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NPC-11 Phase III Trial Concerning Apnea of Prematurity in Japanese Neonates: A Study of Safety, Efficacy and Pharmacokinetics

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Abstract

Objective: To study the safety, efficacy, and pharmacokinetics of caffeine citrate in the treatment of apnea of prematurity in Japanese neonates.

Study design: A non-blind, uncontrolled, multicenter, collaborative clinical trial.

Setting: Three neonatal intensive care units in Japan

Patient inclusion criteria: Neonates at the post conceptional age of 28 weeks to 33 weeks who were diagnosed with apnea of prematurity.

Main outcome measures: 50% or greater reduction in apneic episodes, adverse effects, and pharmacokinetics.

Method: Day 1 - Intravenous (IV) administration of caffeine citrate loading dose of 20 mg/kg, administered over 30 minutes. From day 2 onward - Commencement of administration of maintenance dose (caffeine citrate dose of 5 mg/kg) once daily intravenously over 10 minutes or orally. In the case that event incidence was reduced, the maintenance dose continued to be administered until day 10. If the doctor judged the initial maintenance dose to be ineffective, or its efficacy to be insufficient, the maintenance dose was raised to 10 mg/kg/day.

Results: 23 patients fitting the specifications were found, and dosing was commenced. The reduction rate in apneic episodes during the trial was from 43.5% to 60.9%. Severe adverse effects were not noted. Mean serum concentration was maintained within the therapeutic range, between 11.87 and 18.82 mg/L. Data from clinical trials (Study OPR-001) in the United States, which were similar in methodology to this trial, were used when analyzing population pharmacokinetics. No difference due to race

Conclusion: Caffeine citrate dosing for treatment of apnea of prematurity was effective, produced no safety problems, and showed good tolerability. Additionally, no differences between Japanese and Americans with regard to efficacy, safety and pharmacokinetics were observed

Identifier of this clinical trial: NCT01408173

Keywords: Caffeine citrate; Apnea of prematurity; Japanese neonates; population pharmacokinetics; Adverse effect

Introduction

An episode of apnea of prematurity is generally defined [1-3] as cessation of breathing for 20 seconds or more or cessation of breathing accompanied by bradycardia or cyanosis. Among preterm neonates at the gestational age of 36 weeks or less, it is one of the most frequently encountered medical conditions [4]. Thought to be due to incomplete development of the brainstem, the onset frequency is inversely proportional to birth weight. Apnea of prematurity occurs in 25% of low birth weight infants and in up to 84% of very low birth weight infants [5,6].

Treatment consists first of removing causative factors by controlling body temperature, administering low concentrations of o*xyg*en, or applying physical manipulation. When these treatments were insufficient to the control apnea of prematurity, management of breathing, by administering xanthine type drugs, using mechanical ventilation, nasal CPAP, or nasal DPAP, was carried out. Because there were concerns about artificial respiration devices giving rise to complications such as chronic lung disease (bronchopulmonary dysplasia(BPD)), infection due to long-term intubation, pharynx/trachea stenosis, etc., which constitute significant prognostic factors, carrying out drug treatments before having recourse to ventilation therapy is widespread [6]. In terms of pharmacotherapy, xanthine type drugs (aminophylline, theophylline, caffeine etc.) are the first choice in the treatment of apnea of prematurity both in Japan and overseas.

Caffeine citrate compares with aminophylline and theophylline in the following ways [7-9]: (1) The therapeutic index for caffeine citrate is wide, so the danger of adverse reactions is low; (2) the necessity for therapeutic drug monitoring is low; (3) the efficacy and safety of long-term administration has been proven; (4) because absorption is fast and complete when orally administered, the transition from intravenous to oral administration is easy, and adjustments in dosing at the time of transition are unnecessary; (5) because the serum elimination half-life is long, it is possible to maintain efficacy with a single daily dose. Recently, some authors reported that early caffeine therapy had improved neonatal outcome (death, BPD, retinopathy of prematurity et al). A change in practice toward earlier initiation of caffeine therapy is already occurring [10-12].

Citation: Kondo M (2016) NPC-11 Phase III Trial Concerning Apnea of Prematurity in Japanese Neonates: A Study of Safety, Efficacy and Pharmacokinetics. Pharm Anal Acta 8: 458. doi:10.4172/2153-2435.1000458

In Japan, aminophylline and theophylline agents were commercially available, but caffeine citrate was not. Therefore, to ascertain the safety, efficacy, dosage, and pharmacokinetics of caffeine citrate for use in treating apnea of prematurity in Japan, this trial was designed using the methods of the caffeine group in Study OPR-001 and the CAP trial(a randomized, double-blind, placebo-controlled trial) [13-16].

Method

This trial was carried out, in accordance with GCP, from November, 2011 to October, 2012 in the NICUs of 3 Japanese medical facilities as a non-blind, uncontrolled trial. The drug was administered to neonates satisfying all of the standards of eligibility for the clinical trial: a pause in breathing of greater than 20 seconds, or less than 20 seconds if accompanied by bradycardia (heart rate dropped below 100 bpm) or cyanosis (percutaneous blood oxygen saturation (SpO_2) was at or below 90%).

Included in the study were neonates 24 hours after birth to children at the post-conceptional age of 28 to 33 weeks, neonates who experienced 6 or more confirmed apneic episodes in 24 hours, and neonates whose parents had agreed to allow participate in the clinical trial.

Neonates fitting any of the descriptions below were excluded from the clinical trial: (1) Those having hypoxic encepalopathy, or exhibiting its symptoms, on the grounds of possibly causing secondary apneic episodes; (2) BUN>20 mg/dL and serum creatinine>1.5 mg/dL; (3) serum AST or ALT>triple the upper limit of the normal level; and (4) neonates receiving mechanical ventilation therapy, nasal CPAP or nasal DPAP; (5) those who had been administered a xanthine type drug in the 7 days prior to administration of the loading dose; (6) those who had been administered an H2 receptor antagonist (cimetidine, ranitidine, etc.) within 7 days prior to administration of the loading dose; (7) those being administered a central nervous activator; (8) those already participating in another clinical trial at the time their enrolment was considered. Neonates who were able to be taken off mechanical ventilation, nasal CPAP or nasal DPAP 12 hours or more prior to commencement were not excluded.

The neonates satisfying the selection criteria but not the exclusion criteria were administered an intravenous 20 mg/kg loading dose of caffeine citrate over 30 minutes. 24 hours after the administration of the loading dose, a once daily dose of 5 mg/kg was administered either intravenously over 10 minutes or orally and maintained for 9 days. If the doctor judged the initial maintenance dose to be ineffective, or the efficacy to be insufficient, the maintenance dose could be raised to 10 mg/kg/day. Neonates were to be withdrawn from the study if mechanical ventilation, nasal CPAP or nasal DPAP was required or when the doctors judged them to be at risk of adverse events because the number of apnea episodes in a 24-hour period was greater than 50% of baseline events and adverse effects were observed.

A primary outcome measure of efficacy, the number of Apneic episodes in the 24 hours before administration of the loading dose (the baseline) was recorded. Upon commencing administration, the number of apnea episodes was recorded from day 1 to 10. The change in the percentage of neonates whose number of Apneic episodes had dropped to 50% or less of the baseline was evaluated.

The secondary outcome measures of efficacy were the following: 1) the change from the number of apnea episodes on each study day; 2) the change in the mean duration of Apneic episodes in a 24 hour period on each study day; 3) the change in the mean minimum SpO_2 for the each 24 hour period on each study day; and 4) the change in the

proportion of the number of apneic events having an $SpO_2<85\%$ in a 24 hour period, across the baseline and for the each 24-hour period.

With regards to safety, the number (%) of neonates who experienced at least one type of adverse event during caffeine administrating was determined. The serum concentration of caffeine and its metabolic products (theophylline, theobromine, and paraxanthine) was measured using high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) at the following times: before (0), and 1 and 24 h after, administration of the loading dose, and 24 hours after administering the final maintenance dose. When it was possible, we measured the serum concentration of the caffeine on Days 5 and 8 after administration.

Analysis of the data was carried out using SAS for Windows (Version 8.2 or above). The proportion of neonates whose number of apneic episodes had dropped to 50% or lower (the primary outcome) was determined. However, in the cases in which the maintenance dose (5 mg/kg/day) was changed, or stopped, the Last Observation Carry Forward (LOCF) technique was used. For the secondary outcome measures, the value for the 24 hours preceding the administration of the loading dose was made the baseline; a 95% Confidence interval calculation and a Wilcoxon signed-rank test were carried out for the fundamental statistic and the average value related to the difference between the observed value and that baseline.

The adverse effects were re-coded according to MedDRA/J (Ver. 15.1) and split up into the System Organ Class (SOC) and Preferred Term (PT) groups. Using the serum caffeine concentration measurement data from this trial and the U.S. clinical trial, a nonlinear mixed effects model (NONMEM Version 72.0) assessment based on a 1-component model including covariance was carried out, the individual case pharmacokinetics parameters were determined via Bayes estimator,
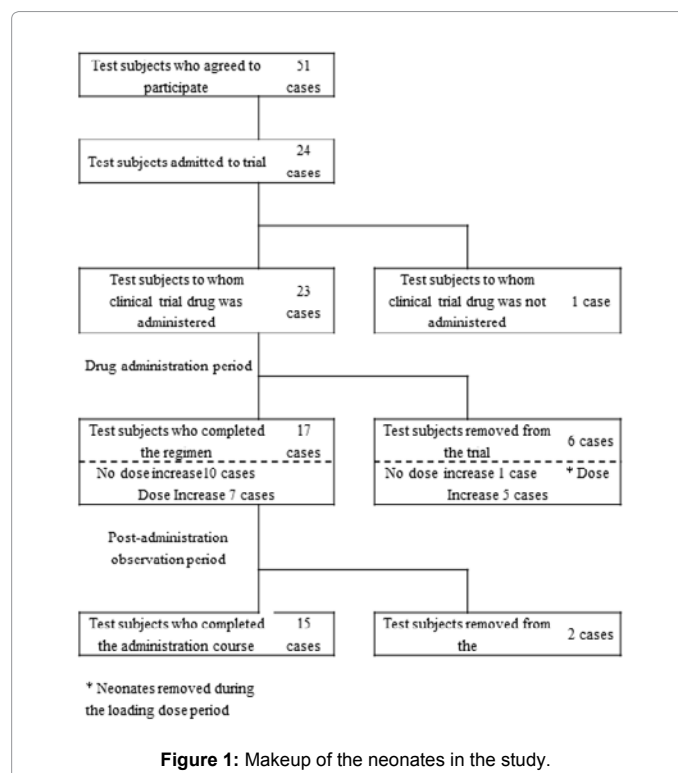

Figure 1: Makeup of the neonates in the study.

and the similarities between Japanese and U.S. subjects were compared.

Results

Of the 51 neonates for whom parental consent for this study had been obtained, 24 were included in the trial, and the caffeine citrate was administered to 23. Of the 23 neonates, 15 (65.2%) completed the trial. The trial was stopped for 6 neonates (26.1%) during administration of the drug, and for 2 neonates (8.7%) during the post-administration observation period (Figure 1). Of these 8 neonates, 5 were removed from the trial because of apparently insufficient efficacy (4 stopped during drug administration, 1 stopped during post-administration observation), 2 were removed because of mechanical ventilation (1 stopped during drug administration, 1 stopped during post-administration observation), and 1 was removed due to an adverse reaction that necessitated mechanical ventilation (stopped during administration).

With regard to dosing, after administration of a loading dose of 20 mg/kg of caffeine citrate, the maintenance dose of 10 mg/kg/day was raised from the initial maintenance dose of 5 mg/kg/day in 12 of the 23 neonates.

Demographic characteristics

Data on the characteristics of the study neonates are presented in Table 1. The 1 minute and 5 minute mean Apgar scores were 6.5 and 7.9, respectively, and were approximately normal at birth. The mean birth weight was 1512.7 g with 56.5% of the neonates being below 1500 g. The mean gestational age was 31.4 weeks (range: 27.7 to 33.6 weeks) and the mean day after birth was 6.8 days (range: 1 to 36 days).

Efficacy

Primary outcome measure: The reduction rate of apneic events from the baseline in a 24 hour period were 60.9% on the first day and second days (Figure 2). From Day 3, the reduction rate of apneic events from the baseline fell into the stable range of 43.5 to 56.5% (Figure 2). In the 12 cases the maintenance dose was increased. In 6 of 12 cases, the caffeine increase was effective.

Secondary outcome measures: The mean number of apneic episodes in a 24-hour period dropped from 14.36 events of the baseline to 8.76 events on the first day, and transitioned to 7.70 or fewer events during the maintenance dose period. The study data confirmed that as the number of the caffeine administration days increased, the number of events decreased. The amount of the change in the mean apneic events compared to the baseline was -5.60 events on the first day of drug administration. During the maintenance dose period, this figure ranged from -6.32 to -11.28. All of these results were statistically significant (Table 2).

Total duration of apneic events during each 24 hour period significantly decreased during the drug administration days, and with an increase in the number of drug administration days, the duration of apneic episodes decreased. The mean change from the 24 hour period before administration of the loading dose was -156.3 seconds on the first day, and during the period the maintenance dose was administered, the figure ranged from -153.8 to -274.6 seconds.

The mean change in the minimum SpO_2 during apneic events over 24 hours was 2.3 to 10.6% higher during the study period (Table 2) while the mean change in the proportional number of apneic events with an $SpO_2 < 85\%$ during a 24 hour period showed a 8.94 to 10.69% decrease (Table 2).

When examining subgroups in terms of efficacy, differences between the sexes were disregarded. As birth weight increased, or as gestational age at birth lengthened or as day after birth became shorter, a trend towards somewhat higher efficacy became evident.

Safety

Table 1: Neonate patient background.

| Item	classification		
Number of test subjects suitable for analysis		n=23	
Sex	M	9	(39.1%)
	F	14	(60.9%)
Apgar Score	1-minute	Number of subjects	23
		Mean	6.5
		Standard deviation	2.2
	5-minute	Number of subjects	23
		Mean	7.9
		Standard deviation	1.6
Body length at birth (cm)		Number of subjects	23
		Mean	39.66
		Standard deviation	3.65
Birth weight (g)		Number of subjects	23
		Mean	1512.7
		Standard deviation	377.7
		Less than 1500g	13	(56.5%)
		1500 to 2500 g	10	(43.5%)
Gestational weeks at birth		Number of subjects	23
		Mean	31.36
		Standard deviation	1.72
		Under 30 weeks	10	(43.5%)
		31weeks to less than 34 weeks	13	(56.5%)
Days after birth		Number of subjects	23
		Mean	6.8
		Standard deviation	8.7
		Under 4 days	14	(60.9%)
		More than 5 days	9	(39.1%)
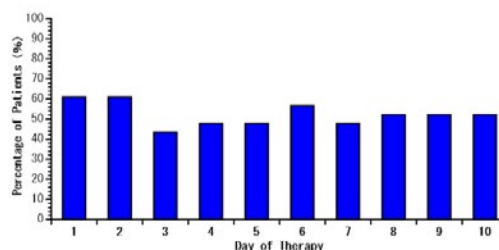
Figure 2: The percentage of infants with at least a 50% reduction in apnea events.

**Table 2:** Change in secondary outcome measures of efficacy.

Efficacy evaluation measurement		Day of dose administration										
		Pre-Admin	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10
Change in number of events during a 24 hour period (events/24 hours)	No.	23	23	22	22	21	19	18	18	17	17	17
	Mean	14.36	8.76	6.75	7.43	7.70	5.54	4.68	4.22	3.55	4.18	3.54
	SD	7.39	8.10	5.87	6.76	11.58	6.23	5.72	3.61	3.24	4.53	4.01
	95%CI	11.17-17.56	5.26-12.26	4.15-9.35	4.43-10.43	2.43-12.98	2.54-8.55	1.84-7.53	2.43-6.02	1.89-5.22	1.85-6.51	1.48-5.60
	Test*	-	0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Duration of apneic event (seconds)	No.	23	23	22	22	21	19	18	18	17	17	17
	Mean	347.2	190.9	179.9	198.3	156.0	154.6	120.7	112.3	84.5	110.2	80.2
	SD	198.9	184.6	184.0	221.2	195.3	199.5	171.1	109.3	87.7	140.7	111.7
	95%CI	261.2-433.2	111.0-270.7	98.3-261.5	100.2-296.4	67.1-244.9	58.4-250.7	35.7-205.8	58.0-166.7	39.4-129.6	37.9-182.5	22.7-137.6
	test*	-	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Minimum SpO$_2$ during apneic event (%)	No.	23	21	20	19	19	16	13	16	15	14	15
	Mean	72.7	75.0	76.7	75.6	78.6	78.8	81.4	80.5	78.7	81.4	79.3
	SD	10.3	10.7	10.0	13.1	13.8	11.7	8.2	10.3	10.9	6.8	7.8
	95%CI	68.3-77.2	70.1-79.9	72.0-81.3	69.3-81.9	72.0-85.3	72.5-85.0	76.4-86.3	75.0-86.0	72.7-84.7	77.5-85.3	75.0-83.7
	test*	-	0.650	0.144	0.547	0.111	0.019	0.005	0.006	0.097	<0.001	0.014
Proportion of events having SpO$_2$ less than 85% (%)	No.	23	21	20	19	19	16	13	16	15	14	15
	Mean	35.00	44.74	42.35	44.90	41.94	40.87	33.25	43.96	37.17	32.76	38.07
	SD	27.86	33.08	36.72	32.61	34.96	33.74	31.58	35.45	42.94	36.85	29.50
	95%CI	22.95-47.05	29.68-59.79	25.16-59.53	29.18-60.62	25.09-58.79	22.89-58.85	14.16-52.33	25.07-62.85	13.39-60.94	11.48-54.03	21.74-54.41
	test*	-	0.099	0.404	0.229	0.548	0.732	0.943	0.715	0.801	0.455	0.413

*Wilcoxon's signed rank sum test; 95%CI=95% confidence interval

The occurrence of adverse events was 78.3% (18/23 neonates), with the most common symptom being gastrointestinal disorder. The adverse events occurring most frequently were suckling sickness (26.1%, 6 neonates), vomiting, high blood pressure, and high body temperature (each 17.4%, 4 neonates). Most adverse events were non-serious; there were 3 cases of mid-level adverse events (metabolic acidosis, rash, circulatory trouble). There were 2 examples (2 cases) of adverse event whose causal relationship was not discounted (1 cases of gastrointestinal bleeding and 1 cases of high blood pressure). No severe adverse effects were acknowledged.

Pharmacokinetics

The change in the serum caffeine concentration of the 23 neonate patients is shown in Figure 3. The mean concentration increased from 1.65 to 11.42 mg/L from before, to 1 hour after, administration of the loading dose. On Day 5 of administration (15 neonates) the mean concentration was 15.09 mg/L, on Day 8 it was 18.82 mg/L (16 neonates) and at 24 hours after the final maintenance dose it was 18.55 mg/L (17 neonates). Serum concentrations of caffeine metabolic products (theophylline, theobromine, paraxanthine) were mostly below the fixed lower limits for neonates.

Figure 3: Change in serum caffeine concentration (Mean ± SD).
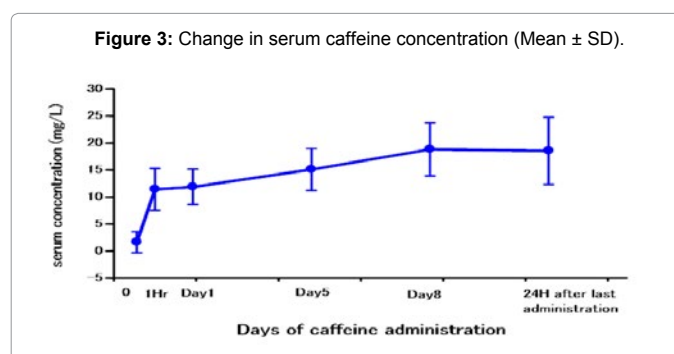
Next, the serum caffeine concentration data from our trial (23 neonates, 110 points) were combined with the serum caffeine concentration data from the U.S. trial (Study OPR-001), (58 neonates, 284 points), and a population pharmacokinetics analysis (NONMEM) was carried out. A fundamental model was constructed using the primary absorption process linear 1-compartment model. An exponent error model was applied to each pharmacokinetic parameter's variation between individuals, an absolute and mixed error model were applied to the

residual error change in the individual, and the pharmacokinetic parameters examined. The neonates' background factors (race, sex, birth weight, gestational age at birth, day after birth, etc.), covariant with the fundamental model, were incorporated. The covariates showing a significant change in target function value (-2 log likelihood of difference; level of significance: <5%) were incorporated in the order of decreasing effect. The forward selection method was employed, and the full model was constructed. Because body weight, birth weight, and body weight at the commencement of drug administration were thought to have multicollinearity, in the cases where one or more of the factors were incorporated as covariates, other factors were not incorporated in the following step. Then, after constructing the full model, using backward elimination (back-step method), covariates were removed one at a time, and non-meaningful covariates (level of significance: >1%) were all removed. The resulting model was considered as the final version.

The standard parameters based on the final model (CL; Clearance, Vd; Volume of distribution, Ka; Absorption rate constant, Foral; Bioavailability) are shown below.

CL (L/hr) = (0.0392 × body weight+0.0000865 × birth age in days) × e0.0472 (CV: 21.7%)

Vd (L) = 0.845 × body weight × exp(0.050) (CV:22.5%)

Ka(/hr) = 0.991 ± 0.355

Foral = 0.895 ± 0.0709

Intra-individual variability: 5.25 ± 1.20 mg/L

In the final model constructed for this analysis, CL increased with an increase in body weight and day after birth, and Vd was proportional to bodyweight.

Because we compared racial differences in pharmacokinetics between Japanese and study OPR-001 subjects, race was examined as a covariate. However, as the covariate proved to be non-meaningful, the caffeine citrate was thought to have no difference in pharmacokinetics between Japanese and American neonates. The Bayesian inference value was determined for the individual test subject pharmacokinetic parameters (CL, Vd, Ka, Foral) used in the final model of this analysis. Additionally, the C_{max} and t1/2 were calculated using the obtained pharmacokinetic parameters (Table 3).

Using the population pharmacokinetic parameters, the actual values obtained in our trial were plotted against a 100-apnea-of-prematurity-case simulation (Figure 4). The change in the individual serum caffeine concentration of the neonates in our trial agreed well with the actual values. The estimability from the final model's Bayes inference parameters was good; a change of 5 to 30 mg/L was recorded in the serum concentration of the drug with a loading dose of 20 mg/kg and maintenance dose of 5 mg/kg/day, corresponding to the textbook estimates of the therapeutic range of the drug.

Discussion

This report is the first clinical trial (trial NPC-11-1) of Japanese neonates with apnea prematurity carried out observing GCP, which was conducted with the goal of examining the safety, efficacy, and

pharmacokinetics of caffeine citrate. 24 Neonates were admitted to the trial and the drug was administered one or more times to 23 neonates (9 boys, 14 girls). The primary outcome measure and main secondary outcome measures (number of apneic events in a 24 hour period) were compared to the results of Study OPR-00113, a randomized, double-blind, placebo-controlled trial period having the same trial period of 10 days. The primary outcome measure, the reduction rate of apneic events from the baseline in a 24 hour period was 60.9 % on the first and second days. Throughout the maintenance dose period from Day 3 onward a stable change was demonstrated. A comparison with the results of Study OPR-001's double blind test period showed that the results were somewhat lower than for the OPR-001's drug group (45 neonates, 62.2% to 75.6%), but higher than for the placebo group (37 neonates, 40.5% to 56.8%). Additionally, the main secondary outcome measures showed a trend to lower values than seen in the Study OPR-001 caffeine group, but higher than in the placebo group.

For the efficacy sub-group examination (sex, birth weight, gestational week at birth, day after birth), sex was ignored. The resulting trend seemed to indicate somewhat higher efficacy as either birth weight increased, or as the number of gestational weeks at birth increased, or as the number of days after birth became decreased. In Study OPR-001, a clear correlation was found with the body weight background factor, whereas for the other background factors, either low, or no correlation was found.

In this clinical trial, death and other severe adverse events did not occur. The safety of this drug was confirmed by these results, which were similar to those of the previous trial (Study OPR-00113 and in an international joint multicenter collaborative trial (the CAP trial)). 14-16 Adverse events (reactions) in which this trial could not exclude the drug as a causative factor, were mild gastrointestinal bleeding (1 neonate, twice) and mild hypertension (1 neonate, twice), but each of these were reported in the previous clinical research [17,18] concerning drug administration for neonates. After commencement of drug administra-
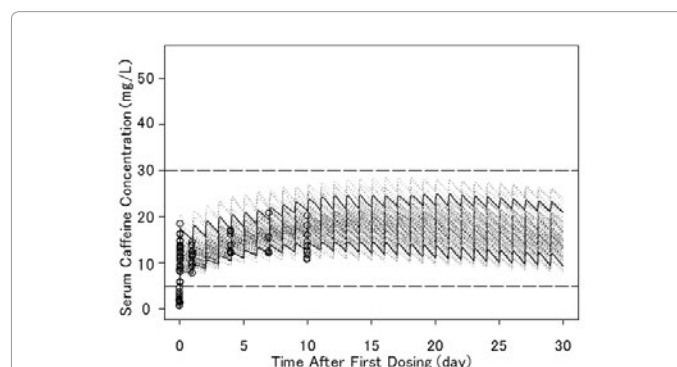

Figure 4: Simulation of population serum caffeine concentration pharmacokinetics positing a loading dose of the drug of 20 mg/kg, followed 24 hours later by a maintenance dose of 5 mg/kg/day.

The dotted, zigzag lines indicate randomly simulated concentration changes in 100 neonates, the upper and lower bold lines are the 95% and 5% values, respectively, ○ is the actual measured caffeine concentration, the bold zigzag lines are the therapeutic range (lower 2 lines) and the lower limit of the toxic range (upper 1 line).

Table 3: Estimated values (Mean ± SD) of pharmacokinetic parameters for neonates included in the analysis.

Trial	N	C_{max} (mg/L)	$t_{1/2}$ (hr)	CL (L/hr)	V_d (L)
Japan Phase 3 Clinical Trial	23	12.41 ± 2.26	133.1 ± 27.4	0.0062 ± 0.0018	1.153 ± 0.302
USA Study OPR-001	58	12.06 ± 2.08	137.0 ± 32.1	0.0054 ± 0.0015	1.041 ± 0.337

C_{max} is the estimated value based on a single dose 20 mg/kg (administered IV: 20 mg/kg/30 minutes)

tion, changes in clinical laboratory examination values, vital signs, and SpO_2 stabilized and remained so during the maintenance dose period, and no effect on the respiratory system, cardiovascular system, or central nervous system was observed. The average serum caffeine concentration value quickly increased to the therapeutic range, and continued to be maintained stably within the therapeutic range for serum concentration. Conversely, the serum concentration of metabolic byproducts was, except in four neonates, below the fixed minimum value, suggesting that preterm neonates have a low ability to metabolize caffeine. The changes in serum caffeine concentration for both this clinical trial and Study OPR-001 were similar.

Caffeine is mainly metabolized in the liver by CYP1A2, CYP2E1, and CYP3A4. Because of this, drugs which either inhibit or induce CYP1A2 etc. could interact with the caffeine. However, because enzymatic metabolism of caffeine in the liver isn't fully developed in neonates, the effect due to drug interaction is thought to be limited. Next, in order to study the pharmacokinetics in the case of IV loading dose and IV or PO maintenance dose application, the serum caffeine concentration data from this trial (23 neonates, 110 points) and Study OPR-001 (58 neonates, 284 points) were combined, and a population pharmacokinetics analysis carried out. In the final model constructed for our analysis, CL increased with an increase in body weight and days after birth. Vd was a linear 1-component model proportional to body weight. Study OPR-001's final model for population pharmacokinetics analysis did not incorporate the effect of day after birth on CL, but some studies [19-22] examining the effect of caffeine in neonates have incorporated the effects of both body weight and day after birth. For this reason, this analysis was designed to incorporate the effect of body weight and day after birth on CL.

To compare any differences in the pharmacokinetics between Japanese and Americans subjects, this analysis used race as a covariate during the study. The result of the analysis proved that race was a non-meaningful covariate on the grounds that no difference between these two groups was found in terms of pharmacokinetics. Caffeine pharmacokinetics are already a topic of investigation in apnea of prematurity among Caucasians [23] and Asians (Chinese, Malay).17 These studies demonstrated differences in the method (IV or PO) of administering caffeine (caffeine citrate or anhydrous caffeine), but revised caffeine pharmacokinetic parameters (serum caffeine concentration, Vd and t1/2) adjusted for body weight were almost identical for Caucasians and Asians. In preterm neonates, metabolic enzymes are not fully developed, and CYP1A2, CYP2E1, and CYP3A4, the principal metabolic enzymes for caffeine, genetic polymorphism frequency showed no clear differences between Japanese and Caucasians [24]. Furthermore, the change in caffeine concentrations among individual neonates in this study agreed well with the actual values.

In the final model constructed for our analysis, predictability based on the relationship between population-predicted values and individual-predicted values, time after administration, relationship between population-predicted values, and conditional weighted residuals was high, and from the bootstrap validation, robustness was also shown to be high, demonstrating the validity of our model for showing caffeine pharmacokinetics in preterm neonates.

Conclusion

Administration of caffeine citrate to treat apnea of prematurity in Japanese neonates demonstrated efficacy in reducing apneic episodes,

no safety problems, and good tolerability. Additionally, no difference in efficacy, safety, or pharmacokinetics due to racial differences between Japanese and Americans was detected.

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