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Pregnancy exposure to quetiapine – Therapeutic drug monitoring in maternal blood, amniotic fluid and cord blood and obstetrical outcomes

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ABSTRACT

Rationale: This prospective study is the first to measure and correlate quetiapine concentrations in maternal blood, amniotic fluid and umbilical cord blood to account for the distribution of quetiapine.

Methods: Concentrations of quetiapine are quantified in seven mother infant pairs at the time of delivery. Data are provided as median values, first (Q1) and third (Q3) quartiles and ranges. To account for the penetration ratio, the concentration of quetiapine in amniotic fluid and cord blood was divided by maternal concentrations. Correlations between daily dosage, maternal serum and umbilical cord blood concentrations were computed for seven patients while calculations for amniotic fluid were only available for six mother-infant pairs.

Results: The median daily dosage of quetiapine was 300 mg (Q1: 300 mg, Q3: 600 mg, range 200–800 mg). There was a strong and significant correlation between maternal serum and cord blood concentrations ($r = 0.893$, $p = 0.007$). The median penetration ratio into fetal circulation was 0.18 (Q1: 0.16, Q3: 0.32; range 0.13–0.42), suggesting a low penetration. The median penetration ratio into amniotic fluid was 0.44 (Q1: 0.15, Q3: 0.96; range 0.09–1.70).

Conclusions: Quetiapine concentrations in amniotic fluid and cord blood give evidence that quetiapine is constantly accessible to the fetus with a relatively low penetration ratio. A high correlation between maternal serum and umbilical cord blood concentrations highlights a predictive role of quantifying drug concentrations in maternal serum for assessing drug concentrations in fetal circulation. Findings support the important role of therapeutic drug monitoring in supporting the efficacy and safety of psychopharmacological treatment strategies in highly vulnerable populations.

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1. Introduction

Second generation antipsychotics (SGA) are less likely to affect fertility than first generation antipsychotics (FGA) and unimpaired fecundity increases the number of pregnancies in patients with schizophrenia spectrum and other psychotic disorders (Huybrechts et al., 2016). Hence, the prescription rates of antipsychotics during pregnancy have increased over the last years (Toh et al., 2013). A recent study by Vigod et al. suggests that antipsychotic drug use in pregnancy does not independently increase the risk for important short term maternal medical and perinatal outcomes (Vigod et al., 2015). However, clinical

practice has evolved without developing comprehensive knowledge about the safety profiles of both, FGA and SGA for pregnant women and their unborn children. Great uncertainty is further rising from discrepancies in pharmacoepidemiological data. More recent data showed no increased risk of congenital malformations (Cohen et al., 2016; Huybrechts et al., 2016), while other studies reported an up to 2-fold enhanced risk for cardiac malformations in children whose mothers were under antipsychotic treatment during pregnancy (Habermann et al., 2013; Kulkarni et al., 2014; Reis and Kallen, 2008). Adverse obstetric outcomes include low birth weight (McKenna et al., 2005), preterm delivery (Sadowski et al., 2013), poor neonatal adaptation (Sadowski et al., 2013) and gestational diabetes (Boden et al., 2012b). Data addressing long-term effects of intrauterine exposure to antipsychotics are inconclusive as well. Older data consistently report no adverse outcomes, while more recent data showed early neuromotor performance deficits (Peng et al., 2013; Stika et al., 1990).

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The mechanisms of underlying drug effects on fetal development remain widely unraveled while confounding factors such as crucial parents' characteristics, e.g. paternal age and smoking habits, are often barely considered (Boden et al., 2012b; Lin et al., 2010b). Hence, the prescription of antipsychotics during pregnancy remains a major challenge for clinicians, who have to consider possible drug-associated effects on both, pregnant women and their unborn infants. The clinical decision-making processes are essentially perplexed by the natural course of the untreated psychiatric diseases and by considering potentially occurring negative effects of a psychopharmacological treatment on the fetus. Data deriving from case reports suggest adverse effects on the children's outcome in untreated maternal affective disorders as well as untreated schizophrenia. Effects appear as intrauterine growth retardation (Grote et al., 2010; Uguz et al., 2011), microcephaly (Boden et al., 2012a), neonatal hypoglycemia (Boden et al., 2012a), increased preterm delivery (Dayan et al., 2006), small gestational age and low birth weight (Diego et al., 2009; Lin et al., 2010a). The discontinuation of psychotropic medication during pregnancy is associated with an increased risk of relapse (Viguera et al., 2007) and the treatment of psychiatric diseases is further complexed by the risk of maternal suicidal behavior due to uncontrolled symptomatology (Khalifeh et al., 2016; Paulzen et al., 2015a). Putting the pieces together, treatment of psychiatric diseases during pregnancy requires balancing of risks between a minimal fetal drug exposure and a maximum of maternal stability, i.e. relapse prevention or improvement of psychopathology.

The placenta acts as the main barrier between the maternal and fetal circulation (Ganapathy et al., 2000) although it is not able to provide a fully protected environment for the fetus and a plethora of drugs manage to cross it (Eshkoli et al., 2011). Placental transfer is particularly affected by the physicochemical properties of a drug (Hutson et al., 2011). Passive diffusion of drugs across the placental barrier mainly depends on structural properties, protein binding or molecular weight of the drugs as well as on compartmental pH value. Changes in pharmacokinetic parameters and physiological conditions throughout pregnancy such as volume of distribution, renal plasma flow and glomerular filtration rate or changes in cytochrome P450 mediated metabolism influence both, drug concentrations in maternal serum as well as intrauterine drug exposition. Moreover the placenta expresses a multitude of transporters such as *p*-glycoprotein, multi-drug-resistance proteins and others facilitating or preventing the passage of xenobiotics (Giaginis et al., 2012). By offering enzyme activity such as cytochromes (CYP) or UDP-glucuronosyltransferase (UGT), the human placenta is able to metabolize a large diversity of pharmacologically active molecules eliciting or inhibiting fetotoxic effects (Giaginis et al., 2012; Reimers et al., 2011).

Evidence for the majority of the commonly prescribed SGAs demonstrates that they are able to cross the placenta to a varying degree, while data for FGAs is lacking (Newport et al., 2007; Nguyen et al., 2011; Uematsu et al., 1991). Quantifying the extent of transplacental passage or knowledge about the accumulation of a drug in amniotic fluid as an important route of fetal exposure can facilitate drug selection and ultimately provide insight into whether or not neonatal complications are directly related to drug exposure with measurable drug concentrations in amniotic fluid or fetal circulation.

Quetiapine is a second generation antipsychotic (SGA) with low potential for extrapyramidal side effects and minimal prolactin increases (Atmaca et al., 2002; Nasrallah et al., 2006). The primary pathway of quetiapine metabolism is a CYP3A4 and CYP2D6 is involved to a lesser extent (Hiemke et al., 2017). Its wide prescription follows the extended licensed indications including schizophrenia, bipolar disorders, major depressive disorder and others (Srisurapanont et al., 2004; Vieta et al., 2010). Out of the SGAs, quetiapine is one of the most frequently prescribed drugs due to its broad indication (Sadowski et al., 2013; Wichman, 2009). Despite some reports of major malformations (Habermann et al., 2013; Kulkarni et al., 2014; Sadowski et al., 2013; Yonkers et al., 2004), it is considered as a safe choice free of increased

relative risk for congenital malformations in first-trimester exposure (Ennis and Damkier, 2015; Lin et al., 2010a). The safety profile of quetiapine may be related to its relatively low placental passage compared to other antipsychotics (Newport et al., 2007).

As data on correlation patterns of quetiapine between maternal serum, amniotic fluid and umbilical cord blood is largely missing, we aimed to unravel pharmacokinetic pattern by measuring drug concentrations in these compartments. We further accounted for the relation between the applied daily doses of quetiapine and the serum- as well as the umbilical cord blood- and amniotic fluid concentrations at the time of delivery under naturalistic/clinical conditions. To account for the placental penetration, the correlation between maternal serum concentrations of quetiapine and cord blood concentration was calculated. Furthermore, the correlation between the concentration in maternal serum and amniotic fluid was calculated to account for the impact of drug accumulation in amniotic fluid as one way of fetal exposure.

2. Materials and methods

2.1. Patients

This investigation is part of an ongoing observational study on the distribution pattern of different psychotropic drugs in maternal blood, amniotic fluid and umbilical cord blood in pregnant women and their infants at the time of delivery (Paulzen et al., 2017a; Paulzen et al., 2015b). It was carried out as a collaboration between the Department of Psychiatry, Psychotherapy, and Psychosomatics, and the Department of Gynaecology and Obstetrics at the University hospital of RWTH Aachen University, Germany, since November 2012. The local Ethics Committee approved the study protocol.

Data of seven pregnant women (2 smokers, 5 non-smokers), age ranging from 24 to 37 years (mean age = 30.1 ± 4.7 ; median = 31), and 7 newborns are presented. Women received quetiapine throughout their pregnancies in daily doses of between 200 and 800 mg and were in stable clinical conditions at the time of delivery. None of the pregnant women suffered from an exacerbation of the psychiatric disease throughout their pregnancies. Last dose adaptations were done >2 weeks before delivery, so steady state conditions were available at time of delivery. One patient was under stable co-medication with 100 mg of sertraline per day and one was co-medicated with 112.5 mg of venlafaxine at the time of delivery. Moreover, two women suffered from a hypothyroidism and one from gestational diabetes and comorbid adiposity. Three of the patients were diagnosed with paranoid schizophrenia (ICD-10: F20.0), two with schizoaffective disorders (ICD-10: F25), one with major depressive disorder in stable remission (ICD-10: F33.4) and one with emotionally unstable personality disorder, Borderline type (ICD-10: F60.31). All seven mother-infant pairs provided maternal serum concentrations and umbilical cord concentrations at delivery with one exception, where amniotic fluid sample was missing (see Table 1).

3. Methods

Maternal blood, umbilical cord blood and amniotic fluid samples were taken simultaneously at the time of delivery under steady-state conditions with regard to the ingested drug but due to clinical circumstances not as trough levels. As indicator for drug concentrations in blood we used serum concentrations. Serum and amniotic fluid were prepared by centrifugation at 14,171g for 15 min. Quetiapine concentrations in maternal serum, amniotic fluid and umbilical cord blood were determined with a validated LC-MS-MS method for the determination of quetiapine as it is described elsewhere (Pan et al., 2012).

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