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ORIGINAL ARTICLE

Antidepressants in breast milk; comparative analysis of excretion ratios

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Abstract

Despite increasing prescription rates of antidepressants in pregnant and breastfeeding women over the past decades, evidence of drug exposure for neonates through lactation is very sparse. Concentrations of three antidepressants citalopram, sertraline, and venlafaxine were measured in maternal blood and breast milk in 17 women receiving antidepressant therapy during breastfeeding period. We also computed concentration-by-dose-ratios (C/D) and milk to serum (plasma) penetration ratios (M/P). Non-parametric tests were applied. Serum concentration of citalopram and daily dosage correlated positively while daily dosage and mother milk concentration did not (rho = 0.939, $p = 0.005$, and rho = 0.772, $p > 0.05$ respectively). A significant correlation was also found between serum and milk concentrations (rho = 0.812, $p = 0.05$). Venlafaxine daily dosage correlated positively with the active moiety milk concentration (rho = 0.949, $p = 0.014$). No significant correlations were reported for sertraline. The amount of antidepressant concentrations to which neonates may be exposed, assessed as absolute infant dose (AID), was particularly low with the highest median AID being 0.16 mg/kg/day for venlafaxine. No significant difference was detected for the M/P ratios between different drugs ($p > 0.05$), whereas the comparison of C/D ratios revealed lower values in the sertraline group, with the highest values reported for citalopram group ($p = 0.007$ for serum concentrations and $p = 0.008$ for mother milk). Findings suggest that breastfeeding under antidepressant treatment constantly exposes children with measurable drug concentrations. As daily dosage and serum concentration of the antidepressants did not predict drug concentrations in mother milk, measuring of drug concentrations in milk helps to quantify drug exposure during breastfeeding. More data—even data of drug concentrations in breastfed children—are needed to better assess the effects of drug exposure on children's development.

Keywords Therapeutic drug monitoring · Pregnancy · Antidepressants · Lactation

Introduction

Antidepressants are increasingly prescribed during pregnancy and lactation (Thomas and Yates 2012, Kallen et al. 2013, Jimenez-Solem 2014). While the effects of in-utero exposition with antidepressants are more frequently investigated (Paulzen et al. 2017a, Paulzen et al. 2017b), data about antidepressant excretion into breast milk and hence the exposition of breastfed infants are sparse and remain inconsistent. Accordingly, recommendations regarding breastfeeding under antidepressant treatment are rarely available and breastfeeding women often choose non-pharmacological treatment options in postpartum depression (Pearlstein et al. 2006). Reported adverse effects include irritability, weight loss or poor weight gain, and infant hypotonia for widely prescribed antidepressants such as doxepin, citalopram, and fluoxetine, while nortriptyline, paroxetine, and sertraline were suggested for postpartum depression in breastfeeding women (Weissman et al.

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2004). A mechanism underlying some of these adverse reactions includes serotonergic overstimulation due to infant exposure with selective serotonin reuptake inhibitors (SSRI) through breastmilk (Müller et al. 2013). Another review of case reports and pharmacokinetic investigations reported no adverse reactions across breastfed infants of mothers receiving antidepressants (Misri and Kostaras 2002), a conclusion replicated in a small study (Berle et al. 2004). However, more recent reviews converge upon a low incidence of serious adverse effects in nursing infants (Whitby and Smith 2005, Payne 2007). Evidence regarding long-term effects of antidepressants via mother milk is barely available (Lanza di Scalea and Wisner 2009).

Despite the lack of evidence implying a clear causality, the effect of psychotropic agents on breastfed infants has been linked with the ability of a drug to penetrate into the mother milk (Whitby and Smith 2005). Consequently, even if there is no definitive consensus regarding the best nursing infant's drug exposure indicator, the drug amount detected in breast milk is referred as a reliable measure for the drug safety profile. Based on an average daily milk intake of 150 ml per kg body weight per day, the daily drug dose ingested by the infant can be calculated using the milk drug concentration (Berle and Spigset 2011). Psychotropic drugs are designed to cross the blood–brain barrier; hence, they represent lipophilic compounds that easily enter breast milk (Nulman et al. 2003). However, the degree of transfer into breast milk may vary for each agent depending on its pharmacological properties such as protein binding, milk lipid content, and maternal drug serum concentration (Whitby and Smith 2005, Stowe et al. 1997). Therefore, a major additional challenge for clinicians is to balance between minimal infant drug exposure and maximum maternal stability, taken into account the increased vulnerability for psychiatric disorders during the postpartum period (Brockington 2004).

Sertraline (SERT) is a highly SSRI without significant affinity to the norepinephrine transporter but with a high affinity to the dopamine transporter. It shows linear pharmacokinetics when prescribed at doses between 50 and 200 mg daily with a half-life of 22–36 h. SERT is primarily metabolized via CYP2B6 and to a lesser extent via CYP2C19, CYP2C9, CYP3A4, and CYP2D6 (Hiemke et al. 2017). It belongs to the most commonly prescribed antidepressants in nursing women (Payne 2007, Eberhard-Gran et al. 2006) and is considered to be a safe treatment option for depression during lactation (Gentile 2007), although data suggest a high interindividual variability of its transfer into mother milk (Whitby and Smith 2005). Adverse reactions following infant exposure to SERT have been barely reported (Kristensen et al. 1998, Whitby and Smith 2005, Hendrick et al. 2003, Wisner et al. 2006).

Citalopram (CIT) acts as SSRI as well. CIT is primarily metabolized via CYP2C19 to desmethylcitalopram without clinical significance (Hiemke et al. 2018). Additional pathways include CYP3A4 and CYP2D6 (Hiemke et al. 2018). CIT displays linear pharmacokinetics with a half-life of 33 h (Baumann 1996). Case reports in mother-infant dyads displayed a considerable penetration ratio in mother milk, while mild symptoms such as restlessness and irritability have been described (Schmidt et al. 2000, Jensen et al. 1997, Spigset et al. 1997, Franssen et al. 2006). In one case, researchers suggested that the adverse reactions were drug withdrawal effects rather than directly drug-induced effects (Franssen et al. 2006). So far, CIT is not considered as a first-line treatment in breastfeeding women (Eberhard-Gran et al. 2006, Gentile 2007). Nevertheless, a study detecting a comparably high transfer into mother milk reported normal development of infants at age of 1 year (Heikkinen et al. 2002). Furthermore, a bigger cohort study concluded that citalopram prescription during lactation was safe (Lee et al. 2004).

Venlafaxine (VEN) is a selective serotonin and noradrenaline reuptake inhibitor (SSNRI) that is mainly metabolized by CYP2D6 leading to formation of the active metabolite O-desmethylvenlafaxine (ODV) (Klamerus et al. 1992). Therefore, the combined concentration of venlafaxine and ODV (active moiety, AM) is the most relevant measure (Hiemke et al. 2018). The half-life time of VEN is 14–18 h, the half-life time of ODV is 10–17 h. Clinical data suggest venlafaxine as an efficient treatment option for postpartum depression (Cohen et al. 2001), although evidence regarding infant exposure are limited. The transfer into mother milk has been reported to be high (Berle et al. 2004, Ilett et al. 1998, Misri et al. 2006).

The aim of our study was to analyze the distribution pattern of three antidepressant agents in maternal serum and mother milk, to account for the relation between the applied daily doses of drugs and the serum—as well as the mother milk concentrations shortly after delivery under naturalistic/clinical conditions. To account for the penetration into breast milk, the correlation between maternal drug concentrations in serum and breast milk was calculated. Penetration ratios were compared between antidepressant agents.

Materials and methods

Patients

This investigation is part of an observational study examining the distribution pattern of different psychotropic drugs in maternal blood and breast milk in women undergoing antidepressant therapy during breastfeeding period. It is 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. Written informed consent was obtained from each patient before collection of maternal serum and breast milk samples. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Data of 17 pregnant women, age ranging from 23 to 40 are presented. Women were treated with different antidepressant agents; a group was medicated with sertraline (R_S, $n = 6$), a group was medicated with citalopram (R_C, $n = 6$), and the third one with venlafaxine (R_V, $n = 5$). No dose adaptions were reported for at least 2 weeks before collection of maternal serum and breast milk samples. Seven patients had a diagnosis of hypothyroidism and were substituted with levothyroxine in fixed daily doses of between 25 and 100 μg, while four of them were receiving oral iron supplementation. One of the patients in the sertraline group presented postpartum hypertension and received ramipril 5 mg/day and methyldopa 1500 mg/day. One of the venlafaxine-medicated mothers was a smoker. In the citalopram group, one patient received an antihypertensive treatment with metoprolol 100 mg/day, while another one suffered from diabetes type I receiving a daily treatment with 26 units of long-acting insulin and 26–28 units of rapid-acting insulin at meal times for regulation of blood sugar levels. All patients were diagnosed with a depressive episode in stable remission, in one case there was a comorbidity of a generalized anxiety disorder.

Methods

The present study is a naturalistic prospective investigation of antidepressant drug concentrations in maternal serum and mother milk in 17 mothers. Samples were collected between day one and day 14 after delivery. In all cases other than one blood was taken simultaneously with mother milk 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. In the case of venlafaxine-medicated mothers, we also measured the concentration of the active metabolite, ODV and consequently calculated the active moiety, AM, (VEN + ODV), consistently reported as of prominent pharmacological action (Hiemke et al. 2018). Moreover, based on the levels in serum and milk, we calculated the metabolite to parent ratio (MPR) of venlafaxine (ODV/VEN), which is considered as a biomarker for the clearance of venlafaxine (Shams et al. 2006). Serum was prepared by centrifugation of blood samples at 14,171 g for 15 min. Drug concentrations in maternal serum and mother milk were determined as described elsewhere (Paulzen et al. 2017b, Paulzen et al. 2017a, Bhatt et al. 2005).

Quantification of antidepressants

Citalopram concentrations in maternal serum and mother milk were determined with an isocratic high-performance liquid chromatography (HPLC) system with ultraviolet detector. Chromatographic separation was conducted with a Waters Acquity® ultra-performance liquid chromatography (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.

Sertraline concentrations in maternal serum and mother milk 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.

Quantitative analyses of venlafaxine and O-desmethylvenlafaxine were carried out by LC-MS/MS. 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 504 ng/mL for venlafaxine and 3.0 ng/mL up to the upper limit of 721 ng/mL for O-desmethylvenlafaxine. Intra- and inter-assay precision across four quality control levels were ≤ 4.4% and ≤ 5.7% for venlafaxine and ≤ 4.2% and ≤ 6.6% for O-desmethylvenlafaxine, respectively.

Statistical analysis

To account for the range of doses of antidepressants received by the patients, we divided the serum and milk concentrations by their applied daily dose (applied once a day), resulting in a concentration-by-dose-ratio (C/D) of antidepressants for serum and mother milk respectively. Additionally, the milk to serum (plasma) ratio (M/P) was calculated. For this purpose, the drug concentration in mother milk was divided by their counterpart values in maternal serum, reflecting the penetration-ratio. The absolute infant dose (AID) was calculated as

the total drug amount excreted in the mother's milk and consumed by the infant assuming a daily infant milk intake of 0.15 l per kg body weight (Bennett 1996) according to $AID = C_{milk} \times V_{milk}$. Data are provided in mg per kg body weight per day (Table 1). Correlations were computed to assess the relation between drug concentrations in maternal serum and breast milk, as well as the relation of these concentrations with the daily dose of antidepressants. In case of venlafaxine, the analysis included the active metabolite (ODV) as well the active moiety (sum of parent compound and active metabolite, VEN + ODV). Due to the small sample size, non-parametric tests such Spearman's rank correlation coefficient (rho), Kruskal–Wallis and Mann–Whitney *U* test were used to analyze the data. Statistical analyses were conducted with SPSS (version 21, IBM, Armonk, NY, USA).

Results

Demographic characteristics, data on daily doses, serum, and breast milk concentrations as well as absolute infant doses are shown in Table 1. The average daily dose of sertraline was 54.16 mg (SD 24.57), of citalopram 21.67 mg (SD 7.53), and of venlafaxine 97.14 mg (SD 50.85).

The daily dose of sertraline neither correlated with the drug concentration in serum (rho − 0.338, $p = 0.512$) nor in milk (rho − 0.169, $p = 0.749$) and no correlation was found between the drug concentration in serum and milk (rho 0.371, $p = 0.468$). Serum concentration of citalopram and daily dosage correlated positively while daily dosage and mother milk concentration did not (rho = 0.939, $p = 0.005$, and rho = 0.772, $p > 0.05$ respectively). A significant correlation was also found between serum and milk concentrations of citalopram (rho = 0.812, $p = 0.05$).

In case of venlafaxine, the daily dose did not correlate with the active moiety drug concentration in serum (rho 0.316, $p = 0.604$), but with the active moiety milk concentration (rho 0.949, $p = 0.014$); this finding was driven by the correlation between daily dosage and the ODVEN mother milk concentration (rho 0.949, $p = 0.014$). In case of the parent drug VEN, the daily dose neither had a predictive role for the VEN concentration in serum nor in milk (rho 0.527, $p = 0.361$ for both). Likewise, no correlation was detected between daily dose and serum ODV concentration (rho 0.527, $p = 0.361$). Finally, no significant correlation was observed between the active moiety serum concentration and the milk concentration of active moiety (rho 0.3, $p = 0.624$).

Especially for venlafaxine, we calculated the metabolite to parent ratio (MPR) in serum and milk. The mean MPR in serum was 7.03 (SD = 5.59), while the mean MPR in milk was 6.81 (SD = 7.5). MPR in serum correlated positively with the corresponding MPR in milk (rho 0.9, $p = 0.037$).

Table 1 Patients' demographic characteristics, median drug serum, and milk concentrations in the different groups

Group	Citalopram	Sertraline	Venlafaxine (VEN)	ODV	AM (VEN + ODV)
Number	6	6	5	5	5
Age (years)	33.17 (25–39)	32.5 (23–37)	32.2 (28–40)		
DD (mg/day), median (range)	20.0 (10–30)	50 (25–100)	75.0 (37.5–150)		
Serum concentration median, (range)	56.45 (36.4–174.0)	9.55 (3.30–17.80)	38.0 (10.0–265.0)	169.0 (84.0–424.0)	240.9 (94.0–462.0)
Milk concentration median, (range)	111.5 (41.5–260.0)	11.3 (3.6–35.7)	102.0 (7.5–568.0)	371.0 (72.0–1031.0)	514.0 (79.5–1086.0)
AID (mg per kg b.w./day), median (range)	0.0167 (0.0062–0.0.0390)	0.0016 (0.0005–0.0054)	0.015 (0.001–0.0852)	0.056 (0.011–0.155)	0.077 (0.0119–0.1629)

AID absolute infant dose per kg body weight, *AM* active moiety, *b.w.* body weight, *DD* daily dose, *ODV* O-desvenlafaxine, *VEN* venlafaxine concentration. Serum concentrations are provided in ng/mL

The concentration-by-dose-ratio (C/D) was calculated using the following formula: antidepressant drug concentration in ng/mL divided by the prescribed dose in mg/day [(n/ml)/(mg/day)] (Reis et al. 2004). C/D ratios and the M/P ratios are shown in Table 2 and Fig. 1.

For all compounds, M/P ratios were above one, reflecting higher milk than blood drug concentrations maybe as a result of the high lipophilicity of the drugs. We then compared the C/D ratios for serum and milk as well as the M/P ratios between the three groups with a Kruskal–Wallis test. For venlafaxine, we used in all cases the clinically relevant active moiety. Regarding the comparison of C/D values, we observed significant differences with values for both, serum and milk being higher in the citalopram-medicated group, followed by venlafaxine patients, while sertraline-medicated mothers had the lowest values ($p = 0.007$ for serum concentrations and $p = 0.008$ for mother milk). No significant difference was detected for the M/P ratio between the groups ($p = 0.487$). Additionally, we compared the M/P ratio of VEN and the M/P ratio of the active metabolite ODV without significant differences ($p > 0.05$).

Discussion

To our knowledge, data on the distribution pattern of antidepressants in maternal blood and in mother milk, hence the exposition of breastfed infants with psychotropic drugs is sparse. Nevertheless, breastfeeding and antidepressants are not considered mutually excluded. Our prospective study is part of an ongoing observational approach to determine the distribution of different psychotropic drugs by comparing maternal blood concentrations and mother milk concentrations to better characterize the degree of transfer into mother milk helping to assess infants' exposure to antidepressants. Therapeutic drug monitoring has proven a valuable clinical tool aiming patient-matched and safe psychopharmacotherapy, even during pregnancy and lactation (Hiemke et al. 2018).

All three antidepressants were found in mother milk contrasting older data that—at least in some cases—reported no measurable concentrations in mother milk ,e.g., for venlafaxine (Ilett et al. 1998). Daily doses of the antidepressants did not correlate with drug concentrations in milk except from venlafaxine. This correlation is driven by active metabolite concentrations since a similar correlation was observed between the applied daily dose and ODV milk concentrations. Apparently, pharmacokinetic and physicochemical properties of ODV account for this finding, although no differences were reported in penetration ratios between parent compound and active metabolite. Nevertheless, the metabolite to parent ratios in serum correlated to the ratios in milk suggesting comparable excretion properties for both compounds. Regarding the relationship between drug serum and milk concentrations of antidepressants, we detected a significant trend in case of citalopram. This finding might be of clinical relevance, since citalopram is regarded as highly penetrative into milk, albeit in our cases not more than other antidepressants. It may be helpful for clinicians to target minimal effective plasma or serum concentrations of citalopram leading to minimal infant exposure via mother milk.

One of the major findings in our study is the very low amount of antidepressant drug concentrations to which infants are exposed, expressed as the absolute infant dose, AID. Even when generously assuming an oral bioavailability of 100% across groups, the highest median AID is 0.16 mg/kg/day in case of active moiety of venlafaxine (corresponding with 0.8 mg/day for an infant weighting 5 kg), with other drugs following. Hence, no clear causality between infant adverse reactions and drug concentrations in milk has been established. Nevertheless, considering this minimal amount of a drug, received by an infant, we conclude that there is no reason not to recommend breastfeeding despite theoretical risks based on pharmacological principles. However, there are hints for enhanced risks for serotonergic toxicity, preterm birth, or major malformations following SSRI exposure (Laine et al. 2003; Eke et al. 2016; Berard et al. 2017), although clinical data are not consistent and less simple to understand (Ornoy and Koren 2017). In particular, the increased risk for some abnormalities may be driven by higher rates for only one agent, e.g., paroxetine for cardiac deficits (Gentile 2005). Although milk to plasma/serum ratios did not differ between the groups, the comparison of the C/D values for serum and milk might support a recommendation of sertraline during breastfeeding period compared to the other two

Table 2 Concentration-by-dose-ratio (C/D) of antidepressants for serum and milk as well penetration ratios (M/P) for each drug (median values with ranges)

Group	Citalopram	Sertraline	Venlafaxine (VEN)	ODV	AM (VEN + ODV)
Serum C/D, median (range)	3.42 (2.45–5.8)	0.23 (0.07–0.39)	0.51 (0.11–1.77)	2.13 (1.13–5.65)	2.89 (1.49–6-16)
Milk C/D, median (range)	4.4 (3.75–9.05)	0.228 (0.07–0.71)	1.36 (0.21–3.79)	3.17 (2.02–6.87)	6.65 (2.23–7.24)
M/P, median (range)	1.65 (0.78–2.83)	1.251 (0.22–2.29)	2.14 (0.75–3.76)	1.49 (0.86–4.96)	1.41 (0.85–4.85)

AM active moiety, *C/D* concentration-by-dose-ratio, *M/P* penetration ratio, *ODV* O-desmethylvenlafaxine, *VEN* venlafaxine concentration. C/D values are provided in (ng/mL)/(mg/day)

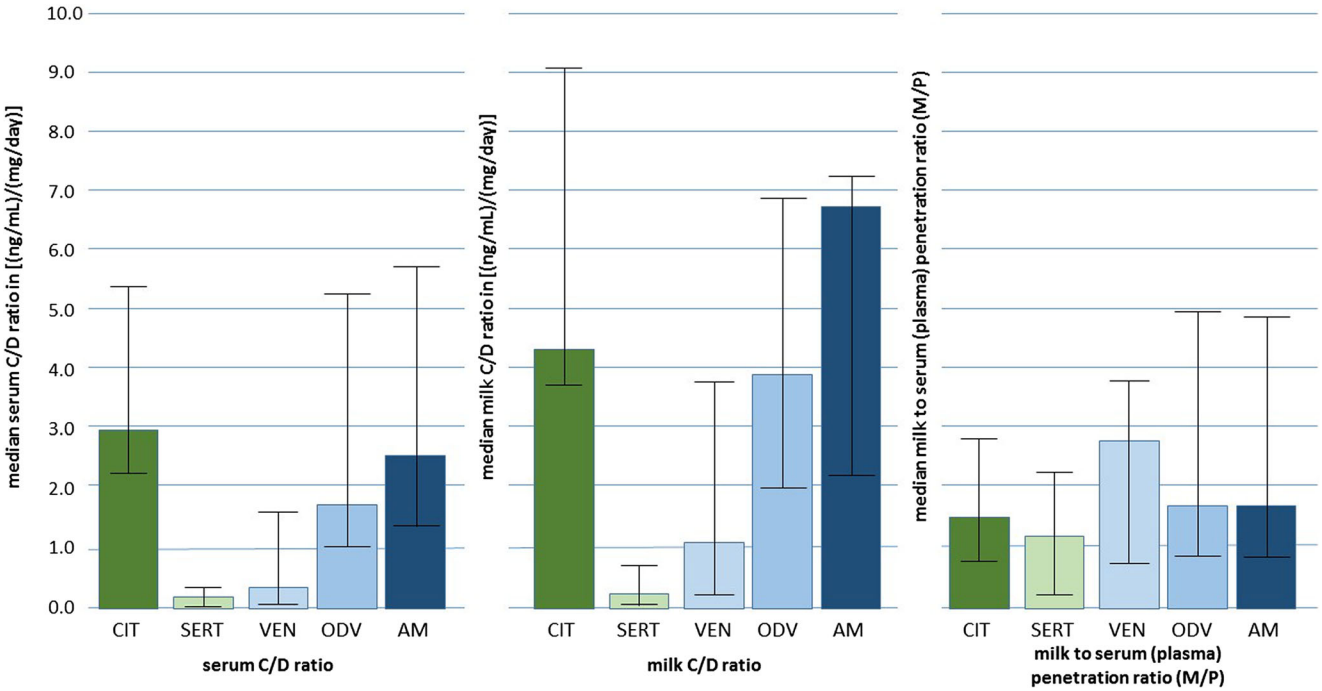

Fig. 1 Serum and milk dose-adjusted serum concentrations (C/D) (left and middle) and milk to serum (plasma) penetration ratio (M/P) right

antidepressants; this follows the lower values for both of parameters in sertraline-medicated nursing mothers. Hence, a minimal infant drug exposure is expected for sertraline. This notion can be juxtaposed with alternative strategies to minimize infant exposure to maternal medication such as discarding milk obtained at the peak serum level, although these strategies are yet to be established (Lanza di Scalea and Wisner 2009). A possible mechanism underpinning the differences for serum and milk C/D ratios might comprise the varying oral bioavailability of the three antidepressants. Pharmacokinetic studies have reported higher oral bioavailability rates for venlafaxine and citalopram than for sertraline (Troy et al. 1997, DeVane et al. 2002, Bezchlibnyk-Butler et al. 2000). These three agents further differ regarding protein binding. Note that sertraline is highly protein bound, while venlafaxine and citalopram are considerably less (Preskorn 1993, Preskorn 1996). Protein binding's role in drug penetration into milk has been already highlighted (Begg et al. 1992). Hence, we would have expected significant differences for the penetration ratio between the three drugs, which was, however, not the case. Apparently, there are additional milk-specific mechanisms underlying the excretion of drugs into mother milk (Burt et al. 2001).

Nevertheless, our data suggest that infant development occurs in a continuous environment of a pharmacologically active drug when breastfeeding mothers are treated with antidepressants. Infant exposure to antidepressant agents can be more clearly defined by an improved understanding of the mechanisms of infant exposure and the factors that influence such pathways. Hence, measuring drug concentrations in milk facilitates the understanding of infant drug exposure during lactation. The need for further research in order to warrant drug safety and efficacy during lactation remains unmet. Regardless of the therapeutic regimen, the cardinal aspect of the postpartum depression treatment remains the careful monitoring of mother and infant including therapeutic drug monitoring.

Bigger samples are undoubtedly necessary. Another limitation of our data regards the lack of an incomplete description of the history of the mother's depression. Data such as onset and duration of illness as well as pharmacological treatment were not always present and could therefore not be included. When interpreting the drug milk determinations and the penetration ratio, there is a considerable limitation. Daily drug milk fluctuations have been consistently reported over the course of the day (Whitby and Smith 2005, Stowe et al. 1997). Therefore, multiple measurements at different times of the day would have provided a more precise determination of the penetration ratio. However, in our case, only single measurements were conducted failing to overcome the fluctuation shortcoming. Finally, we lacked data from long-term follow-up assessments.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained by all patients participating in this study.

Conflict of interest Gerhard Gründer has served as a consultant for Boehringer Ingelheim (Ingelheim, Germany), Cheplapharm (Greifswald, Germany), Eli Lilly (Indianapolis, Ind, USA), Lundbeck (Copenhagen, Denmark), Ono Pharmaceuticals (Osaka, Japan), Roche (Basel, Switzerland), Servier (Paris, France), and Takeda (Osaka, Japan). He has served on the speakers' bureau of Eli Lilly, Gedeon Richter (Budapest, Hungary), Janssen Cilag (Neuss, Germany), Lundbeck, Roche, Servier, and Trommsdorf (Aachen, Germany). He has received grant support from Boehringer Ingelheim and Roche. He is co-founder of Pharma Image GmbH (Düsseldorf, Germany) and Brainfoods UG (Selfkant, Germany). Georgios Schoretsanitis received a grant from the bequest "in memory of Maria Zaoussi," State Scholarships Foundation, Greece, for clinical research in Psychiatry for the academic year 2015–2016. The authors declare that they have no conflict of interest.

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