Accuracy and Reliability of Dosing Equations to Individualize Theophylline Treatment of Apnea of Prematurity

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Apnea of prematurity is associated with high morbidity and mortality. Treatment generally includes supplemental oxygen and theophylline or caffeine. The half-life of theophylline is prolonged in newborns because of their immature cytochrome P-450 system, and there is considerable variation in the drug's metabolism in infants. We compared the accuracy, precision, and reliability of two equations that use postnatal age (PNA) to determine a maintenance dosage of theophylline with a standard maintenance dosage (SMD) that produced a steady-state serum theophylline concentration (STC) of 8 μg/ml for apnea of prematurity in 46 infants less than 34 weeks' gestational age (GA) and less than 36 weeks' postconceptional age (PCA). The two equations were mg/kg/day = [(0.2 x PNA in wks) + 5], and mg/kg/day = [(0.3 x PNA in wks) + 8]. Their reliability to predict the SMD was determined by correlation analysis. The precision and accuracy with which they predicted SMD were determined and analyzed by χ^2. The SMD did not correlate with the maintenance dosages calculated by equations 1 and 2 (r=0.296 and 0.296, p>0.05 in both cases). Multiple linear regression of SMD versus GA , PNA, and PCA was not significant (r=0.33, p=0.32). After stratifying data based on GA and performing correlation analysis of SMD versus PNA, a weak but significant correlation (r=0.42, p=0.0517) was found for infants with GA between 31 and 34 weeks. Poor correlation was found between SMD versus PNA for infants 27–30 weeks' GA. Two new equations of the best fit line were generated using the same data. Currently available equations for determining maintenance dosages of theophylline in infants and children are not reliable for premature newborns, in whom two new equations based on GA and PNA have been developed. The equations will be evaluated for their utility, and employed to accrue data to determine if better ones can be developed.

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Because of its associated high morbidity and mortality, apnea of prematurity is of major concern in preterm infants. Of premature infants weighing less than 2500 g at birth, 25% will experience at least one episode of apnea, which increases to 84% for infants weighing under 1000 g.[1,2] Morbidity and mortality increase with the number and duration (> 20 sec) of apneic episodes.[3] The disorder has many possible etiologies in infants;

however, the most probable one is an underdeveloped medullary respiratory center that does not adequately respond to hypoxia and hypercapnia.[4]

Treatment of apnea may be supportive or pharmacologic. Supportive treatment generally includes supplemental oxygen therapy, continuous positive airway pressure, or mechanical ventilation. Pharmacologic management consists primarily of theophylline or caffeine; doxapram hydrochloride is a second-line agent that has also been given to stimulate the respiratory center.[5] For the treatment of apnea, the therapeutic serum theophylline concentration (STC) ranges from 6.6–13 μg/ml.[6, 7] The toxic effects of theophylline are dose related, generally progressing from gastrointestinal disturbances to abnormalities of cardiovascular rate and rhythm, to central nervous system toxicity often manifested as intractable seizures.[8]

The drug's half-life is prolonged in the newborn secondary to an immature cytochrome P450 (C-P450) system and ranges from 13–29 hours.[8] Intrapatient and interpatient theophylline metabolism varies considerably. Because of the low level of activity of the C-P450 system, the newborn methylates a portion of theophylline to caffeine, which has an even longer half-life, ranging from 100–200 hours.[8] The additive pharmacologic effect of caffeine in the treatment of apnea, in conjunction with its extended half-life, complicates the dosing requirements of theophylline in the newborn. According to one group,[9] although the activity of the C-P450 system in the newborn increased from 28–42 weeks' postconceptional age (PCA), there was no concomitant decrease in the methylation of theophylline to caffeine. Therefore, it would be advantageous to identify predictors of theophylline dosing requirements in neonates.

Although theophylline has been the mainstay of the pharmacologic treatment for apnea of prematurity since the early 1970s, no consensus exists as to the best method to predict the appropriate maintenance dosage in premature newborns. Numerous studies have evaluated the agent's pharmacokinetics in premature infants with apnea and led to the development of empiric dosage guidelines based on weight to include a loading dose of 5.0–6.0 mg/kg and a maintenance dosage of 1.1–2.0 mg/kg every 12 hours.[10–14]

We compared the accuracy, precision, and reliability of two equations using postnatal age (PNA) to calculate the maintenance dosage of theophylline to an established standard maintenance dosage (SMD) that produced a serum theophylline concentration (STC) of 8–10 μg/ml for the treatment of apnea of prematurity.

Methods

Infants less than 34 weeks' gestational age (GA) diagnosed with apnea of prematurity and requiring intravenous aminophylline therapy were screened between December 1992 and June 1993. They were enrolled in the study if they had initially received 6 mg/kg intravenous aminophylline as a loading dose, were not receiving any other drugs such as phenobarbital that might influence the clearance of theophylline, had no significant perinatal events that could affect theophylline metabolism (e.g., birth asphyxia), and had normal renal and hepatic function. Since the STC was measured as part of routine patient care and data collection was retrospective, informed consent was not required by the investigational review board, which approved the study.

The initial maintenance dosage of aminophylline corresponded to PNA. Premature infants 30 days PNA or younger received 1.6 mg/kg intravenously every 12 hours, and those over 30 days PNA received 2.4 mg/kg intravenously every 12 hours. All doses were infused over 15–30 minutes using a syringe pump, and a steady-state trough STC was obtained for all subjects.

Steady-state condition was defined as that point at which the patient had received a loading dose followed by at least four maintenance doses before a trough STC was obtained, based on an assumed half-life of 13–29 hours. If this steady-state STC was less than the desired trough STC of 8 μg/ml, the midtherapeutic range for treatment of apnea of prematurity, the initial maintenance dosage was adjusted using principles of first-order pharmacokinetics to reach this range. The new trough STC was determined after the patient had received at least four new maintenance doses. If the target level (8–10 μg/ml) was achieved, at this point the patient was entered in the study and data collection started.

A fluorescence polarization immunoassay (TDx, Abbott Laboratories) was used to analyze all STCs. Data collected on each subject included PNA, PCA, GA, weight, STC, and the actual dose required to reach therapeutic STC (8–10 μg/ml).

Equations

For the purpose of comparison with study equations, the target STC was set at 8 μg/ml. When a trough STC of 8–10 μg/ml was reached, the patient was entered into the study, and the dosage required to achieve the target trough STC of

8 μg/ml (determined by first-order kinetics) was calculated. This was called the standard maintenance dosage (SMD). It was then compared with the dosage calculated by each of the following equations:

$$\text{mg/kg/day} = [(0.2 \times \text{PNA in wks}) + 5]^{7} \quad (1)$$

and

$$\text{mg/kg/day} = [(0.3 \times \text{PNA in wks}) + 8],^{15} \quad (2)$$

using the study population's PNA. Of note is the fact that equation 1 is derived from equation 2 by performing a 37% reduction in the constant parameters. Since equation 2 was designed to produce a STC of 10–20 μg/ml, one would expect equation 1 to produce a STC of 7–13 μg/ml. The dosages predicted by these two equations were analyzed for the precision, bias, and reliability with which they might predict the SMD calculated to produce a target trough STC of 8 μg/ml.

Table 1. Patient Demographics

Characteristic	Mean (±SD)
Postnatal age (wks)	3.05 (2.24)
Postconceptual age (wks)	33.07 (2.26)
Gestational age (wks)	30.02 (2.28)
Weight (kg)	1.55 (0.39)

Table 2. Standard and Predicted Doses of Theophylline Using Published Equations

Dose	Mean (± SD) (mg/kg/day)
Actual dose	5.60 (1.09)
SMD	5.73 (1.37)
Equation 1	5.61 (0.45)
Equation 2	8.91 (0.67)

SMD = standard maintenance dosage.

Data Analysis

The squared prediction error (precision) of each equation to predict the SMD was calculated as follows. The theophylline dosage (mg/kg/day) predicted by equation 1 for each patient was subtracted from the SMD (mg/kg/day) and the absolute difference was squared. The mean of the sum of squared differences was determined and analyzed using Student's *t* test.[16] The same procedure was performed for equation 2. The equation with the smaller mean difference was considered to be the more precise. The precision of the equations to predict the desired STC was also compared. The frequency with which they predicted a theophylline dosage, based on a linear relationship to the SMD, that would have produced a STC of 8–10 μg/ml was determined. These frequencies were compared using McNemar's χ^2 analysis for correlated data. The equation with the higher percentage was considered the more precise.

Bias was determined by calculating the mean prediction error.[16] The reliability of each equation to predict the SMD was determined by correlation analysis. The equation with the coefficient closest to 1 was considered to be more reliable.

Results

A total of 46 premature newborn infants were evaluated in a prospective manner. Patient demographics are presented in Table 1. The mean, standard deviations, and range of theophylline dosages calculated from equations 1 and 2 and SMD and the actual doses are shown in Table 2.

The means of the squared absolute differences were 1.7 and 12.1 for equations 1 and 2, respectively. Equation 1 was significantly more accurate than equation 2 (Student's *t* test $p \leq 0.05$). Equations 1 and 2 predicted the desired STC in 46% and 2% of patients, respectively, indicating that equation 2 was less precise than equation 1 (Mc Nemar's χ^2 $p<0.05$).

The SMD did not correlate with the maintenance dosages calculated by either equation ($r=0.296$ and 0.296, $p>0.05$ in both cases). Because of the poor correlation, multiple linear regression was performed with the SMD versus GA, PNA, and PCA, and also was not significant ($r=0.33$, $p=0.32$). Linear regression of the SMD versus PNA revealed a weak but significant correlation ($r=0.3$, $p=0.04$). Due to the weak correlations obtained with above variables and SMD, we used the same data to generate two new equations of the best fit line.

Pearson correlation analysis was performed on two separate sets of data formed by stratifying the existing data based on GA. The stratified data included GA of 27–30 weeks or 31–34 weeks. For infants 27–30 weeks the correlation was poor ($r=0.05$; $p=0.78$; mean square prediction error 1.1). However, for infants 31–34 weeks' GA, the correlation although weak, was much improved ($r=0.42$; $p=0.05$; mean square prediction error 1.18). The predicted equations are as follows.

27–30 weeks:

$$\text{mg/kg/day} = 5.81 - (0.02 \times \text{PNA in wks}) \quad (A)$$

and

31–34 weeks:

$$\text{mg/kg/day} = 4.82 + (0.28 \times \text{PNA in wks}) \quad (B)$$

Discussion

Currently, a number of dosage guidelines are available for calculating theophylline maintenance dosages in newborns and infants. However, they must be evaluated because of the wide variability of the patient populations, dosing intervals, and routes and methods of administration (i.e., intermittent vs continuous infusions). The Food and Drug Administration recommends a loading dose of 1 mg/kg theophylline for each 2-μg/ml increase in STC desired, followed by 1.0 mg/kg every 12 hours maintenance for preterm infants (≤ 36 weeks PCA). For full-term infants (either at birth or 40 wks PCA) the recommended dosage is 1–2 mg/kg every 12 hours.[17] These guidelines generally result in subtherapeutic STCs.[11, 18]

Alternative methods for calculating theophylline maintenance dosages in newborns have been proposed. An alternative for infants less than 1 year of age is an equation (equation 1) that also incorporates PNA in weeks as a variable.[7] It is designed to achieve a therapeutic STC of 7–13 μg/ml. Although there is no primary reference for it or targeted STC in the literature, this equation, which is a modification of the equation derived by Hendeles et al,[19] is a 37% reduction of the original one derived by Nassif et al,[15] presumably expected to produce a trough STC that is 37% less than that produced by the equation of Nassif (i.e., 37% of 10–20 μg/ml, which is 7–13 μg/ml). This original equation (equation 2) was obtained from the least squares regression of the oral theophylline dose in mg/kg/day versus PNA in weeks in infants 6–48 weeks' PNA being treated for asthma. It aimed for STC of 10–20 μg/ml and produced a mean STC of approximately 15 μg/ml. For the very premature infant this STC could be toxic and produce side effects such as tachycardia.

Another study[20] compared three equations that incorporated either PNA or PCA to determine the maintenance theophylline dosage after continuous intravenous infusion. The dose based on PNA was the most accurate in producing STCs of 10–20 μg/ml in infants ranging from 4.5–54.3 weeks' PNA.

The majority of equations that have been evaluated to date for accuracy of theophylline dosing are either empiric or incorporate PNA as the only patient-specific variable, which may not be sufficient to individualize therapy in the premature infant. The age range of the patients studied and the therapeutic STCs obtained in these studies are also different from the variables primarily involved in treating apnea of prematurity (i.e., PCA < 40 wks, STC 6–12 μg/ml).

The accuracy of equation 1 is statistically significantly better than that of equation 2. Its precision is also better for predicting maintenance dosages that yield STCs of 8–10 μg/ml. The results of our study indicate that these equations for dosing theophylline in newborns are not reliable and correlated poorly in our study population. We subsequently derived equations A and B for premature newborns based on GA and PNA. They were generated from the best fit lines of the regression of PNA and the SMD after stratifying the data for GA 27–30 and 31–34 weeks. The SMD of theophylline for premature newborns with apnea of prematurity that they predict is expected to achieve a desired therapeutic STC of approximately 8–10 μg/ml. Our patient population is homogeneous and the target STC is narrow. Both of these factors provide a more accurate and safer prediction of theophylline maintenance dosage for treatment of apnea of prematurity. It is probable that the difference observed between equations A and B may be related to differences in the degree of maturation of the cytochrome P-450 system as a function of gestational age.

We realize that the correlation for these newly generated equations, especially for infants less than 30 weeks, is weak. However, we intend to evaluate their utility and accrue data to see if we can develop better ones.

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