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CASE REPORTS

Evaluating Transfer of Modafinil Into Human Milk During Lactation: A Case Report

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We present a case of a 27-year-old woman in whom idiopathic hypersomnolence was diagnosed in adolescence with adequate symptomatic control on daily dosage of 250 mg of modafinil. She maintained this dosage throughout her pregnancy and during the peripartum period, but did not breastfeed her newborn because of a lack of information on the transmission of modafinil in human breast milk. Samples of her breast milk were obtained at various times over a 24-hour period and analyzed using liquid chromatography mass spectrometry. The relative infant dose was calculated to be 5.3%, below the threshold of concern for drug passage via breast milk. This is the first reported case of modafinil transfer into human breast milk. Given the drug's use in a variety of sleep disorders, the results of this case can be used to advise breastfeeding mothers prescribed modafinil.

Keywords: armodafinil, human breast milk, idiopathic hypersomnia, modafinil

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INTRODUCTION

Idiopathic hypersomnia (IH) is one of the central sleep disorders characterized by excessive daytime sleepiness (EDS) in the absence of disturbances in circadian rhythm or sleep-wake cycle.[1–3] The International Classification of Sleep Disorders, Third Edition (ICSD-3) characterizes IH as a diagnosis of exclusion because of the variety of diseases and comorbid lifestyle factors contributing to hypersomnolence and hypersomnia. Additionally, IH lacks pathognomonic symptoms such as cataplexy and sleep paralysis, or a biological marker akin to orexin of narcolepsy. Because of these factors, ICSD-3 requires the following criteria for positive diagnosis of IH[2]:

- a report of subjective sleepiness, mean sleep latency time showing a mean latency of < 8 minutes with fewer that two sleep-onset rapid eye movement periods (SOREMP), including any on polysomnogram from the preceding night;
- absence of cataplexy and hypocretin deficiency, if measured;
- no other identifiable cause.

Given the difficulty in making definitive diagnoses of IH, its prevalence is unknown, though it is thought to occur more frequently in females of reproductive age.[1] Treatment options for IH are similar to those of narcolepsy, with modafinil being the most common. Its efficacy in the management of IH was first proven in 1988, and several studies since have given similar results.[1,3,4] It is the first-line treatment for the reduction of excessive sleepiness in IH and narcolepsy types 1 and 2, and in many cases can bring patients at or near their baseline activity status prior to the onset of their symptoms.[4–6]

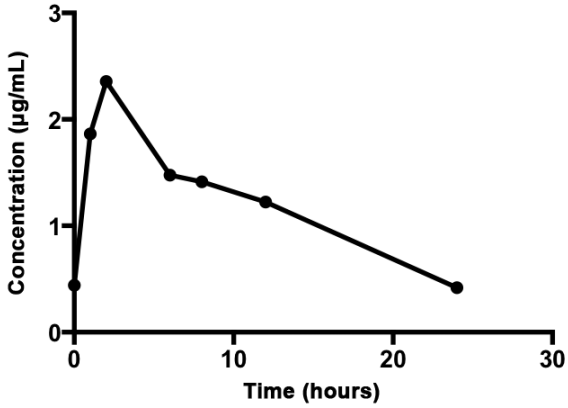
Modafinil is classified as a wakefulness-promoting agent that interacts with a variety of neurotransmitter receptors.[5,6] Armodafinil is the R-enantiomer of modafinil, which is composed of a racemic mixture of the R- and S-enantiomers. Armodafinil is the active form, and the S-enantiomer is the inactive form. Both are rapidly absorbed, reaching peak concentrations within 2 to 4 hours after administration and undergoing almost 90% metabolism in the liver. It is only moderately bound to plasma protein, about 60%, and it is widely distributed with a volume of distribution of approximately 0.9 L/kg. Modafinil reaches a steady state in humans in 2 to 4 days and has a half-life of 15 hours.

Modafinil is the first-line treatment not only for IH, but also for narcolepsy types 1 and 2, and has been used to alleviate symptoms of EDS in patients suffering from obstructive sleep apnea and shift-work disorder. As many patients in whom these conditions are diagnosed are of reproductive age, it is a worthwhile endeavor to measure modafinil levels in human breast milk.

REPORT OF CASE

In May 2017 a 27-year-old woman delivered an infant at 37 weeks gestational age by normal spontaneous vaginal delivery. This was reported as her second pregnancy. The mother had a previous diagnosis of idiopathic hypersomnia during adolescence after reporting instances of falling asleep while driving and during other activities, with significant disruption of her

Figure 1—Mean milk concentration-time profile of armodafinil in human milk following the oral administration of a 250-mg dose.



daily tasks. Her diagnosis was confirmed during a sleep study demonstrating a lack of SOREMPs on Multiple Sleep Latency Tests and a sleep latency of 2 minutes. According to the information provided by her sleep specialist she did not have either circadian rhythm disorder or sleep apnea. Since her diagnosis more than 10 years prior to her pregnancy she had adequate symptomatic control on a daily dose of 250 mg of modafinil. In addition, the patient had Hashimoto thyroiditis for which she took 75 µg of levothyroxine per day, and mild intermittent asthma controlled with albuterol on an as-needed basis. She also had a diagnosis of obsessive-compulsive disorder and major depressive disorder, which were well controlled on sertraline at 200 mg per day.

Concerned about the effects of modafinil on the infant, the patient's provider contacted the InfantRisk Center to evaluate the safety of the drug. Because of the lack of published information regarding drug transfer of modafinil into human milk, the mother agreed to provide samples of her breast milk. The mother consumed 250 mg of modafinil daily prior to, during, and after her pregnancy as prescribed and was therefore at a steady state. Nineteen days after the infant was delivered, milk samples were collected at 0, 1, 2, 4, 6, 8, 10, 12, and 24 hours. The patient was also taking levothyroxine and sertraline at the time these samples were taken. The mother ultimately decided against breastfeeding her infant and her lactation period ended shortly thereafter.

METHODS

The samples of the patient's breast milk were analyzed for armodafinil (the active form of modafinil) concentration levels by high-performance liquid chromatography mass spectrometry (LCMS). The Agilent 6120 Quadrupole LCMS system was used, equipped with an atmospheric pressure ionization electrospray source. Chromatography conditions were isocratic, with a mobile phase consisting of water: acetonitrile (50:50 vol/vol) at a flow rate of 1 mL/min on a biphenyl column, 100 × 4.6 mm, 5 µm (Phenomenex, Torrance, California, United States).

Table 1—Pharmacokinetic parameters of armodafinil in a breastfeeding woman.

Parameter (units)	Value
AUC (µg.hr/mL)	28.96
C_{avg} (µg/mL)	1.2
C_{max} (µg/mL)	2.4
T_{max} (hours)	2
Infant dose (mg/kg/day)	0.18
RID (%)	5.3

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, T_{max} = time at which maximum concentration is observed, RID = relative infant dose for armodafinil in milk.

The analyte was quantified by comparison of the area obtained against a standard curve of breast milk spiked with known concentrations of armodafinil (0.156–5 µg/mL) with correlation coefficient as 0.99. The intrasample and intersample coefficients of variation were less than 5% and 10% respectively. Analysis of blank milk used for the standard curve did not reveal any peaks that could interfere and was specific for compound to be analyzed. A simple protein precipitation method was followed for sample preparation. The milk samples were collected at 0, 1, 2, 4, 6, 8, 10, 12, and 24 hours. The single ion monitoring was done at m/z 167.4, set up in the positive mode with capillary voltage of 4,000 volts.

RESULTS

Following a dose of 250 mg, the maximum concentration measured of armodafinil in milk was 2.4 µg/mL and was observed at 2 hours. This level decreased gradually over 24 hours. As the patient was in steady state, we observed 0.43 µg/mL at zero hour just before she administered her daily dose. **Figure 1** represents the mean milk concentration-time profile of armodafinil. The calculated area under the curve was 28.96 µg.hr/mL. The average infant dose was 0.181 mg/kg/day based on the assumption of the infant's daily intake of 150 mL/kg/day. The relative infant dose (RID) was estimated to be 5.3%. **Table 1** reports the pharmacokinetics parameters observed.

DISCUSSION

To our knowledge this is the first quantitative description of armodafinil transfer into breast milk. Levels of armodafinil were found to be low, with an average concentration C_{avg} of 1.2 µg/mL. The estimated infant dose was 0.18 mg/kg/day, and the RID was 5.3%. This is below the theoretical level of 10% where there is concern for medications in breastmilk.[7] Approximately 90% of modafinil is metabolized in the liver. As the infant receives medication via breast milk, the medication undergoes first-pass metabolism following first-pass uptake in the liver. Though it is below theoretical threshold for concern,

it is still worth watching the infant for problems such as insomnia, jitteriness, poor weight gain, or anorexia. In the case of these events we recommend the mother either discontinue the drug, or discontinue breastfeeding.

Because of its structure, modafinil is likely to cross over to breast milk due to its low molecular weight of 273 Da, moderate protein binding of 60%, and long terminal half-life of approximately 15 hours. Because of its central mechanism of action on various neurotransmitter receptors there is some concern about passage of the drug via the blood-brain barrier to the newborn.[6] However, as the drug is received via breast milk it enters the gastrointestinal tract and must undergo first-pass metabolism through the liver. Because of its high rate of metabolism, it is unlikely large quantities of armodafinil will enter milk or cross the blood-brain barrier.

In animal studies pregnant rats and rabbits given modafinil throughout the pregnancy did produce offspring with a higher incidence of skeletal and visceral abnormalities, though many of these occurred when modafinil was given at doses higher than the recommended 200 mg. In another study, authors found that human mothers who took modafinil during pregnancy showed no change in complications in comparison with unexposed mothers.[8] However, this study did not mention the effects of breastfeeding on the infant while the mother was taking modafinil. In our study, with an RID of only 5.3% there is probably minimal risk of infant toxicity. However, it is still recommended to observe the infant for any clinical changes during exposure to modafinil.

This is the first known case report determining amount of armodafinil transfer into human milk. Because modafinil is used for a number of disorders characterized by EDS, and not limited to only idiopathic hypersomnia as in this case, further studies regarding the transmission of armodafinil into human milk and its effect on breastfeeding infants are required.

ABBREVIATIONS

API, atmospheric pressure ionization
EDS, excessive daytime sleepiness
ICSD, International Classification of Sleep Disorders
IH, idiopathic hypersomnia
LCMS, liquid chromatography mass spectrometry
RID, relative infant dose
SOREMP, sleep onset rapid eye movement periods

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DISCLOSURE STATEMENT

Work for this study was performed at Texas Tech University Health Sciences Center. All authors have reviewed this manuscript and approved it for submission. The authors report no conflicts of interest.