BRIEF REPORT

Placental Passage of Tricyclic Antidepressants

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Background: *The use of antidepressants during pregnancy continues to garner considerable attention, though there are limited investigations that have sought to quantify fetal exposure.*

Methods: *Maternal and umbilical cord sera were collected at delivery from ten women taking nortriptyline and seven taking clomipramine. Placental passage was calculated as the ratio of umbilical cord to maternal serum concentration. Obstetrical outcome data were gathered from subjects at delivery.*

Results: *The placental passage ratio of nortriptyline and its active metabolite, cis-10-hydroxynortriptyline, were .68 ± .40, 1.40 ± 2.40, respectively. Clomipramine and desmethylclomipramine ratios were .60 ± .50, .80 ± .60. Obstetrical complications, such as pre-term delivery and pregnancy induced hypertension, were increased compared to the national average.*

Conclusions: *The in vivo ratios of umbilical cord to maternal serum drug concentrations demonstrate considerable fetal exposure and differ greatly from previous results utilizing ex vivo perfusion.*

Key Words: Nortriptyline, clomipramine, antidepressants, pregnancy, placental passage

There has been increased focus on the use of medications during pregnancy, particularly those requiring chronic prenatal administration. This has extended to the in vivo quantitative estimation of fetal drug exposure using placental passage (ratio of umbilical cord to maternal serum concentration). Quantifying the extent of placental passage might inform medication selection based on the extent of fetal drug exposure and ultimately provide insight into whether or not neonatal complications are directly related to medication exposure. Similarly, the pharmacological feasibility of purported neonatal withdrawal syndromes related to specific medications can be tested (Webster 1973; Misri and Sivertz 1991; Stiskal et al 2001; Jacqz-Aigrain and Koren 2005; Sanz et al 2005).

An initial report on nine women taking tricyclic antidepressants (TCAs) at delivery (7 imipramine, 2 clomipramine) described irritability, cyanosis, tachypnea, and hypotonia in several infants (Misri and Sivertz 1991). Subsequent reports have focused on the selective serotonin uptake inhibitors (SSRIs). A review of the World Health Organization Registry of Adverse Drug Reactions (Sanz et al 2005) identified 93 reports of presumed neonatal withdrawal, and proposed that the higher representation of paroxetine ($n = 64$) was secondary to higher antimuscarinic potency compared to the other SSRIs. While it is premature to claim that any particular pattern of neurotransmitter receptor affinity would account for neonatal outcome, quanitification of fetal exposure to other antidepressants with higher affinity for such receptors (e.g. the tricyclics) serves to clarify this issue.

An early nortriptyline case report (Sjoqvist et al 1972) suggested 43% placental passage in a woman following overdose proximate to delivery. Subsequent in vivo case series (Stowe et al 1997; Hendrick et al 2003) and ex vivo perfusion studies (Heikkinen et al 2002) have focused on the SSRIs, demonstrating considerable differences between the two methods with ex vivo perfusion showing <15% placental passage compared to 60–80% for in vivo delivery collection. The current study sought to determine if a similar disparity exists for TCAs.

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Methods and Materials

Subjects

Pregnant women treated with TCA monotherapy were recruited from the Emory Women's Mental Health Program. Each subject was informed of the potential risks associated with fetal/neonatal exposure to maternal mental illness, TCAs, and alternative treatments. Written consent was obtained prior to data collection. The study was approved by the Emory University School of Medicine Institutional Review Board.

Sample Collection

Maternal and umbilical cord sera were obtained at delivery, prepared and coded as previously described (Stowe et al 1997). These samples were collected over a 6-year period from women treated with TCAs through delivery. Samples were stored at −80°C until assay. Obstetrical outcome data were collected for all participants.

Determination of TCA Concentrations

Calibration curves for high-performance liquid chromatography (HPLC) analysis were constructed by spiking drug free human serum with varying concentrations (0–1000 ng/ml) of the compounds of interest. A standard curve and 2 quality control samples were included in each assay run. Assay sensitivity for analyzed compounds was 2 ng/mL, and the procedures were linear to 1000 ng/mL. Nortriptyline and its 10-hydroxy metabolites were analyzed by a previously validated method (Ritchie et al 1996). Intra-assay imprecision averaged 7.6% and 5.6% for samples containing 65 and 400 ng/ml of each compound. Interassay imprecision averaged 9.6% and 7.5% for the same samples. Clomipramine and its active demethylated metabolite, desmethylclomipramine, were assayed by modification of a previous method (Mazhar and Binder 1989). Using low (130 ng/mL) and high (360 ng/mL) quality control serum pools, the intraassay coefficients of variation (CV) were 3 to 7.5% while the interassay CV's ranged from 5 to 9.75%.

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Table 1. Ratio of Medication Concentration in Umbilical Cord Blood to Maternal Serum and Obstetrical Outcomes for Study Participants

			PLACENTAL PASSAGE DATA									OBSTETRICAL OUTCOME DATA					
			Maternal Sample Concentration (MS) (ng/mL)			Umbilical Cord Concentration (ng/mL)			Umbilical Cord:MS Ratio					APGAR Scores			
Subject	Dose (mg/d)	Time Post Dose (hrs)	Nortriptyline	cis-10-Hydroxy Nortriptyline	trans-10-Hydroxy Nortriptyline	Nortriptyline	cis-10-Hydroxy Nortriptyline	trans-10-Hydroxy Nortriptyline	Nortriptyline	cis-10-Hydroxy Nortriptyline	trans-10-Hydroxy Nortriptyline	Gestational Exposure to Medication (weeks)	EGA (wks)	1 min	5 min	Birth Weight (kg)	Complications
A	30	15.08	38.0	9.5	<2.0	9.4	<2.0	<2.0	.25	.20	NA	39	39.0	9	9	3.74	None
B	40	12.00	54.5	20.4	<2.0	66.4	31.5	7.9	1.20	1.54	NA	39	38.6	10	10	3.44	None
C	60	3.83	71.3	32.7	3.2	36.3	3.6	<2.0	.51	.11	.60	29	36.3	9	9	2.60	None
D	70	16.83	25.8	8.5	<2.0	26.4	61.8	<2.0	1.02	7.30	NA	8	39.6	7	8	3.60	Neonatal lethargy, Poor suck reflex
E	75	6.83	69.4	132.0	<2.0	21.2	44.0	<2.0	.31	.33	NA	38	37.9	9	9	3.31	None
F	75	26.50	27.9	109.1	<2.0	27.5	118.6	<2.0	.99	1.09	NA	36.5	41.0	8	9	4.11	None
G	80	19.58	<2.0	4.6	<2.0	17.0	<2.0	<2.0	NA	.44	NA	21	36.0	8	9	2.22	Pregnancy induced hypertension
H[a]	100	12.80	2.8	<2.0	<2.0	74.0	108.0	17.3	26.30	NA	NA	10	38.3	6	9	3.80	None
I	125	29.37	15.2	<2.0	<2.0	4.7	<2.0	<2.0	.31	NA	NA	39	39.3	9	9	4.14	None
J	150	24.87	42.3	25.9	<2.0	35.5	16.2	<2.0	.84	.63	NA	25	36.9	8	9	2.89	Poor suck reflex, Special Care Nursery with feeding tube for 9 days
Mean	78	17.21	38.5	38.3	2.1	27.2	31.3	2.7	.68	1.40	NA	28.5	38.3	8.3	9.0	3.39	
SD	38.0	8.78	23.6	48.1	−.4	18.2	39.2	2.0	.40	2.40		12.1	1.6	1.2	.5	.64	

			Maternal Sample Concentration (MS) (ng/mL)		Umbilical Cord Concentration (ng/mL)		Umbilical Cord:MS Ratio				APGAR Scores			
Subject	Dose (mg/d)	Time Post Dose (hrs)	Clomipramine	Desmethyl Clomipramine	Clomipramine	Desmethyl Clomipramine	Clomipramine	Desmethyl Clomipramine	Gestational Exposure to Medication (weeks)	EGA (wks)	1 min	5 min	Birth Weight (kg)	Complications
K	50	28.15	25	<2.0	38	<2.0	1.50	NA	5	39.0	6	8	4.31	None
L	50	NA	41	73	6	40	.15	.60	22	33.3	9	9	2.51	None
M[a]	50	24.28	78	186	3	91	.04	.50	36	36.1	NA	NA	3.09	NICU (1 day) labored breathing, neonatal tachycardia
N	100	16.42	84	56	70	30	.80	.50	38	38.6	5	7	3.60	NICU (2 days), aspiration
O	100	37.67	63	93	25	165	.40	1.80	3	38.9	8	9	3.19	None
P	175	NA	100	141	40	88	.40	.60	37	36.6	NA	NA	2.74	Premature rupture of membranes
Q	175	25.41	144	71	58	38	.40	.50	38	37.7	NA	NA	3.15	Pregnancy induced hypertension
Mean	108.0	26.91	76	73	40	61	.60	.80	25.6	37.2	7.0	8.3	3.23	
SD	56.0	8.75	43	46	23	58	.50	.60	15.8	2.0	1.8	1.0	0.60	

NA, not available; EGA, estimated gestational age.

[a]statistical outliers excluded from analysis.

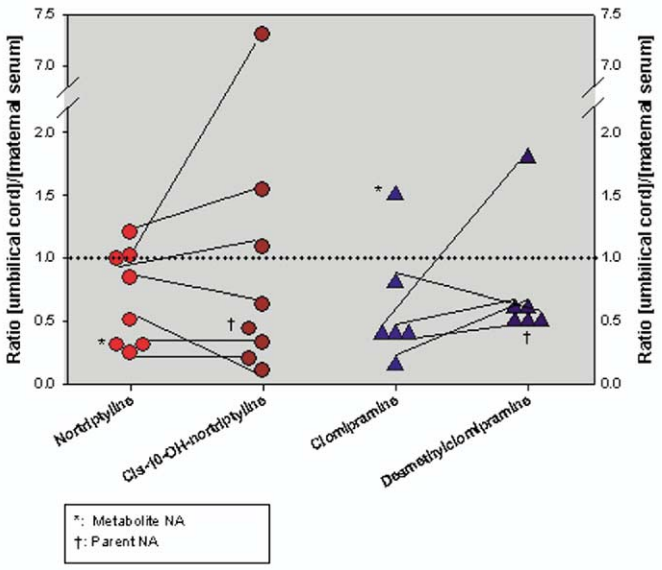

Figure 1. The individual placental passage ratios for the parent compound and metabolite are shown. The lines connect the ratios obtained from a single individual and demonstrate that parent compound ratio is not predictive of metabolite ratios. The dotted line at a ratio of 1.0 is provided for reference, e.g. above the line the umbilical cord concentration > maternal serum concentration (excessive placental passage). The two subjects determined to be statistical outliers are not included in the figure. NA, not available.

Data Analysis

Placental passage was calculated as the ratio of drug concentration in the umbilical cord (UC) to maternal serum (MS). Descriptive statistics including means, standard deviations, and frequencies were tabulated. Pairs with undetectable maternal concentrations were excluded from placental passage analysis, as maternal compliance could not be confirmed and an UC:MS ratio could not be estimated. Undetectable umbilical cord concentrations were converted to the limit of detection (2.0 ng/ml), a conservative approach erring toward overestimation of fetal exposure.

Results

Seventeen women participated in the study. Paired maternal and umbilical cord sera were collected (nortriptyline $n = 10$, clomipramine $n = 7$). Women in the nortriptyline group were treated for major depression. Five women were treated with nortriptyline for failure to respond to an SSRI, three women were taking nortriptyline at the time of conception, and two women did not tolerate SSRIs secondary to insomnia. In contrast, four of the women treated with clomipramine had a history of obsessive-compulsive disorder, two had significant obsessions in conjunction with depression, and one was taking clomipramine at the time of conception. The average ages of the women treated with nortriptyline and clomipramine were 35 ± 2.8 and 30 ± 4.3 years, respectively. The daily dose was adjusted based on clinical response and side effects.

Three subjects were excluded from placental passage analyses (cf. Table 1). The parent compound was undetectable in one maternal sample (Subject G), and initial analyses identified two ratios as statistical outliers (H, M). The placental passage ratios are shown in Figure 1.

Obstetrical outcome data are presented in Table 1. Obstetrical complications included: 1) preterm delivery (<37 weeks gestation) − 6/17 (35.3%); 2) low birth weight (<2.50 kg) − 1/17 (5.9%); 3) pregnancy induced hypertension − 2/17 (11.8%); and 4) premature rupture of membranes − 1/17 (5.9%). Neonatal complications included: 1) Neonatal intensive care unit (NICU) admission − 3/17 (17.7%); 2) poor suck reflex − 2/17 (11.8%); 3) respiratory difficulties − 2/17 (11.8%); and 4) tachycardia − 1/17 (5.9%). No structural malformations were observed. By comparison the obstetrical complications in these subjects were more than twice the national averages of preterm delivery (12.1%) and pregnancy induced hypertension (3.78%). Similarly, neonatal respiratory difficulties were higher than the 3.1% cited for respiratory admissions to the NICU (Martin et al 2003). No statistical correlations were found between parent and metabolite cord blood concentrations and obstetrical outcome.

Discussion

Although SSRIs are recommended as the drugs of choice for treatment of depression, TCA use continues around the world. Thus, evaluating the placental passage of any antidepressants to which a fetus may be exposed remains clinically relevant. These results demonstrate that in vivo placental TCA transfer occurred in all study participants. The considerable variability of both parent and metabolite placental passage may reflect differences in time post dose at delivery, fetomaternal metabolic capacities, or maternal distribution volume. Ex vivo placental perfusion has been a widely used alternative for estimating fetal exposure. In a detailed investigation using 9 placentae, one group estimated the transplacental transfer of nortriptyline at only 6% (Heikkinen et al 2001), compared to 68% in the current study. The SSRI data with citalopram and fluoxetine demonstrates a similar degree of underestimation between the two methods, <10% with ex vivo (Heikkinen et al 2002) and >63% for in vivo (Hendrick et al 2003).

In this small sample no clear pattern of complications was correlated with fetal exposure (ng/ml) or with placental passage ratio. A nonsignificant trend ($p = .07$) between birth weight and parent compound ratios warrant further attention. In the current study, each patient's clinical circumstances tipped the balance of risk in favor of treatment with a TCA rather than risk potential adverse sequelae of untreated maternal mental illness. Previous prenatal TCA studies have failed to demonstrate any consistent adverse effects on obstetrical outcome (Altshuler et al 1996), though neonatal complications have been reported (Misri and Sivertz 1991). In contrast, extended follow-up studies (>60 months) have demonstrated no adverse neurodevelopmental effects of prenatal TCA exposure (Nulman et al 1997; Nulman et al 2002).

Results from the current study and our previous collaboration (Hendrick et al 2003) suggest that ex vivo methodology underestimates antidepressant placental transfer. Furthermore, in vivo collection affords an opportunity to assess fetal metabolic capacity. There is considerable variability in the extent of fetal exposure, and the parent compound exposure did not reliably predict exposure to the metabolite. Extended pharmacokinetic studies may ultimately provide the greatest information regarding the individual variability of serum concentrations during pregnancy, placental passage, the determinants of fetal exposure, and the potential relationship of such exposure to outcome.

In summary, concerns regarding neonatal antidepressant syndromes, published for over 3 decades, remain speculative at best. Although no consistent pattern of neonatal effects was identified

in this small prospective study, it is noteworthy that the TCA placental passage resulted in considerable fetal exposure. Indeed, this substantial exposure casts doubt as to whether any antidepressant-associated syndromes arising within minutes to hours of delivery are a consequence of acute withdrawal from the tricyclic antidepressant. Adult antidepressant discontinuation syndromes are not described within 12 hours of peak serum concentrations (Lejoyeux and Ades 1997), and it is unlikely that the neonate's metabolic capacity to clear these medications exceeds that of an adult. Nevertheless, the potential for a neonatal antidepressant syndrome warrants further attention (Webster 1973). Delineating the etiology of adverse outcomes will require that future studies utilize in vivo collection to confirm fetal exposure to the medication, and detailed documentation of the course of maternal depression and concomitant illness-associated exposures known to be more common among pregnant women with mental illness including operative deliveries (Chung et al 2001), poor prenatal care, and illicit substance use (Zuckerman et al 1989).

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