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Transfer of epinastine to infants through human breast milk

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The purpose of this study was to develop an analytical method for analyzing epinastine in breast milk and maternal plasma samples to determine the safety of epinastine in breastfed infants. Six nursing mothers took epinastine hydrochloride (20 mg) once a day for 7 days, while a nursing mother took it for 30 days. Breast milk and blood samples were collected 2, 4, and 10 h after administration from the volunteers. A liquid chromatography-mass spectrometry system was used to analyze samples pretreated by liquid-liquid extractions. The concentration of epinastine in human milk was 10.3–33.5 ng/mL after 2 h, 9.1–63.8 ng/mL after 4 h, and 8.3–28.9 ng/mL after 10 h. The increase achieved 4 h after administration indicates that epinastine was transferred into human breast milk. However, the milk-to-plasma ratio had a wide range (0.82–3.39), while the relative infant dose at 4 h was 0.36–2.49%, which is lower than the safety level of transferability (10%). Moreover, the plasma levels of epinastine in two infants were slightly below the quantification limit. Overall, our results suggested that epinastine can safely be used by nursing mothers without affecting their infants.

1. Introduction

Breastfeeding is of great benefit to both mothers and infants. Unfortunately, one of the factors preventing commencement or continuation of breastfeeding is drug therapy in mothers (Mortensen et al. 2002; Mackie et al. 1999; Hoddinott et al. 2008; WHO press. 2013). Many drugs such as amiodarone (Moretti et al. 1995), atenolol (Eyal et al. 2010), cimetidine (Somogyi and Gugler 1979; Oo et al. 1995), lamotrigine (Morita et al. 2013), zonisamide (Ando et al. 2014), and morphine (Feilberg et al. 1989) can be transferred through human breast milk. However, few clinical studies on drug use and lactation have been reported (Ito 2000), perhaps owing to ethical considerations, research environments, and the mental state of mothers. The influence of drugs on babies is also unclear, even for the small amounts that could be found in breast milk. The lack of information about the effects of drugs on babies has various impacts, including a physician's reluctance to prescribe medication or discontinuation of breastfeeding. Discontinuing breastfeeding without appropriate breast care can lead to problems such as mastitis. Consequently, detailed information about drug use and lactation is required to help guide decisions on drug therapy.

The following recommendations are often given for medical therapy during lactation: "use only if necessary" "use only for the amount of time needed" and "use topical drugs rather than oral drugs" (American Academy of Pediatrics 2001). In the case of allergies, topical drugs are not ideal because allergies often require prolonged therapy. Although nursing mothers may take antihistamines, concerns exist. For example, the website LactMed® (Toxnet 2017) and the book Drugs in Pregnancy and Lactation (Briggs et al. 2014) recommend that breastfeeding women use the antihistamine epinastine (EPN) only in the form of eye drops. Of note, in commercially available oral EPN, the Japanese package insert advice to "avoid use during lactation" is based on an excretion experiment in rats, not humans (Oiwa et al. 1992). When maternal rats were orally administered radioactivated EPN at doses 15 to 30 times larger than clinically equivalent human doses, transfer to maternal milk was approximately 0.08% (Oiwa et al. 1992). However, the composition of maternal milk differs between humans and animals (Wilson et al. 1980), so human data are needed.

It is unclear whether mothers with allergies can take EPN while breastfeeding, which is unfortunate because EPN is easy to use. The oral formulation is taken once a day and causes less drowsiness than the first-generation H1 antihistamines. This option has spread to 20 countries worldwide and has been accepted as an over-the-counter prescription since October 2011 in Japan. If the safety of EPN for breastfeeding could be demonstrated by measuring its concentration in human milk samples, the anxiety of nursing mothers could be alleviated.

Ohtani et al. (1996) reported on plasma concentrations of EPN in rats measured by using a high-performance liquid chromatography-ultraviolet detection (HPLC-UV) method with the pretreatment of dichloromethane extraction. However, the EPN concentration in human breast milk has not been mentioned so far.

The present study describes a method for measuring EPN concentrations in human breast milk and plasma that utilizes liquid

Table 1: Recovery rates of EPN and DPN obtained using different liquid-liquid extractions as the pretreatment of the HPLC-UV method

	Recovery (%)		
	2-propanol / chloroform	*n*-hexane/ MeOH	*n*-hexane/0.1% AcOH in MeOH
EPN	51.7 ± 4.5*	80.6 ± 0.8	81.7 ± 1.9
DPN	47.4 ± 3.3	55.4 ± 1.2	79.1 ± 2.1

*Each value was expressed by mean ± SD (n = 4).
MeOH: methanol, AcOH: acetic acid

chromatography-mass spectrometry (LC/MS) to analyze samples pretreated by liquid-liquid extraction with n-hexane and 0.1% acetic acid in methanol. The safety of EPN in infants was further evaluated based on milk-to-plasma (M/P) ratios and relative infant doses (RIDs).

2. Investigations and results

2.1. Measurement of EPN concentration in commercially available milk samples

In order to evaluate the safety of EPN on infants, an analytical method for the measurement of EPN in human breast milk and plasma was established using a liquid chromatographic method that included pretreatment of the samples. Based on the results by Ohtani et al. (1996), who used a dichloromethane extraction for pretreatment of plasma, different liquid-liquid extractions of commercially available milk samples were analyzed using HPLC-UV. Table 1 summarizes the recovery rates of EPN and DPN from the commercial milk samples. Among the extraction media, the *n*-hexane / 0.1% acetic acid in methanol system yielded better recoveries (81.7% for EPN and 79.1% for DPN) than did other systems. This liquid-liquid extraction system was chosen as the pretreatment method for the present study.

A series of experiments utilizing the chosen pretreatment method revealed that HPLC-UV was not sensitive enough to detect EPN. In addition, with HPLC-UV did not produce satisfactory separation of EPN owing to the interference of other components in the milk samples. For this reason, we used a LC/MS system for determination of EPN, with DPN as the internal standard.

2.2. Measurement of EPN concentration in human breast milk and plasma

2.2.1. Background of the mothers and their infants

Seven nursing mothers volunteered to provide breast milk samples. The mothers were aged 31–38 years and had taken EPN hydrochloride (20 mg/d) once a day for more than 7 days before collection. Informed consent was received from the mothers for themselves and their infant.

Table 2 lists basic information of the seven mothers and their infants, aged 4–21 months. Six mothers took EPN hydrochloride for pollen allergy, and one mother took EPN for allergic rhinitis; none took concomitant oral medications. Four infants were breastfed only. The other three infants had a mix of breast milk and baby food or a mix of breast milk and infant formula. All the infants were healthy, of average size, and were without congenital disease or low birth weight. The health condition of each infant was checked by interviewing the mother after 6 months and 1 year, as following;

(1) How long did you breastfeeding your infant?
(2) What do you feed your infant now (i.e., breast milk, formula, or other)?
(3) Did your infant have any illness while you were taking medication?
(4) Does the pediatrician have any comments about your infant?

2.2.2. Calibration curve for the measurement of EPN in human breast milk and plasma

Figure 1 illustrates the chromatograms of EPN and DPN obtained from human breast milk (Fig. 1A) and plasma samples (Fig. 1B). Each peak was selectively detected at a retention time of 7.07 min for EPN and 7.54 min for DPN without any interference from other components. Figure 2 illustrates the calibration curves for EPN in breast milk (Fig. 2A) and plasma samples (Fig. 2B). Both curves showed excellent linearity in the range of 0.1–25 ng/mL for the breast milk sample and 0.5–50 ng/mL for the plasma sample.

2.2.3. Determination of EPN in human breast milk and plasma

Table 3 summarizes the concentrations of EPN in human breast milk samples obtained from seven nursing mothers who took EPN hydrochloride daily for 7 days. Two hours after administration, the EPN concentration in breast milk ranged from 10.3 to 33.5 ng/mL; 4 h after administration, most EPN concentrations increased (range 9.1–63.8 ng/mL). By 10 h after administration, the EPN concentrations declined (8.3–28.9 ng/mL). These results revealed that EPN breast milk concentrations peaked 4 h after intake.

The mothers' plasma EPN concentrations were also determined by LC/MS analysis. As summarized in Table 3, their plasma EPN concentrations ranged from 8.2 to 14.9 ng/mL.

The plasma concentrations of EPN obtained from the infants of mothers corresponding to samples 2 and 7 were 0.0189 and 0.0449 ng/mL (average, n = 3), respectively. Both concentrations were under the quantification limit. No change in health conditions of the seven infants was observed during the present study.

Table 2: Background information of seven volunteer nursing mothers and their infants

Sample number	1	2	3	4	5	6	7
Infant age (months)	21	4	9	4	4	9	7
Maternal age (years)	35	32	38	37	31	38	31
Breast milk intake	BM:BF 10:90	BM only	BM:BF 40:60	BM only	BM only	BM only	BM:IF 98:2
Symptom for EPN intake	allergic rhinitis	pollen allergy	pollen allergy	pollen allergy	pollen allergy	pollen allergy	pollen allergy
Infant body weight (kg)	10.8	6.8	8.5	5.4	8.1	9.0	7.0
Maternal body weight (kg)	52.0	65.0	52.0	48.0	62.0	46.0	50.0
Complications in infant	no	no	no	no	no	no	no
Congenital disease in infant	no	no	no	no	no	no	no
Concomitant oral medications taken by mother	no	no	no	no	no	no	no
Time of milk sampling (days)	7	7	30	7	7	7	7
Time of maternal blood sampling (hour after dose)	4	2	10	10	10	2	2

BF, baby food; BM, breast milk; EPN, epinastine; IF, infant formula.

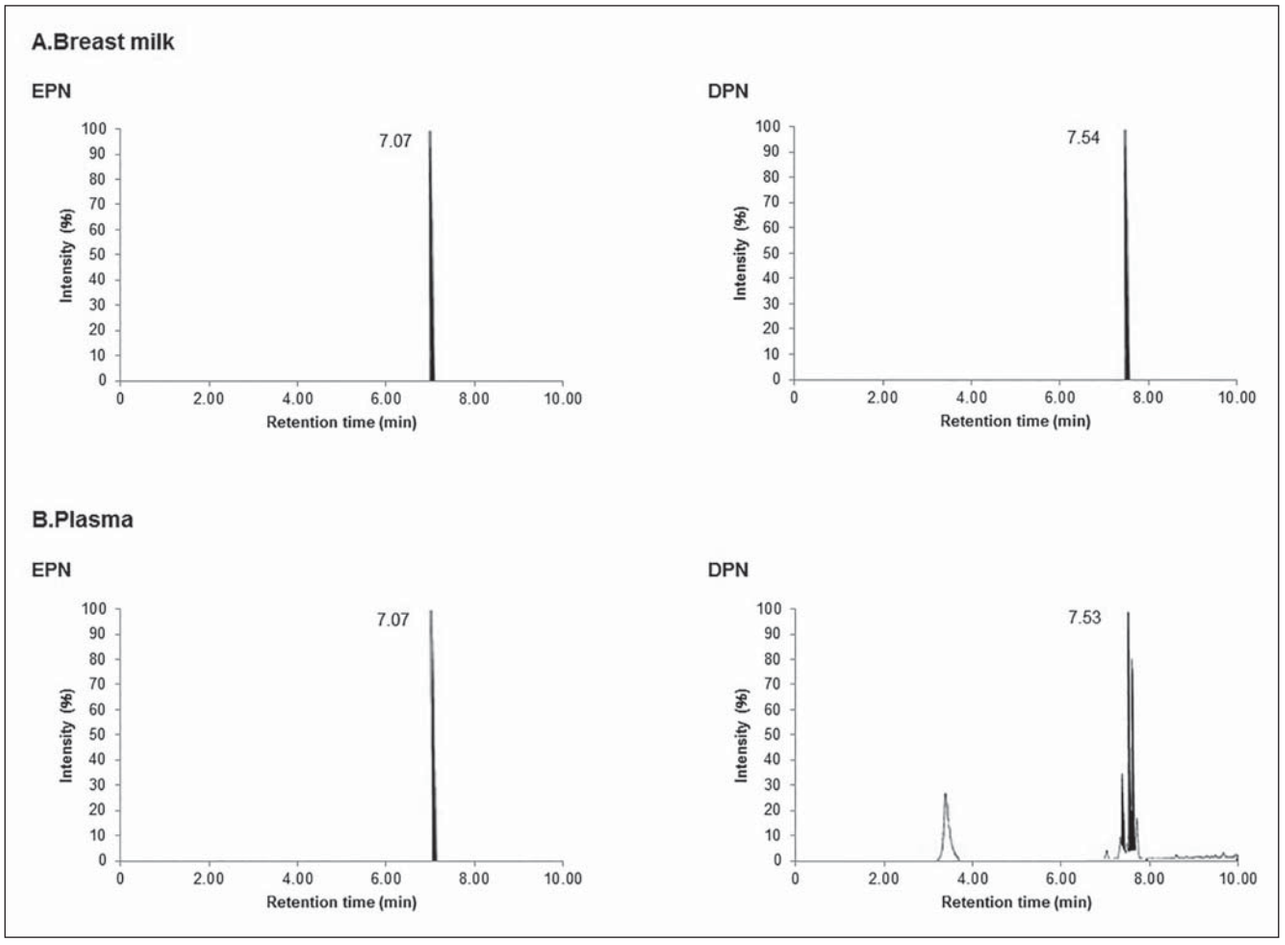

Fig. 1: Liquid chromatography–mass spectrometry chromatograms of epinastine (EPN) and diphenidol (DPN) obtained from human breast milk (A) and plasma (B).

Table 3: Concentration of epinastine in human breast milk at three different collection times after administration

Sample number	Concentration of EPN* (ng/mL)			
	In human breast milk			In maternal plasma (sampling time)
	after 2 h	after 4 h	after 10 h	
1	10.3±1.3	9.1±1.0	15.3±2.2	8.2±1.5 (after 4 hour)
2	---**	18.7±1.1	8.3±0.4	9.5±0.8 (after 2 hour)
3	14.5±1.4	63.8±9.2	28.9±3.3	8.5±0.9 (after 10 hour)
4	33.5±1.0	45.2±1.8	25.9±1.2	11.1±0.7 (after 10 hour)
5	15.7±0.2	38.2±1.8	14.3±2.8	9.3±2.0 (after 10 hour)
6	19.4±0.8	22.7±1.8	16.3±1.4	8.3±0.8 (after 2 hour)
7	12.2±0.7	19.1±1.9	11.3±0.2	14.9±1.3 (after 2 hour)

*Each value is expressed as the mean ± standard deviation (the average of three replicate samples).
**No data. EPN, epinastine.

2.2.4. Calculation of M/P ratio and RID

The M/P ratio and RID were calculated according to the following formulae (Hale and Rowe 2016):

(1) M/P ratio = drug level in breast milk / drug level in maternal plasma

(2) RID (%) = infant dose (mg/kg/day) / maternal dose (mg/kg/day) × 100,

where the infant dose was calculated as follows:

(3) infant dose = drug level in mother's milk × daily breast milk intake

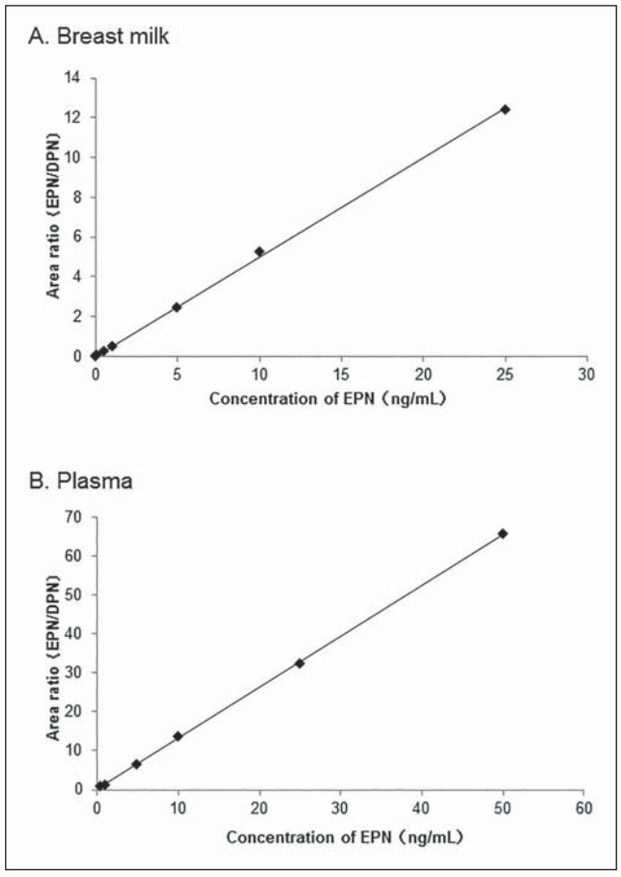

Fig. 2: Calibration curves for epinastine (EPN) in human breast milk (A) and plasma (B). The linear equations were as follows: A: y = 0.4991x + 0.0078 (r2 = 0.9995); B: y = 1.3108x + 0.0658 (r2 = 0.9999). DPN=diphenidol

The estimated average daily intake of breast milk was 150 mL/kg/d, which was used as the daily breast milk intake (Hotham and Hotham 2015).

Table 4 summarizes the M/P ratios and the RIDs calculated from Table 3.

3. Discussion

The transfer of drugs into breast milk is generally evaluated based on two values: M/P ratio and RID. Traditionally, M/P ratios are used for evaluating transferability into maternal milk. In our study, the M/P ratios ranged from 0.82 to 3.39. Among the six values, five M/P ratios were greater than 1, signifying high transferability of the drug into maternal milk (Hale and Rowe 2016). This result suggested that EPN is concentrated in maternal milk. However, M/P ratios are insufficient as the standard of transferability, because they are easily affected by the maternal plasma concentrations of the medications (Ito 2000; Atkinson et al. 1988).

In general, medications with a basic pH (e.g., EPN) are concentrated in maternal milk because of "ion trapping" (Hale and Rowe 2016) Nevertheless, drugs transferred into maternal milk are generally considered safe if the RID is under 10%, a value clinically used as the standard of transferability (Hotham and Hotham 2015). In our study, RIDs varied in the ranges of 0.40–1.21%, 0.36–2.49%, and 0.40–1.13% at 2 h, 4 h, and 10 h after EPN intake, respectively. Thus, although the M/P ratio of EPN was greater than 1, the maximum RID obtained after 4 h was 2.49%, which is lower than 10%. Drugs such as acyclovir (Sheffield et al. 2002), sumatriptan (Wojne-Horton et al. 1996), and escitalopram (Rampono et al. 2006) have M/P ratios greater than 1 and RIDs under 10% and are considered "probably compatible" with breastfeeding (Hale and Rowe 2016). Therefore, our results suggested that EPN is safe for use by nursing mothers.

Table 4: M/P ratios and RIDs calculated from analytical values obtained from seven volunteer nursing mothers

Sample number	M/P ratio	RID (%)		
		after 2 h	after 4 h	after 10 h
1	1.11	0.40	0.36	0.60
2	---*	---*	0.91	0.40
3	3.39	0.56	2.49	1.13
4	2.34	1.21	1.63	0.93
5	1.37	0.73	1.78	0.67
6	2.35	0.67	0.78	0.56
7	0.82	0.46	0.72	0.42

*No data. M/P, milk/plasma; RID, relative infant dose.

In addition to M/P ratios and RIDs, we evaluated EPN concentrations in breast milk. Peak breast milk concentrations, which corresponded to maximum maternal blood concentrations, were obtained 4 h after dosing for all maternal milk samples. Sample 3 had the highest concentration (63.8 ng/mL; RID = 2.49%). In that case, the infant received milk and baby food at a ratio of 4:6 (Table 2). Therefore, we calculated that the adjusted maternal milk concentration was 25.5 ng/mL and the adjusted RID was 1.00%. The age of the infant is related to the quantity of milk intake. Therefore it is necessary to consider the age of the infant when administering a drug to a nursing mother.

At equilibrium, drug levels in human breast milk generally correlate to drug plasma levels; however, they did not correlate in our study (Table 3). Transfer into breast milk depends on various factors such as degree of protein binding, molecular weight, and lipid solubility. Hydrophilic drugs take a longer time to transfer into breast milk than nonhydrophilic drugs do. EPN is hydrophilic, because its *n*-octanol/water partitioning value is 9.2×10^{-2} (Atkinson et al. 1988). This may be responsible for the gap in drug peak concentrations between maternal milk and plasma.

Finally, we evaluated the plasma EPN concentrations of nursing infants. In Japan, powdered EPN is used in infants. It does not easily transfer into the brain, and its central depressant effect is weak. However, neonates require careful observation during the intake period owing to the immature blood-brain barrier and metabolism–excretion system. As mentioned above, the plasma EPN concentrations of two infants in our study were under the quantification limits. At approximately 3.4% and 5.3% of the maternal EPN concentrations, the values were extremely low compared to effective blood concentrations. Indeed, there were no changes in the health conditions of the two infants.

It is not easy to collect a satisfactory number of milk and blood samples from nursing mothers in drug therapy because of ethical issues as well as the busy schedule of mothers and the complexity of samplings. At present, an improved sampling method is being applied to the study of other antihistamine drugs in breast milk (Saito et al. 2016). This method facilitates the transfer of samples from lactating women from distant locations, thereby increasing the availability of samples. However, this method may introduce the risk of sample damage during transport. Therefore, various approaches to obtaining samples from lactating women will be required in the future.

In summary, an analytical method for evaluating the transfer of EPN through breast milk was developed using an LC/MS system with ESI in positive mode. The samples were pretreated by liquid-liquid extraction that utilized *n*-hexane and 0.1% acetic acid in methanol. Then, separation of EPN and DPN was achieved using an ODS-silica column with an eluent composed of aqueous 0.1% formic acid/acetonitrile solution. This method was applied to the quantification of EPN in human breast milk and plasma. From those analytical values, we calculated a maximum M/P ratio of 3.39 and a maximum RID of 2.49% for EPN. Our results suggested that nursing mothers can take EPN during breastfeeding without affecting their breastfeeding infants.

The information from our study will benefit patients requiring allergy therapy during lactation. We recommend that further studies be performed on other antihistamines that lack such information to reduce the anxiety of nursing mothers.

4. Experimental

4.1. Measurement of EPN concentration in commercially available milk samples

4.1.1. Materials

EPN hydrochloride (used as the standard) and diphenidol (DPN; internal standard, IS) (Ohtani et al. 1996) were purchased from Tokyo Chemical Industry Co. (Tokyo, Japan) for chromatographic analysis. All other reagents were of reagent grade. The milk samples used the commercial available one that we got from a supermarket

4.1.2. Preparation of samples for the calibration curve

Each EPN standard solution was prepared at the desired concentration by dissolving with purified water. A constant volume of aqueous standard solution was added into the test tube and evaporated under a vacuum. Then, the EPN residue was dissolved in milk. The standard milk solution was prepared at final concentrations of 0, 12, 16, 24, 32, 40,48, and 56 ng/mL of EPN. The IS solution was prepared by dissolving DPN with purified water at a concentration at 0.1 ng/mL.

4.1.3. Measurement

Five-hundred microliters of milk samples was mixed with 20 µL of the IS solution. Two milliliters each of *n*-hexane and methanol containing 0.1% acetic acid was then added to each sample, and the sample solutions were mixed vigorously for 1 min. After centrifuging at 3000 rpm for 10 min, the sample solutions were left to stand to form two layers. The upper *n*-hexane-rich phase was removed from the test tubes, and the lower methanol-rich phase was evaporated under vacuum. The residues were dissolved with 50 µL of water. Then, the sample solutions were subjected to HPLC analysis. As follows: column, Intertsil ODS-SP(150×4.6 mm, 5 µm, GL Sciences); eluent, aqueous methanol / 1% triethylamine solution (pH4.5, 36 : 64); detection, UV 215 nm).

4.2. Measurement of EPN concentration in breast milk and plasma

4.2.1. Materials

EPN hydrochloride (used as the standard) and diphenidol (DPN; internal standard, IS)(Ohtani et al. 1996) were purchased from Tokyo Chemical Industry Co. (Tokyo, Japan) for chromatographic analysis. All other reagents were of reagent grade.
Breast milk samples were collected at 2, 4, and 10 h after taking EPN hydrochloride. Within the same day, blood samples from the mothers were collected in test tubes containing heparin at 2 or 10 h after taking EPN hydrochloride (Table 2) (Azuma et al. 1992). Infant blood samples were collected at the same time as maternal blood samples. Each blood sample was centrifuged at 3000 rpm for 6 min. Then, the plasma was separated. Both breast milk and plasma were frozen and stored at -80 °C until measurement.

4.2.2. Preparation of samples for the calibration curve

Each EPN standard solution was prepared at the desired concentration by dissolving with purified water. A constant volume of aqueous standard solution was added into the test tube and evaporated under a vacuum. Then, the EPN residue was dissolved in human milk or plasma. The standard human milk solution was prepared at final concentrations of 0, 0.1, 0.5, 1, 5, 10, and 25 ng/mL of EPN. The standard plasma solution was also prepared at final concentrations of 0, 0.5, 1, 5, 10, 25, and 50 ng/mL of EPN. The IS solution was prepared by dissolving DPN with purified water at a concentration at 0.1 ng/mL.

4.2.3. Measurement

Five-hundred microliters of milk or plasma samples was mixed with 20 µL of the IS solution. Two milliliters each of *n*-hexane and methanol containing 0.1% acetic acid was then added to each sample, and the sample solutions were mixed vigorously for 1 min. After centrifuging at 3000 rpm for 10 min, the sample solutions were left to stand to form two layers. The upper *n*-hexane–rich phase was removed from the test tubes, and the lower methanol-rich phase was evaporated under vacuum. The residues were dissolved with 200 µL of methanol. Then, the sample solutions were subjected to LC/MS analysis. The operating conditions of the LC/MS instrument (Waters) were established according to the method by Do et al. (2015). as follows: column, ACQUITY UPLC® BEH C18 (1.7 µm i.d.); eluent, aqueous 0.1% formic acid solution / acetonitrile; detection, electrospray ionization (ESI) positive mode (target ions: m/z 250.134 for EPN and m/z 310.217 for DPN).

4.3. Ethical considerations

This study was conducted according to study protocols approved by the Ethics Review Boards of the Saiseikai Narashino Hospital (Chiba, Japan; no approval number was provided; date of approval was August 12th, 2015) and the School of Pharmacy, Nihon University (Chiba, Japan; No. 15-007). Efforts were made to maintain the privacy of the participants in the present study.

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Conflicts of interest: The authors declare no conflict of interest.

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