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LETTER TO THE EDITOR

Agomelatine in breast milk

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Introduction

Postpartum depression with a prevalence of 10–15% (Gavin *et al.* 2005) is characterized by social retreat, feelings of hopelessness and guilt as well as the inability to feel gratification in the mother's role. A combined treatment of postpartum depression with antidepressant psychopharmacotherapy and psychotherapy is to be preferred in moderate to severe depressive episodes and is the choice of the majority of mothers (Lanza di Scalea & Wisner, 2009). Under breastfeeding, pharmacotherapy of postpartum depression is restricted to a limited number of substances with current favouritism of sertraline, paroxetine and nortriptyline (Burt *et al.* 2001; Lanza di Scalea & Wisner, 2009), although all three show detectable levels in the infant's plasma (Fortinguerra *et al.* 2009).

The efficacy of the antidepressant agomelatine has broadly been demonstrated both in preclinical and clinical trials (Fornaro *et al.* 2010; Kennedy & Emsley, 2006). Due to the small impact on other receptors, only a few side-effects and good tolerance, the rates of discontinuation of treatment are low (Kennedy & Rizvi, 2010). Agomelatine has a short plasma half-life of 1–2 h and an absolute bioavailability of 5–10% due to its high hepatic first-pass metabolism.

Because neither preclinical nor clinical data exist, we sought to investigate the levels of agomelatine in the breast milk of a patient suffering from a depressive syndrome, hypothesizing that levels of agomelatine in breast milk show a plasma-equivalent early depletion.

Case report

The investigation was conducted in a 30-yr-old patient who was suffering from a depressive syndrome in the framework of a postpartum psychosis after her second delivery. Psychotic symptoms, predominately consisting of paranoia, derealization, depersonalization, auditory and visual hallucinations as well as thought disorder, lessened with 200 mg/d quetiapine. Due to a growing depressive syndrome with anhedonia, lack of affect towards the child, loss of drive and appetite as well as sleep disturbances, agomelatine was added on the seventh day of treatment. On the first three consecutive days of treatment with 25 mg agomelatine, probes of breast milk were sampled within a strict time schedule 10 min before (T1) and 30 (T2), 60 (T3), 90 (T4), 120 (T5) and 240 (T6) min after medication. Using a manual pump, 20 ml breast milk were pumped, alternating the breast at each collection. After manual mixing, probes were immediately aliquoted in non-absorbing polypropylene tubes of 1500 μl, shock-frozen in liquid N_2 and stored in a freezer at $-80\,^{\circ}C$ until further measurements were conducted. Serum probes of days 1 and 3 of the investigation were drawn 90 min (T4) after medication and also shock-frozen in fluid N_2 and stored in a freezer at $-80\,^{\circ}C$.

For the measurement, high performance liquid chromatography (HPLC) coupled with tandem mass spectrometry was performed. In brief, 0.5 ml sample (plasma or breast milk) was extracted with 5 ml diethylether including the internal standard methabenzthiazurone. The organic extract was evaporated and the residue was resolved in 0.2 ml mobile phase acetonitrile/5 mM acetate-buffer pH 3.9 (60:40). Ten μl were injected onto the HPLC-system with a chromolith C18 column (50×4.6 mm) as stationary phase. Quantification was performed after electrospray ionization with an API 4000 tandem mass spectrometer in the positive MRM mode, with ion transitions of 244.3 to 185.2 m/z for agomelatine and of 222.0 to 165.0 m/z for the internal standard, respectively. The limit of quantification as signal:noise ratio of 10 for this method was $<0.1\,\mu g/l$.

On all 3 d, concentrations of agomelatine in the milk were below the detection limit of $<0.1\,\mu g/l$ before the drug was administered (T1). Levels of agomelatine on day 1 rose after 30 (T2; $0.4\,\mu g/l$), 60 (T3; $0.8\,\mu g/l$) and 90 min (T4; $1.2\,\mu g/l$) and C_{max} with $2.0\,\mu g/l$ was reached 120 min (T5) after administration. On day 2, concentrations were under the detection limit at T2 and C_{max} of 0.78 was reached at T3. On day 3, levels of agomelatine were first detected at T4 ($1.63\,\mu g/l$) and reached C_{max} with $1.71\,\mu g/l$ at T5. On all 3 d of sampling, concentrations of agomelatine were below the detection limit within 240 min after medication (T6; see Fig. 1). Concentration of the drug in the blood, drawn at T4, was $6.4\,\mu g/l$ on day 1 and $0.2\,\mu g/l$ on day 3. Due to safety concerns, breast feeding

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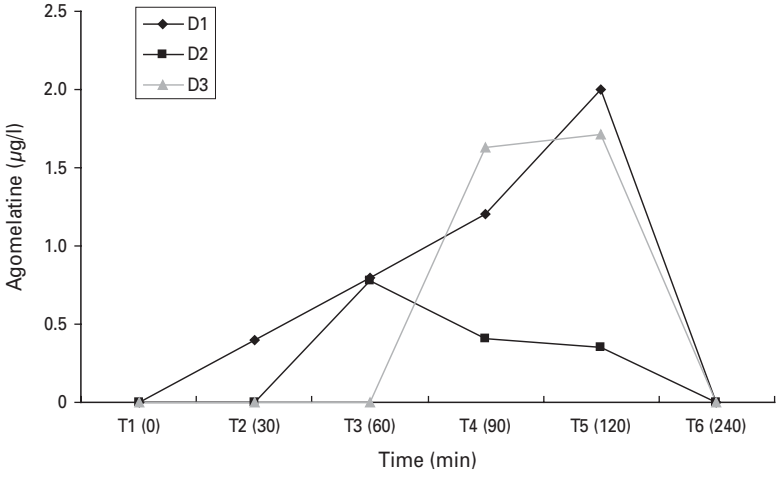

Fig. 1. Three-day course of levels of agomelatine in maternal breast milk.

was abandoned and, therefore, measurements of agomelatine levels in the infant were not conducted. The patient gave written informed consent to perform the investigation.

Discussion

In this case report, we investigated the levels of agomelatine in the breast milk in a patient suffering from a depressive syndrome within a postpartum psychosis over the course of 3 consecutive days with six measures daily. Peak levels of agomelatine in the breast milk were reached 1–2 h after medication, resembling the reported half-life in the blood (Hiemke *et al.* 2011). On all 3 d, no traces of the drug were residual 4 h after medication.

Studies investigating the long-term exposure to low doses of antidepressants are missing to date (Fortinguerra *et al.* 2009; Lanza di Scalea & Wisner, 2009). Due to the immature renal and hepatic systems, blood–brain barriers and developing neurological systems in infants, it is advisable only to apply pharmaceuticals that do not enter the child's organism and therefore lead only to undetectable infant plasma levels (Weissman *et al.* 2004). Based on our data, this requirement is achieved 4 h after medication, making the discontinuation of breast feeding during treatment with agomelatine unnecessary. This conclusion is stated under the requirement that the milk is continuously detached and discarded, as in our investigations, in the first 4 h. Whether agomelatine levels are upheld, detectable or accumulating in the milk over time when no pumping is performed beforehand, shall be studied in a further investigation. Limitations that have to be considered when interpreting the data are the possible inter-individual variation of agomelatine levels. Whether our preliminary assumption is a general finding needs to be investigated in a larger sample of breast-feeding patients. Further, the milk investigated was a mixed sample of fore-milk and hind-milk. According to the different relations of fats and proteins as well as the high protein binding of agomelatine, we should not underestimate changes in agomelatine concentrations depending on the type of milk and the point of nursing. Although investigations in other psychotropic drugs partitioning the milk showed no significant effect of detected concentrations of the drug (Rampono *et al.* 2007). Intriguingly, the plasma concentrations on day 1 were above and on day 3 below the concentration in the milk at T4. The maternal plasma levels of agomelatine found were relatively low whereas universally valid thresholds and mean values for agomelatine are not established and missing for the dose of 25 mg. A diluting effect due to the use of uncentrifugated frozen plasma probes may also have influenced the concentrations of the drug.

In conclusion, our data point to the use of agomelatine in breast-feeding mothers. Studies investigating larger samples of patients including plasma probes of the child in order to minimize the risk of harm to the infant are warranted.

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Statement of Interest

None.

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