resulted in a significant decrease in scaling and itching but did not affect extension of the eruption. DMFAE, 240 mg daily, produced a significant amelioration and prevented extension. Side effects of FA treatment were nausea, diarrhea, general malaise, and severe stomachache. Mild disturbances of liver and kidney function during treatment were observed with the 720 mg dosage of MEFAE and with the 240 mg dosage of DMFAE. Moreover, a relative lymphopenia with a selective decrease of suppressor T lymphocytes occurred in about 50% of the patients treated with DMFAE. Although oral therapy with FA derivatives has to be considered experimental, it may be a new possibility in the systemic treatment of psoriasis. (J Am Acad Dermatol 1989;20:601-8.)

HISTORY AND SUMMARY OF THE LITERATURE

A new therapy, called the *fumaric acid* (FA) *therapy,* has become popular in the past 20 years in Western Europe among thousands of patients with psoriasis. This therapy was initiated by Schweckendiek, a biochemist who himself had psoriasis.[1] In further publications he introduced monoethylfumaric ester (MEFAE) and dimethylfumaric ester (DMFAE) because FA was poorly absorbed by the gastrointestinal tract.[2] This therapy was standardized by Schäfer, a German general practitioner, who added a strict diet in which patients were told to avoid several species, nuts, etheric oils, and wine.[3] A clinic specializing in this therapy was founded in Leysin, Switzerland.

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Previously reported results

With this regimen, called *fumaric acid compound therapy* (FACT), Schäfer[4] claimed a considerable improvement in 70% of his 900 patients, with 20% total remission. Approximately 15% showed a moderate improvement, and 15% did not respond. In addition, a considerable improvement of psoriatic arthritis was noted in many patients. In The Netherlands, Kunst[5] saw similar results in 62 patients. Both Schweckendiek[6] and Schäfer support the systemic therapy with topical application of 1% to 3% FA and/or MEFAE in bathing oils and ointments.[6] The FA therapy initially was rejected by dermatologists on the grounds of contradictory results[7] and of nephrotoxic and hepatotoxic side effects,[8,9] but the need for more reliable information was pointed out.[10] Recently a 50% success was described in an open long-term study in 13 patients.[11] Up to now double-blind studies have not been performed.

Pharmacology and treatment

The systemic prescription consisted initially of several mixtures of FA, DMFAE, and salts of MEFAE: calcium (Ca), ferrous (Fe), potassium (K), zinc (Zn), magnesium (Mg), cupric (Cu), manganese (Mn), and lithium (Li). Later this was simplified into two prescriptions: (1) enteric-coated tablets containing 120 mg DMFAE and MEFAE (FAE-forte): 87 mg Ca, 5 mg Mg, and 3 mg Zn and (2) enteric-coated tablets with 30 mg DMFAE and MEFAE (FAE-mitis): 56 mg Ca, 5 mg Mg, and 3 mg Zn. Usually medication was started with one FAE-mitis tablet a day. This dosage was increased weekly or monthly to a maximum dose of six FAE-forte tablets. When remission took place, the dosage was gradually reduced to a maintenance dose, usually one to three FAE-forte tablets a day. The pharmacologic and pharmacokinetic properties of the FA esters are unknown. Schweckendiek[12] based his therapy on the hypothesis that psoriasis is characterized by a defective carbohydrate metabolism in which the fumaric acid cycle, especially it oxidation, is disturbed. FA was thought to stabilize this reaction. Schäfer[13] assumed a relative cellular FA deficiency in psoriasis. Experimental evidence for these hypotheses was not produced, however. In vitro experiments showed that MEFAE exhibited DNA synthesis in phytohemagglutin-stimulated lymphocytes.[14,15] FA appeared to cause a 50% to 80% inhibition of the solid growth of Ehrlich tumor cells in mice.[16] In contrast it had no deleterious effect on the monolayer development of mouse and chicken embryo cells but exhibited a protective effect against toxic agents such as mitomycin C and aflatoxin.[17] Pharmacokinetic studies with 1 gm FA showed no change in the serum FA levels in men.[18] No pharmacokinetic studies have been performed with DMFAE and MEFAE, which probably are absorbed more readily than FA because of their better lipophilic properties.[19]

Side effects and toxicity

The occurrence of serious side effects is a controversial matter. In mice the LD_{50} of FA is 0.266 mg/gm body weight,[16] and the LD_{50} for MEFAE is 6.88 mg/gm body weight, whereas dosages of more than 0.086 mg/gm caused toxic reactions in the heart muscle and the renal tubuli.[15] With a solution of the FAE-forte tablets a similar LD_{50} occurred in mice and rats. In female animals the LD_{50} was higher than in males.[11] In human beings side effects[20] included flushing, which appeared 10 to 15 minutes after intake and lasted for half an hour in more than 50% of patients, and gastric and esophageal pain, nausea, and vomiting in 5% to 10%. These effects have led many patients to stop FA therapy. The use of enteric-coated tablets diminished these complaints considerably. In an inquiry of 32 patients who were treated in Leysin, van Dijk[20] noted general malaise (7/32), dizziness (3/32), and initial rise of body temperature. Proteinuria was noted in three of six patients with extensive psoriasis after topical application of 3% MEFAE in ointment.[8] Other authors did not observe nephrotoxicity even after long-term systemic use of FA derivatives.[11,13] Rise of the serum guanosine triphosphate level was seen by Kunst in 19 of 62 patients and a drop in the peripheral lymphocyte count in 31 patients,[5] both of which disappeared after therapy was discontinued. Contact of MEFAE and DMFAE with normal skin caused an itching maculopapular erythema around psoriatic lesions.[4] A few hours after pharmacy technicians had been capsulating FA derivatives, an itching erythema on their faces and arms also was noted.[21]

Present study

There were several reasons for our group to investigate FA therapy despite lack of knowledge of its

pharmacologic and toxicologic properties. The first was strong pressure from the Dutch Federation of Psoriasis Associations, and the second was based on the results of two "protocolled" inquiries done by van Dijk; his first protocol was published in 1985.[20] Both appeared to confirm the results reported by Schäfer. Third, we observed that a distinct deterioration occurred in eight former Leysin patients after withdrawal of MEFAE from the FACT therapy.[22] Finally, an increasing number of patients with psoriasis were being treated with a possibly potent and perhaps dangerous therapy without sufficient medical supervision.

This report comprises one open study of the FACT therapy, three controlled studies with MEFAE and DMFAE, one dose-finding comparative study with MEFAE, and one long-term open study with DMFAE. To the best of our knowledge this is the first report of controlled studies with FA esters in the treatment of psoriasis.

PATIENTS

Only patients older than 18 years of age with stable nummular and plaque psoriasis with at least 10% involvement of the body surface were included. Excluded were patients with erythrodermic psoriasis and generalized pustular psoriasis. FA treatment was started after previous therapy had been discontinued at least 2 weeks. The studies were performed under a protocol approved by the Hospital's Ethical Committee.

MATERIALS AND METHODS

Patients were advised to take the FA medication in two daily divided dosages after meals. Topical treatment consisted of the application of bland creams or ointments. Mild topical corticosteroids were allowed only on the face and the hands.

Patients were seen at 4-week intervals. At each visit evaluation was done according to a psoriasis severity score based on extension of the eruption, scaling, redness, thickness of the lesions, and itching. In this system zero (0) represents the absence of signs or symptoms. The extension of the eruption was scored from 0 to 5, depending on the percentage of the body surface involved (1, 1% to 10%; 2, 10% to 20%; 3, 21% to 35%; 4, 36% to 50%; and 5, >50%). Zero to 3 was scored for the scaling (1, mild; 2, moderate; 3, heavy), redness (1, rose; 2, red; 3, purple-red), thickness (1, slight induration; 2, moderate induration; 3, induration and elevation), and itching (1, slight; 2, moderate; 3, severe). The minimal score was 0, the maximal 17.

After the final visit the effect of the treatment was estimated according to the final score and expressed as a percentage of the initial score. Statistical analysis was carried out with the chi-square test. Laboratory tests performed monthly included urinalysis; WBC count with differential; determination of hemoglobin, serum creatinine, blood urea nitrogen (BUN), transaminase, and alkaline phosphatase levels; and prothrombin and glucose times. At each visit the presence of following side effects were noted: flushings, nausea, stomachache, dizziness, and headache.

In the 12 patients in whom lymphopenia developed, the percentage of T and B cells and the thyroid serum ratio were determined.

Study I: an open study with FACT therapy. This study included 36 patients, 15 women and 21 men, of whom 34 were evaluable. The average observation time was 9.7 months (1 to 32 months). Previous treatments had been unsatisfactory according to the patients. Medication started with one enteric-coated FAE-forte tablet a day the first week, two the next, and three during the third week. Depending on the results the dosage was increased to a maximum of six tablets a day. The average maintenance dosage was three to four tablets a day. In case of serious gastrointestinal complaints FAE-mitis tablets were given during the first few weeks. All patients received a printed diet list.

Study II: controlled study with MEFAE sodium (Na). In a double-blind study 240 mg MEFAE-Na was compared with placebo in 38 patients (22 women and 16 men). Treatment started with one capsule of 60 mg MEFAE-Na or placebo a day for a week. The dosage was increased in 3 weeks to a maximum of 240 mg. The observation time was 4 months, from September until January.

Study III: controlled study with DMFAE. In a double-blind study 240 mg DMFAE was compared with a placebo in 42 patients, 19 women and 23 men. The treatment schedule was similar to that in study II. The medication consisted of capsules filled with 60 mg enteric-coated granulate of DMFAE or with placebo granulate to a maximum dosage of up to four capsules a day. The observation time was 4 months, from October until February.

Study IV: comparative study of 720 mg MEFAE-Na compared with 240 mg MEFAE-Na. This dose-finding study was performed because the daily 240 mg dosage of MEFAE was ineffective. It was performed in 20 patients, 12 women and 8 men: 10 had been treated with 240 mg MEFAE and 10 with placebo in the previous 4 months. The first group was given 720 mg daily, the latter 240 mg. The observation time was 3 months, from January until April.

Study V: open continuation study with DMFAE. This open study comprised 56 patients. Thirteen of them had not responded to MEFAE-Na therapy, and DMFAE therapy was begun in September. After study III was finished in January a group of 30 patients, 20 from the placebo group and 10 from the DMFAE group, entered the continuation study. The remaining 26

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