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Pharmacokinetic assessment of alprazolam-induced neonatal abstinence syndrome using physiologically based pharmacokinetic model

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Abstract

Sustained benzodiazepine use during pregnancy can induce neonatal abstinence syndrome (NAS). In this study, the association between NAS and plasma alprazolam concentration was examined using the measured neonatal concentrations in the time series as well as simulated plasma concentrations of pregnant woman and neonate by physiologically based pharmacokinetic (PBPK) modeling. A neonate born to a mother taking alprazolam daily throughout pregnancy exhibited symptoms such as apnea and vomiting from 9 h to 4 days after birth. Finnegan score was 7 at birth and decreased to 0 by day 4. Apnea improved by 24 h post-delivery and gastrointestinal symptoms disappeared by day 4. The plasma alprazolam concentration in the neonate was 15.2 ng/mL immediately after birth and gradually decreased over 3 days. Measured neonate and estimated maternal plasma alprazolam concentrations were within the 90% prediction intervals of each concentration by PBPK simulation using “pregnancy” and “pediatrics” population parameters including in Simcyp population-based ADME simulator. In conclusion, NAS symptoms such as apnea and digestive events disappeared in parallel with the decrease of the neonate’s plasma alprazolam concentrations. Moreover, PBPK modeling and simulation is a useful methodology for toxicological assessment in special characteristics populations lacking specific experimental data.

Keywords

neonatal abstinence syndrome, alprazolam, plasma concentration, PBPK, simulation

1. Introduction

Alprazolam is a benzodiazepine anxiolytic used for the treatment of psychosomatic disorders, dysphoria, anxiety, and sleep disorders. Regular and prolonged use of benzodiazepines can induce neonatal abstinence syndrome (NAS) in the infant if taken during pregnancy [1]. Therefore, benzodiazepine prescriptions for pregnant women are limited to cases in which the benefits are deemed to exceed the risk of neonatal harm.

NAS occurs due to the sudden interruption of placental drug delivery at birth [1,2]. Within hours after birth, these neonates begin to express neurological symptoms such as tremor, irritability, anxiety, or excitement; digestive symptoms such as poor feeding, vomiting, or diarrhea; autonomic symptoms such as diaphoresis or fever, and in serious cases, apnea or spasm [1]. Although benzodiazepine-induced NAS generally last only 1–3 days, a neonate must be monitored carefully for a period that depends on the offending drug [3]. It is reported that neonates with NAS due to *in utero* benzodiazepine exposure secrete the drug in urine for 1–7 days after birth [2], but the associations between plasma concentration and abstinence syndrome symptoms are unclear.

In this report, we evaluated the plasma concentrations of alprazolam in a neonate with NAS born to a mother who took alprazolam routinely throughout pregnancy to clarify whether abstinence symptoms depend on systemic drug concentrations and its elimination rate. We also examined if a physiologically based pharmacokinetic (PBPK)

simulation is useful for prediction of plasma alprazolam concentrations in neonates as well as pregnant women.

2. Methods

2.1. Blood sampling and measurement of alprazolam concentrations

The mother gave written informed consent for the measurement of plasma drug concentrations of herself and her baby and publication of these data. Blood samples were collected from the neonate as routine care right after birth and daily thereafter. A blood sample was collected from the mother on day 100 after delivery. Alprazolam concentrations were measured by liquid chromatography-tandem mass spectrometry in LSI Medience Corporation (Tokyo, Japan).

2.2. PBPK modeling and simulation

PBPK simulations of plasma alprazolam concentration were performed using Simcyp population-based ADME simulator version 15 (Certara UK Limited, Simcyp Division, Sheffield, UK) with the compound model of alprazolam and population parameters for “pregnancy”, “pediatrics”, and “Japanese”.

Simulation of plasma alprazolam in the mother was performed using the population “Sim-Pregnancy” parameters with our modifications. Age and height of the population were adjusted according to this patient’s values. Abundances of cytochrome P450

(CYP) 3A4 and CYP3A5 in the liver and gastrointestinal tract, the main enzymes metabolizing alprazolam, were modified to the values contained in the "Sim-Japanese" parameter set. Oral alprazolam dose was set as 0.8 mg three times a day, the routine dose for this patient.

Simulation of plasma alprazolam concentration in the neonate was performed using the population "Sim-Paediatrics" set with "0 year" and "female". Administration route was set intravenous, and the dose was set so that peak alprazolam concentration reached 15.2 ng/mL, the measured concentration right after birth. Simulation in the neonate was performed by re-defining the individual enzyme abundance over the study period.

3. Cases

The mother was 30 years old and taking benzodiazepines for the treatment of her panic disorder. She took alprazolam 2.4–3.2 mg/day during mid-pregnancy and 2.4 mg/day in late pregnancy until the day of delivery. She also took lorazepam 0.5–1.0 mg/day as needed in mid-pregnancy. Final administration of alprazolam was 20 min prior to delivery. The baby was delivered vaginally at 40 weeks' gestation and weighed 3400 g. The events after birth are summarized in **Fig. 1A**. At birth, Apgar score was 9. Two hours after birth, the neonate was given supplemental oxygen for apnea in the incubator. At that time, the Finnegan score was 7. From 9 h to 2 days after birth, vomiting and poor feeding occurred, so intravenous fluid was administered. On day 3

after birth, we assessed that her feeding and respiratory status got improved because of the relief of apnea and digestive symptoms, so the neonate was free from the incubator. By day 4, the Finnegan score reached 0 (**Fig. 1B**).

The neonate's plasma alprazolam concentration was 15.2, 10.0, and 4.5 ng/mL on day 0, 1, and 2, respectively, and under the detection limit thereafter (**Fig. 1B**). The simulation assumed a fetal:mother alprazolam plasma concentration ratio of 0.72 in rats based on the interview form of alprazolam (Solanax, Pfizer, Tokyo, Japan). Using this value and assumed fetal concentration of 15.2 ng/mL as the same as neonate concentration, the mother's plasma concentration was estimated to be 21.1 ng/mL at the time of delivery. Actual measured concentration on day 100 in the mother was 36.0 ng/mL (**Fig. 2**). The estimated maternal plasma concentration at the delivery, measured neonate plasma concentration 24 and 48 h after birth, and measured maternal plasma concentration all fell within 90% prediction intervals by the Simcyp simulator.

4. Discussion

The mother took high-dose alprazolam regularly throughout her pregnancy. Improvement of apnea and digestive symptoms were paralleled by a decrease in plasma alprazolam concentration. Some reports indicated that alprazolam can increase the risk of NAS if mothers took alprazolam throughout their pregnancy [4]. There are few reports evaluating the exposure−response relationship of alprazolam. The EC_{50} values

of alprazolam for sedation and stimulation are reported to be 27 and 30 ng/mL in rats, respectively [5]. The lower threshold of alprazolam therapeutic range is estimated as 2–25 ng/mL [6], suggesting that the neonate's plasma concentration was sufficient to induce pharmacological effects. These findings implicate that NAS in this neonate, at least apnea and digestive symptoms, was possibly induced by alprazolam. However, there are possibilities that several other symptoms may last for a certain period of time even after most of the drug eliminates from the body. A further investigation is needed to clarify whether the plasma drug concentrations can be directly linked to the symptoms (side-effects) of NAS.

The calculated half-life of alprazolam in the neonate was 39.7 h in the first 24 h and 20.7 h in 24 to 48 h after delivery, showing that time values were far longer than in healthy adults [7]. Alprazolam is metabolized by CYP3A4 and CYP3A5 in the fetal liver [8], and its metabolite is excreted in urine following conjugation to glucuronic acid by uridine diphosphate glucuronosyltransferase (UGT) 1A4 [9]. Expression and activity of CYP3A4 and UGT1A4 are lower in neonates than in adults [10,11]. Therefore, the prolonged half-life of alprazolam was likely caused by the inadequate expression of metabolic enzymes. The physiological maturation rapidly occurs in the first few days after birth; consequently, the pharmacokinetic parameters also rapidly change during this time [12,13]. Therefore, the shortened half-life of alprazolam in 24–48 h after delivery may reflect the rapid maturation of CYP3A4 and CYP3A5 in this neonate. Our

simulation of neonate's plasma alprazolam concentration by PBPK reflected the time-varying physiology of neonates using default setting values in Simcyp simulator and the reported values [12,14], however, we cannot successfully simulate the neonate's concentration at 72 h after birth. Maturation speed of CYP3A4 and CYP3A5 expression in this neonate may be more rapid than reported values. Although alprazolam is metabolized by CYP3A7, an enzyme expressed in fetus for a few days after birth, the contribution of this enzyme is small compared to those of CYP3A4 and 3A5 [15]. Therefore, CYP3A7 was not included in alprazolam elimination pathway in our simulation.

Actual concentrations were close to those predicted by the PBPK model incorporating parameters for "pregnancy", "pediatrics" , and "Japanese women". Thus, PBPK modeling is a useful methodology for toxicological assessment in special characteristics populations for which experimental data is difficult to obtain. However, a limitation of this PBPK modeling was that "Sim-Pregnancy" and "Sim-Paediatrics" population settings were derived from Caucasians. Although we changed the CYP3A4 and CYP3A5 expression levels in the liver and gastrointestinal tract to the Japanese parameters implemented in Simcyp simulator from the default Caucasians values, there are also differences in placental and other tissue volumes, CYPs activity, and glomerular filtration rate between Caucasians and Japanese. Another limitation is that the estimated concentration in this pregnant woman was based on the fetal:mother alprazolam plasma

concentration ratio of 0.72 in rats.

In conclusion, we could observe the relation between the neonate's plasma alprazolam concentrations in the time series from delivery and symptoms of NAS, and elucidated the usefulness of PBPK modeling for toxicological assessment in special characteristic populations. This is a first case report about the measured plasma alprazolam concentration of a neonate born to a mother taking alprazolam daily.

Conflict of Interest

All authors have no conflicts of interest to disclose.

Authors' contributions

Dr. Yamamoto designed and carried simulation of plasma drug concentration, drafted the initial manuscript, and reviewed the manuscript. Ms. Mishima, Ms. Hashimoto, Ms. Yamakawa and Dr. Fukushima collected data and revised the manuscript. Dr. Fujioka and Prof. Iijima coordinated and supervised data collection and reviewed and revised the manuscript. Prof. Yano supervised conception of this report and interpretation of data and critically revised the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figure Legends

Fig. 1. Clinical course after birth (A) and plasma concentrations of alprazolam and Finnegan scores in the case neonate (B).

The gray bars indicate Finnegan scores and the gray circles indicate plasma concentrations of alprazolam from day 0 to day 4.

ALP: alprazolam

Fig. 2. Physiologically based pharmacokinetic simulations of plasma alprazolam concentration using parameters for "pregnancy", "pediatrics", and "Japanese women" .

Gray area indicates the 90% prediction intervals and the gray line indicates the mean concentration (conc.) of alprazolam in the 100 simulations. The closed black circles indicate actual measured plasma concentrations. (A) PBPK simulation for maternal plasma alprazolam concentration during pregnancy using parameters for "pregnancy". Gray triangle indicates the estimated plasma concentration at delivery. (B) PBPK simulation of neonatal plasma alprazolam concentration using "pediatric" parameters. In the simulation, alprazolam was administered intravenously at a dose yielding a peak plasma concentration of 15.2 ng/mL, the concentration right after birth. (C) Post-delivery maternal PBPK simulation using the parameters for "Japanese women". The closed black square indicates the measured value at day 100 after delivery.

ALP: alprazolam

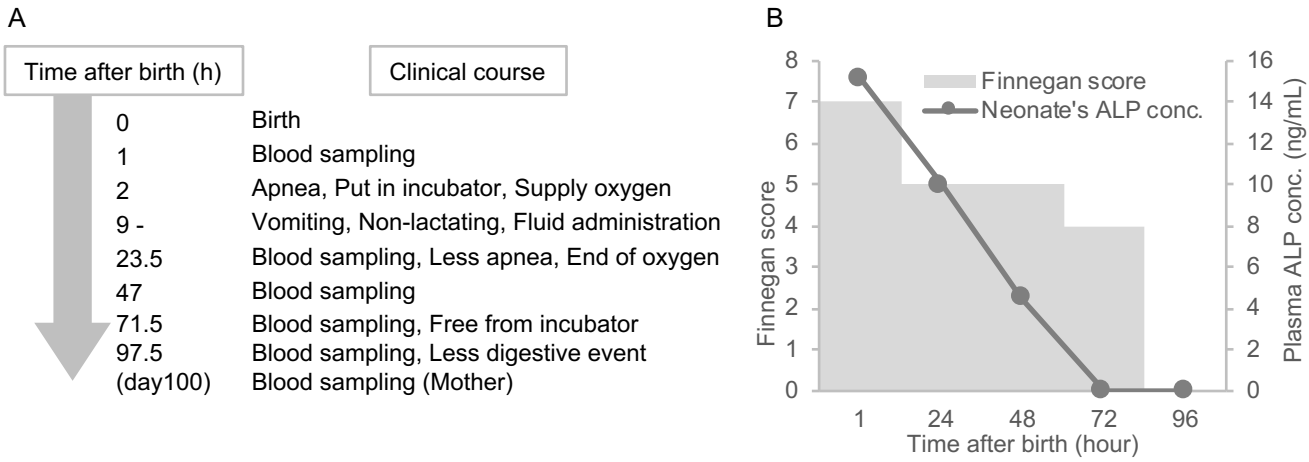
A
Time after birth (h)
Clinical course
0
Birth
1
Blood sampling
2
Apnea, Put in incubator, Supply oxygen
9 -
Vomiting, Non-lactating, Fluid administration
23.5
Blood sampling, Less apnea, End of oxygen
47
Blood sampling
71.5
Blood sampling, Free from incubator
97.5
Blood sampling, Less digestive event
(day100)
Blood sampling (Mother)
B
Finnegan score
Neonate's ALP conc.
Finnegan score
Plasma ALP conc. (ng/mL)
Time after birth (hour)
0
1
2
3
4
5
6
7
8
0
2
4
6
8
10
12
14
16
1
24
48
72
96

Figure 1

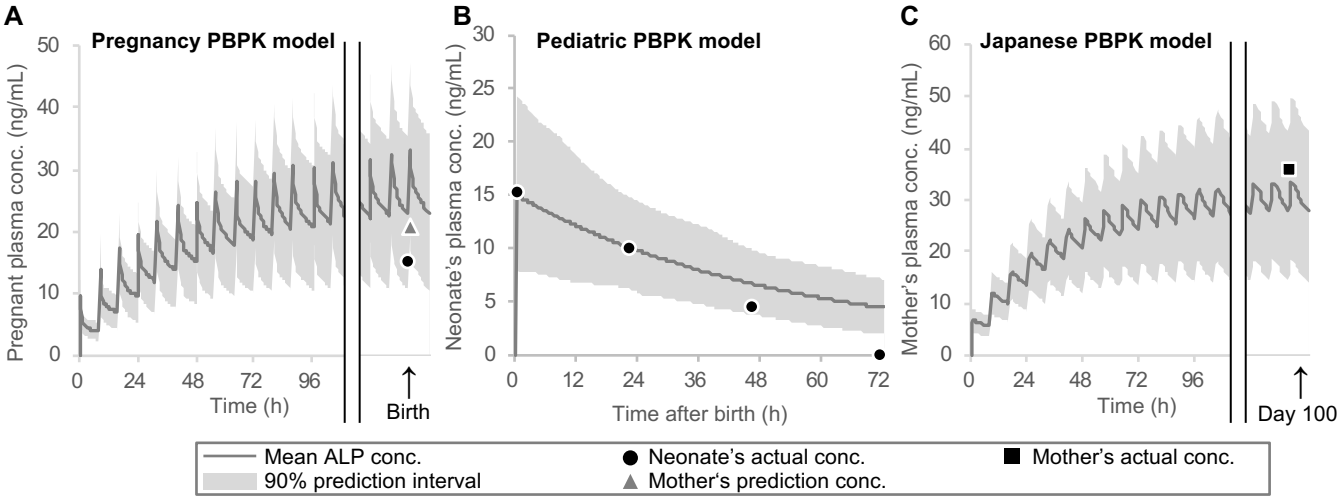
A
Pregnancy PBPK model
Pregnant plasma conc. (ng/mL)
Time (h)
Birth
B
Pediatric PBPK model
Neonate's plasma conc. (ng/mL)
Time after birth (h)
C
Japanese PBPK model
Mother's plasma conc. (ng/mL)
Time (h)
Day 100
Mean ALP conc.
90% prediction interval
Neonate's actual conc.
Mother's prediction conc.
Mother's actual conc.

Figure 2