Treatment of Multiple Sclerosis with Tecfidera in Breastfeeding Mother

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Introduction

Multiple sclerosis is a chronic demyelinating disease of the central nervous system. With an unknown etiology, treatment is targeted at suppressing the immune response. In March 2013, Tecfidera was approved by FDA for the treatment of relapsing multiple sclerosis. The mechanism by which dimethyl fumarate exerts its therapeutic effect in multiple sclerosis is unknown although it is believed to produce antioxidant and anti-inflammatory properties. After oral administration of 240 mg, twice daily, dimethyl fumarate (DMF) is rapidly converted to its active metabolite, monomethyl fumarate (MMF).The most common side effects of Tecfidera are flushing and gastrointestinal problems at the start of therapy, but decrease with time.

There are no adequate and well controlled studies in pregnant and lactating women. We present a case report, measuring the levels of Monomethyl Fumarate into human milk collected from a lactating woman.

Case Report

Case 1:
A 38-year-old woman breastfeeding her 4-month-old female infant was prescribed Tecfidera for multiple sclerosis. Her symptoms such as numbness appeared in 2009. She was diagnosed with multiple sclerosis and was prescribed Tecfidera in 2018. She experienced slight flush as a side effect of the drug. She volunteered to donate her milk samples after 11 months of treatment, at 0, 1, 2, 4, 8 and 12 hours following her intake of her dosage.

Methods:

- Quantification of monomethyl fumarate was determined using an Agilent 1260 Quadrapole mass spectrometer.
- A Phenomenex Luna C-18 column, 50 x 2 mm, 3-micron particle size was used.
- Isocratic elution was followed using water and acetonitrile with a flow rate of 0.5 mL/min.
- Single ion Monitoring for monomethyl fumarate at m/z 129.1 was analyzed in the negative mode.
- Extraction from milk was accomplished using protein precipitation with acetonitrile.
- Blank milk was spiked with appropriate concentrations of monomethyl fumarate for determining the calibration curve.

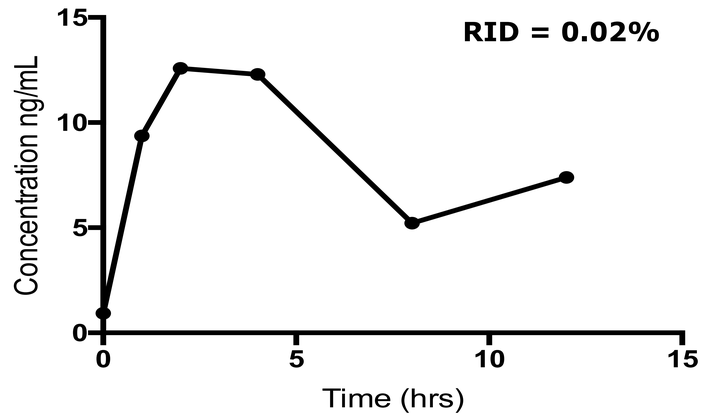

Figure 1: Mean concentration-time profile of monomethyl fumarate over 12 hours in human milk.

Parameters (units)	Value
AUC (ng.hr/mL)	101.2
C_{avg} (ng/mL)	8.43
C_{max} (ng/mL)	12.58
T_{max} (hr)	2
Infant dose (mg/kg/12hrs)	0.00063
RID%	0.02

Table 1: The pharmacokinetic parameters are summarized above.

AUC = Area under the Drug Concentration-Time Curve
Cavg = Average Drug Concentration across the Dose Interval
Cmax = Maximum Drug Concentration across the Dose Interval
Tmax = Time at which maximum concentration is observed
RID = Relative Infant Dose.

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Results

- The maximum concentration of monomethyl fumarate (MMF) in milk was 12.58 ng/mL and was observed at 2 hours as evident by Figure 1. The average concentration of MMF in the milk was 8.43 ng/mL.
- Based on the assumption of infant's daily milk intake of 75 ml/kg/12hr, the infant dose was calculated at 0.00063 mg/kg/12hr.
- The relative infant dose (RID) was calculated to be 0.02%, well below the standard theoretical level of concern of 10%.[2]
- The pharmacokinetic parameters are described in Table 1.

Discussion

- Following oral administration, dimethyl fumarate is rapidly hydrolyzed to the active metabolite, monomethyl fumarate and therefore was not quantifiable in human milk samples.
- The active drug component, monomethyl fumarate (MMF) has a low molecular weight of only 129 Daltons and low protein binding (27-45%).
- Exhalation of CO_2 is the primary route of elimination of MMF. It has a terminal half-life of 1 hour and accumulation does not occur with multiple doses.
- In our study, the MMF concentration levels observed were very low with relative infant dose of 0.02%.

Conclusion

- Tecfidera, a treatment for relapsing forms of multiple sclerosis, has not been approved for breast-feeding mothers. The FDA recommends that the mother and her physician weigh the benefits of breast-feeding with the need for Tecfidera as a treatment for multiple sclerosis.
- The relative infant dose (RID) observed is 0.02%, which is below the theoretical level of concern (RID of <10%).[2] This suggests that the transfer of monomethyl fumarate (MMF) into breast milk is unlikely to pose a risk to the breastfeeding infant.
- There are no previous studies reporting transfer of MMF into human milk. Further studies are needed to determine long-term effects of MMF on breastfed infants.

References
1. Hale, Thomas. Drug Entry into Human Milk. Infant Risk Center. Texas Tech University Health Sciences Center.
2. Bennett, P. N. "Use of the monographs on drugs." Drugs and human lactation 2 (1996): 67-74.