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Levonorgestrel pharmacokinetics in plasma and milk of lactating women who take 1.5 mg for emergency contraception

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BACKGROUND: Progestin-only methods are among the contraceptive options available for breastfeeding women, however the doses of progestin used in emergency contraception (EC) have not been evaluated in nursing mothers. We therefore investigated the pharmacokinetics of 1.5 mg levonorgestrel (LNG) in lactating women. METHODS: Twelve healthy exclusively breastfeeding volunteers received 1.5 mg LNG. Women refrained from nursing for 72 h after dosing and fed their infants with milk frozen beforehand. Serial blood and milk samples were collected for 120 h and assayed for LNG and sex hormone binding globulin. RESULTS: LNG concentrations peaked in plasma and in milk 1–4 h and 2–4 h after dosing, respectively. Concentrations in milk (M) paralleled those in plasma (P) but were consistently lower (mean M:P ratio 0.28). Estimated infant exposure to LNG is 1.6 μg on the day of dosing (1 μg in the first 8 h), 0.3 μg on the second day and 0.2 μg on the third day. CONCLUSIONS: Nursing mothers may need EC. These results suggest that to limit infant exposure to the period of maximum LNG excretion in milk, mothers should discontinue nursing for at least 8 h, but not more than 24 h, after EC.

Keywords: breastfeeding/emergency contraception/lactation/levonorgestrel/pharmacokinetics

Introduction

The benefits of breastfeeding for infants and mothers are myriad, including optimal nutrition and protection against infection for infants and temporary decreased fertility for mothers (Battin *et al.*, 1985; American Academy of Pediatrics, 1997; Tommaselli *et al.*, 2000).

Ovulation may occur before menses resume in breastfeeding women, and women may recover menstrual cycles while fully breastfeeding (Díaz *et al.*, 1988, 1999; Gray *et al.*, 1990; Campbell and Gray, 1993). For women who have resumed menstruating, lactation alone is unreliable in preventing conception after the ninth week post-partum, and with sexual intercourse resuming for a majority of women around the sixth week, methods of family planning complementary to breastfeeding need to be considered (Chao, 1987; World Health Organization, 1999; Connolly *et al.*, 2005). In terms of hormonal methods, combined oestrogen–progestin oral contraceptives have been shown to impair milk secretion (Croxatto *et al.*, 1983; Díaz *et al.*, 1983; WHO, 1988), whereas contraception with progestin alone, whether delivered by oral, subdermal or intrauterine routes, appears to have no deleterious effects on milk production or infant growth when used by breastfeeding women (WHO, 1984, 1994a,b, 2004; Díaz *et al.*, 1985, 1997; Shaaban *et al.*, 1985; Affandi *et al.*, 1986; McCann *et al.*, 1989; Fraser, 1991; Shaaban, 1991; Díaz and Croxatto, 1993; Dunson *et al.*, 1993; WHO, 1994a,b, Sivin *et al.*, 1997; Curtis *et al.*, 2002; Jordan, 2002; Schiappacasse *et al.*, 2002). Current recommendations call for the introduction of progestin-only contraceptive methods starting from 6-weeks post-partum (WHO, 2004).

Nursing women at risk of pregnancy are candidates for post-coital emergency contraception (EC) following a barrier method failure or intercourse without contraception. Levonorgestrel (LNG) administered at a dose of 1.5 mg (given either as a single dose or two 0.75 mg doses, 12–24 h apart) within 72 h after unprotected intercourse is the reference method of hormonal EC (Cheng *et al.*, 2004; von Hertzen *et al.*, 2002; WHO, 2004), and as a progestin-only method LNG EC is indicated for breastfeeding women. Approved prescribing information for various LNG EC products all mention that LNG is secreted

into human milk, but contain a variety of recommendations for reducing the exposure of the nursing infant, ranging from no specific guidance to detailed instructions (prescribing information for Plan B®, Levonelle®, NorLevo®). These recommendations are based on empirical evidence with progestin-only regular contraceptive methods; no specific data are available regarding the extent and duration of transmission of LNG in human milk following EC use.

We therefore set out to obtain data upon which to base clinical recommendations for nursing mothers who present for EC. We employed a lactating women (plasma and milk) study design (Food and Drug Administration, 2005) to investigate the pharmacokinetics of LNG EC in healthy breastfeeding women volunteers and the amount of drug transferred into human milk. Infant sampling was not performed in this type of study, therefore the total dose could be estimated, but systemic exposure of the infant could not be measured directly.

Materials and Methods

Overview of the clinical study

The clinical phase of this study was performed at the Instituto Chileno de Medicina Reproductiva (ICMER, Santiago, Chile). We set out to enroll 12 healthy, non-smoking, exclusively breastfeeding women who were between 6 and 12 weeks post-partum, in lactational amenorrhea, not on hormonal contraception or any other hormonal treatment, had healthy babies and provided informed consent. Women who participated in the study were reimbursed for any travel costs incurred and received financial compensation for their time spent participating in the study. The protocol, volunteer information and informed consent form were approved by the Institutional Review Board of the ICMER and the Scientific Ethics Committee of the Chilean Ministry of Health, Central Metropolitan Health Service.

The study consisted of a screening visit, in which eligibility for the study was confirmed and baseline physical examinations of the mother–infant dyad and laboratory tests (haematology and clinical chemistry) of the women were performed; a pretreatment phase, during which each volunteer was instructed to pump milk and conserve it frozen until she obtained an adequate volume of milk ($450\ ml^{-1}$ kg infant bodyweight) to allow her baby to be breastfed during the first 72 h after the LNG dosing; a treatment phase, described in more detail below; and a post-study phase, which was a visit performed within 72 h of completion of the treatment phase, consisting of a safety evaluation including physical examinations of the mother–infant dyad and laboratory tests for the mother.

Pharmacokinetic sampling phase

Women reported to the clinic with their infants at 0800–1000 hours on the day of the scheduled treatment phase; they were allowed to eat breakfast that morning as long as it was before 0600 hours. Body temperature, pulse rate and blood pressure were recorded. After collection of pre-dose blood and milk samples, women received one tablet of NorLevo (1.5 mg LNG) with 240 ml water. Women received a standardized meal 3 h after administration of the study medication and standardized fluids in the first 4 h after treatment. Volunteers left the research centre 8 h after LNG dosing, with the proviso that they return for the subsequent blood and milk sample collections.

Venous blood samples (6 ml) were collected by venipuncture into heparinised, labelled, glass tubes according to the following time schedule: before administration of study medication and 1, 2, 4, 6, 8, 24, 48, 72, 96 and 120 h thereafter. The actual blood sampling times were registered. Blood samples were centrifuged and plasma stored at −20°C until the LNG and sex hormone binding globulin (SHBG) assays were performed.

Milk samples (6 ml) were collected by manual expression before administration of the study medication and at 2, 4, 6, 8, 24, 48, 72, 96 and 120 h after treatment, immediately after blood samples were obtained. Outside of the designated sampling times during the first 72 h after treatment, women were requested to empty both breasts and to store all the milk collected at −4° C. The total milk collected was measured and pooled by 24-h period (0-24 h = pool 1; 25–48 h = pool 2; 49–72 h = pool 3) and an aliquot of each pool was kept. All milk samples were stored at −20°C until LNG assay.

During this 72-h period, women bottle-fed their infants the milk that they had reserved during the pretreatment phase. Women resumed breastfeeding after the blood sample was taken at 72 h.

SHBG assays

Quantitative analysis of SHBG in plasma was performed at Endocrinology Laboratory, Catholic University of Chile, using a commercial assay kit (SHBG 125I IRMA Kit, Institute of Isotopes Ltd., Budapest, Hungry). SHBG was quantified prior to LNG administration and thereafter in one sample per 24-h interval (at 1, 24, 48, 72, 96 and 120 h). Sensitivity of the assay was $0.22\ nmol\ l^{-1}$.

Drug assays

The analysis of the study samples was performed at CEPHAC (St Benoît, France). The analytical procedures for the determination of LNG in human milk and in human plasma had been previously developed and validated (CEPHAC internal standard operating procedure). Briefly, the milk and plasma samples underwent a liquid/liquid extraction followed by a purification step. The samples were then analysed by gas chromatography (Hewlett Packard 6890 gas chromatograph and 7683A automatic sampler) with tandem mass spectrometric detection (Hewlett Packard 5973 mass spectrometer). The analytical procedure was shown to be linear from 0.02 to $5.0\ ng\ ml^{-1}$ in milk and from 0.1 to $20.0\ ng/ml^{-1}$ in plasma. Pre-study assay qualifications were carried out for each of the two matrices prior to analysis of the study samples; a single batch, consisting of calibration standards and intra-batch samples at four concentrations, was analysed for each matrix to test the performance (linearity, imprecision and inaccuracy) of the method. In-study validation included (i) examination of representative chromatograms obtained from calibration standards, blank samples and a study sample for retention times of LNG and the internal standard (norethindrone); (ii) verification of instrument performance by the injection of three reference samples at the same concentration when starting the injection of a batch of samples; (iii) evaluation of carryover for each analytical batch using blank matrix samples injected after the first series of calibration standards and after each high quality control sample; (iv) examination of linearity of the relationship between peak signal ratio and concentration of LNG, using determination coefficient (r^2) and (v) calculation of the concentration, imprecision and inaccuracy of quality control samples.

Pharmacokinetic and clinical data analysis

The pharmacokinetic analysis was carried out by the Pharmacokinetic Unit of ASTER (Paris, France). Data on plasma and milk LNG concentrations were transferred directly from the bioanalytical software (Watson® LIMS 7.0.0.01) into the pharmacokinetic software (WinNonLin V 5.0, Pharsight Corporation) for processing and pharmacokinetic data generation.

For the calculation of the pharmacokinetic parameters and characteristics, the actual (not theoretical) blood sampling times were used. A series of pharmacokinetic parameters were derived for each subject from plasma and milk LNG concentrations. The rate and extent of absorption of LNG (plasma values) and secretion into milk was measured by: the maximum plasma or milk concentration (C_{max}); the time taken to reach C_{max} (t_{max}), obtained directly from the concentration–time data; the terminal plasma or milk half-life ($t_{1/2}$); the area under the concentration–time curve from time zero (pre-dose) to specific time points or the time of last quantifiable concentration (AUC_{0-24}, AUC_{24-48}, AUC_{48-72}, AUC_{0-t}), calculated using a linear trapezoidal method; the area under the plasma or milk drug concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$); and the apparent clearance, Cl/F, calculated as dose divided by $AUC_{0-\infty}$. Plasma and milk concentrations were compared using the milk/plasma ratio, calculated by dividing the $AUC_{0-\infty}$ of milk by the $AUC_{0-\infty}$ of plasma. The total exposure of the suckling infant to LNG, per 24 h, was estimated by multiplying AUC_{0-24}, AUC_{24-48} and AUC_{48-72} by the volume of milk production during each of the three corresponding time intervals. Moreover, the data from the pooled milk samples were used to estimate the total amount (Ae) excreted in milk over each interval calculated by Ae = conc × vole, and the fraction (*fe*) of the dose excreted in milk over each interval calculated by fe% = (Ae/dose) × 100.

For descriptive statistics of plasma and milk concentrations (mean and SD), concentrations below the limit of quantification (LOQ) were substituted by one-half of the LOQ if at least two-thirds of the plasma or milk values per time-point were above the LOQ. For descriptive statistics performed on pharmacokinetic parameters, results are presented as mean, SD, median, minimum (min) and maximum (max) values.

Clinical data from the Case Report Forms were double-key entered and transferred to SAS version 8.2 for analysis. Safety data were summarized by tabulating adverse events reported during the study. Full blood count and clinical chemistry profile variables were summarized for baseline, endpoint and for the change from baseline to end of exposure.

Results

A total of 18 women provided informed consent and were screened for enrollment into the study, 12 of whom were included and completed the study. The six screen failures were due to irregular menstrual cycles before pregnancy (1), inadequate baby weight increase (2), moderate hypercholesterolemia (1), excess weight (1) and menstruation (1).

Mothers who participated were on average 25 years old and 11 weeks post-partum at the time of LNG treatment (Table 1). They and their infants all had vital signs within the normal range and normal or clinically insignificant findings for general physical exam at screening, during the treatment phase and at the post-study visit (data not shown). No serious adverse events related to the use of the medication occurred during the study, however, one woman was diagnosed with choledocolithiasis as a result of a clinical condition that arose in the post-treatment phase. Four women and six infants experienced adverse events during the course of the study, none of which were deemed to be related to the study drug. All infants resumed breastfeeding after 72 h of nursing interruption. Three out of 12 women presented 2–5 bleeding or spotting days starting 2–6 days after treatment, and after this event they continued in amenorrhoea.

Table 1. Demographic characteristics and gynaecological history of participants

Characteristic	Mean ± SD (range) or *n* (%)
Age (years)	24.7 ± 4.8 (18–32)
Weeks post-partum	
At screening	7.0 ± 1.0
At treatment	11.1 ± 0.8
Body mass index (kg m^{-2})	24.9 ± 2.5 (21–30)
Sexually active at screening	8 (67%)
Contraceptive method	
Copper IUD	10 (83%)
Condoms only	1 (8%)
Condoms + copper IUD	1 (8%)
Parity	
1	4 (33%)
2	7 (58%)
3 +	1 (8%)

Milk and plasma samples were analysed for LNG concentrations according to the protocol, with in-study method validation performed successfully. The retention times of syn and anti-isomers of LNG and of syn and anti-isomers of norethindrone were approximately 7.60, 7.75, 7.25 and 7.40 min, respectively. Before starting the injection of a batch of samples, the instrument performance was verified by the injection of three reference samples at the same concentration. If several batches were injected consecutively, the system suitability determined before the first batch was used for the following batches. In each case, the imprecision was within acceptance criteria (i.e. imprecision lower than or equal to 10%). No significant carryover effect was observed, and the system suitability was demonstrated. The analysis met the acceptance criteria for the determination coefficient ($r^2 > 0.98$), the imprecision (<5% for milk, <6% for plasma) and the inaccuracy (within ±16% at the LLOQ and within ±10% at the other concentration levels for milk, within ±8% for plasma) calculated from the back-calculated data of the calibration standards obtained during the analysis of the study samples. Within each batch of study samples for both milk and plasma, all quality control samples were within ±15% of their respective nominal values. For each quality control concentration level, the imprecision (<5% for milk, <6% for plasma) and the inaccuracy (within ±3% for milk, within ±5% for plasma) met the acceptance criteria.

Mean plasma and milk concentration–time curves of LNG are shown in Figure 1. LNG milk concentrations paralleled those of plasma but were lower than plasma concentrations, with an overall mean milk-to-plasma ratio of 0.28 ± 0.09. Mean pharmacokinetic parameters are summarized in Table 2. Progestin concentrations increased after dosing to reach a peak between 1 and 4 h in plasma and between 2 and 4 h in milk. The maximal LNG concentrations ranged from 9.8 to 22.3 ng ml^{-1} and 4.1 to 10.7 ng ml^{-1} in plasma and milk, respectively. The mean terminal half-life of LNG was 29 h in plasma and 26 h in milk.

At 120 h after dosing, plasma concentrations (mean ± SD) of LNG were still above the lower LOQ for all subjects

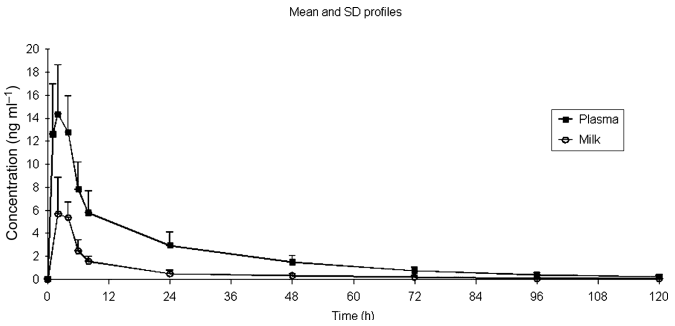

Figure 1. Concentration—time curves of levonorgestrel (LNG) in plasma and milk before treatment and at 2, 4, 6, 8, 24, 48, 72, 96 and 120 h after receiving a dose of 1.5 mg LNG.

(0.23 ± 0.07 ng ml^{-1}), while milk concentrations were very low (0.06 ± 0.4 ng ml^{-1}) and reached undetectable levels for two subjects out of 12. The mean AUC at the last quantifiable concentration (AUC_{0-t}) is similar to that extrapolated to infinity ($AUC_{0-\infty}$) (percentage extrapolation is 3.9% in plasma, 2.6% in milk), indicating that the sampling time period was adequate to characterize the pharmacokinetic profile of the dose administered.

The amount of LNG excreted in milk over the first 24 h was 0.09% of the dose administered. This amount decreased rapidly with time, with only 0.01% of the given dose being recovered in milk over the 49–72 h interval. The concentration of LNG (mean ± SD) measured in pooled milk samples was 1.7 ± 0.5 ng ml^{-1} on the first day, decreasing to 0.4 ± 0.1 ng ml^{-1} on the second day and to 0.2 ± 0.05 ng ml^{-1} on the third day. Based on the AUC per 24-h interval, the estimated mean amount of progestin potentially absorbed by an infant suckling about 800 ml of milk per day was 1.6 μg in the 0–24 h interval after dosing (1.0 μg in the first 8 h and 0.6 μg in the interval of 8–24 h after dosing), 0.3 μg in the 24–48 h interval and 0.2 μg in the 48–72 h interval (Table 3). The mean total amount of LNG excreted in milk was 1830 ± 522 ng over the 3 days following the administration of 1.5 mg LNG.

On average, plasma SHBG concentrations remained essentially unchanged 1 h after the dose of LNG (56.3 ± 21.5–57.5 ± 23.0 nmol l^{-1}) and then decreased consistently for all subjects over the 120 h sampling time period to a mean of 35.9 ± 12.8 nmol l^{-1}, which corresponds to a mean 64% of pre-dose values (Fig. 2).

Table 3. Estimated infant exposure to levonorgestrel in breast milk after a dose of 1.5 mg

Time interval (h)	AUC (ng h ml^{-1})		Exposure (μg)	
0–24	45.0	(8.3)	1.6	(0.4)
0–8	28.6	(7.2)	1.0	(0.3)
8–24	16.5	(3.4)	0.6	(0.2)
24–48	9.6	(4.5)	0.3	(0.2)
48–72	6.1	(2.9)	0.2	(0.1)

Values are mean (SD).

Discussion

The results of this study show that LNG passes rapidly into the milk of nursing women following a dose of 1.5 mg. LNG reached peak concentrations in milk 2–4 h after dosing, with peak values nearly half as great as the peak concentrations measured in maternal plasma. LNG concentrations in milk declined rapidly thereafter to less than one-quarter of peak values at 8 h and one-tenth of peak values at 24 h after dosing. Milk concentrations paralleled those of plasma at a milk-to-plasma ratio of nearly 30%; this ratio represents more than double the 10 to 15% of LNG transferred from plasma to milk reported in previous studies of progestin-only pills (Nilsson *et al*., 1977; Shikary *et al*., 1987) and is within the range reported for LNG implants of 8–33% transfer during the first 40 days of use (Díaz *et al*. 1985).

Because this study included sampling of lactating mothers without infant sampling, the total dose ingested by an infant could be estimated, but the systemic exposure of the infant could not be measured. In comparison with the up to 140 ng day^{-1} daily dose estimated to be ingested by infants whose mothers use progestin-only pills for regular contraception (daily dose of 30 μg LNG) (Díaz, 2002), the estimated dose ingested after LNG EC was 10 times higher on the day of dosing (1409 ± 450 ng for the 0–24 h interval after dosing) and decreased rapidly to roughly equivalent levels of oral regular contraception two days later (135 ± 62 ng for the 48–72 h interval).

The LNG absorption profile in breastfeeding women is similar to that obtained in previous studies with healthy cycling women volunteers in terms of peak plasma concentration (C_{max} of 15.4 ng ml^{-1} in this study, 12.3 ng ml^{-1} (reported as 39.3 nmol l^{-1}) in Johansson *et al*. 2002; 17.5 ng ml^{-1} in HRA Pharma unpublished data) and time to reach C_{max} (2 h in this study, 2.5 h in Johansson *et al*. 2002; 2 h in HRA Pharma

Table 2. Pharmacokinetic parameters of levonorgestrel following a dose of 1.5 mg in lactating women

	Biological matrix					
	Plasma			Breast milk		
t_{max} (h)	2.0		(1.0–4.0)	3.9		(1.9–4.1)
C_{max} (ng ml)$^{-1}$	15.4	(3.9)	(9.8–22.3)	7.0	(2.3)	(4.1–10.7)
AUC_{0-t} (ng h ml)$^{-1}$	252.8	(79.9)	(158.5–392.9)	65.3	(11.4)	(41.3–77.4)
$AUC_{0-\infty}$ (ng h ml)$^{-1}$	262.6	(80.4)	(166.0–401.4)	67.0	(12.9)	(42.6–79.5)
$t_{1/2}$ (h)	29.3	(5.6)	(21.3–37.0)	26.3	(7.1)	(14.8–38.9)

Values are arithmetic mean (SD) (min–max) except t_{max} which is median (min–max).

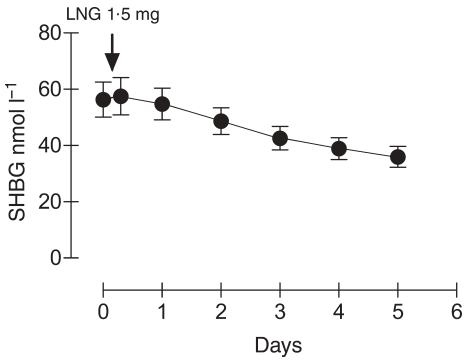

Figure 2. Mean (SEM) plasma sex hormone binding globulin concentrations after a single dose of 1.5 mg LNG.

unpublished data). The sum of the plasma and milk bioavailability ($AUC_{0-\infty}$) measured in this study is also very close to the total plasma bioavailability measured in previous studies of non-breastfeeding volunteers (360 ng h ml^{-1} in this study; 340 ng h ml^{-1} in HRA Pharma unpublished data).

LNG is highly bound to plasma proteins and in particular SHBG (42–68%), upon which it is also known to exert an inhibitory effect on production (Alvarez *et al*., 1998). SHBG levels are significantly elevated during pregnancy and diminish gradually during the months that follow delivery (Uriel *et al*., 1981; Campino *et al*., 2001). In this study, SHBG levels decreased after LNG dosing in all women, a pattern similar to that seen with the introduction of LNG contraceptive methods in non-breastfeeding women (Alvarez *et al*., 1998; Johansson *et al*., 2002).

The published literature contains a number of studies indicating no detrimental effects of progestin-only contraceptive methods used by nursing mothers on lactation or infant growth (Díaz *et al*., 1985; Shaaban *et al*., 1985; Shikary *et al*., 1987; McCann *et al*., 1989; WHO, 1994b; Kelsey, 1996), and LNG is generally regarded as a drug compatible with breastfeeding (American Academy of Pediatrics, 2001). With respect to infant development, infants exposed to progestins in milk do not exhibit any impairment of gross motor, vision and fine motor, hearing, language and concept development, or self-help and social skills (WHO, 1994b). Nevertheless, conflicting reports hint at potential adverse consequences of chronic infant exposure to LNG via milk, including decreased thyroid hormones in breast-fed male infants (Shikary *et al*., 1986; Bassol *et al*., 2002), suppressed infant hepatic drug metabolizing enzyme depending on infant age (Patel *et al*., 1994; Toddywalla *et al*., 1995), and increased rates of infection (Abdulla *et al*., 1985; Schiappacasse *et al*., 2002;). Concern about the impact of steroid intake on infant reproductive development has its origins in studies of the effect of intrauterine and post-natal administration of sex steroids to animals (Shapiro *et al*., 1976; Harlap, 1987) and is reinforced by data indicating that the children of women treated with progestins during pregnancy for the prevention of miscarriage exhibit a variety of physical, psychological and behavioural differences compared to unexposed subject (Reinisch, 1981; Reinisch and Karow, 1987).

In contrast to other situations of chronic fetal or infant progestin exposure, LNG used for EC is administered as a single dose. It is not known whether a single bolus exposure following a mother's use of LNG for EC could affect liver metabolism or alter an infant's pituitary-thyroid axis, thereby influencing the maturation of the neural centres that regulate gonadal function. Current recommendations call for the initiation of steroid contraceptives by mothers no earlier than 6 to 8 weeks post-partum, and the same is true for LNG EC (WHO, 2004). The first post-partum weeks are the period in which the liver and other systems are less mature, so delaying intake increases the chances that the infant will be able to absorb and metabolize the LNG efficiently (Patel *et al*., 1994). Treatment no earlier than 6 weeks post-partum also avoids the critical immediate post-partum period in human development during which the central nervous system has its highest extra-uterine growth rate and is thereby potentially more susceptible to deleterious stimuli (Davison and Dobbing, 1968). Although the daily milk concentrations achieved in this study decreased rapidly to levels of chronic exposure with other LNG contraceptive methods, women may wish to limit their infants' exposure to LNG following their use of it for EC.

As is the case for any medication taken by nursing women, the risks and benefits of taking the drug must first be weighed which, in the case of EC, involves assessing the risk of pregnancy based on time since delivery, menstrual status and breastfeeding and supplementation patterns in order to decide whether EC is indicated in the first place. Based on the data generated in this study, recommendations can be made to reduce potential infant exposure to LNG. The peak milk concentrations are not reached until 2–4 h after dosing, LNG decreased to 27% of the maximum level achieved at 8 h after dosing, and the diminution reached 9% at 24 h. Accordingly, women can be advised to breastfeed immediately before EC administration and to discard ('pump and dump') milk thereafter for a period of at least 8 h and up to 24 h. Discarding milk in these first 8 h avoids a bolus effect due to the accumulation of LNG in milk (Toddywalla, 1995). The duration of 'pumping and dumping' beyond 8 h of EC administration should be decided on a case-by-case basis, taking into account infant age, breastfeeding patterns and supplementation practices. Prolonging the interval of 'pumping and dumping' beyond 24 h may create unnecessary barriers to the benefits of breastfeeding for mothers and their infants.

Nursing mothers may need EC. This is the first study that shows the levels of LNG attained in milk after the administration of a single dose of LNG for EC in breastfeeding women. It suggests that, to avoid the period of maximum LNG excretion in milk, nursing should be discontinued and milk discarded for an interval of at least 8 h, but not longer than 24 h, after the use of EC.

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