Serotonin Modulator Vortioxetine transfers into Human Milk

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Introduction

- Vortioxetine (Trintellix) is a novel antidepressant that works through serotonin modulation, inhibiting the reuptake of serotonin and acting as an agonist at the 5-HT1A receptor and as an antagonist at the 5-HT3 receptor.[1]
- This medication is approved to treat major depressive disorder in adults and has fewer side effects compared to other antidepressants including lack of weight gain, lack of changes in the QTc, and low incidence rate of sexual dysfunction.[2] A typical dose is 5 to 20 mg once daily.
- The prevalence of major depression is 12.7% among pregnant women and 4.8% among nonpregnant women of childbearing age.[3] Major depressive disorder affects a woman's quality of life, and maternal depression adversely affects mother-child bonding and child socioemotional development.
- There are no previous studies on the transfer of vortioxetine into human breast milk. The present study determined the drug concentration-time profile in the milk samples collected from two lactating mothers taking 10 mg and one taking 20 mg, all at steady-state.

Case Report

- Patient 1: A 35-year-old woman weighing 63.6 kgs gave birth to a female infant after 40 weeks of gestation. She was diagnosed with depression and anxiety in 2005 and was prescribed 20 mg vortioxetine once daily in March 2018. She donated her milk samples in September 2019, her blood levels well in steady state. At time of the study, she was exclusively breastfeeding her 2-month-old infant. Her other medications included vitamins, aspirin 81 mg, and levothyroxine 50 mcg.
- Patient 2: A 28-year-old woman weighing 93 kg gave birth to a female infant after 39 weeks of gestation. She had history of depression and anxiety since 7 years of age and was prescribed vortioxetine in March 2018, initially 20 mg once daily but due to side effects was reduced to 10 mg once daily. She donated her milk samples in July 2019 in steady state. At time of the study, she was exclusively breastfeeding her 6-month-old infant. Her other medications included magnesium glycinate 120 mg twice a day and vitamins.
- Patient 3: A 28-year-old woman 73 kg gave birth to a male infant after 37 weeks of gestation. She was diagnosed with depression at 15 years of age and was prescribed 10 mg of vortioxetine once daily in June 2015. She donated her milk samples in May 2018 in steady state. At the time of the study, she was exclusively breastfeeding her 1-month-old infant. Her other medications included 2 mg of Subutex, fish oil and clonazepam.
- The participants donated milk samples at 0, 5, 7, 10, 12, and 24 hours after the dose for both the doses.

Methods:

Quantification of vortioxetine was determined using Agilent 1260 Quadrapole mass spectrometer. A Phenomenex Biphenyl column, 100 x 4.6 mm, 5 µm was used. Isocratic elution was followed using water and acetonitrile with a flow rate of 0.5 mL/min. Single ion monitoring at m/z 299.3 for vortioxetine was determined. Milk samples were extracted using protein precipitation. Blank milk was spiked with appropriate concentrations of vortioxetine and internal standard for determining the calibration curve.

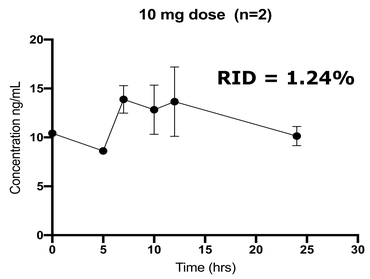

Figure 1: Mean milk concentration-time profile of vortioxetine following the oral administration of 10 mg taken once daily (n=2).

Parameters (units)	Value
AUC (ng.hr/mL)	279.4
C_{avg} (ng/mL)	11.64
C_{max} (ng/mL)	13.89
T_{max} (hr)	7
Infant dose (mg/kg/day)	0.002
RID%	**1.24**

Table 1: The pharmacokinetic parameters for dose 10 mg (n=2)

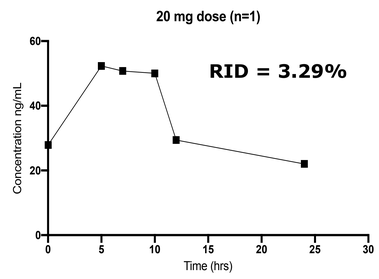

Figure 1: Mean milk concentration-time profile of vortioxetine following the oral administration of 20 mg taken once daily (n=1).

Parameters (units)	Value
AUC (ng.hr/mL)	842.8
C_{avg} (ng/mL)	35.12
C_{max} (ng/mL)	52.32
T_{max} (hr)	5
Infant dose (mg/kg/day)	0.005
RID%	**3.29**

Table 2: The pharmacokinetic parameters for dose 20 mg (n=1).

Antidepressant	Relative Infant Dose range
Vortioxetine	1.24 – 3.29%
Sertraline	0.2 – 2.4%
Paroxetine	1.1 – 3.2%
Citalopram	13.2 – 18.4%
Fluoxetine	13.1 – 20.0%
Venlafaxine	8.8%

Table 3: Comparison of Relative infant dose (RID) for SSRI/SNRI antidepressants

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Results

- At a dose of 10 mg daily, the maximum concentration of Vortioxetine was 13.89 ng/mL with peak concentration observed at 7 hours. The average concentration was 11.64 ng/mL and the concentration of vortioxetine remained relatively stable over the twenty-four-hour time course (Figure 1).
- At a dose of 20mg daily, the maximum concentration of Vortioxetine was 52.32 ng/mL with peak concentration observed at 5 hours. The average concentration was 35.12 ng/mL and the concentration of vortioxetine drops to a steady state after 10 hours (Figure 2).
- The infant dose calculated was 0.002 mg/kg/day for 10 mg dose and 0.005 mg/kg/day for 20 mg dose based on the assumption of infant's daily milk intake of 150 ml/kg/day.
- The relative infant dose (RID) was calculated to be 1.24% for 10 mg dose and 3.29% for 20 mg dose, showing a dose-dependent increase in RID as described in Table 1 & 2.

Discussion

- Vortioxetine has linear and dose proportional pharmacokinetics. The half-life is 66 hours and steady-state plasma concentration is reached in 2 weeks.[4] Vortioxetine is well absorbed orally and the time to maximal serum concentration is within 7 to 11 hours. It is mostly bound to plasma protein in the serum (98%), reducing the likelihood of transfer.
- Sertraline and paroxetine are the current first-line treatment for lactating patients starting an antidepressant.[5] Other SSRIs such are considered generally compatible with breastfeeding but have higher accumulation in breast milk. SNRIs appear to be safe for breastfeeding women based on lack of adverse events in infant observational studies, but infant exposure is greater than most SSRIs.
- Table 3 shows the relative infant dose for other antidepressants. Vortioxetine has similar RID to sertraline and paroxetine[6].
- There are no studies on the effects of serotonin modulators in infants, but in SSRIs adverse events are rare. One review found adverse events in 0.9% of paroxetine cases and in only 1 case out of 279 for sertraline[5]. The most common effects are irritability and lethargy.

Conclusion

- This case report of three lactating mothers is the first study on the transfer of vortioxetine into human breast milk. While vortioxetine shows a dose-dependent increase in infant exposure, both RID for 10 mg and 20 mg (1.24% and 3.29%, respectively) fall below the 10% theoretical level of concern[7].
- These findings suggest a low risk of infant toxicity, and the RID for vortioxetine is similar to sertraline and paroxetine, the current first-line treatments for depression in lactating patients, and lower than most antidepressants. Additionally, no adverse effects were reported by the mothers.
- However, caution should be exercised as this is a small patient sample and further studies are required to report any adverse effects of vortioxetine on breastfeeding infants.

References:

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