Journal of Affective Disorders 212 (2017) 1–6

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Sertraline in pregnancy – Therapeutic drug monitoring in maternal blood, amniotic fluid and cord blood

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ARTICLE INFO

Keywords:
Pregnancy
Depression
Antidepressants
Sertraline
Pharmacokinetics
Therapeutic drug monitoring
Amniotic fluid
Cord blood
Placental transfer

ABSTRACT

Rationale: This study is the first to measure and correlate sertraline concentrations in maternal blood, amniotic fluid and umbilical cord blood and account for distribution of the drug between these three compartments.
Methods: Concentrations of sertraline were measured in six mother infant pairs at the time of delivery. Data are provided as median values, first and third quartiles as well as ranges. To account for the penetration ratio into amniotic fluid and cord blood, the concentration of sertraline in both environments was divided by the concentration in maternal serum. Daily doses were correlated with maternal serum- and umbilical cord blood-concentrations, and serum levels were correlated with levels in amniotic fluid.
Results: The median daily dose of sertraline was 75 mg (Q1: 43.75 mg, Q3: 100 mg; range 25–100 mg). Amniotic fluid concentrations of sertraline strongly correlated with the daily dose ($r=0.833$, $p=0.039$) while neither maternal serum concentrations nor cord blood concentrations correlated with the daily dose ($p > 0.05$). The median penetration ratio for sertraline into amniotic fluid was 0.57 (Q1: 0.28, Q3: 0.75; range: 0.22–0.88). The median penetration ratio into the fetal circulation, calculated on the basis of umbilical cord blood-concentrations, was found to be 0.36 (Q1: 0.28, Q3: 0.49; range: 0.17–0.65).
Conclusions: Sertraline concentrations in amniotic fluid gave evidence that maternally administered sertraline is constantly accessible to the fetus via amniotic fluid in a manner not previously appreciated. A relatively low penetration into fetal circulation may contribute to a sufficient safety profile of sertraline during pregnancy although in our study APGAR Scores were relatively low in three infants. Our data support the important role of therapeutic drug monitoring in maintaining the safety of pregnant women and exposed infants.

1. Introduction

Extensive data regarding the safety of selective serotonin reuptake inhibitors (SSRI) provide minimal absolute risk rates, so that SSRIs are suggested as a first line medication for antenatal depression (Ram and Gandotra, 2015). A recent bayesian analysis of an enormous sample reassured the safety of the prescription of SSRIs in pregnancy with the exceptions of paroxetine and fluoxetine (Reefhuis et al., 2015).

Despite a high prevalence of depressive disorders during pregnancy and the increasing use of antidepressant drugs during pregnancy over the last years (Jimenez-Solem, 2014; Kallen et al., 2013; Thomas and Yates, 2012), there is still a lack of clinical data regarding safety of these drugs for both, pregnant women and unborn children. Furthermore, evidence supporting prescription strategies of psychotropic agents during pregnancy remains inconclusive (Schaefer, 2011). Accordingly, to enhance both, safety and efficacy of antidepressant drug treatment during pregnancy there is a need for more comprehensive data on the short- and log-term effects of antidepressant exposure during pregnancy.

Apart from possible drug-associated effects on pregnant women and their infants, pregnancy outcomes and clinical decision-making processes are also affected by the natural course of the untreated psychiatric diseases. Due to methodological limitations of relevant studies, data investigating the risks of untreated depression on both, the expectant mothers and their infants remain sparse and rather unclear. However, adverse perinatal effects such as intrauterine growth retardation (Grote et al., 2010; Henrichs et al., 2010; Uguz et al., 2011), increased preterm delivery (Dayan et al., 2006; Diego et al.,

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http://dx.doi.org/10.1016/j.jad.2017.01.019
Received 18 October 2016; Received in revised form 16 January 2017; Accepted 19 January 2017
Available online 21 January 2017
0165-0327/

2009) or low birth weight (Diego et al., 2009) have been reported. Furthermore, children of mothers with untreated or inadequately treated psychiatric diseases such as depression or psychosis might be at risk of future psychopathology (Nulman et al., 2012) or even at risk for maternal suicidal behavior due to uncontrolled symptomatology (Paulzen et al., 2015a). Hence, a major challenge for clinicians is to balance between a minimal fetal drug exposure and a maximum maternal stability, i.e. relapse prevention or improvement of psychopathology.

Although limiting the exchange of xenobiotics between mother and infant, the placenta is not able to provide a fully protected environment for the fetus (Eshkoli et al., 2011) and a plethora of drugs has shown teratogenic effects in the past. However, the placenta constitutes the sole structural barrier at the maternal-fetal interface (Ganapathy et al., 2000) and separates the maternal and fetal circulations. It performs many functions that support the maintenance of pregnancy and the normal development of the fetus but various factors can influence placental transfer, including the physicochemical properties of a drug (Hutson et al., 2011). Additional factors include pharmacokinetic parameters and physiological conditions such as protein binding, volume of distribution, renal plasma flow and glomerular filtration rate. 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). Through 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).

All available antidepressant drugs are able to cross the placenta to a varying degree (Hendrick et al., 2003; Newport et al., 2001). 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.

Sertraline (SERT) is a naphthalenamine derivative, acting as SSRI. It belongs to the most commonly prescribed antidepressants and has been shown to provide various comparative advantages in terms of efficacy comparing to other antidepressants (Cipriani et al., 2009; Kaplan and Zhang, 2012). Recent data support a sufficient reproductive safety profile (Gadzhanova and Roughead, 2015; Reefhuis et al., 2015) with daily dosages below 150 mg suggested as a safe treatment option during pregnancy (Roca et al., 2011). Sertraline is primarily metabolized through the liver by N-desmethylation, catalysed via CYP2B6 and to a lesser extent via CYP2C19, CYP2C9, CYP3A4, and CYP2D6 (Kobayashi et al., 1999; Xu et al., 1999) with a terminal half-life time of 26 h. *In vitro* data suggest a high affinity of sertraline for the efflux transporter P-glycoprotein (*p*-gp) (Wang et al., 2008). This might explain a lower fetal access of sertraline compared to other antidepressants (Hendrick et al., 2003), since P-gp comprises a major efflux transporter on the maternal side of the placenta limiting the passage of various xenobiotics (Mason et al., 2011). An increase of P-gp activity during ongoing pregnancy may essentially contribute to this function (Hebert et al., 2008) but sertraline may above that inhibit a P-gp activity with undetermined maternal and fetal consequences (Feghali et al., 2015). Umbilical cord serum samples support a lower extent of placental transfer of sertraline and thereby lower infant exposure for sertraline compared with other antidepressants (Hendrick et al., 2003; Rampono et al., 2004, 2009). The low infant exposure may contribute to the sufficient reproductive safety profile eventually lacking infant serotonergic overstimulation outcomes such as neurodevelopmental symptoms as reported for other SSRIs (Laine et al., 2003).

Aim of our study was to analyse the distribution pattern of sertraline in maternal serum, amniotic fluid and umbilical cord blood, to account for the relation between the applied daily doses of sertraline and the serum- as well as the umbilical cord blood concentrations and concentrations in amniotic fluid at the time of delivery under naturalistic/clinical conditions.

2. Materials and methods

2.1. Patients

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

Data of six pregnant women, age ranging from 23 to 37 years (mean age =31.66 ± 5.2; median =32.5), and 6 newborns are presented. Women were treated throughout their pregnancies with sertraline in daily doses of between 25 and 100 mg. The last dose adaptions were done more than 2 weeks before delivery so steady state conditions were available at time of delivery. One patient was under stable co-medication with 900 mg quetiapine per day at the time of delivery. Five of the patients were diagnosed with a depressive episode in stable remission, one with schizoaffective disorder. All six mother-infant pairs provided maternal serum concentrations, amniotic fluid concentrations and umbilical cord concentrations at delivery (see Table 1).

2.2. Methods

The present study is a naturalistic prospective investigation of sertraline concentrations in maternal serum and amniotic fluid in six women and umbilical cord blood of their six newborns. Blood was taken at the same time as delivery at steady-state conditions with regard to the ingested drug but due to clinical circumstances not as trough levels. As indicator for drug levels in blood we used serum concentrations. Serum was prepared by centrifugation of blood samples at 14,171*g* for 15 min. Sertraline 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 1.0 ng/mL up to the upper limit of 392 ng/mL for sertraline. Intra- and inter-assay precision across four quality control levels were ≤5.7% and ≤7.6%, respectively.

2.3. Statistical analysis

To account for the placental penetration, the correlation between maternal serum concentrations of sertraline and the cord blood concentration was calculated. Furthermore, the correlation between maternal serum and amniotic fluid was computed to account for the impact of drug accumulation in amniotic fluid as one way of fetal exposure.

A concentration-by-dose- (C/D) ratio [in (ng/mL)/(mg/day)] for sertraline in maternal serum (MS), amniotic fluid (AF) and cord blood (CB), was calculated by dividing the serum-, amniotic fluid- and cord blood-concentrations of sertraline by the applied dose of sertraline. Additionally, the penetration ratio into the amniotic fluid and cord blood of sertraline was calculated. For this purpose the concentration of sertraline in AF as well as in CB were divided by their counterpart values in MS, reflecting the penetration-ratio into amniotic fluid and cord blood, respectively. Data are provided as median values, first