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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

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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.

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## 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.

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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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