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Agomelatine for postpartum depression and breastfeeding

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***Abstract*:** Postpartum depression (PPD) is a common and serious mental health problem that is associated with maternal suffering and numerous negative consequences for offspring. The benefit of breastfeeding for the infant and mother is well documented; therefore, the information about the risk–benefit of antidepressants, if used while mothers are breastfeeding, is necessary for the clinician's decision. The case series and systematic data on antidepressants in breastfeeding consist mainly of selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and mirtazapine, whereas information on newer antidepressants such as agomelatine in pregnant or lactating women is rare, especially the adverse effects on the infant of the mother with PPD treated with agomelatine. To add to the limited available data, we report the case of agomelatine treatment in a breastfeeding woman with PPD. In this case report, we took advantage of the short half-life of agomelatine to reduce the potential effect on infant in the treatment of a nursing woman with PPD. The results confirm the effectiveness of agomelatine in the treatment of PPD and demonstrate the safety in breastfeeding.

Keywords: agomelatine, breastfeeding, postpartum depression

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Introduction

Postpartum depression (PPD) affects approximately 10–30% of women and impairs mother–infant interactions that in turn are important for child development.[1] Untreated PPD is likely to recur, and recurrent depression of mothers is associated with behavioral problems in offspring.[2] The management of PPD includes sleep protection, exercise, psychosocial support, cognitive–behavior therapy, interpersonal therapy, and pharmacological intervention; however, for severe PPD, antidepressants alone or with psychological intervention is recommended.[3] The US Food and Drug Administration approval of brexanolone is a breakthrough in the treatment of moderate-to-severe PPD.

Breastfeeding and treatment with antidepressant medications are not mutually exclusive. The benefits of breastfeeding for maternal and infant health are well established. Infant exposure through lactation must be considered when using antidepressants. Therefore, clinicians must carefully weigh up risks and benefits of antidepressant use in mothers who wish to breast-fee. The case series and systematic data on antidepressants in breastfeeding consist mainly of selective serotonin reuptake inhibitors (SSRIs),[4–7] serotonin–norepinephrine reuptake inhibitors (SNRIs),[8–10] and mirtazapine.[11–13] The safety profile of SSRIs during lactation is confirmed; all SSRIs pass minimally into breastmilk at a level considered compatible with breastfeeding and have no severe adverse events reported in exposed, healthy full-term infants.[14] In all SSRIs, paroxetine and sertraline are preferred as first-line choice in nursing women who need an antidepressant treatment,[15] whereas there are not enough data available to come to a conclusion on the safety of SNRIs and mirtazapine during lactation.[10,12]

To date, information on newer antidepressants such as agomelatine during lactation is rare. To add to the limited available data, we report the case of agomelatine treatment in a breastfeeding woman with PPD. In this case report, we review the case of a woman with severe PPD who was effectively treated with agomelatine, and no

adverse event associated with agomelatine was found in her or her infant with breastfeeding during treatment.

Case report

A 33-year-old Chinese woman was suffering from a severe depressive episode, with sleep disturbance and guilt 4 weeks after her first delivery. The patient and her family had no history of psychiatric disorders. A routine examination, including a physical examination and laboratory tests, was normal. She was diagnosed with major depressive disorder (MDD) with peripartum onset according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition. She agreed to take antidepressants but insisted on continuing to breastfeed her child. She was treated with agomelatine, 25 mg per night, at home. To avoid concentration of agomelatine in breastmilk and potential effect on her baby, she was instructed to feed the infant before taking agomelatine, then stop breastfeeding until she pumped all milk the next morning. She could breastfeed her child during daytime as usual. She took agomelatine for 12 weeks and came back to see her doctor every 2–4 weeks for assessment with the Quick Inventory of Depressive Symptomatology-Self Report (16-items).

At week 4, most of the symptoms were greatly improved, especially sleep disturbance. She achieved remission after 8 weeks treatment. The biochemical tests were normal for her and the infant. The development of the infant was normal. No adverse event related to agomelatine was reported during 12 weeks' treatment and after discontinuation of agomelatine.

This case report was approved by the Ethics Committee Review Board of Beijing Anding Hospital (approval no. 2020-ky-1h) and written informed consent for publication of the medical data was obtained from the patient.

Discussion

Agomelatine is a new antidepressant with unique melatonin-receptor type M1 and M2 agonism in suprachiasmatic nucleus and serotonergic receptor 5-hydroxytryptamine receptor 2C (5-HT-2C) antagonism. Agomelatine has higher efficacy compared with SSRIs and SNRIs in the treatment of MDD.[16] In a recent meta-analysis, agomelatine was proved to have better acceptability with fewer dropouts than placebo and other antidepressants.[17] Because of its unique chronobiotic effects on sleep and circadian disturbance, agomelatine is the only one recommended as a first-line treatment for MDD with sleep disorders.[18] Moreover, agomelatine has advantages in improving anhedonia, cognition, and less effects on sexual function and weight. Unfortunately, studies regarding the safety profile of agomelatine in pregnant or lactating women are scarce.

In this case, we selected agomelatine as the first choice for the following reasons. Firstly, agomelatine has the shortest half-life among all antidepressants. It also has high protein-binding ability. Both properties may minimise the potential plasma concentration in the infant. In general, from a pharmacokinetic point of view, medications with shortest half-life and highest protein-binding ability are recommended for nursing infants.[19] Secondly, the patient suffered from severe sleep disturbance, and the potential of agomelatine to regulate sleep and restore circadian rhythm could reduce the use of hypnotics.

To our knowledge, this is the first case report of agomelatine use in breastfeeding. We took advantage of the short half-life of agomelatine to reduce the potential infant exposure to drug. As reported, the half-life of agomelatine is 1–2 h in the blood and breastmilk, and concentrations of agomelatine in breastmilk were undetectable within 240 min after medication.[20] Although strategies to reduce infant exposure to antidepressants have been suggested (i.e. discarding the breastmilk obtained during the peak serum level), whether such strategies produce a clinically meaningful reduction in an already low exposure has not been established.[21] This case demonstrates no adverse effects of agomelatine on the infant using reducing exposure strategy. Regarding maternal outcomes, we confirm the efficacy of agomelatine in the treatment of MDD. Moreover, this case without using any hypnotics highlights the effect of agomelatine on sleep disturbance.

The benefits of treating depression during pregnancy and lactation should be balanced against the risks associated with the treatment itself.[22] So far, pharmacotherapy of postpartum depression under breastfeeding is restricted to a limited number of antidepressants; sertraline, paroxetine, nortriptyline and imipramine are the most evidence-based medications for use during breastfeeding,[21] although they were still detectable in infant plasma.[23] According to our data and Schmidt *et al.*'s[20] findings of early depletion of agomelatine in breastmilk, it is safe for the infant

when the milk is discarded in the first 4 h. It is unnecessary to discontinue breastfeeding during treatment with agomelatine. However, the limitation of our study not having monitored the concentration of agomelatine in the breastmilk or infant's plasma should be considered when interpreting the data.

The information on the effects of agomelatine in breastfeeding is only applicable to healthy babies born at term. For those who may be potentially susceptible to adverse effects of agomelatine taken by the mother, such as premature babies or those with cardiac disease or hepatic impairment, the mothers should seek specialist advice before deciding to breastfeed. Furthermore, agomelatine does pose a risk of liver injury, which is usually reversible. Rare cases of severe and life-threatening hepatotoxicity have also occurred. Therefore, it is essential that clinicians monitor liver function frequently while prescribing agomelatine.

In conclusion, this case introduces a strategy of agomelatine for PPD and demonstrates a potentially safe option for women to continue during lactation. The data also expand the existent literature on agomelatine in breastfeeding. Further studies investigating larger samples of patients, including plasma concentration of the child to minimize the risk of harm to the infant, are needed. This case might instigate larger studies to replicate these findings.

Conflict of interest statement

The author declares that there is no conflict of interest.

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