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Pharmacokinetics and pharmacodynamics of medications used in children: a systematic review

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ABSTRACT

Which methylated xanthine is safe and effective for treating apnea of prematurity in underdeveloped nations is still up for debate. The majority of newborns in developing nations are small for gestational age. For both Appropriate for Gestational Age and Small for Gestational Age infants, many doctors use the same dosage of methylxanthines. In order to optimize the dosages of caffeine and aminophylline in preterm infants with apnea, population PKPD models for these drugs must be developed and qualified. The study also aimed to examine the safety and effectiveness of routine prescribed doses of aminophylline and caffeine for apnea of prematurity. Caffeine at the usual suggested dosages for treating preterm apnea can be maintained. Since postnatal age had a major impact on Vd, it was clear that time-related developmental factors had a considerable impact on the pharmacokinetics of aminophylline. Doses determined using mg/kg would be biased. The current study's calculated dose of aminophylline can be used as a substitute for the commonly advised dosage. Comparative evaluation indicates that caffeine and aminophylline are similarly efficient at lowering apnea. There were noticeably fewer tachycardia episodes when caffeine was consumed.

Keywords: *Pediatric formulation, pediatric investigation, medication adherence.*

1. INTRODUCTION

In neonates under 37 full weeks of gestation, apnea of prematurity (AOP) is generally described as abrupt, brief (at least 20 seconds) respiratory cessation accompanied by bradycardia and desaturation [1]. 85% of newborns under 34 weeks of gestation have been reported to have AOP. It has also been documented as a prevalent and severe condition in low birth weight (LBW) preterm infants. Approximately 25% of newborns have birth weight (BWT). Prone positioning, kinesthetic stimulation, methylxanthines, bag mask ventilation (BMV), non-invasive ventilation (NIV), and invasive mechanical ventilation (IMV) are among the few available intervention modalities.

Mechanical ventilation, which helps preterm infants' undeveloped lungs compete with extrauterine life, is an often recommended strategy in neonatal respiratory distress [2]. Many babies must be kept on a ventilator for a variety of lengths of time, ranging from a few days to several weeks or more. Long-term ventilation raises the risk of barotraumas, and chronic lung illnesses and pulmonary infections are examples of possible pulmonary morbidity [10]. Aminophylline and caffeine, two methylxanthines, are used to treat AOP, avoid apneic episodes, and reduce the chance of extubation failure by preparing for planned or unplanned extubation [3]. Caffeine and aminophylline both have crucial pharmacological roles in assisting newborns in transitioning off of ventilation [4]. These are thought to function by enhancing respiratory drive, decreasing the threshold of sensitivity to hypercapnia, and boosting the diaphragm's contractility [15]. Each medication's therapeutic benefit also lessens the requirement for artificial ventilation by avoiding the onset of recurring apneas [14]. However, caffeine's broader therapeutic range, lower dosage frequency, prevention of bronchopulmonary dysplasia (BPD), decreased risk of symptomatic PDA, decreased risk of stage 4 or 5 Retinopathy of Prematurity (ROP), and minimal adverse effect profile have all contributed to its increased popularity [11].

Traditional pharmacokinetic studies mostly concentrate on carefully chosen patients or healthy volunteers [13]. Premature infants present a number of special difficulties when conducting clinical studies, including frequent invasive blood sample collection, limited blood volume, ongoing developmental changes, clinical problems, health issues, and—most importantly—ethical concerns that impede data collection as required by the conventional pharmacokinetic protocol [5]. The study of the causes and correlates of drug concentration fluctuation among the target patient population receiving clinically

appropriate dosages of a medicine of interest is known as population pharmacokinetics, or PPK [9]. The pharmacokinetic (PK) and pharmacodynamic (PD) profiles of target groups, including premature neonates, are reportedly amenable to investigation using PPK techniques in contemporary contexts [17]. This practical method allows for the estimation of the PK parameters using flexible, less invasive blood collecting techniques [18]. As a result, it is much more moral and least inconvenient for the subjects. This effective method not only enables the simultaneous estimate of average values of PK parameters and the analysis of pooled data with flexible sampling patterns, but it also aids in determining and quantifying the extent of variability that contributes to variations in the dose-concentration relationship [19].

2. SYSTEMATIC REVIEW ON EFFECTIVENESS AND SAFETY STUDIES

All of the early research showed that methylxanthines might be used to cure apnea. However, the small number of participants in these studies prevented a thorough examination of the safety profile of the targeted medications. These medications were recognized as neurostimulators and were thought to cause long-term neurodevelopmental effects in newborns. Furthermore, the PK disposition of these medications in preterm infants was not well understood, making it difficult to start with safe and suitable dosages. Despite the silver bullet, neonatologists still had a lot of issues to address before using methylxanthines. By showing therapeutic control on apnea at a plasma theophylline concentration of 6.6 mg/L and noticing tachycardia with a range of 13 to 32 mg/L, Shannon et al. highlighted the limited therapeutic range of theophylline. Shannon and colleagues first recommended an oral theophylline dosage of 2.5 mg/kg every 6 hours [6] based on these findings in 17 premature infants.

Eight LBW preterm infants with apnea had their theophylline PK profiles studied by George Giacoia et al. According to the authors, theophylline has a half-life of 13–29 hours, a higher Vd of 0.65–2.86 L/kg, and a CL value of 23–68 ml/hr/kg. The authors recommended a loading dose of 6 mg/kg and a maintenance dose of 2 mg/kg/12 hours, with dosage adjustments depending on TDM, in light of these findings [7]. Bory et al. reported on the metabolism and interconversion of theophylline to caffeine in newborns with apnea who were treated with theophylline. They showed that a third of the theophylline dose was converted to caffeine. Caffeine levels in this trial reached a maximum of 8 mg/L, which was thought to be within a therapeutic range for treating apnea [8]. The identified interconversion routes, according to the authors, may lower the toxicity threshold of aminophylline and help to explain tachyarrhythmias found in infants with mild theophylline plasma concerns [12]. Turmen et al. showed in a later trial that caffeine reduces apnea even at lower plasma levels (3 to 4 mg/L) and suggested caffeine as a safer xanthine than theophylline [16]. Theophylline's therapeutic range was proven to be 5–12 mg/L, while caffeine's was reported to be 5–20 mg/L, based on all the quick follow-up investigations on methylxanthine. The loading dose of aminophylline was chosen at 5 mg/kg given intravenously in order to target their respective drug levels. Additionally, after starting the loading dose, the recommended maintenance dose of 1.5 mg/kg is administered every eight hours. In contrast, a loading dose of 20–40 mg/kg of caffeine citrate—which is equal to 10–20 mg/kg of caffeine base—can be given orally or intravenously. Caffeine citrate (5–10 mg/kg), which is equal to caffeine base (2.5–5 mg/kg), is given once daily after a 24-hour loading dose start period.

2.1 Objectives of the research are

In preterm newborns with AOP below or equivalent to 34 weeks of gestation, the Population Pharmacokinetic and Pharmacodynamic models of caffeine and aminophylline will be developed and qualified.

Primary objective: Examine the safety and efficacy of conventional dosages of aminophylline and caffeine for preterm newborns with gestational ages of less than or equal to 34 weeks who have apnea of prematurity.

Secondary objectives: to evaluate methylxanthine's safety and efficacy in various preterm growth (AGA, SGA) characterizations.

3. METHODOLOGY

General procedure and follow up: During their stay in the NICU, all preterm neonates under 34 weeks were exposed to the following standard procedure. 92% target saturation was upheld. Electrolytes and the sixth hourly Glucometer Random Blood Sugar (GRBS) were measured at 48 hours of life and repeated if necessary. Septic screening was performed upon admission and, if necessary, later on in accordance with clinical evaluation. If respiratory distress occurred, a chest X-ray was conducted; if signs and symptoms of RDS were present together with radiological characteristics, surfactant replacement therapy was taken into consideration. When an infant's Downe's score indicated minor respiratory distress, CPAP was taken into consideration.

Randomization: Blocks of ten neonates, five in each of the caffeine and aminophylline groups, were randomly assigned using computer-generated block randomization. Sequentially numbered, opaque, sealed envelopes were used to blind the

participant/caretaker and the outcome assessor. The size and shape of these envelopes matched. A statistician who was unconcerned with the current study, management, or recruited infants carried out the random allocation sequence and concealment. The study's principal investigator recruited the participants.

Interventions: A loading dose of 20 mg/kg of caffeine citrate (10 mg/kg caffeine base) diluted in 5% dextrose was administered to neonates assigned to the caffeine group for 30 minutes. They were then given a maintenance dose of 5 mg/kg (2.5 mg caffeine base) every 24 hours via intravenous or oral preparation of caffeine citrate solution (20 mg/ml); if no satisfactory response was obtained, the dose was increased to 7.5 mg/kg.

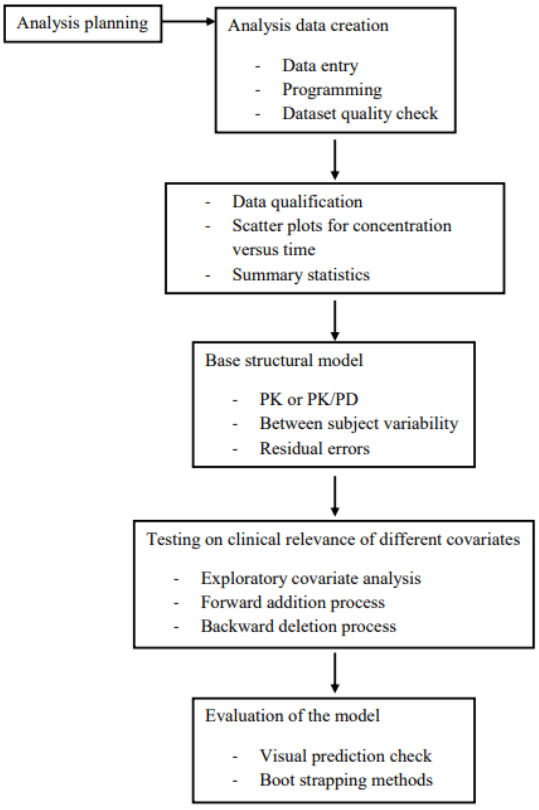


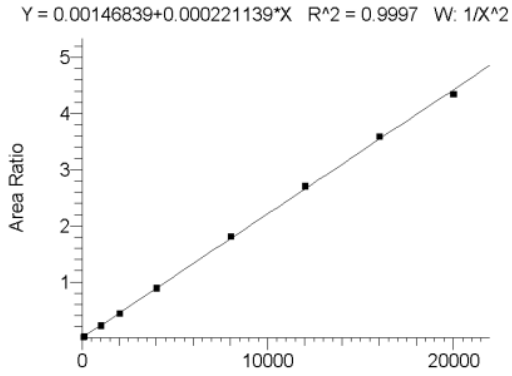
Figure1: Flow representing the development of Population PK-PD models

Sampling: The "full population PK design" was used for PK screening. Another name for it is experimental population PK design, in which blood was drawn at different intervals after the medication intervention. A sparse sampling strategy was used to conduct the sampling, which usually involved 1–5 blood samples. The sampling strategy was utterly unstructured and out of balance. On one or more days during methylxanthine therapy, including the day of the loading dose, blood collection was requested.

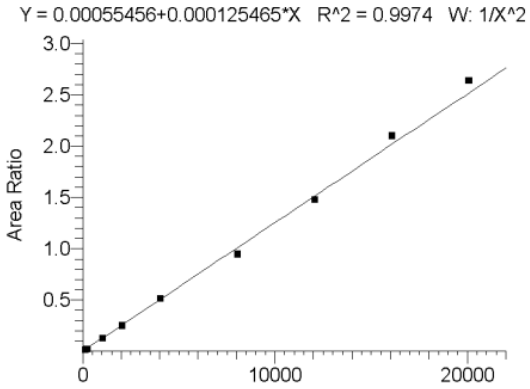
3.1. Bio-analytical assay

For covariate modeling, the impact of baseline demographic characteristics, specific concurrent medications, and other exogenously supplied nutrition data were gathered. Evaluating the impact of all gathered developmental, physiological, pathological, and pharmacological factors on methylxanthine PK values was the aim. To do this, every event or factor pertaining to preterm newborns was documented in the NONMEM dataset. PNA, fluids, feed, total fluids supplied, current body weight, urine output, FIO2, PEEP, delivery of sodium, potassium, amino acids, dextrose, and calcium, as well as GA, BWT, APGAR at 1 minute, APGAR at 5 minutes, and time varying continuous variables were recorded. During the study period, the following binary variables were included: gender, prenatal steroids, birth cry, rescue surfactant therapy, intubation, phototherapy, intralipid administration, ampicillin, amikacin, pipzo (piperacillin and tazobactam), and the existence of NIV assistance. We used growth categories (AGA=1, SGA=2, and LGA=3) as a categorical variable. The covariate-parameters correlation graphs were then used to determine which of the possible explanatory factors in the gathered dataset should be included in the models. In the structural model, every continuous variable was added using an exponential function in a linear additive method. In a linear additive fashion, binary covariates were incorporated. In contrast, the

categorical covariates were defined using the FLAGS, IF, and ELSEIF commands. The improvement in fit was assessed for each covariate added to the structural base model. If the Objective Function Value (OFV) decreased by more than 3.84, which is equivalent to a statistical significance of p, covariates were included. The negative logarithm of twice the log likelihood is known as OFV. When compared to two hierarchical models, this is regarded as a model-specific and significant technique for determining the improvement in fit. A more cautious statistical significance threshold was applied during the following backward elimination of variables (OFV> 6.64, p.



(a)



(b)

Figure 2: Calibration curve

A total of 296 samples from 61 newborns treated with caffeine were examined. The current observational study included preterm newborns with a mean weight of 1197 grams and a gestational age of 29 weeks. At the median postnatal age of 8 days, neonates took part.

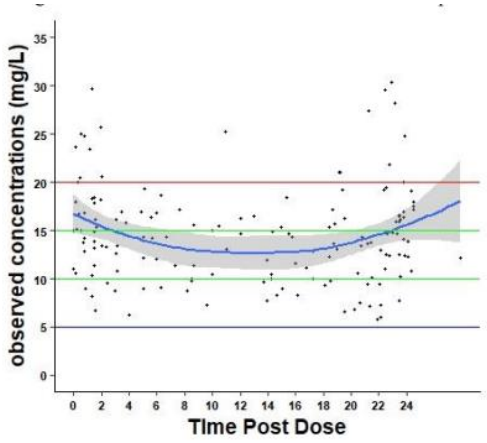


Figure 3: Plasma caffeine concentration versus weight of the participants

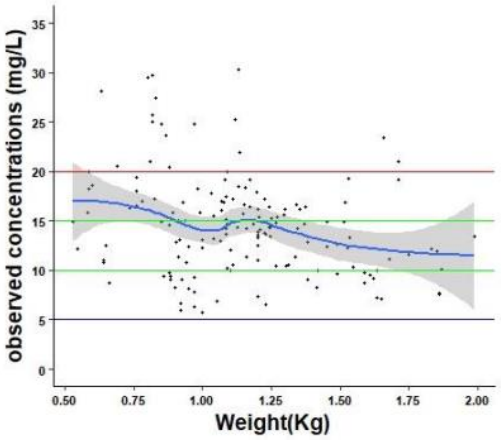
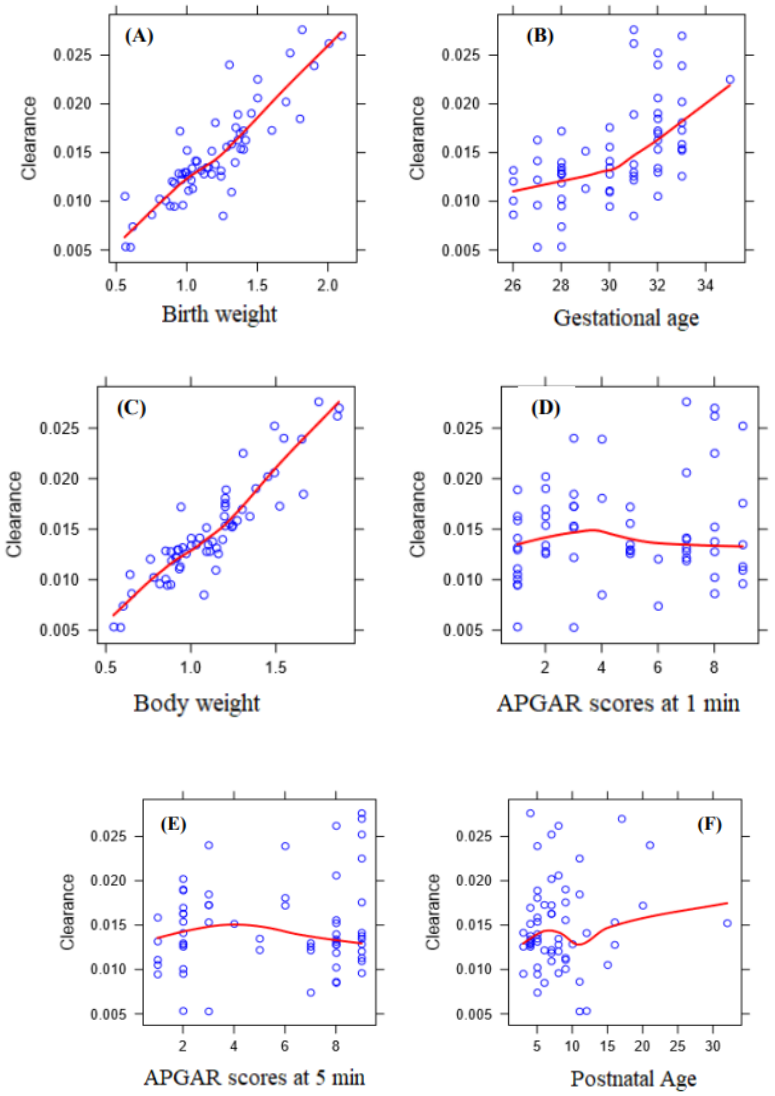
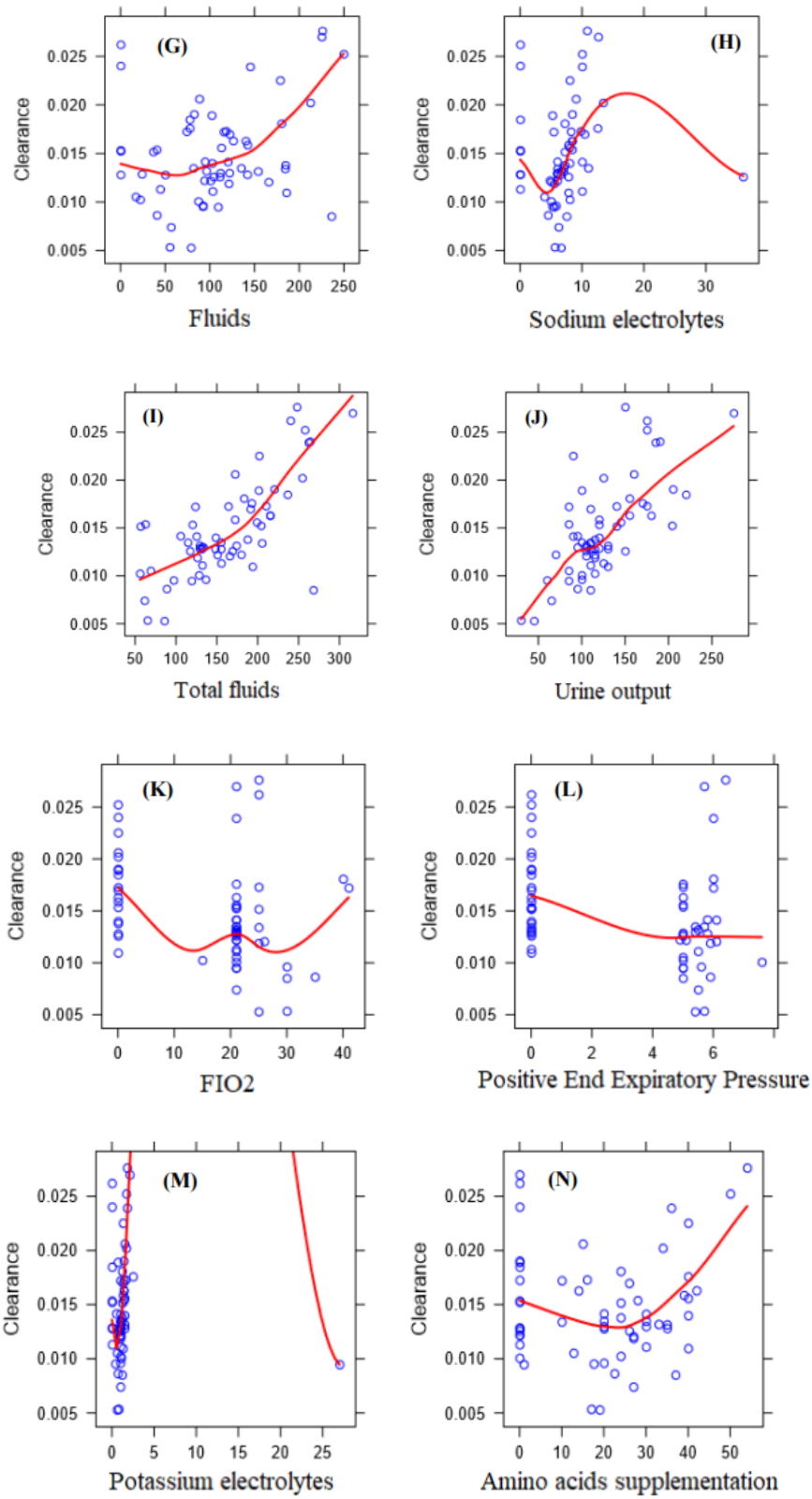


Figure 4: Plasma caffeine concentration versus weight of the participants

Plotting box plots for categorical variables and scatter plots for continuous covariates allowed for the observation of trends between covariates and PK parameters. Individual covariate versus CL graphs were plotted (figure 5). In order to assess best fit, any covariates that were thought to have correlations with the parameters were then chosen and gradually introduced to the model.




(G)
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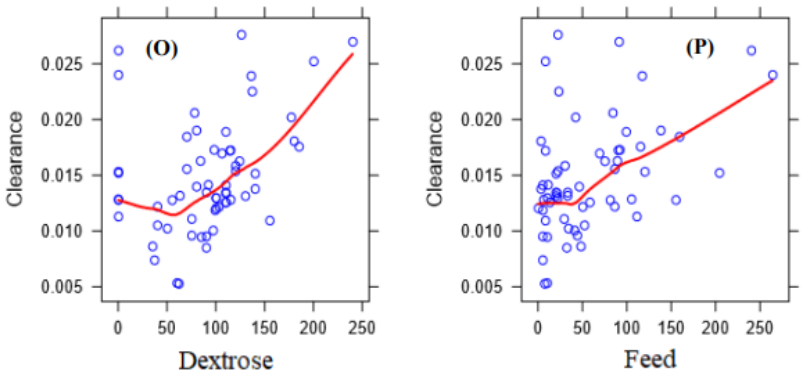

Figure 5: Covariate versus caffeine clearance

These diagnostic graphs demonstrated how well the data fit the finished model. The profile that was produced as a consequence of the 1000 simulations adequately reflected the data that was layered from observations made during the normal dosage regimen. VPC plots (Figure 6) with bootstrap 95% CI were used to illustrate this. The values derived from the population model and the median estimates of PK parameters acquired during bootstrapping were in close agreement. When the model was fitted to several participant sample data sets, this demonstrated the model's stability.

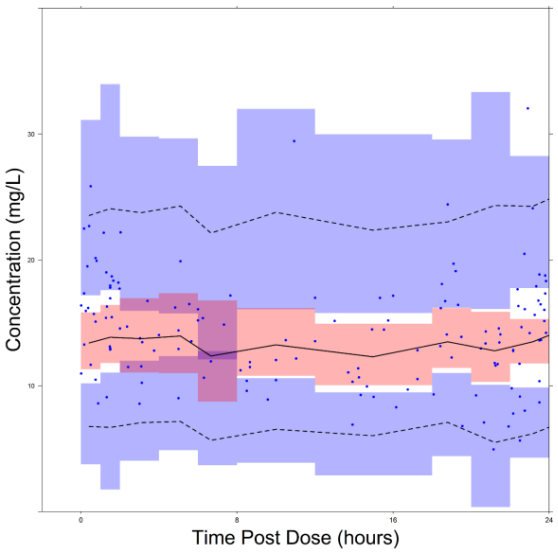

Figure 6: Visual predictive check

In the meantime, studies showed that the start of methylxanthine treatment increased the output of respiratory neurons. However, the well-researched discovery that methylxanthine functions as an adenosine receptor antagonist and phosphodiesterase inhibitor enzyme inhibitor caused these pharmacological effects. Even though methylxanthines are frequently used in neonatal care settings, the majority of neonatologists in underdeveloped nations struggle to decide which methylated xanthenes are best for treating AOP. An ancient medication used to treat AOP is theophylline (116,279,280). In the years that followed, numerous research focused on the use of caffeine as a preventative medication to avoid apnea (2,213,246) and as a therapeutic medication to treat AOP (3,157,233,281). There aren't many studies focusing on caffeine's safety and effectiveness.

4. CONCLUSION

Premature infants with AOP, a developmental disease, exhibit immaturity in respiratory control. The precise mechanism of AOP is still unclear due to limitations in the animal model of spontaneous apnea and a dearth of research on premature neonates in humans. However, it has been observed that the immaturity of breathing affects various levels of respiratory control based on the data available from preclinical tests and physiological research on preterm neonates. Preterm infants' immaturity has been shown to cause hypoxia, poor ventilatory responses to hypercapnia, and exaggerated inhibitory responses to activation of the airway receptors. This includes pulmonary afferents that are central, peripheral, and inhibitory.

Methylxanthine treatment is a pharmacological management technique. Since the 1970s, methylxanthine has been advised as the medicine of choice for the treatment of AOP. There are several physiological and pharmacological factors that have been demonstrated to underlie the current therapeutic approach. Methylxanthines improve diaphragmatic activity, decrease hypoxic depression, raise CO2 sensitivity, and improve minute ventilatory responsiveness.

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