Case Report

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Maternal Transfer of Cetirizine Into Human Milk

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Abstract

Introduction: Cetirizine hydrochloride is a second-generation H1 histamine antagonist with Food and Drug Administration approval for treatment of allergic rhinitis and urticaria. Currently, the Food and Drug Administration does not recommend use of cetirizine during breastfeeding, as there are insufficient studies on both the transference of cetirizine into human milk and the effects of cetirizine in infants.

Main issue: To determine the concentration of cetirizine in human milk, samples were analyzed using high performance liquid chromatography mass spectrometry.

Management: Based on calculations, relative infant dose was found to be 1.77% at 24 hr. In addition, there were no reported adverse effects seen in the infants.

Conclusion: We suggest that transfer of cetirizine into human milk is minimal and unlikely to pose a significant risk to the breastfeeding infant. This is the first report presenting the transfer of cetirizine in human milk.

Keywords

breastfeeding, human milk, mother-to-child transmission

Introduction

Cetirizine is the active metabolite of hydroxyzine, a second-generation H1 histamine antagonist. Its effects are mediated via selective inhibition of peripheral H1 receptors. This antihistaminic activity has been well documented for the majority of allergy conditions. Allergic rhinitis, also referred to as "hay fever" or simply seasonal allergies, is a condition that affects an estimated 10%–20% of the population (Kakli & Riley, 2016). Symptoms include rhinorrhea, nasal itching, nasal congestion, sneezing, and headache. While symptoms may be minimal in some people, it may be severe and debilitating in others. In fact, a researcher survey found that 50% of patients reported significantly impaired sleep and 74% reported an influence on school/work performance in severe allergies (Schatz, 2007).

The parent drug, hydroxyzine, is known to be extremely sedating. Cetirizine is generally administered orally, reaching a maximum plasma concentration in about 1 hr. It is water-soluble and is primarily renally excreted. As expected for hydrophilic molecules, plasma accumulation was not observed in a study involving once daily 10 mg dosing of cetirizine for 10 days (Zhang et al., 2013). Common side effects of cetirizine include sedation, dizziness, and xerostomia, although these effects tend to be less pronounced than in first generation antihistamines, as the second-generation drugs do not cross the blood–brain barrier (Simons & Simons, 2008).

Currently, the manufacturer does not recommend use of cetirizine during breastfeeding, as there are insufficient studies on both the transference of cetirizine into human milk and the effects of cetirizine in infants. While safety and efficacy has been studied in the pediatric population, evidence is lacking in infants less than 6 months of age. These data are the first published on the transfer of this antihistamine to human milk. Each mother discussed below has given consent for publication.

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History and Observational Assessment

Case 1

A 33-year-old woman weighing 59.1 kg, exclusively breastfed her 6-month-old child. The infant's weight at the time of study was 7 kg. She had a 20-year history of seasonal allergies, with symptoms including sneezing and itching of the eyes and nose. She was taking cetirizine, 10 mg by mouth, once daily, for more than 6 months prior to this study. The only side effect reported by her was occasional nasal dryness. Other maternal medications included ibuprofen prn and iron supplementation daily.

Case 2

A 35-year-old woman weighing 59.8 kg was exclusively breastfeeding her 5-month-old infant and taking cetirizine 10 mg by mouth daily for 2–3 years prior to this study. The infant's weight at the time of study was 7.2 kg. She has a history of seasonal allergies and recurrent sinusitis over the past 12 years and reported no side effects. Other medications included budesonide nasal spray, montelukast, docusate calcium, prenatal vitamins, and probiotics.

Case 3

A 38-year-old woman weighing 49.8 kg, with a history of recurrent sinusitis was taking cetirizine, 10 mg by mouth daily, while breastfeeding a 6-month-old infant. The infant's weight at the time of study was 6 kg. She reported taking cetirizine for 3.4 years prior to this study without reported side effects. Other medications included pantoprazole, calcium supplementation, and a postnatal vitamin. Of the concurrent medications consumed by these participants, there were no known interactions with cetirizine (Lexicomp Drug Interactions Online, 2020).

All milk samples from the participants were collected at 0, 1, 2, 4, 6, 8, 10, 12, and 24 hr after administration of 10 mg by mouth, with sample 0 being just before drug administration. They were advised to express milk from both the breasts, and gently mix and collect 30-60 mL into a collection tube. Samples were stored in the freezer and shipped overnight to our facility. The samples were stored at −80 °C until further analysis. Chronological summary of collection of samples is described in Figure 1.

Management

Samples of human milk were analyzed for cetirizine by high performance liquid chromatography mass spectrometry. AB Sciex QTTRAP 5500 UHPLC tandem MS/MS was used in positive ion mode. An Agilent poroshell C-18 column was used for reverse phase separation. The mobile phase consisted of acetonitrile–water at 65:35 (v/v) and was pumped at the flow rate of 0.5 mL/min. Data were analyzed using multiple reaction monitoring (MRM) as m/z 389.26–165.16 for cetirizine and m/z 397.1–165.16 for cetirizine-d8 (internal standard). Calibration standards were prepared freshly in blank milk at concentration range of 0.19 ng/mL–100 ng/mL. A simple protein precipitation method was followed for extraction of analyte.

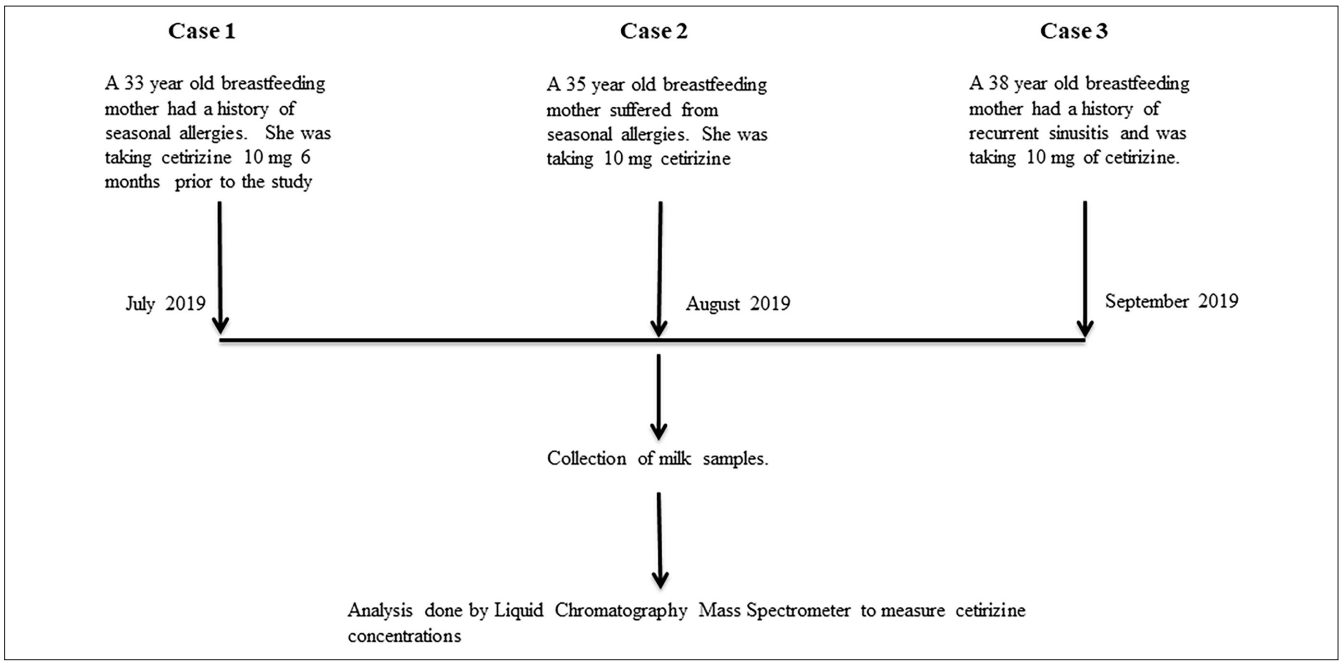

Figure 1. Chronological Summary Timeline (*N* = 3).

Table 1. Pharmacokinetic Parameters of Cetirizine (*N* = 3).

Parameter (Units) Cetirizine	Value (*M*)
Dose	10 mg once daily
AUC (ng·hr/mL)	506.8
C_{avg} (ng/mL)	21.1
C_{max} (ng/mL)	49
T_{max} (hr)	2
Infant dose (mg/kg/day)	0.0031
RID (%)	1.77

Note. AUC = Area under curve; C_{avg} = average drug concentration; C_{max} = maximum drug concentration; RID = relative infant dose of cetirizine.

Outcome

The concentration of cetirizine was determined in milk samples obtained from all the participants. The trapezoidal method was used to calculate the area under the milk concentration-time curve (AUC) taking the average of concentration at different time points for all the three participants. The derived pharmacokinetic parameters are described in Table 1. The maximum concentration of cetirizine in milk of 49 ng/mL was observed at 2 hr following the dose. Total infant dose was calculated as 0.0035 mg/kg/day using the average weight of participants (*M* = 56.2 kg). Based on the above calculations the mean relative infant dose over 24 hr was 1.77%. Cetirizine concentrations declined over a 24-hr period, as shown in Figure 2.

Discussion

Our results suggest that the transfer of cetirizine into human milk is minimal, as estimated by the average relative infant dose of only 1.77% in three participants, following a single oral dose of 10 mg. Assuming milk intake by an infant is 150 mL/kg/day, (Begg et al., 1992) the maximum infant dose of cetirizine present in human milk was estimated to be 3.1 μg/kg daily. In addition, none of the participating mothers in this study reported any adverse effects in their infants.

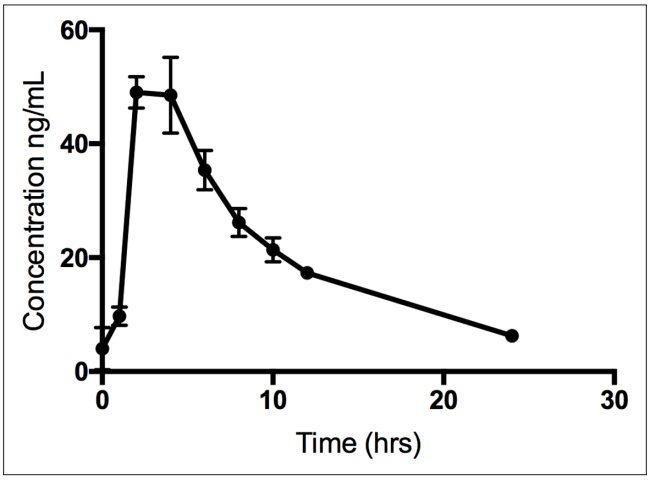

Figure 2. Mean Concentration–Time Profile of Cetirizine (10 mg Daily) Over 24 hr in Human Milk (*N* = 3).

The reason for low levels of drug transfer into human milk is likely associated with the structure of the molecule and its high protein binding. It is well known that the transfer of drugs into human milk is largely a function of their structure, which includes lipid solubility, protein binding, and the molecular weight of the drug (Hale, 2018). Due to its structure, cetirizine is highly lipophilic at a physiological pH, is moderately water soluble at 101 mg/L and has a high plasma protein binding at 93% (Wishart et al., 2018). Taken together, these physicochemical components indicate that milk levels will be low. While cetirizine has a plasma elimination half-life of approximately 8–9 hr, plasma levels do not change much with multiple dosing. As it is less extensively metabolized than other antihistamines, more than 60% of an administered dose is secreted unchanged in 24 hr. Cetirizine does not have any known active metabolite. The maximum plasma concentration (C_{max}) in adults has been reported to be around 300 ng/mL at 1 hr with no accumulation reported (Derakhshandeh & Mohebbi, 2009).

Although seasonal allergies are not life-threatening, some precautions need assessing during the use of medications during pregnancy and lactation. There is unfortunately minimal data available on the transfer of second-generation antihistamines in human milk. From our data, we believe the amount of cetirizine transferred into human milk is unlikely to result in any adverse effects in nursing infants. Caution must be taken with reliance on the relative infant dose alone in interpreting the risk to the breastfed infants. While the relative infant dose is useful, it can only estimate exposure to the infant and does not take into account the differences in bioavailability or metabolism in a particular infant, or the absolute oral intake of human milk for that matter. Additionally, our study is limited by a small sample size and no corresponding plasma samples were available, which would have allowed us to calculate the milk:plasma (M:P) ratio. This value defines the extent of transfer of medication from mother's milk to her infant's plasma. We were unable to calculate M:P ratio because participants refused to provide plasma samples. A more thorough investigation with a larger sample is required to draw definitive conclusions regarding risks involved when taking cetirizine while breastfeeding.

Conclusion

With a relative infant dose of only 1.77%, our findings indicated that transfer of cetirizine into human milk was minimal and unlikely to pose a significant risk to the breastfeeding infant. To date, no researchers have reported transfer of cetirizine into human milk. The data provided in this case series

adds important information that may be used to advise breastfeeding mothers taking this drug.

Authors' Note

First author Hannah will graduate from Medical school of Texas Tech University in May 2021.

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Declaration of Conflicting Interests

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