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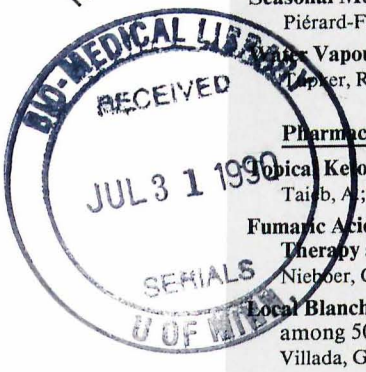

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Fumaric Acid Therapy in Psoriasis: A Double-Blind Comparison between Fumaric Acid Compound Therapy and Monotherapy with Dimethylfumaric Acid Ester[1]

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Key Words. Psoriasis · Dimethylfumaric acid ester · Monoethylfumaric acid ester · Fumaric acid therapy

Abstract. In a 4-month double-blind study the effects of dimethylfumaric acid esters (DMFAE-EC) and DMFAE plus salts of monoethylfumaric acid esters (fumaric acid combination, FAC-EC) in enteric-coated tablets were compared in 22 respectively 23 patients with psoriasis. In both groups about 50% showed a considerable improvement, i.e. the initial score was more than halved. The therapeutic effects showed no significant differences in both groups with respect to the total psoriasis score or the different parameters. In the FAC-EC group the effects were obtained more rapidly. Most frequently observed side effects in both groups were flushings, stomachache and diarrhea. Due to these complaints 3 respectively 8 patients discontinued therapy. Eosinophilia, leukopenia and lymphopenia were the most frequently observed differences in lab tests. It was concluded that FAC-EC had no significantly better effect than monotherapy with DMFAE-EC. Moreover, enteric coating of the tablets did not prevent stomach complaints. Until more information has been obtained about the pharmacokinetics, the toxicity and optimal composition of the drug, the fumaric acid therapy in psoriasis should be seen as experimental.

The fumaric acid (FA) therapy is a new systemic medication with FA derivatives that has gained an increasing popularity among psoriasis patients in several countries in western Europe.

Several double-blind studies have indeed shown that dimethylfumaric acid ester (DMFAE) and salts from monoethylfumaric acid (MEFAE) combined with DMFAE [2] have a positive therapeutic effect on psoriasis [1, 2]. The same studies showed that DMFAE was clearly more effective than the Na salt of MEFAE, which only produced some effect when given in higher dosages [1].

The mechanism of the effects of these substances is unknown. The view, originally held by Schweckendiek [3], was that these substances influenced the citric acid cycle. This could not be confirmed by us in a number of unpublished experiments with both isolated mitochondria and hepatocytes. It is a known fact, however, that MEFAE and DMFAE [unpubl. observation] inhibit the mitosis of PHA-stimulated lymphocytes [4] and epithelial cell lines [5]. Little is known about the pharmacokinetics of the FA derivatives.

Both DMFAE and MEFAE salts form the active ingredients of enteric coated (EC) tablets that are usually prescribed in FA therapy. This combination seemed to be based on historical factors rather than a rational therapeutic approach. The question arose whether this combination was not too complicated and monotherapy was just as effective. The aim of our study was therefore to assess the therapeutic efficiency of DMFAE monotherapy compared to that of DMFAE combined with MEFAE salts using the same DMFAE dosage and dosage form (EC tablets).

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Table 1. Comparative study on the effects of DMFAE-EC (n = 22) and FAC-EC (n = 23) on 45 psoriasis patients

Medication	n	Improvement			Deterioration	Discontinuation
		<25%	25–50%	>50%		
DMFAE-EC	22	5 (22)	3 (14)	10 (45)	0	4 (18)[1]
FAC-EC	23	1 (4)	2 (9)	12 (52)	0	8 (35)[2]

Figures in parentheses are percentages.
Dosage DMFAE-EC: 120–480 mg/day.
Dosage FAC-EC: 1–4 tablets/day.
[1] All discontinued because of side effects.
[2] Discontinued because of side effects, 1 for other reasons.

Material and Methods

Medication

The two different drugs for this study were supplied in EC tablets which were indistinguishable in size, form and color. The monotherapy tablets (DMFAE-EC) contained DMFAE, 120 mg per tablet. The combination therapy tablets (FAC-EC) contained an equivalent amount of 120 mg DMFA and an additional amount of 5 mg magnesium-MEFA, 3 mg zinc-MEFA and 87 mg calcium-MEFA. The latter combination is used most frequently in FA therapy. The two batches of DMFAE-EC and FAC-EC were produced by the Kethel Pharmacy, Schiedam, The Netherlands. Quality control on both batches was done at the pharmacy laboratory, Free University, Amsterdam, The Netherlands. The quality control consisted of identification (on DMFAE for DMFA-EC and DMFAE, MEFAE, magnesium, zinc and calcium for FAC-EC), quantitation of contents (between 95 and 105% of the declared amount) by high-performance liquid chromatography (DMFAE content for DMFAE-EC and DMFAE – and total MEFAE content for FAC-EC) and control on enteric coating according to the USP XXI [6]. Both batches passed the tests in the quality control.

Patients

Before entering the study patients were informed verbally and gave their consent. Randomization into two groups was made between 45 patients, 25 female, 20 male, aged between 18 and 70 years: 22 were treated with DMFAE-EC, 23 with FAC-EC. At the end of the study 33 patients could be evaluated, 18 had been treated with DMFAE-EC and 15 with FAC-EC. At least 10% of the body surface was affected. At the beginning of the study 22 of these 33 patients showed the plaque type, 10 the macular type and 1 the guttate type of psoriasis. 11 patients had joint complaints, 6 in the DMFAE-EC group and 5 in the FAC-EC group. The study was performed under a protocol approved by the hospital's Ethical Committee.

Dosage

The starting dosage was 1 tablet a day. This was increased weekly up to a maximum of 4 tablets a day handed out in 2 administrations. 6 patients of the DMFAE-EC group and 4 patients of the FAC-EC group did not tolerate this dosage. They were treated with 1 tablet twice a day.

Evaluation

A simplified 'psoriasis area and severity score' was applied, in which 5 parameters were evaluated: Extent: 0 = entirely clean, 1 = < 10% body surface affected, 2 = 10–25%, 3 = 25–35%, 4 = 35–50%, 5 = > 50% body surface affected; scaling: 0 = none, 1 = slight, 2 = moderate, 3 = severe, spontaneous; thickness of patches: 0 = no infiltration, 1 = slight infiltration, 2 = apparent infiltration, not raised, 3 = raised; redness: 0 = none, 1 = pink, 2 = bright red, 3 = fiery red or red-purple; itching: 0 = none, 1 = slight, 2 = moderate, 3 = strong. The maximum total score was 17, the minimum 0. The patients were examined every 4 weeks and the psoriasis score as well as the side effects were registered.

Apart from this score a general evaluation was given at the end of the examination by the investigator and the patient (deteriorated, no change, slight improvement, strong improvement, full clearance). The effect on joint complaints was judged on the basis of the impressions of the patients: deteriorated, unchanged, improved, considerably improved.

During each visit the following laboratory tests were carried out: blood: peripheral leukocytes plus differential count; serum: BUN, alkaline phosphatase, LDH, ALAT, ASAT, γ-GT; urine: protein and sediment.

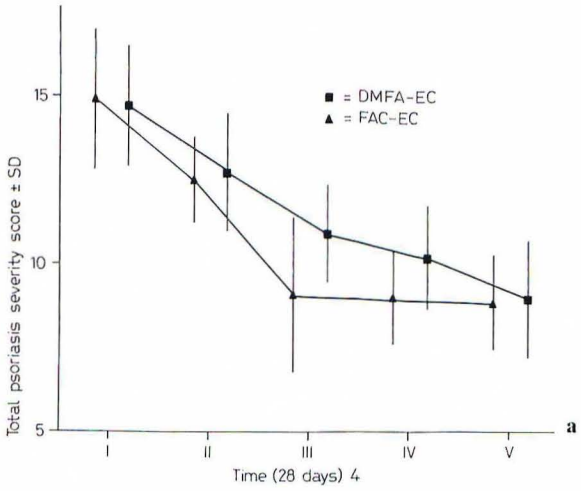
The study was carried out in the months from October to April, the duration of the study was 4 months per patient. Statistical analysis was carried out using Fischer's exact test and the χ^2 test.

Results and Side Effects

The individual results are shown in table 1. Compared to the initial population score, a considerable improvement (i.e. score more than halved) was observed in 45% of the patients treated with DMFAE-EC and in 52% of the treated with FAC-EC. This improvement was statistically significant.

In both groups 4 patients (18 and 15%) showed a full clearance. Considerable improvement occurred in 15 out of 22 (68%) patients with the plaque type and in 4 out of 10 (40%) of those with the macular type. The patient with the guttate type showed a full clearance after a treatment of 2 months with FAC-EC, but had an extensive relapse 1 month later even though the therapy had been continued. For 5 patients (22%) in the DMFAE-EC group and 1 patient (4%) in the FAC-EC group the psoriasis did not show any reaction to the therapy. The observed differences between the two groups appeared to be not significant. Deterioration, that is an increase of the score up to more than 125%, was not observed in either of the groups.

The course of the score in both groups with regard to the total average score and the separate parameters is shown in figure 1a, b. It covers the observations of those patients who could be evaluated after 4 months: 18 in the DMFAE-EC group and 15 in the FAC-EC group. The



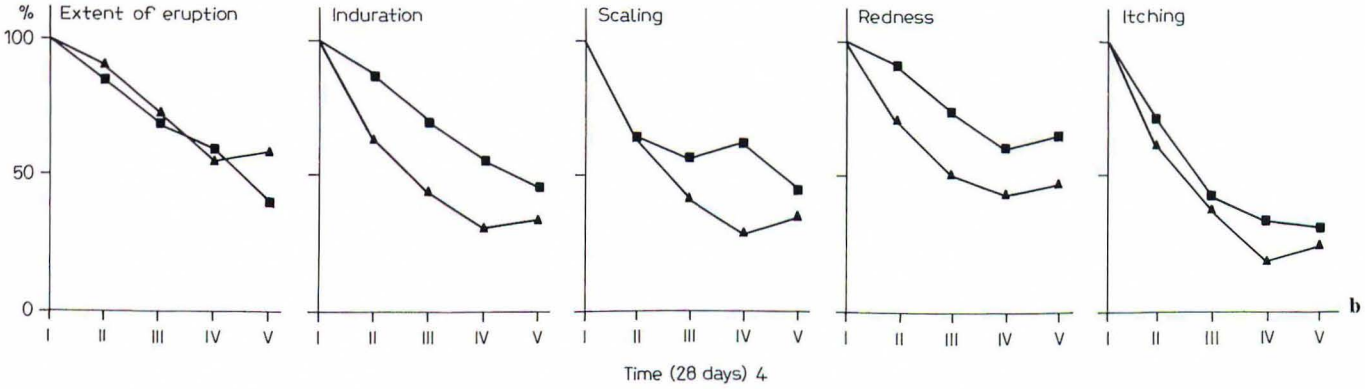


Fig. 1. Course of the total psoriasis score and of the 5 parameters in patients treated with DMFAE-EC (n = 18) or FAC-EC (n = 15) during 4 months. **a** Total psoriasis severity score. **b** Percent decrease of the 5 parameters of the severity score.

total average score in the DMFAE-EC group dropped from 9.7 to 4.1 and in the FAC-EC group from 10.5 to 4.1. The course of this score in both treatment groups was not significantly different at any time point (I–V). Subsequently the separate parameters too did not show a significant difference in time course. The results after 4 months were not statistically different.

The joint complaints of the 6 patients in the DMFAE-EC group showed considerable improvement for 2 patients, and some for 1, and deteriorated or remained unchanged for the other 3. In the 5 patients in the FAC-EC group a considerable improvement occurred in 2 cases and a slight improvement in 3 cases.

The general evaluation of the therapy by the patients usually corresponded with that of the investigators.

The subjective and objective side effects are shown in table 2. The flushings started 3–4 h after the tablets were taken. They involved a feeling of tingling heat, accompanied by diffuse redness, which continued for about half an hour mainly localized in the face, arms and the upper part of the body. This symptom was not constantly present and in the course of the treatment its frequency decreased. One patient was troubled by this symptom to such an extent that he discontinued the treatment. The gastrointestinal complaints, on the other hand, presented a real problem. More than half the patients were troubled by serious stomach complaints, involving gastralgia, but also nausea, vomiting and diarrhea. For 14% (n = 3) of the patients in the DMFAE-EC group and 30% (n = 7) in the FAC-EC group these complaints were a reason to discontinue the therapy. Another patient had to discontinue the DMFAE-EC therapy because his tablets had been stolen.

The abnormalities which were registered in the blood most generally were: leukopenia ($<3.0 \times 10^9$/l), lymphopenia (<15%) and eosinophilia (>5%). The former two developed in the course of the 3rd and 4th months. The eosinophilia usually began in the first 2 months and disappeared spontaneously in most of the cases.

Table 2. Side effects during treatment of psoriasis with DMFAE (n=22) or FAC-EC (n=23) over a period of 4 months

	DMFAE-EC (n=22)		FAC-EC (n=23)	
	n	%	n	%
Symptoms				
Flushing	19	86	20[1]	87
Diarrhea	12[2]	55	14[3]	61
Nausea/stomache	11[2]	50	14[3]	61
General malaise	2	9	1	4
Dizziness	1	5	0	0
Headache	1	5	1	4
Laboratory				
Urine				
Albuminuria	0	0	2	9
Blood				
Leukopenia	3	14	3	13
Lymphopenia	3	12	2	8
Eosinophilia	8	35	3	13
Increase of				
Creatinine/urea	0	0	0	0
Alkaline phosphatase	1	5	0	0
ASAT/ALAT	0	0	1	4

[1] 1 Patient discontinued the treatment as a result of this symptom.
[2] 3 Patients discontinued the treatment as a result of these symptoms.
[3] 7 Patients discontinued the treatment as a result of these symptoms.

Discussion

In this study the treatment of psoriasis with FA esters led to evident improvement in about 50% in the patients. This percentage was even higher when one did not consider the initial study population, but only those patients who could be evaluated after 4 months. In that calculation the improvement percentage (i.e. a psoriasis severity score more than halved) was 55% in the DMFAE-EC group and 80% in the FAC-EC group. The course of the total score and of the separate parameters during the 4 months of the study showed a tendency towards a more rapid result with FAC-EC than with DMFAE-EC monotherapy. However, this difference was not significant and the final score in both groups was the same.

Of the side effects the frequently occurring gastrointestinal symptoms should be mentioned first. Fairly often the diarrhea, frequently accompanied by stomachaches, formed the main reason to discontinue the therapy. In a number of cases these side effects disappeared spontaneously in due course, for other patients loperamide resolved this complaint. Some patients had predominantly serious gastric complaints, despite the use of EC tablets. In a number of cases Antagel (Solutio Antacida, Dutch Pharmacist Formulary) could prevent stomach complaints. Another way to prevent these complaints is lowering of the starting dosage to 30 or 60 mg DMFA with subsequent weekly increases. The gastric complaints must be taken seriously as we observed aggravation of ulcera ventriculi and even once a perforation of the stomach during treatment with noncoated capsules with DMFAE.

The experience of the flushings was less serious, flushing did not occur each time the drug was taken and it often decreased in the course of the study. General malaise (without complaints of the digestive tract) was experienced by several patients, but was taken for granted because of the positive therapeutic results.

The most striking differences in lab tests were those in the blood count: leukopenia, lymphopenia and eosinophilia. The latter mainly occurred in the first 2 months and usually disappeared spontaneously. It did not involve allergic symptoms, neither of the skin nor of the respiratory tract. The leukopenia was in most cases the result of a considerable decrease of the lymphocytes. It is a well known fact that MEFAE inhibits the proliferation of PHA-stimulated lymphocytes among other things. We noticed that DMFAE had the same effect. It was remarkable that the lymphopenia in this study occurred far less frequently than in an earlier study, in which more than 50% of the patients showed this phenomenon [1]. In this earlier study, instead of the EC tablets, capsules filled with a coated granulate were used, which already released DMFAE in the stomach. It was demonstrated there that the lymphopenia was caused by a selective decrease of T suppressor (Ts) lymphocytes and, less explicitly, of the B lymphocytes, whereas the number of T helper cells remained constant. An explanation for these phenomena could be that the Ts and B lymphocytes are a population of cells with a rapid proliferation of which the cell division is inhibited by relatively high serum levels of DMFAE after prompt resorption due to prepyloric release. So far the lymphopenia has disappeared in all patients in the course of 2–4 months after discontinuation of the therapy.

In 2 patients of the FAC-EC group, albuminuria occurred which was not accompanied by a rise of the serum creatinine and urea. One should, however, not rule out the possibility of serious nephrotoxicity. Acute tubulus necrosis has been reported in 4 patients and could very probably be ascribed to FA therapy [7].

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