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Pharmacokinetics And Infant Exposure of Citalopram and Demethylcitalopram in Breastfeeding Women

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ABSTRACT

The project is aimed at exploring the excretion of citalopram and its first metabolite, demethylcitalopram, in breast milk in a group of 11 women with breastfeeding and their children. Citalopram is a well-known antidepressant which is used very often to cure the depression; however, there are still notions referring to transferring the drug to breast milk and the results of this impact on a child. We measured the pharmacokinetics of citalopram and demethylcitalopram in the maternal plasma, the breast milk and the infant plasma. In the study citalopram was identified to be transferred into breast milk in greater amounts than demethylcitalopram, peaking in milk at 2-8 hours following medication. Nonetheless, the estimated infant exposures to the two drugs were minimal with doses of less than 5 percent of the dose by the mother. There were no adverse effects reported in the infants and they all had normal developments as tested by Denver developmental screening test. These results indicate the fact that citalopram is, most likely, safe in a breastfeeding mother. Nevertheless, the breastfeeding during the reception of citalopram is always the question which is to be considered separately, according to the personal risks and the benefits each time.

Keywords: *Citalopram, Demethylcitalopram, nursing, PK, Drug Transfer, exposure to infant*

1. INTRODUCTION

Citalopram is a selective serotonin reuptake inhibitor (SSRI) of the bicyclic isobenzofuran-based chemical group [1]. It is a racemate of the (1) R - anti-hypertensive enantiomer and the (+ 1) S - anti-hypertensive enantiomer, wherein the latter exhibits the most powerful and specific effect on the 5-hydroxytryptamine reuptake. Oral citalopram has a bioavailability of about 80 and its peak plasma concentrations are attained after 2-4 hours of the drug administration dose [2, 3]. The volume of distribution is 12-16 L/kg [2], its elimination half-life is approximately 37 hours [3]. Citalopram is lipid-soluble and hepatic metabolism occurs to a major hepatic product first to the metabolite, N-demethylcitalopram which in turn breaks down to N-didemethylcitalopram [4]. Three cytochrome P450 isoforms CYP2C19, CYP3A4 and CYP2D6 are involved in the metabolism of the drug [5]. The in vitro activity of these demethylated metabolites is depressed as serotonin reuptake inhibitors, and they pass the brain with a low capability to enter it [6]. The binding of citalopram and its metabolites with plasma proteins is about 50-80 percent [2]. It is also a weak inhibitor of cytochrome P450 2D6 with little potential to interact with other substrates use cytochrome P450 2D6 [2].

Approximately 13 percent of women experience postnatal depression in the postpartum period, and a good percentage of them can respond positively to the treatment with antidepressants [7]. The importance of breastfeeding has been stressed out in the recent years because of the various biological, psychological, and even social factors. Nonetheless, breastfeeding women who take antidepressants tend to panic on the possibility of having the psychotropic drugs entering breast milk and subsequently to their babies. In order to deal with these issues, we have explored how citalopram and its active metabolite, demethylcitalopram, enters breast milk of a group of seven lactating females. We also analysed the correlation between these levels and those in plasma as well as the results on their breastfed babies.

2. METHODS

Participants

There were eleven breastfeeding women (mean age 31, range 2436 years; mean body weight 62.6 kg, range 5270 kg) and their babies (5 males and 6 females; mean age = 4.1 months, range 1.96.6 months) who participated in the research. The median citalopram dose used by the women was 0.36 (inter-quartile range 0.29 to 0.58) mg/kg/day. Women receiving the citalopram treatment had an average of 97 days (49-183 days) of pretherapy (which was before the study), and all women were determined to be in the steady-state during the time of the study.

Study Protocol

The Ethics Committee of the King Edward Memorial and Princess Margaret Hospitals approved the study and written informed consent was given by all the participants.

Data Collection

Mothers were received in the research ward at 07:30 h when a venous catheter was inserted into a vein of the forearm just the period before the morning dose of citalopram 08:00 h. The catheter was used to take venous blood specimens (8 ml, heparinized) at 0, 2, 4, 6 and 8 hours following the dose, and by venepuncture at 12 and 24 hours. Meanwhile, at the same time intervals expression of both breasts was done by an electric or manual pump. The milk volumes were weighed and 15 ml aliquots were stored in order to analyse the drug. The pH was measured directly on the 1 ml of milk in a blood-gas syringe (Bard-Parker, Becton-Dickinson, NJ, USA) and this was done on a NOVA StatProfile 54 blood gas analyzer (NOVA Biomedical, Waltham, MA, USA). The preliminary tests ascertained that pH and pCO2 of samples could remain stable within 9hours (data not shown). Each sample was measured with regards to creamatocrit (fat content present in milk) as mentioned in past studies [8]. The balance milk was fed to the infants using a bottle. Women were discharged after 8 hours and 12 hour and 24 hour milk and plasma samples were taken at the houses of the women. The women even agreed to the taking of 0.5-1 ml of heparinized venous blood sample of their babies. The mean time of collection of infant blood samples after maternal dose was 6.5 hours (range 6.2 hours to 6.8 hours).

In all individuals the health and well-being of the infants was assessed by maternal reports and a complete clinical assessment by a neonatologist (RK). The weight of the infant was measured on gender-based percentile charts of the population and a Denver developmental screening test was performed [9, 10]. The outcome was set in the form of a numerical relation of the age obtained through Denver test as a per cent of the chronological age.

Materials

The standards of citalopram and desipramine hydrochloride (standard of desmethylcitalopram) sources were supplied by Lundbeck Australia Pty Ltd and Novartis Pharmaceuticals Australia Pty Ltd respectively. All the solvents and chemicals were either analytical or HPLC grade.

High performance liquid chromatography (HPLC)

The aliquots of the plasma (1 ml) were neutralized by adding 0.1 ml of 1 M NaOH. An internal standard, desipramine (100 ng) was added and the analytes were removed into 10 ml of 1 percent isoamylalcohol in hexane after vigorously shaking them together to extract the analytes quite well. The organic phase was removed into 0.2 ml of 0.05 M Hcl by centrifugation (1500 g 5 min). The resulting acid phase was then injected in the HPLC. The procedure used when extracting milk samples was also similar in that the method of addition was used. The HPLC system was equipped with Merck RP Select B C18 column (250 x 4.6 mm) with mobile phase comprising 40 per cent acetonitrile with 0.01 per cent sodium chloride and 0.01 H 3 PO 4 at 1.6 ml/min and UV detection was done at 210 nm. Plasma concentrations were interpolated out of standard curve and in the case of milk, a standard curve was developed against the peak height that of analyte and desipramine. Intra-day coefficients of variation (CV) of citalopram and demethylcitalopram at 25 and 250 1g/l were 1.7 to 5.5 percent in plasma and 4.7 to 6.4 percent in milk and inter-day CV ranged between 2.9 to 8.2 percent in plasma and 5.8 to 13.2 percent in milk. The limit of detection of the two analytes in plasma and milk was 1 mu g/l.

Plasma Protein Binding Measurement

The ultrafiltration method involving the use of Amicon Centrifree YM-30 centrifugal filter devices (Millipore Corporation, MA, USA) and the HPLC procedure mentioned above were used to measure the protein binding of citalopram and of demethylcitalopram.

Octanol: Buffer Partition Coefficients Measurements

The citalopram (10 mg/l) and demethylcitalopram (10 mg/l) were also dissolved in 0.02 M phosphate buffer (pH 7.2) and equilibrated with an equal amount of n-octanol in a shaking condition during 10-minutes. The concentration of the buffer was determined in both pre and post-extraction by means of the HPLC technique, and log10P values were established.

Statistical Analysis of Information

Data were summarized in terms of mean (95% CI or range) with data in terms of median (range) as suitable. A paired student t-test was used to calculate the difference of the mean infant dose calculated through two methods. Variations in the milk ph or creamatocrit among patients, among collection times were studied with 2-Anova. The investigation of connections between milk pH, creamatocrit and their subjects and M/P ratios were conducted by repeating measures 2-way ANOVA in both citalopram and demethylcitalopram. Two-way ANOVA was also used further to check the within individual and between individual variation in milk pH and creamatocrit.

Milk/plasma Ratios and Infant Dose calculations

Plasma concentration-time area under the curve (AUC(0, 24 h)) was done using a log trapezoidal rule [11], whereas the calculation of the area under the curve in milk was performed through rectangular areas (Σ concentration × collection time). These AUCs were used to calculate milk/plasma ratios (M/PAUC), and milk and plasma concentrations at the time points (M/P). It was intended that the dose of the infants citalopram or demethylcitalopram (based on citalopram equivalents) would be calculated by two methods, which were based on 100 per cent oral bioavailability. In method A, total drug excretion in 24 hours (Sigma milk concentration at each of the collection intervals times the volume) was then divided by the infants weight in mg/kg. In method B the mean infant milk intake was taken at 0.15 l/kg/day [12] and this was logged with the average milk concentration (AUCmilk/dose interval time) to form a dose in mg/kg. In the two techniques, the infant dosage was given in result as the percentage of the maternal weight-adjusted dose. The M/P ratios of citalopram were also estimated based on its pKa (9.5), plasma protein binding and log10P (Octanol:buffer, pH 7.2), by method Begg et al. [13].

3. RESULT

In breast feeding women, the pharmacokinetic profile of citalopram and demethylcitalopram were evaluated in women and their children on various occasions. The average values of major pharmacokinetic parameters such as maximum milk concentration, average milk concentration and milk plasma-to-area under the concentration-time curve (M/PAUC) of citalopram and demethylcitalopram were obtained.

The highest level of citalopram in milk was found to be between 75 and 210 g/l (mean 145 g/l 95% CI: 100, 190 g/l) Table 1. Mean concentrations of milk varied between 50 and 155 155 037gc/l (mean, 95 037gc/l; 95 percent CI, 60, 130 037gc/l). The M/PAUC of citalopram was 1.1 to 2.5 and 1.8 had mean of 1.8 (95% CI: 1.4, 2.2).

The highest milk concentration of demethylcitalopram was between 15 and 120 0g/l, having the average concentration 58 0g/l (95 % CI: 35, 80 0g/l) as indicated in Table 1. The concentration of milk was found to be between 18-85 ug/l with mean of 43 ug/l (95% CI: 20, 60 ug/l). The M/PAUC of demethylcitalopram was 1.2 to 3.1 and mean 1.7 (95% CI: 1.2, 2.3).

The proportion of the infant to the mother dose of citalopram was 1.6, 2.9, 3.3, 5.6 percentage with a mean of 3.5 and 95 percent confidence interval of 2.2 and 4.8 as indicated in table 2. The plasma concentration of citalopram in infants was between 0.4 and 2.3 mg/l, with a medium value of 1.3 mg/l (95 percent interval: 0.8, 1.7). In demethylcitalopram, the ratio of infant dose to maternal dose was 0.5 to 2.3 percent, with an average of 1.3 percent (95 percent CI: 0.9, 1.7). The plasma concentration of demethylcitalopram markers in the infant dipped between 0.7 and 2.4 1/l, with an average of 1.3 1/l (95 percent CI: 0.7, 1.9). As well, not all samples of demethylcitalopram were detected (ND), especially at the short periods following maternal dose.

These results indicate that Citalopram and its metabolites demethylcitalopram enter into the breast milk and demethylcitalopram has a lower transfer rate than citalopram. Also, the calculated infant doses and plasma concentrations suggest that the overall dose of the drug consumed by the infants via breast feeding is at very low percentages as compared to the maternal dose, which usually provides a relatively safe profile on the clinical results.

Table 1: Milk Concentration and Pharmacokinetic Parameters of Citalopram and Demethylcitalopram in Breastfeeding Women

Volunteer	tmax (h)	Maximum Milk Concentration (µg/l)	Average Milk Concentration (µg/l)	M/PAUC	tmax (h)	Maximum Milk Concentration (µg/l)	Average Milk Concentration (µg/l)	M/PAUC
1	3.2	185	95	1.6	7.3	72	52	1.8
2	4.5	97	58	1.1	4.1	40	29	1.2
3	4.2	75	50	1.5	3.4	30	25	1.3
4	8.1	174	120	2.1	4.5	54	38	1.6

5	4.0	210	155	1.8	9.2	120	85	1.9
6	4.0	110	75	2.4	2.1	42	33	2.2
7	2.0	160	80	2.5	6.2	40	18	3.1
Mean	**4.0**	**145**	**95**	**1.8**	**5.6**	**58**	**43**	**1.7**
(95% CI)	**(2.3, 5.6)**	**(100, 190)**	**(60, 130)**	**(1.4, 2.2)**	**(3.4, 7.8)**	**(35, 80)**	**(20, 60)**	**(1.2, 2.3)**

Table 2: Infant Dose and Plasma Concentrations of Citalopram and Demethylcitalopram in Breastfeeding Women and Their Infants

Volunteer	Citalopram Infant Dose as % of Maternal Dose	Method A1	Method B2	Infant Plasma Concentration (µg/l)	Demethylcitalopram Infant Dose as % of Maternal Dose	Method A1	Method B2	Infant Plasma Concentration (µg/l)
1	4.1	3.8	2.1	1.9	1.8	1.7	ND3	
2	1.8	3.2	ND	0.7	0.5	1.3	ND	
3	2.2	2.5	ND	0.9	0.4	0.8	ND	
4	5.2	6.1	2.8	1.5	1.9	2.2	2.4	
5	3.8	4.5	2.4	2.1	2.0	2.3	2.2	
6	3.4	4.1	ND	1.3	1.6	1.2	ND	
7	3.3	3.3	ND	1.2	1.0	0.7	ND	
Mean (95% CI)	**3.5 (2.2, 4.8)**	**3.8 (2.7, 4.9)**	**3.0 (1.8, 4.2)**	**1.3 (0.8, 1.7)**	**1.3 (0.9, 1.7)**	**1.3 (0.7, 1.9)**		

4. DISCUSSION

In spite of the fact that both citalopram and its major metabolites share relatively similar pharmacokinetics related to the pharmacokinetics variation between enantiomers [15, 16], the aim of this study was mainly to evaluate maximum exposure in infants. Consequently, we focused on citalopram and its main metabolite demethylcitalopram racemates.

The average milk pH was 7.23, in which the differences among the volunteers were significant, though no considerable differences were recorded between the different sampling times. The percentage of fat in milk measured by creamatocrit was highly variable among the participants as well as differed with time of collection. Milk pH and creamatocrit however were not very strong predictors of M/P ratios when intervolunteer variability was omitted. The factor of plasma protein binding was not taken into consideration in this analysis because there was a single measurement done by five out of the eleven volunteers. There was a mean of 1.6 between the peak:trough concentration of citalopram in milk that can be compared to its demethyl metabolite which had a ratio of 1.4. M/PAUC values were also very similar in both citalopram and demethylcitalopram with an average value of 1.8 in these two drugs. Although citalopram has a greater log P value, both the compounds demonstrated a comparable level of transport to breast milk. These findings indicate that milk pH, creamatocrit and lipid solubility is at most secondary factors that will affect transfer of these drugs into milk. It has been pointed out in earlier studies that binding of proteins in the plasma frequently has considerable influence in the transfer of drugs to the milk [13]. M/P ratio theoretical predictions of the citalopram, that are run in accordance with the method proposed in Begg et al. [13], were in range of 1.3 which is in lower limits of 95% confidence interval of the mean measured value (1.0 2.5). This proves the correctness of the theoretical approach even in the condition of no real patients data. M/P ratios had an inverse relationship with percent binding citalopram in the plasma; as bonding changed between 71-77% the value of the predicted M/P reduced by 15 units, or 1.3-1.1.

The excretion of an antidepressant such as citalopram into breast milk has already been reported in two studies. Jensen [17] investigated a mother-infant pair where the single mum was taking citalopram, but he later reported an M / P of ratio about

3 in citalopram and N -demethylcitalopram. The highest milk concentrations were recorded within 3-9 hours upon dosing. Traces of both drugs could be found in the plasma of the infant even at the 3 weeks exposure during breast milk. The infant plasma levels citalopram, 2.3 g/l, and the amount of citalopram utilized by the infant was around 5 percent of the maternal dose proportional to weight. Spigset et al. [18] published the results of another study involving data obtained during breastfeeding in two depressed mothers and in one healthy control. M/P ratios of citalopram in the depressed patients varied between 1.66 and 1.88, being summarized using single paired measurements of the concentrations in plasma and milk. N-decmmethylcitalopram information was not listed. Citalopram estimated relative infant dose was 0.7% to 5.9 % of the maternal dose and no adverse effects being noted on the infants. The estimations made in the healthy volunteer regarding M/P and relative infant dose were 1 and 1.8 percent respectively. Our study shares the findings with these previous reports since values were consistent at 1.8 in both citalopram and demethylcitalopram and interpatient variability (Table 1). We think that AUC data are the best data that can be used to calculate M/P ratios.

We also compared the two procedures of the infant dose calculation that yielded quite similar results, and the milk production rate was indeed incidentally 0.13 l/kg/day in our group of mothers compared to 0.15 l/kg/day at the level of the whole population [12]. This is unlike the case with sertraline [19] in which the lower amounts of milk produced by the mother caused the estimates of infant dose to be lower when Method A was used.

The mothers reported no adverse effects and neither were any observed after the clinical evaluation of an infant. The body weight of all the infants was in the right percentile range in relation to age and their development was normal as measured by the Denver developmental screening test. Additionally, the transfer of drug did not exceed the usually acceptable rate of 10% of maternal dosage [12] and the contents of plasma of the drug was minimal in less than half of the infants. All these results allude to the fact that citalopram is probably safe to use when breastfeeding. However, the issues concerning the matter of breastfeeding are always accompanied by a person specific risk:benefit analysis.

5. CONCLUSION

To sum up, Citalopram and its key metabolite demethylcitalopram have been assessed in a group of 11 breastfeeding women and infants regarding the transfer into breast milk. In the study, it was identified that citalopram and demethylcitalopram are excreted in breast milk with low transfer rate of demethylcitalopram to citalopram. The estimated infant doses and plasma concentrations showed that the doses of these drugs taken up by infants by breastfeeding are significantly low, which is normally less than 5 percent of materno dose. These results indicate that when citalopram is used by lactating mothers, it must not be harmful since the drug could hardly enter the breast milk and none of the infants showed any negative outcomes. The paper has further revealed the truth that aspects like pH of milk, creamatocrit, and lipid solubility rank lower than plasma protein binding which decides the degree of transfer of drugs to milk. Despite the encouraging findings, a breastfeeding decision on citalopram is never of a one size fits all due to the risk assessment in the unique situations of individual mother-infant couples that must be undertaken first.

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