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Original Article

Transfer of vaginal chloramphenicol to circulating blood in pregnant women and its relationship with their maternal background and neonatal health

Satoe Harauchi [a], Takashi Osawa [a], Naoko Kubono [a], Hiroaki Itoh [b], Takafumi Naito [a, *], Junichi Kawakami [a]

[a] Department of Hospital Pharmacy, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan
[b] Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

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ABSTRACT

Few clinical studies have determined the quantitative transfer of vaginal chloramphenicol to circulating blood in pregnant women. This study aimed to evaluate the plasma concentration of chloramphenicol in pregnant women treated with trans-vaginal tablets and its relationship with maternal background and neonatal health. Thirty-seven pregnant women treated with 100 mg of trans-vaginal chloramphenicol once daily for bacterial vaginosis and its suspected case were enrolled. The plasma concentration of chloramphenicol was determined using liquid chromatography coupled to tandem mass spectrometry at day 2 or later after starting the medication. The correlations between the maternal plasma concentration of chloramphenicol and the background and neonatal health at birth were investigated. Chloramphenicol was detected from all maternal plasma specimens and its concentration ranged from 0.043 to 73.1 ng/mL. The plasma concentration of chloramphenicol declined significantly with the administration period. The plasma concentration of chloramphenicol was lower at the second than the first blood sampling. No correlations were observed between the maternal plasma concentration of chloramphenicol and background such as number of previous births, gestational age at dosing, and clinical laboratory data. Neonatal infant health parameters such as birth-weight, Apgar score at birth, and gestational age at the time of childbearing were not related to the maternal plasma concentration of chloramphenicol. Vaginal chloramphenicol transfers to circulating blood in pregnant women. The maternal plasma concentration of chloramphenicol varied markedly and was associated with the administration day, but not with maternal background or her neonatal health.

1. Introduction

Chloramphenicol is an antibiotic widely used to treat the bacterial infections caused by gram-negative coccoid bacterium, bacilli, rickettsia, mycoplasma, and chlamydia. In Japan, trans-vaginal chloramphenicol is used to treat the bacterial vaginosis [1]. Bacterial vaginosis is a disease in which the normal vaginal flora is replaced by anaerobic bacteria [2], and is the most common vaginal infection in both pregnant and non-pregnant women [3]. The compositions of vaginal microbiome differ between non-pregnant women and pregnant women, and the prevalence of bacterial vaginosis ranges from 10 to 20% in pregnant women [4–6]. According to the drug package insert of vaginal tablets containing chloramphenicol, the drug does not transfer to circulating blood [7]. Vaginal tablets containing chloramphenicol or metronidazole are widely used to treat bacterial vaginosis in pregnant women in Japan. In pregnant women, chloramphenicol as secondary choice easily passes through placenta, and therefore may have an effect on neonatal infants [8].

Chloramphenicol causes several serious adverse effects including aplastic anemia, bone marrow suppression, and leukemia

Abbreviations: IQR, interquartile range; LC–MS/MS, liquid chromatography coupled to tandem mass spectrometry; HPLC–UV, high performance liquid chromatography coupled to ultraviolet detection.

* Corresponding author. Department of Hospital Pharmacy, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, Shizuoka 431-3192, Japan. Fax: +81 53 435 2764.
E-mail address: naitou@hama-med.ac.jp (T. Naito).

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in adults. Gray baby syndrome is a known adverse effect of chloramphenicol in neonatal infants [9,10]. Chloramphenicol is metabolized by uridine 5′-diphospho-glucuronosyltransferases in the liver and converted to the glucuronate conjugate. Gray baby syndrome is a result of the inability to conjugate glucuronate by neonatal infants, especially immature babies. The occurrence of gray baby syndrome is potentially associated with the plasma concentration of chloramphenicol in pregnant women [11]. The effect of chloramphenicol on neonatal infants is an issue that must be addressed when administering trans-vaginal chloramphenicol to pregnant women.

Trans-vaginal chloramphenicol was not transferred into the general circulation in an earlier observation [7]. In this earlier observation, 34 women including 10 pregnant women who were treated with 100 mg of trans-vaginal chloramphenicol were investigated. The plasma concentration of chloramphenicol was determined using high performance liquid chromatography coupled to ultraviolet detection (HPLC–UV) and its lower limit of quantification in human plasma was 100 ng/mL. Although HPLC–UV has several advantages in terms of lower running cost, larger dynamic range, and non-destructive detection, disadvantages include a lower detection limit and a lack of structure-specific detection. This earlier report did not quantitatively determine the transfer of chloramphenicol in circulating blood in pregnant women treated with trans-vaginal chloramphenicol. In contrast, liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS) can detect analytes structure-specifically and sensitively compared with HPLC–UV.

Few previous reports have examined the quantitative transfer of trans-vaginal chloramphenicol to the maternal general circulation using LC–MS/MS. In the present study, we developed a highly specific and sensitive method for determining the plasma concentration of chloramphenicol by an LC–MS/MS in humans. This study evaluated the transfer of chloramphenicol to circulating blood in pregnant women treated with trans-vaginal chloramphenicol, and we investigated the correlations with maternal background and the health of neonatal infants.

2. Patients and methods

2.1. Ethics

The study was performed in accordance with the Declaration of Helsinki and its amendments, and the protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine (approval number, 25-324). The patients received information about the scientific aim of the study and each patient provided written informed consent.

2.2. Patients and study schedule

The present study was an observation study conducted at Hamamatsu University Hospital. A total of 37 Japanese pregnant women receiving chloramphenicol vaginal tablets (Clomy® Vaginal Tablet, Daiichi Sankyo Pharmaceutical Co., Ltd, Tokyo, Japan) for bacterial vaginosis and its suspected case were enrolled. Bacterial vaginosis was assessed by vaginal secretion characteristics according to WHO diagnostic criteria. Each patient received 100 mg chloramphenicol once daily trans-vaginally. Exclusion criteria were as follows: patients (1) in whom obtaining the blood on schedule for pharmacokinetic analysis was difficult; (2) who were being co-treated with a drug metabolizing enzyme modifier; (3) with impaired renal function (serum creatinine > 2.0 mg/dL); and (4) with hepatic dysfunction (total bilirubin > 2.0 mg/dL). Blood samples were obtained on day 2 or later after starting the medication. A 2-mL blood specimen was withdrawn into tubes containing EDTA dipotassium salts at 24 h post-dose. A second plasma specimen was obtained from some patients after the first blood sampling. This study is registered in the University Hospital Medical Information Network (UMIN-CTR UMIN000021034).

2.3. Materials and solutions

Chloramphenicol was purchased from Wako Pure Chemicals (Osaka, Japan). Chloramphenicol-*d5* as an internal standard (IS) was obtained from Sigma Aldrich (St. Louis, MO, USA). All other reagents were of analytical grade and commercially available. Stock solutions of chloramphenicol and IS were prepared with methanol. Standard solutions of chloramphenicol were obtained by the dilution of a stock solution with methanol. Calibration standards were prepared in drug-free pooled plasma (Kohjin-Bio Co., Ltd, Sakado, Japan).

2.4. Plasma preparation for chloramphenicol measurement

Plasma was separated by centrifugation of the EDTA-treated blood samples at 1670 × *g* at 4 °C for 10 min. For sample deproteinization, to 200 μL of plasma, 100 μL of IS solution (10 ng/mL) and 1000 μL of methanol were added into a microtube. After vortexing, the mixture was then sonicated and cooled. Then the mixture was vortex-mixed and centrifuged at 17,900 × g, and the supernatant was evaporated to dryness. The residue was reconstituted with 120 μL of mobile phase and centrifuged at 17,900 × *g*. The supernatant was injected into the LC system.

2.5. Determination of plasma chloramphenicol

Chloramphenicol in human plasma was determined using an LC system ($UFLC_{XR}$, Shimadzu Corporation, Kyoto, Japan) coupled to a triple quadrupole mass spectrometer (3200 QTRAP®, AB Sciex, Foster City, CA, USA) with an electrospray probe. Separation was performed using TSKgel ODS-100V (particle size 3 μm, 2.0 mm I.D. × 75 mm, Tosoh, Tokyo). The mobile phase consisted of 20% acetonitrile containing 5 mM ammonium acetate (pH 3.5), and the flow rate was 0.2 mL/min. Chloramphenicol and IS were monitored by the respective transitions of *m/z* 320.7–151.9 and 325.8–156.8 with collision energy levels of −20 eV, respectively. The linearity of chloramphenicol was observed at concentration ranges of 0.1–100 ng/mL. The intra- and inter-assay accuracies of chloramphenicol were 100.5–107.1% and 100.7–106.0%, respectively. The intra- and inter-assay precisions of chloramphenicol were 1.39–4.98% and 3.99–8.78%, respectively. The lower limit of quantification for chloramphenicol in human plasma was 100 pg/mL.

2.6. Factors related to plasma chloramphenicol

This study investigated the quantitative transfer of chloramphenicol to the maternal general circulation and assessed the relationships between the maternal plasma concentration of chloramphenicol and maternal background. The parameters of maternal background included the number of previous births, gestational age at the first dosing, and clinical laboratory data. The clinical laboratory data consisted of aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) as hepatic dysfunction, serum creatinine as renal function, C-reactive protein (CRP) and white blood cell count (WBC) as inflammatory markers, and serum albumin. To assess the influence of chloramphenicol treatment on neonatal infants, the relationships between the maternal plasma concentration of chloramphenicol and birth-weight, Apgar score at birth, and the gestational age at the time of childbearing were investigated.

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2.7. Statistical analysis

All statistical analyses were performed using IBM SPSS 22.0J Statistics (IBM Japan Ltd, Tokyo). The relationship between the maternal plasma concentration of chloramphenicol and the factors except for the birth experience and condition classification of neonatal infants by Apgar score was analyzed using Pearson's test. The number of previous births and condition classification of neonatal infants by the Apgar score were analyzed using the Mann–Whitney *U* test. All values are expressed as the median and interquartile range (IQR) unless otherwise stated. A $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Maternal characteristics

Table 1 shows the maternal characteristics of the study population. All patients enrolled were pregnant women with bacterial vaginosis and were being co-treated with urinastatin vaginal suppository. The medians of the maternal and gestational ages at dosing were 31 years (IQR, 28–36 years) and 30 weeks and 3 days, respectively. The subjects did not receive any medications other than chloramphenicol and urinastatin.

Table 1
Maternal backgrounds.

Maternal parameters	Values
Age (years)	31 (28–36)
Body weight (kg)	54.4 (49.3–63.0)
Body height (cm)	158 (154–162)
Primipara/multipara	18/19
Total administration period (days)	7 (7–7)
Gestational ages at dosing (w.d)	30w.3d (24w.2d–32w.5d)
Aspartate aminotransaminase (U/L)	15 (13–21)
Alanine aminotransferase (U/L)	10 (7–18)
Serum creatinine (mg/dL)	0.43 (0.40–0.46)
Serum albumin (g/dL)	2.9 (2.8–3.3)
C-reactive protein (mg/dL)	0.27 (0.12–0.74)
White blood cell count (μL)	8220 (7180–9710)

Data are expressed as the median and interquartile range in parentheses. The clinical laboratory data were obtained at the first blood sampling.

3.2. Maternal plasma concentration of chloramphenicol

Fig. 1A shows the plasma concentration of chloramphenicol in the subjects. The chloramphenicol concentration ranged from 0.043 to 73.1 ng/mL. Chloramphenicol was detected from all plasma specimens. The median plasma concentration of chloramphenicol was 10.1 ng/mL (IQR, 4.06–18.0 ng/mL) at the first sampling. The median and IQR of the dose-normalized plasma concentration of chloramphenicol were 5.71 and 2.34–8.85 ng/mL per mg/kg, respectively. Fig. 1B shows the plasma concentration of the chloramphenicol-administration day profile at the first sampling. The median administration day was 7 days (IQR, 7–7 days). The median days of the first and second sampling were day 3 (IQR, day 2–4) and day 7 (day 4–7), respectively. The maternal plasma concentration of chloramphenicol declined significantly with the administration day. The plasma concentration of chloramphenicol was significantly lower at the second than the first sampling ($P = 0.009$).

3.3. Maternal backgrounds and clinical laboratory data

The maternal plasma concentration of chloramphenicol was not significantly correlated with maternal age ($R^2 < 0.001$, $P = 0.94$), number of previous births ($P = 0.36$), or gestational age ($R^2 = 0.16$, $P = 0.13$). There was no correlation between body weight ($R^2 = 0.040$, $P = 0.24$) or height ($R^2 = 0.012$, $P = 0.52$) and the maternal plasma concentration of chloramphenicol. No significant correlation was observed between the maternal plasma concentration of chloramphenicol and clinical laboratory data that included AST ($R^2 = 0.042$, $P = 0.23$), ALT ($R^2 = 0.068$, $P = 0.12$), serum creatinine ($R^2 = 0.003$, $P = 0.77$), and serum albumin ($R^2 = 0.13$, $P = 0.68$). The medians of CRP and WBC in patients at first sampling were 0.27 mg/dL (IQR, 0.12–0.74 mg/dL) and 8220/μL

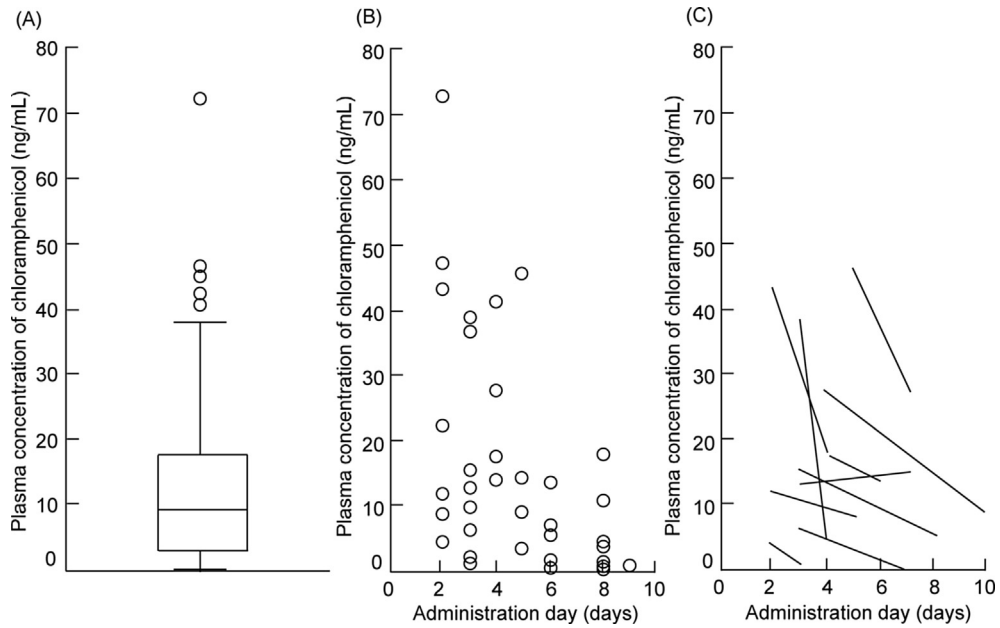

Fig. 1. Maternal plasma concentration of chloramphenicol (A) and its relationship with administration period of trans-vaginal chloramphenicol at first blood sampling (B, $n = 37$), and multiple blood sampling (C, $n = 10$). Box plots represent the median (bold line), 25th, and 75th percentiles, and the whiskers indicate the range and extend within 1.5 times the length of the inner quartiles.

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(7180–9710/μL), respectively. No significant correlations were observed between the plasma concentration of chloramphenicol and CRP and WBC (Fig. 2).

3.4. Neonatal health

The medians of birth weight and Apgar score at birth were 2312 g and 8, respectively (Table 2). No infants were diagnosed as gray baby syndrome at birth. Significant associations were not observed between the maternal plasma concentration of chloramphenicol and birth weight ($R^2 = 0.008$, $P = 0.58$) or Apgar score ($P = 0.79$) of the neonates. The gestational age at the time of childbearing was not correlated with the maternal plasma concentration of chloramphenicol ($R^2 < 0.001$, $P = 0.90$).

Table 2
Neonatal health parameters.

Parameter	Value
Gestational age at birth (w.d)	36w.2d (34w.1d–38w.4d)
Body weight at birth (g)	2312 (1954–2846)
Apgar score at 1 min after birth	8 (7–9)
6 points and less: asphyxia ($n = 9$)	4 (3–5)
7 points and over: healthy ($n = 29$)	8 (8–9)

Data are expressed as the median and interquartile range in parentheses ($n = 38$). Four pregnant women were not assessed because of patient transfer and stillbirth. Five postpartum women had twins.

4. Discussion

Vaginal tablets containing chloramphenicol or metronidazole are commonly used for the treatment of bacterial vaginosis in pregnant women [12,13]. Chloramphenicol for bacterial vaginosis easily passes through placenta and potentially has an effect on neonatal infants. This study investigated the plasma concentration of chloramphenicol in pregnant women treated with trans-vaginal tablets and its relationships with maternal background and the health of their neonatal infants at birth. In the present study, plasma chloramphenicol was detected at the range of 0.043–73.1 ng/mL and there was a large variation in its concentration. The maternal plasma concentration of chloramphenicol decreased over time after first dose. No correlations were observed between the maternal plasma concentration of chloramphenicol and the maternal background or neonatal health at birth. These findings suggest that there is a large variation in the uptake of trans-vaginal chloramphenicol into the general circulation. To the best of our knowledge, this is the first report to determine quantitatively the transfer of chloramphenicol to circulating blood in pregnant women treated with trans-vaginal tablets.

Chloramphenicol was detected from all plasma specimens of the women in this study. Our LC–MS/MS method has a 1000-fold sensitivity compared with an earlier study using HPLC–UV [5]. Our data indicate that vaginal chloramphenicol transfers to circulating blood in pregnant women. In addition, the maternal plasma concentration of chloramphenicol showed a large variation (IQR, 4.06–18.0 ng/mL). The maternal plasma concentration of chloramphenicol in this study population was much lower than the therapeutic range of chloramphenicol (5–20 μg/mL) in typhoid fever [14]. Oral chloramphenicol is metabolized to the glucuronate conjugate in the liver. Approximately 90% of the drug excreted in the urine was reported to be in the form of glucuronide [15]. The chloramphenicol clearance in humans was found to be dependent on both renal and liver function, and renal and liver function potentially cause the interindividual variability in the plasma concentration of chloramphenicol [14]. No patient enrolled in this study had kidney or liver dysfunction, and none were receiving any medications that are known to have an effect on chloramphenicol pharmacokinetics. These data indicate that the clinical condition of bacterial vaginosis and pregnancy itself potentially affects the variability of the maternal plasma concentration of chloramphenicol.

The plasma concentration of chloramphenicol declined with the number of administration. In 10 patients with multiple blood samplings, the maternal plasma concentration of chloramphenicol

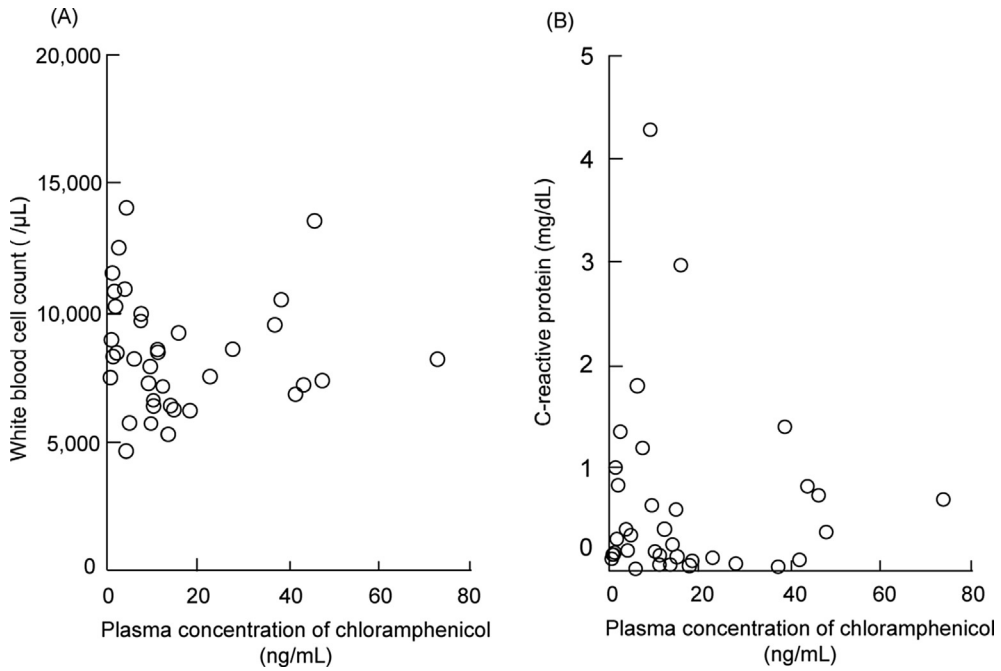

Fig. 2. Relationship between maternal plasma concentration of chloramphenicol and clinical laboratory data. (A) White blood cell count and (B) C-reactive protein.

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was significantly lower at the second than the first sampling. Generally, improvement of the inflammatory condition of the gut mucous membrane reduces drug absorption [16]. The trans-vaginal absorption of chloramphenicol through the vaginal mucous membrane may also be increased by the inflammation caused by bacterial vaginosis. Our data suggest that normalization of the self-defense function in the vaginal mucous membrane after the treatment of vaginal chloramphenicol decreases the maternal plasma concentration of chloramphenicol in pregnant women.

The gestational age in this study population ranged from 16 to 36 weeks, classified as the second and early third trimester. In the late second trimester, cardiac output and renal blood flow increase, while hepatic blood flow does not change [17]. There were slight differences in the gestational age and serum creatinine levels in this study population. These data suggest the gestational age and changes in renal function during pregnancy do not strongly affect the individual variation in the maternal plasma concentration of chloramphenicol. The parameters maternal background including maternal age, number of previous births, and gestational age did not influence the plasma concentration of chloramphenicol. In addition, physical characteristics such as body weight and height related to drug distribution were not associated with the plasma concentration of chloramphenicol. These results indicate that the physiological alterations during pregnancy are not responsible for the interindividual variation in the maternal plasma concentration of chloramphenicol.

No association between the maternal concentration of chloramphenicol and inflammation markers such as CRP and WBC was observed in the present study. These inflammation markers may not reflect the condition of local inflammation caused by bacterial vaginosis [18–20]. Mild bacterial vaginosis and its suspected case have not been routinely graded using the clinical parameters including inspection in clinical settings. The clinical parameters would confirm that the absorption of chloramphenicol through vaginal mucous membrane is affected by the degree of the inflammation level and the cervical lesions. The trans-vaginal chloramphenicol is administrated to pregnant women in order to prevent premature birth induced by the inflammation of bacterial vaginosis. In four women, the flora color of vagina secretions changed from yellow or pinkish to colorless or white and the volume decreased in the present study. Changes in the color and volume may indicate an improvement of the symptoms of bacterial vaginosis by treatment of trans-vaginal chloramphenicol administration. While CRP and WBC as clinical laboratory data are not associated with an improvement of local vaginal inflammation, a decline in the maternal plasma concentration of chloramphenicol may be a useful as biomarker that reflects the improvement of bacterial vaginosis.

The maternal plasma concentration of chloramphenicol was not associated with neonatal health such as gestational age, body weight, and Apgar score at birth. In reproduction test in rats, 300 mg/kg of chloramphenicol for 4 weeks was found to potentially cause miscarriage and premature birth [21]. Chloramphenicol is recognized as Class C in the United States FDA pregnancy category [22]. In the present study, pregnant women with gestational ages ranging from 16 to 36 weeks were exposed to by 100 mg of trans-vaginal chloramphenicol per day for 7 days. However, those treated with trans-vaginal tablets had much lower plasma concentrations of chloramphenicol, compared with oral or intravenous administration. In addition, our clinical study revealed that the maternal plasma concentration of chloramphenicol did not affect the health of the neonates at birth.

The present study has several limitations. First, the maternal plasma specimens were collected just before administration of trans-vaginal chloramphenicol. Also, we did not evaluate the plasma concentration time-profile after medication. Chloramphenicol has a short half-life of 3–4 h [23] and a high concentration is not maintained in human plasma. The maternal trans-vaginal chloramphenicol level was considered to have little influence on neonatal health at birth. Second, this study did not determine the concentration of chloramphenicol in the umbilical cord blood. Maternal chloramphenicol readily crosses the placenta [22]. However, the maternal plasma concentration of chloramphenicol after trans-vaginal treatment was one one-thousandth that of the therapeutic concentration in oral and intravenous treatments. The umbilical cord blood concentration in this study is expected to be lower than the therapeutic concentration. Third, pregnant women with bacterial vaginosis were enrolled in this study. Trans-vaginal chloramphenicol is also administrated to non-pregnant women. Absorption of the drug through the vaginal mucous membrane in non-pregnant women may not be identical to that in pregnant women because pregnancy may affect the condition of the vaginal mucous membrane [24,25]. The transfer of vaginal chloramphenicol to circulating blood in women who are not pregnant needs to be clarified in further studies.

In the present study, the transfer of vaginal chloramphenicol into the general circulation was quantitatively evaluated in pregnant women and the plasma concentration of chloramphenicol was found to be in the range of 0.043–73.1 ng/mL. Based on the quantitative transfer data of trans-vaginal chloramphenicol to circulating blood, physicians can explain the administration of trans-vaginal chloramphenicol to pregnant women from the viewpoint of the risk-benefit balance. Our findings may be helpful as safety information for the use of trans-vaginal chloramphenicol in pregnant women.

In conclusion, this study established a highly specific and sensitive method for determining the plasma concentration of chloramphenicol using LC–MS/MS in humans. Vaginal chloramphenicol transfers to circulating blood in pregnant women and we observed a large variation in the maternal plasma concentration of chloramphenicol that was correlated with the administration day, but not maternal background or health of the neonate.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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