

MOTHERISK ROUNDS

Can Venlafaxine in Breast Milk Attenuate the Norepinephrine and Serotonin Reuptake Neonatal Withdrawal Syndrome?

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Abstract

A newborn infant whose mother had used venlafaxine, a selective inhibitor of both norepinephrine and serotonin reuptake, throughout pregnancy exhibited signs consistent with the norepinephrine and serotonin reuptake withdrawal syndrome. Is it possible that mother's milk can help mitigate the effects of norepinephrine and serotonin reuptake withdrawal? Pharmacokinetic analysis and review of the only published case with active treatment of a baby with venlafaxine suggest that breastfeeding may mitigate the neonatal withdrawal syndrome.

Résumé

Un nouveau-né dont la mère avait pris de la venlafaxine (inhibiteur sélectif du recaptage tant de la norépinéphrine que de la sérotonine) tout au long de la grossesse présentait des symptômes correspondant à un syndrome de sevrage associé au recaptage de la norépinéphrine et de la sérotonine. Est-il possible que le lait maternel contribue à l'atténuation des effets du sevrage associé au recaptage de la norépinéphrine et de la sérotonine? L'analyse pharmacocinétique et l'étude du seul exposé de cas publié concernant le traitement actif d'un nouveau-né à la venlafaxine laissent entendre que l'allaitement naturel pourrait atténuer le syndrome de sevrage néonatal.

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THE CASE

At two days of age, a full-term infant born to a 95 kg mother who was being treated for depression with venlafaxine (Effexor) 375 mg daily exhibited lethargy, jitteriness, rapid breathing, poor ability to suck, and dehydration. Clinical and laboratory investigations ruled out sepsis, respiratory distress syndrome, aspiration pneumonia,

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and metabolic problems. It was suggested that this clinical picture might be indicative of serotonin toxicity from the effects of venlafaxine, in which case breastfeeding might worsen the clinical picture by exposing the baby to more of the drug.

With the use of a high-performance liquid chromatographic method, a single milk sample provided by the mother 19 hours after ingestion of venlafaxine 375 mg showed a level of venlafaxine (and its two active metabolites) of 0.69 µg/mL. This serum level was within the therapeutic range. Assuming milk consumption of 1L/d, the baby received 0.14 mg/kg/d of venlafaxine. The mother received 3.95 mg/kg/d; hence the baby was exposed to 3.5% of the maternal weight adjusted dose. The mother breastfed the baby, and the symptoms subsided gradually and spontaneously over one week.

DISCUSSION

At present, the mechanism leading to these observed abnormalities in a neonate is not understood. Theoretically the abnormal behaviour in the infant may result either from serotonin toxicity or from serotonin withdrawal.¹ In adults, serotonin syndrome has been characterized by confusion, restlessness, myoclonus, hyperreflexia, diaphoresis, tremor, incoordination, and hyperthermia.² It occurs mostly while patients are taking more than one medication that causes elevation in brain serotonin. In neonates, however, serum concentrations of selective serotonin reuptake inhibitors have been reported to be low or undetectable after maternal use in late pregnancy,¹ suggesting that in most cases the syndrome in neonates is associated with serotonin withdrawal

Analysis of neonatal withdrawal as cause of symptoms*

| Question | Yes | No | Don't know | Score |
|---|-----|----|------------|-----------|
| 1. Previous conclusive reports of this reaction | X | | | 1 |
| 2. Did the adverse event appear after the suspected drug's exposure? | X | | | 2 |
| 3. Did the adverse reaction improve when the drug was removed? | X | | | 1 |
| 4. Did the adverse reaction reappear when the drug was re-administered? | X | | | 2 |
| 5. Were alternative causes r/o? | X | | | 2 |
| 6. Did reaction reappear with placebo? | | | X | 0 |
| 7. Was drug absent from blood when the ADR occurred? | X | | | 1 |
| 8. Was the reaction more severe with higher dose? | | | X | 0 |
| 9. Similar reaction with previous exposure? | | | X | 0 |
| 10. Adverse event confirmed objectively? | X | | | 1 |
| Total score | | | | 10 |

*The Naranjo Adverse Drug Reactions Probability Scale,¹⁰ was modified (questions 3, 4, and 7) to allow evaluation of causality of withdrawal for the de Moor case.⁹

Scores: ≤ 0: doubtful; 1–4: possible; 5–8: probable; > 9: highly probable.

rather than serotonin toxicity.^{3–8} This is consistent with the only published report of neonatal venlafaxine withdrawal syndrome, described below.⁹ In contrast, we have recently encountered rigidity in a neonate with high serum levels of paroxetine; the rigidity subsided when the paroxetine levels decreased.¹

The amount of venlafaxine ingested by the baby through breast milk is very unlikely to cause serotonin syndrome. Even after correcting the weight-adjusted dose for the probably slower metabolism of venlafaxine in the baby, this dose is too small to cause serotonin toxicity.

Because the mother used venlafaxine throughout pregnancy, the steady state levels in the fetus were likely similar to maternal levels, as there was ample time for transplacental equilibration. After birth, the amount of venlafaxine supplied to the neonate in breast milk would have been much less than that supplied transplacentally so it should not be surprising that the falling levels of venlafaxine in the neonate may be associated with emergence of a withdrawal syndrome. But might the amount of venlafaxine present in breast milk mitigate or minimize the neonatal withdrawal syndrome?

An exhaustive literature search revealed a recent Dutch case that may shed a light on this question.⁹ A clinical picture consistent with withdrawal symptoms occurred in a neonate after maternal use of venlafaxine (300 mg daily) during pregnancy. The signs of withdrawal included restlessness, hypertonia, jitteriness, tremor, irritability, poor feeding, and

hypoglycemia. Glucose was administered intravenously but, despite normalizing serum glucose levels, the tremors continued. Clinical and laboratory examination ruled out infection. Electroencephalography showed normal findings for a neonate. The serum venlafaxine level in the baby was undetectable, excluding toxicity.

To confirm the diagnosis of neonatal withdrawal, 1 mg of venlafaxine was given orally to the baby. Over the subsequent two to three days the irritability and restlessness subsided. The baby was not given a second dose of venlafaxine, and on the following day the abnormal findings reappeared. Thereafter the irritability and restlessness subsided gradually over eight days.

The case by de Moor provides convincing evidence for the causality of the symptoms. Using the Naranjo scale for causality of adverse drug effects,¹⁰ this case confirms causation at high probability (see the Table).

The baby described in the Dutch case reacted favourably to an oral venlafaxine dose of 0.33 mg/kg of body weight. The neonate described in our case received an estimated dose of 0.14 mg/kg through breast milk. It is possible that the dose ingested by the baby in breast milk was higher, as the single venlafaxine level in the baby was measured at trough, namely 19 hours after the maternal dose.

CONCLUSION

Venlafaxine provided in breast milk may mitigate the effects of venlafaxine withdrawal in the neonate.

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