CHAPTER 17

FUMARIC ACID ESTERS IN DERMATOLOGY

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INTRODUCTION

Fumaric acid (FA) is a simple organic dicarbonic acid with a simple structure widely used in the food, agriculture, pharmaceutical and chemical industries today.[1] In humans, it plays a role in an important step of the citric acid cycle. It has been also in use as a drug since 1959 when it was discovered to be effective in the treatment of psoriasis. Schweckendiek, a German chemist, suggested that the lack of FA may play a role in the etiopathogenesis of psoriasis. Using an oral mixture made of FA esters (FAE) he developed himself, Schweckendiek has cured his own psoriatic lesions and shown the efficacy of the FAEs in psoriasis.[2, 3]

When administered through the oral route, the bioavailability of FA is not satisfactory and it may cause gastrointestinal irritation. Therefore, the FAE used for treatment is manufactured in the form of enteric-coated tablets. There are three types of FAE, namely dimethyl fumarate (DMF), methyl hydrogen fumarate (MHF) and ethyl hydrogen fumarate (EHF).[2] The therapeutic preparation containing FAEs have been one of the prominent drugs used for the systemic treatment of psoriasis since 1994 in Germany, the only country where it is registered. The preparation includes DMF and a blend of the three monoethyl fumarate (MEF) salts. Under the brand name Fumaderm®, it is presented in two different strengths including a low-dose starting treatment and a high-dose tablet (Table 2). The active ingredient effective for the treatment is DMF.[3]

TABLE 1. The contents of the preparation of fumaric acid esters

	Dimethyl-fumarate (mg)	Mono-ethyl-fumarate Ca-salt (mg)	Mono-ethyl-fumarate Mg-salt (mg)	Mono-ethyl-fumarate Zn-salt (mg)
Fumaderm Initial®	30	67	5	3
Fumaderm®	120	87	5	3

TABLE 2. Diseases of the fumaric acid ester is indicated.

Approved indications (Licenced only in Germany)	Psoriasis vulgaris
Off-Label indications	Granulomatous diseases Sarcoidosis[48, 49, 50, 51] Granuloma annulare[52, 53,54, 55, 56] Necrobiosis lipoidica[57, 58,59] Cheilitis granulomatosa[60] Annular elastotic giant cell granuloma[60] Other Skin diseases Malign melanoma[61, 62, 63, 64] Lupus erythematosus[65, 66, 67] Pityriasis rubra pilaris[68] Alopecia areata[69] Hidradenitis suppurativa[70]

PHARMACOKINETICS

Following the oral administration, FAE is almost completely absorbed through the small intestine. From the enteric-coated tablets, the DMF is released in the small intestine and a portion of it is hydrolysed to MMF in the alkaline pH environment of the intestines. In the pH 7.4 environment consistent with the human serum, DMF is rapidly hydrolysed to its active metabolite monomethyl fumarate (MMF). This hydrolysis does not occur in an acidic environment.[3, 4] The half-life of DMF is 12 minutes and it is not detectable in the plasma. Following the oral intake, its metabolite MMF is detected in the plasma.[5] The plasma concentrations of DMF and fumaric acid are negligible. In a study conducted on the pharmacokinetics of FAEs on healthy volunteers, the postprandial pharmacokinetics of a single tablet containing 120 mg DMF and 95 mg calcium monoethyl fumarate was observed to greatly vary between individuals. Therefore, fumarate doses were recommended to be taken before meals [(6)]. Following the oral intake, the peak plasma MMF levels are reached within 5-6 hours. In the serum, 50% of MMF is bound to proteins and its half life is 36 hours. No teratogenicity was observed in the therapeutic doses in animal studies. MMF enters the citrate cycle and is metabolised to carbondioxide and water. It main route of excretion is through respiration. A small fraction is excreted through the urine and faeces.[7]

effects are complaints related to the gastrointestinal system and flushing. Flushing and gastrointestinal side effects are more common among the patients with good treatment response.[5,7,72] Gastrointestinal side effects are observed in two-thirds of the patients and comprise abdominal pain, increased frequency of stool and tenesmus, bloating, diarrhea and nausea. The other reported side effects include headaches, malaise, fatigue, hair loss, exacerbation of the disease and palpitations.[34]

A significant decrease in lymphocyte count is observed in 94% of the patients and necessitates a dose adjustment in 3.1% of the patients. Lymphopenia is also parallel to the efficacy of the drug and reduces both the T and B cells.[7,16] Approximately half of the patients develop temporary eosinophilia. Elevations in the liver enzymes were observed in psoriatic patients under long-term treatment.[7]

Acute kidney failure was reported in patients under treatment with FAE. Kidney failure is more frequent in female patients and was associated with high doses.[74] Although not reported in large patient series, proteinuria developed in three patients in a study conducted on 20 patients and attributed to the differences among regional populations.[75]

Method of administration and dose:

In order to minimize the side effects, standard treatment with FAE is stared at low doses and increased stepwise to the therapeutic dose.[34] The first week, therapy is initiated with Fumaderm initial® once a day and the treatment is continued with Fumaderm initial® twice a day through the second and third weeks. On the fourth week, Fumaderm® tablet is administered once a day and the dose increased to Fumaderm® tablet twice a day during the fifth week and three times a day in the sixth week. The dose is recommended to be increased at weekly intervals. The maximum dose is 1.2g/day (6 strength tablets). After the treatment response is achieved, the dose is adjusted according to the individual.[5, 7]

Patients under treatment with FAE should be followed up through monthly laboratory tests during the first 6 months and tests should be repeated every two months after this period. The routine hematology tests including serum creatinine, blood urea nitrogen, alanine and aspartate aminotransferases, gamma glutamyl transferase and the white blood count a complete urine test are among the parameters to be examined during the follow up visits. If the leukocyte count is below 3x109/L, lymphocyte count is 0.5x109/L and the eosinophil count is above 25%, the serum creatinine is 30% above the baseline value and proteinurea is observed, the dose should be reduced. If abnormal laboratory parameters prevail after the dose adjustment, the treatment should be discontinued.[7]

No evidence of teratogenicity or mutagenicity was found in the toxicology studies with FAE. Still, since the data at hand is limited, it should not be prescribed during gestation and the lactation period. No metabolic interaction is known with another agent. Nevertheless, it is not recommended to be used concurrently with the drugs with an impact on the kidney function.[76]

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