

Dimethyl fumarate transfer into human milk

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Abstract: Dimethyl fumarate (DMF) is approved for the treatment of relapsing-remitting multiple sclerosis. It is unknown whether DMF or its primary metabolite monomethyl fumarate (MMF) are excreted into human milk. We present two cases of lactating patients who donated milk samples to study the transfer of MMF into human milk following a week of 2×240 mg daily oral dose. Samples were analyzed using liquid chromatography mass spectrometry. The calculated relative infant dose was 0.019% and 0.007%. This is the first study to demonstrate that MMF is transferred into human milk, with only limited exposure to an infant.

Keywords: Multiple sclerosis, tecfidera, dimethyl fumarate, lactation, human milk

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Introduction

Dimethyl fumarate (DMF) is a fumaric acid derivative approved for the treatment of relapsing forms of multiple sclerosis (MS) in the United States (US) and relapsing remitting multiple sclerosis (RRMS) in the European Union (EU) for 5 years.^{1,2} Previously, this substance was used for the treatment of psoriasis but in a slightly different formulation.³

Following oral intake, DMF is metabolized rapidly to its primary active metabolite monomethyl fumarate (MMF) due to esterase-mediated hydrolysis.^{2,4} The drug's immune modulatory and antioxidative effects are believed to be induced by activation of the transcription factor 'nuclear factor erythroid-derived-2-like 2' (Nrf2).^{2,4} The exact mechanism of action is still under investigation.⁵

For the treatment of RRMS, DMF is administered orally with a recommended twice daily dosage of 240 mg.^{1,2} As the beginning of the treatment is often accompanied by gastrointestinal side effects, a lower starting dose is increased for at least 1 week until the final maintenance dose is reached.

Currently, data on excretion of DMF or MMF in human milk are lacking. In European prescribing

information, mothers are advised to choose between breastfeeding and DMF therapy²; the US label proposes a risk–benefit assessment.¹ As the relapse rate increases after delivery in women with MS, the secretion of MS disease-modifying drugs into human milk is of interest.

Herein, we present the first case report of MMF transfer and its pharmacokinetics in breast milk of two RRMS patients.

Case report

Case 1

A 35-year-old lactating woman from the German MS and pregnancy registry (DMSKW) was restarted on DMF treatment postpartum for RRMS.

In 2009, due to hypesthesia of the left side of her body, cranial (cMRI) and spinal (sMRI) magnetic resonance imaging (MRI) was performed revealing several cranial and spinal lesions. Analysis of cerebrospinal fluid suggested positive oligoclonal bands. The patient was diagnosed with RRMS and interferon-beta treatment was initiated. She discontinued interferon-beta treatment in September 2014 when she became pregnant. In December 2015, a follow-up MRI after

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delivery suggested new T2 lesions in cMRI and therapy was switched to DMF. Therapy was discontinued again in October 2016 during her second pregnancy; in July 2017 the patient delivered a healthy female infant in gestational week 40 by normal spontaneous vaginal delivery. During pregnancy she was relapse-free. She breastfed the infant exclusively for almost 6 months during which she was still relapse-free. However, follow-up MRI 6 months after delivery indicated new lesions, so she decided to wean her infant and restart oral Tecfidera (DMF) treatment. She continued to pump to retain her supply and donated milk samples for this study. Milk samples were collected before the very first DMF intake postpartum, and on the 8th day of 240 mg twice daily dosage at 1, 2, 4, 8, and 12 h after the intake.

At 1 year postpartum the patient reported no postpartum relapse.

Case 2

A 36-year-old lactating woman from the DMSKW who restarted DMF treatment postpartum for RRMS.

In May 2016 the patient was diagnosed with clinically isolated syndrome due to hypesthesia of her left leg. In August 2016 a follow up MRI revealed several new cranial lesions. She was diagnosed with RRMS and DMF treatment was started. DMF was discontinued in June 2017 because of pregnancy; her male infant was born at gestational week 36 by normal spontaneous vaginal delivery in January 2018. The infant was breastfed for 5 months. In June 2018 the patient decided to discontinue breastfeeding and restart DMF treatment. She continued to pump to retain her supply and donated milk samples for this study. Milk samples were collected before the very first DMF intake postpartum and on the 8th day of 240 mg twice daily dosage at 1, 2, 4, 8, and 12 h after the intake. Seven months after delivery, a follow-up MRI revealed five new cranial lesions. Further follow-up MRIs until 1.5 years postpartum, revealed stable lesion load. The patient has been relapse-free since June 2016.

Methods

The DMSKW is a nationwide prospective cohort study for pregnant women with MS or neuromyelitis optica spectrum disorders (NMOSD), approved by

the local ethics committee of the Ruhr-University Bochum (18-6474-BR). Written informed consent – including consent to publish medical data – was obtained from both patients presented in this report.

Milk samples were analyzed for MMF using high performance liquid chromatography tandem mass spectrometry (MS). AB Sciex QTTRAP 5500 UHPLC tandem MS/MS was used in negative ion mode. A Biphenyl column from Phenomenex was used followed with gradient elution methodology. Data were analyzed using multiple reaction monitoring (MRM) as m/z 128.9–84.7 for MMF and m/z 132.1–84.7 for MMF-d4 (internal standard). A simple protein precipitation method was followed for extraction of analyte. A calibration curve was determined in blank milk with a correlation coefficient of 0.99. Relative infant dose (RID) was calculated as a percentage of infant dose (mg/kg/day) divided by maternal dose (mg/kg/day).

Results

DMF is metabolized completely into its active metabolite MMF. DMF is not quantifiable in plasma; therefore, all pharmacokinetic analyses were performed using MMF concentrations. The levels determined in both the patients varied; in patient 1, the maximum concentration found was 11.23 ng/ml, whereas in patient 2 it was 3.7 ng/ml (Figure 1); however, peak concentration for both was at 2 h. Patient 2 levels were lower as compared with those of patient 1, apparently due to interpatient variability.

Derived from the area under the curve, the average concentration (C_{avg}) was used to calculate the RID. The RID calculated in this study was 0.019% and 0.007%, respectively, at 12 h following drug treatment (Table 1).

Discussion

The RIDs of 0.019% and 0.007% calculated in this study were far below the theoretical threshold of concern of 10%.⁶ MMF is a small molecule (129 Da) with low plasma protein binding of only 27–40% and a high volume of distribution.^{1,2} Due to its short terminal half-life of only 1 h, MMF apparently does not accumulate.^{1,2} Peak MMF plasma concentration occurred after 2–2.5 h following oral administration,^{1,2} and our results suggest that likewise in breastmilk, the maximum

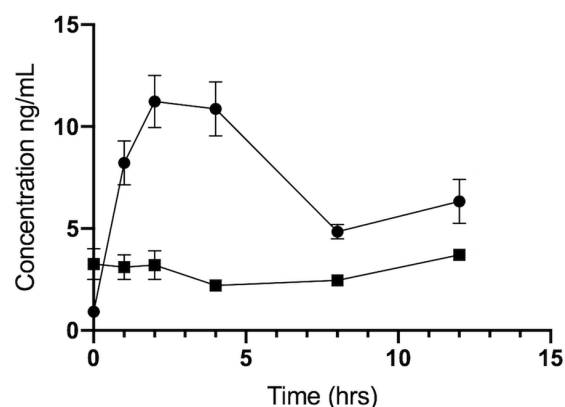


Figure 1. Concentration–time profile of MMF in human milk ($n=2$). MMF concentrations (in ng/mL; bars indicate SEM in milk of patient 1 [O] and patient 2 [X] over a time course of 12 h after intake of 240 mg DMF. DMF, dimethyl fumarate; MMF, monomethyl fumarate; SEM, standard error of mean.

concentration probably occurs after 2 h. Our results suggest that DMF is likely compatible with breastfeeding.

To date, interferon-betas are the only MS-treatment approved during lactation.⁷ In other medical fields, treatment of autoimmune diseases with immunomodulatory therapies during breastfeeding is more common, unfortunately not regarding fumaric acids for which neither human nor animal data are published. Although large studies are lacking, the use of several immunomodulating substances including, for example, hydroxychloroquine, sulfasalazine and azathioprine, are

presently recommended or considered compatible during lactation.^{8,9} The amount of drug present in human milk is quite low for these substances, ranging mostly from undetectable to a few milligrams per liter – corresponding RIDs were unfortunately not calculated by default. Although the sample size is limited, no harmful side effects were reported in exposed infants.^{8,9} This is very reassuring, as exposure to immunomodulators might raise concerns about an impeded immune system function.

The small sample size and the lack of maternal plasma levels are limitations of our case report. Because both infants were weaned before re-initiation of DMF-therapy, we cannot accurately assess to what degree these minimal levels of MMF in milk would affect breastfed children. Still, as this is the first report of MMF transfer in human milk, these data provide valuable information, assisting neurologists and patients in their decision-making process regarding treatment during lactation.

In both cases, we found very low concentrations in milk and thus the RIDs of MMF in human milk were even lower than theoretically expected from such chemical properties as low molecular weight. However, it is true that low RIDs alone should not be automatically interpreted as being absolutely safe. Many other factors such as oral bioavailability of the drug, and its overt toxicity in milk should also be considered. In addition, our results suggest a certain interindividual variability, which has to be investigated more thoroughly before generalizing recommendations. Larger sample sizes and especially follow-up data on exposed breastfed

Table 1. Pharmacokinetic parameters of MMF ($n=2$).

Parameter (units)	Value (patient 1)	Value (patient 2)
Dose	240 mg twice daily	240 mg twice daily
AUC (ng.hr/ml)	90.15	33.33
C_{avg} (ng/ml)	7.5	2.7
C_{max} (ng/ml)	11.23	3.7
T_{max} (hr)	2	2
Infant dose (mg/kg/12 h)	0.00056	0.0002
RID (%)	0.019	0.007

AUC, area under the drug concentration–time curve; C_{avg} , average drug concentration across the dose interval; C_{max} , maximum drug concentration across the dose interval; MMF, monomethyl fumarate; RID, relative infant dose; T_{max} , time at which maximum concentration is observed.

infants are needed to confirm these findings, but our results suggest that DMF treatment might be compatible during lactation. Until more data are available, caution should be advised as MMF is orally bioavailable and infants' immature gastric function might reduce degradation of the substance. While it is possible that even small amounts of DMF ingested *via* breast milk could potentially lead to untoward pharmacological effects, as with almost all other situations, side effects are almost invariably a function of dose. With DMF, these would include flush and gastrointestinal discomfort.² In addition, as shown in a case series of DMF use in pediatric MS patients, side effects correspond to those in adults.¹⁰ Due to the lack of published reports of DMF therapy during lactation, it is not known if such adverse effects in infants are to be expected. However, with such minimal levels, as described in this study, the risk of major side effects is very unlikely. However, the younger the infant, the more unstable or (chronically) ill and the higher the dosage, the more likely adverse effects would seem.

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Conflict of interest statement

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Palika Datta declares that there is no conflict of interest.

Kathleen Rewers-Felkins declares that there is no conflict of interest.

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