TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER™ *at* Amarillo

Cladribine Transfer into Human Milk

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Introduction

Cladribine is among a number of disease-modifying drugs recently approved for the treatment of relapsing Multiple Sclerosis (MS)[1]. It acts as an immunosuppressant via cytotoxic effects on both proliferating and resting lymphocytes. MS markedly affects the female population, often beginning during childbearing years. Thus far, there are no published data determining the transfer of cladribine into human milk. This study presents the pharmacokinetic transfer of cladribine from maternal plasma to breastmilk of a patient undergoing therapy for Relapsing-remitting multiple sclerosis.

Case Report

- 29-year-old female with history of MS delivered a healthy male infant at 42 weeks gestational age by normal vaginal delivery.
  - During her pregnancy, she did not experience any MS relapses.
  - 4 months postpartum, she developed a MS relapse with a new contrast-enhancing thoracic spinal cord lesion.
  - She was diagnosed with relapsing-remitting multiple sclerosis (RRMS).

- **Treatment of patient's RRMS:**
  - Oral cladribine (dosed according to her body weight: 93 kg)
  - 1st treatment: 20 mg once daily on days 1-4 and 10 mg on day 5
  - 2nd treatment (5 weeks after 1st treatment week): 20 mg once daily on days 1-3 and 10 mg on days 4-5
  - Patient discontinued breastfeeding once she began cladribine treatment, however, continued to pump to retain supply and donated milk samples for this study.

- **Methods:**
  - Breast milk samples were collected daily at 0, 1, 2, 4, 6, 8, 12, and 24 hours after cladribine intake in the 2nd treatment week.
  - Samples were collected, frozen, and transported in dry ice to the InfantRisk Center laboratory in Amarillo, Texas.
  - After administration of her last dose, selective analysis was done for single samples collected at 48, 72 and 96 hours.

- **Analysis:**
  - Rapid, high-throughput mass spectrometry assay for detection of cladribine along with internal standard in human milk samples
    - Quantitation was determined using ABSciex QTRAP 5500 UPLC MS\MS mass spectrometry
    - The precursor-product ion transition for cladribine m/z 286.1 -134.0 and m/z 304 - 170.0 for the internal standard clofarabine were used
    - A Phenomenex Biphenyl column 100x4.6mm, 5µm used as an analytical column
  - Milk samples were prepared using a protein precipitation standard technique.
  - A calibration curve was determined in blank milk with the concentration range of 1.5 – 400 ng/mL with a correlation coefficient of 0.99.
  - Average concentration (Cavg) was used to calculate the Infant dose, which was calculated as the product of the average concentration in milk and an assumed milk intake of 0.15 L/kg/day.
  - Maternal dose was calculated as daily dose (amount) by maternal body weight.
  - Relative Infant dose (RID) was estimated as absolute infant dose expressed as a percentage of maternal dose (mg/kg/day).

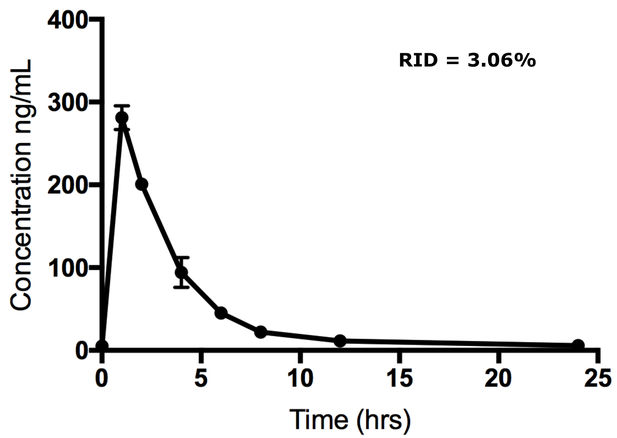

Figure 1. Average milk concentration-time profile of cladribine in human milk (n=1) following the oral administration of 20 mg daily from Day 3 of five-day treatment course.

Parameter (units) Cladribine	Value
Dose	20 mg once daily
AUC (ng.hr/mL)	1056
C_{avg} (ng/mL)	44
C_{max} (ng/mL)	281.2
T_{max} (hr)	1
Infant dose (mg/kg/day)	0.0066
RID (%)	3.06

Table 1. Pharmacokinetic parameters of cladribine from Day 3 of five day treatment course.

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Results and Discussion

- **Results:**
  - Cladribine levels in milk reached maximum concentration of 281.2 ng/mL at 1 hour following a 20 mg dose, with a rapid decline in milk concentration over a period of 12-24 hours (Figure 1).
  - Milk samples analyzed at 48, 72, and 96 hours post-administration of the drug revealed to be below the quantifiable concentration.
  - Based on values shown in Table 1, a relative infant dose (RID) of 3.06% of cladribine was found in the milk within a 24 hour period.

- **Discussion:**
  - Cladribine is rapidly absorbed after oral administration and maximum plasma concentration is reached within 0.5 – 1.5 hours[2].
  - Once taken up by lymphocytes, cladribine undergoes phosphorylation to its active form, making it virtually impossible to quantify in plasma. Thus, only traces of active metabolites have been identified in plasma or urine after acting on the target cells[3].
  - Cladribine has an estimated half-life of 1 day and the drug does not accumulate following once-daily administration.

- Cladribine level in human milk rapidly declines over a period of 24 hours.
  - The levels were undetectable in the milk samples collected at 48, 72 and 96 hours after administration of the patient's last dose.

- **Limitations include:**
  - Lack of corresponding plasma samples at times of milk collection.
  - Small sample size.

Conclusion

- This is the first case report suggesting the transfer of cladribine in human milk, and also adds a significant information for its use during lactation.
- As there is no data available regarding cladribine's clinical effect on breastfed infants, caution should be advised when breastfeeding mothers are treated with the drug.
- Due to the rapid decline of drug levels in human milk within 24 hours, several days of withholding breastmilk after the last dose may be sufficient to avoid ingestion of cladribine by the infant.

References:

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