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Pregnancy exposure to citalopram – Therapeutic drug monitoring in maternal blood, amniotic fluid and cord blood

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ABSTRACT

Rationale: Aim of the study was to measure and correlate citalopram concentrations in maternal blood, amniotic fluid and umbilical cord blood to account for the distribution of the drug between these three compartments.
Methods: Concentrations of citalopram were measured in twelve mother infant pairs at the time of delivery. Data are provided as median values, first (Q1) and third (Q3) quartiles as well as ranges. To account for the penetration ratio into amniotic fluid and cord blood, the concentration of citalopram in was divided by the concentration in maternal serum. Correlations between daily dosage, maternal serum concentrations and umbilical cord blood concentrations were computed for twelve patients. As amniotic fluid was only available for nine mother infant pairs, appropriate calculations are provided for these mother-infant pairs.
Results: The median daily dosage of citalopram was 20 mg (Q1: 10 mg, Q3: 20 mg; range 10–40 mg). The relation between the daily dosage of citalopram and its concentrations in maternal serum was highly significant ($r = 0.667$, $p = 0.018$). Maternal serum concentrations and cord blood concentrations were positively correlated ($r = 0.790$, $p = 0.002$) with a median penetration ratio into the fetal circulation of 0.78 (Q1: 0.52, Q3: 1.16, range 0.46–1.66). The median penetration ratio into amniotic fluid was 1.8 (Q1: 1.07, Q3: 2.64; range 0.52–6.97).
Conclusions: Citalopram concentrations in amniotic fluid and cord blood give evidence that maternally administered citalopram is constantly accessible to the fetus via amniotic fluid. A high correlation between maternal serum concentrations of citalopram and umbilical cord blood concentrations highlights a predictive role of quantifying drug concentrations in maternal serum for assessing drug concentrations in the fetal circulation. Findings support the important role of therapeutic drug monitoring in maintaining the safety of pregnant women and exposed infants.

1. Introduction

Major Depressive Disorder is a leading cause of the disease burden for women of childbearing age and clinical depression occurs in 10–15% of pregnant women (Evans et al., 2001). The use of antidepressants during pregnancy has increased over the last decade with reported prevalence rates of 8 to 13% in the United States (Kallen et al., 2013; Jimenez-Solem, 2014; Huybrechts et al., 2013). The most commonly used psychotropic drugs during pregnancy are selective serotonin reuptake inhibitors followed by benzodiazepines or benzodiazepine-like drugs (Hanley and Mintzes, 2014). Antidepressant treatment strategies with selective serotonin reuptake inhibitors (SSRI) seem to be associated with minimal absolute risk rates for birth defects with the exceptions of paroxetine and fluoxetine (Alwan et al., 2016). Hence, the treatment of depression during pregnancy remains a major challenge for clinicians, who have to consider possible drug-associated effects on both, pregnant women and their infants. Clinical decision-making processes need to balance the risks of the natural course of the

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psychiatric diseases and potentially occurring negative effects of a psychopharmacological treatment. Data deriving from case reports have demonstrated adverse perinatal effects for untreated depression such as intrauterine growth retardation (Grote et al., 2010; Uguz et al., 2011), increased preterm delivery (Dayan et al., 2006) and low birth weight (Diego et al., 2009). Additionally, long-term effects such as an increased risk of future psychopathology needs to be considered (Nulman et al., 2012) and the complexity of treating psychiatric disorders is further increased by the risk of maternal suicidal behavior (Paulzen et al., 2015a; Khalifeh et al., 2016).

Although rarely investigated, some studies have demonstrated that all available antidepressants are able to cross the placenta to a varying degree (Newport et al., 2001; Hendrick et al., 2003; Ewing et al., 2015). Quantifying the extent of transplacental passage or knowledge about the accumulation of a drug in amniotic fluid as an important route of fetal exposure (Loughhead et al., 2006) 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. Two own studies have shown that measuring maternal plasma or serum concentrations of psychotropic drugs such as lamotrigine and sertraline help to predict the in-utero exposition of the infants (Paulzen et al., 2015b, 2017). The placental transfer of (psychotropic) drugs is thereby affected by the physicochemical properties of a drug (Hutson et al., 2011) as well as by pharmacokinetic parameters and physiological conditions such as protein binding, volume of distribution, renal plasma flow and glomerular filtration rate. 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 (Reimers et al., 2011; Giaginis et al., 2012).

Citalopram was introduced as one of the first second-generation antidepressants acting as a serotonin reuptake inhibitor that clinicians use for routine depression care. The primary pathway of citalopram metabolism is a CYP2C19-catalyzed *N*-desmethylation (Hiemke et al., 2011). CYP2C19 is a genetically polymorphic enzyme with extreme metabolizer genotypes contributing to variability in pharmacokinetics. Hence, dose adjustments for citalopram based on CYP2C19 have been proposed (Hicks et al., 2015). Pharmacokinetic changes during pregnancy with reduced CYP2C19 activity give particular attention to changes in citalopram concentrations during pregnancy whereas most other drugs (that are not metabolized by CYP2C19 or CYP1A2) show an increased drug clearance (Pariente et al., 2016). Citalopram has been reported to be highly penetrative into umbilical cord blood compared to other SSRIs with penetration ratios between 0.17 and 1.42 (Hendrick et al., 2003; Rampono et al., 2009) leading to a considerable fetal exposure. The prominent detection in umbilical cord blood may be explained by its pharmacological properties as citalopram is lowly protein bound compared to other SSRIs (DeVane, 1998). Prospective data for mothers under citalopram in early pregnancy reported no increased risk of major malformations (Einarson et al., 2009). Nevertheless, retrospective cohort studies demonstrated an association between citalopram prescription and congenital malformations such as neural tube and cardiac defects (Alwan et al., 2007; Pedersen et al., 2009; Louik et al., 2007) while the debate about potential effects on the newborns is still ongoing (Larsen et al., 2015). Nonetheless, the relative risk of neonatal adverse effects is considered to be relatively low (e.g. with an odds ratio (OR) between 0.86 and 1.06 for different malformations) (Reis and Kallen, 2010) and citalopram is widely prescribed in pregnant women (Larsen et al., 2015).

As data on the correlation patterns of citalopram between maternal serum, amniotic fluid and umbilical cord blood is sparse, we aimed to unravel pharmacokinetic patterns by measuring drug concentrations in these compartments. We further accounted for the relation between the applied daily doses of citalopram 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 citalopram and cord blood concentrations was calculated. Furthermore, the correlation between drug levels 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 psychotropic drugs in maternal blood, amniotic fluid and umbilical cord blood in pregnant women at the time of delivery (Paulzen et al., 2015b, 2017). It is 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. The local Ethics Committee approved the study protocol.

Data of twelve pregnant women, age ranging from 23 to 37 years (mean 31.5 ± 3.84), and 12 newborns are presented. Women received citalopram throughout their pregnancies in daily doses of 10–40 mg. Steady state conditions for drug concentrations were available at time of delivery. One patient was under stable co-medication with 15 mg of mirtazapine per day, while two suffered from an insulin-dependent gestational diabetes, both under stable insulin doses. Eight patients were diagnosed with a major depressive disorder in stable remission (ICD-10: F33.4), four with a panic disorder (ICD-10: F41.0). All twelve mother-infant pairs provided maternal serum concentrations and umbilical cord concentrations at delivery (see Table 1); while in three cases amniotic fluid samples were missing and therefore not included in the analysis.

3. Methods

Samples of maternal blood, umbilical cord blood and amniotic fluid were taken simultaneously at the time of delivery under steady state conditions 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 14,171*g* for 15 min. Citalopram concentrations in maternal serum, amniotic fluid and umbilical cord blood were determined with an isocratic HPLC system with UV detector. Chromatographic separation was conducted with a Waters Acquity® UPLC system with gradient elution on a Waters Acquity® UPLC BEH-C18 column (2.1 mm × 50 mm, 1.7-µm particle size). For quantification, a Waters Acquity® TQ detector was used. The method is linear from the designated limit of quantification of 4.0 ng/mL up to the upper limit of 612 ng/mL for citalopram. Intra- and inter-assay precision across four quality control levels were ≤ 7.6% and ≤ 6.6%, respectively.

3.1. Statistical analysis

To account for the range of daily doses of citalopram received by the patients, we divided the serum, amniotic fluid and cord blood concentrations of citalopram by the applied dose of citalopram (applied once a day), resulting in a concentration-by-dose-ratio (C/D) for citalopram in maternal serum (MS), amniotic fluid (AF) and cord blood (CB), respectively. Data are provided as median values, first (25th percentile, Q1) and third quartiles (75th percentile, Q3) as well as ranges between min and max values. The penetration ratio into amniotic fluid (for 9 patients) and cord blood of citalopram was calculated. By dividing the concentrations of citalopram in AF as well as CB by their counterpart values in MS, reflecting the penetration-ratio into amniotic fluid and cord blood, respectively. Correlations were computed to assess associations between the drug concentrations in