Iranian Journal of Pharmaceutical Sciences
Summer 2011: 7(3): 151-163
ijps.sums.ac.ir

Original Article

Pharmacokinetic Evaluation of Two Doses of Aminophylline/Theophylline Administered as Multiple Intermittent Infusions to Iranian Apneic Premature Neonates

Afsaneh Vazin[a,*], Mohammad Moslehi[a], Mehrdad hamidi[b], Narjes Pishva[c]

[a]*Clinical Pharmacy Department, Faculty of Pharmacy; and Pharmaceutical Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[b]*School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran.*
[c]*Department of Pediatrics, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.*

Abstract

Many premature neonates suffer from apnea, and aminophylline is administrated for them. The objective of this study was to reveal pharmacokinetic (PK) parameters of theophylline in Iranian premature neonates. Premature neonates (68) who were admitted in the Neonatal Intensive Care Unit (NICU) of Namazi, Hafez, and Zeinabieh Hospitals were included in the study. All of them received 5 mg/kg aminophylline. One group received 1 mg/kg/8 h and the other group received 2 mg/kg/8 h as maintenance dose. One blood sample was taken in steady-state on just before eleventh dose. Theophylline level was determined with immunoassay kit. There was a significant difference in average serum concentration (C^{ave}_{ss}) between two dosing levels (7.69±2.92 µg/ml *vs*. 11.44±3.80 µg/ml). Furthermore, the total clearance and volume of distribution were significantly different in two groups. No significant correlation could be found between the gender and C^{ave}_{ss} in different dosing levels. Postnatal age and postconceptional age have significant relationship with C^{ave}_{ss} just in the second group. According to theophylline serum concentrations, these two dosages produce therapeutically safe and effective blood levels. Pharmacokinetic parameters in these patients – in two dosing groups – approximately are correlated with other reported and recommended amounts.

Keywords: Aminophylline; Apnea; Pharmacokinetics; Premature neonates; Theophylline.
Received: February 3, 2011; *Accepted:* April 20, 2011

1. Introduction

Many research efforts have been devoted to theophylline pharmacokinetics. These studies have covered several aspects such as basic or clinical studies, single or multiple dose studies, linear or non-linear pharmacokinetic evaluations, molecular pharmacokinetic studies, dose-response titrations, etc. Overall,

*Corresponding author: Dr. Afsaneh Vazin, Clinical Pharmacy Department, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, 71345-1583, Iran.
Tel. (+98)9171128120, Fax: (+98)711-2424126;
E-mail: vazeena@sums.ac.ir

it seems that many factors can affect theophylline pharmacokinetics and, therefore, one can see huge variations in pharmacokinetics findings [1, 2].

Therapeutic window for theophylline - especially in premature neonates- is very narrow, whereas there is no agreement on a fixed serum level range with this respect. Consequently, there is not a single recommended dose for achievement of the therapeutic range, which has the boundaries of 4-7 µg/ml as minimum (minimum effective concentration; MEC) and 11-14 µg/ml as maximum (minimum toxic concentration; MTC). For example, Jones and Baillie recommended 5 µg/ ml for MEC and 17 µg/ ml for MTC [3]. Shannon *et al*., however, have found that levels above 12 µg/ ml are unnecessary and may be associated with unwanted effects [4]. Lagercrantz *et al*. recommended 7.25 µg/ ml for MEC [5].

In medical literature, we find various methods of treating apnea with aminophylline and there is no clear cut protocol. The aim of the current study is comparing the pharmacokinetic parameters between two maintenance doses of aminophylline (1 mg/kg versus 2 mg/kg) in Iranian premature neonates.

2. Method and material

2.1. Patients and methods

This study was approved by ethics committee of Shiraz University of Medical Sciences. The consent form was signed by parents of neonate prior the patients enrolled in this study.

Neonates with gestational age ≤36 weeks who were admitted in the Neonatal Intensive Care Unit (NICU) of Namazi Hospital, Hafez Hospital, and Zeinabieh Hospital, Shiraz University of Medical Sciences, were eligible for this study. Apnea had diagnosed in all eligible patients by neonatologist. Patients received 5 mg/kg aminophylline as loading dose (LD), and 1 or 2 mg/kg/8 h as maintenance dose (MD) up to the eleventh dose. Patients who had previously received any methylxanthine were excluded from this study. Patients who had changed dose before the eleventh repeated dose were excluded from the study, too.

Loading dose was administered intravenously (IV) during 20 min. The maintenance doses in two levels mentioned were started 8 h after the loading dose, and then were repeated every 8 h as intermittent IV infusion within 20 min. Neonates were randomized to receive one of the maintenance doses of 1 mg/kg or 2 mg/kg of aminophylline. Maintenance dose amounts

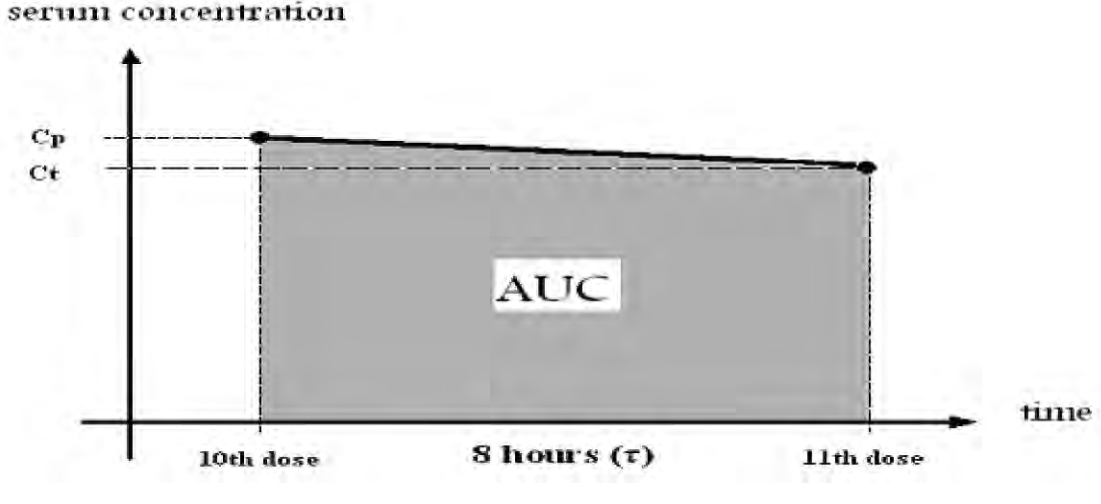

Figure 1. Schematic representation of the trapezoidal shape of AUC (area under the curve) between eleventh and twelfth doses of aminophylline.

were calculated for each patient based on the patient weight, and then the ampoules were diluted (in 6 ml that is the volume of extension tube) with 5% dextrose infusion and were administered by extension tube in about 20 min. For each patient, just before the eleventh dose, one 1-ml blood sample was obtained from peripheral vein via broken needle. The blood samples were left to clot for 45 min., centrifuged at 1000 g for 5 min, and serum was separated by aspiration and maintained in freezer at -25 °C until drug assay time.

The utilized kit principles are based on immunoassay. The Quantex Theophylline used in this study works based on a latex inhibition assay. The reagent is a suspension of polystyrene latex particles of uniform size coated with theophylline which agglutinates with the theophylline antibodies contained in the buffer. When a serum containing theophylline is previously mixed with buffer, the agglutination is inhibited in proportion to the theophylline concentration.

Theophylline assay methods should be of precision enough to produce a CV (Coefficient variant) <10% and preferably ~ 5%, if pharmacokinetic analyses are being used to adjust dosage. The precision and accuracy over several days should be such that the CV is <5% [6]. The CV of our kit was 1.6%. In this kit, the results between 1.5 to 320 µg/ml with automatic rerun were linear.

A stock solution of theophylline was prepared from which the concentrations of 2.5, 5, 10, 20, 40 µg/ml were prepared by serial dilution. These solutions were analyzed by auto-analyzer for making a standard curve. In fact, it measures the absorbance of each concentration 25 times and the average values are used for equipment calibration automatically.

It was recommended to use two levels of controls. The quality control samples were analyzed at least once each. The control values were within established range. Otherwise, corrective measures were taken by the user, for identification and resolution of out-of-control situations.

Based on similar studies, practical considerations, and statistical principles (α= 0.05) for an open label and purpose-to-treat clinical trial study, sample size was determined. Sixty-eight neonates were divided into two groups based on dosing level: 34 subjects received 1 mg/kg and 34 subjects received 2 mg/kg. For randomization in this study, patients 1 to 34 were belonged to group 1 and patients 35 to 68 were belonged to group 2.

For pharmacokinetic analysis, considering

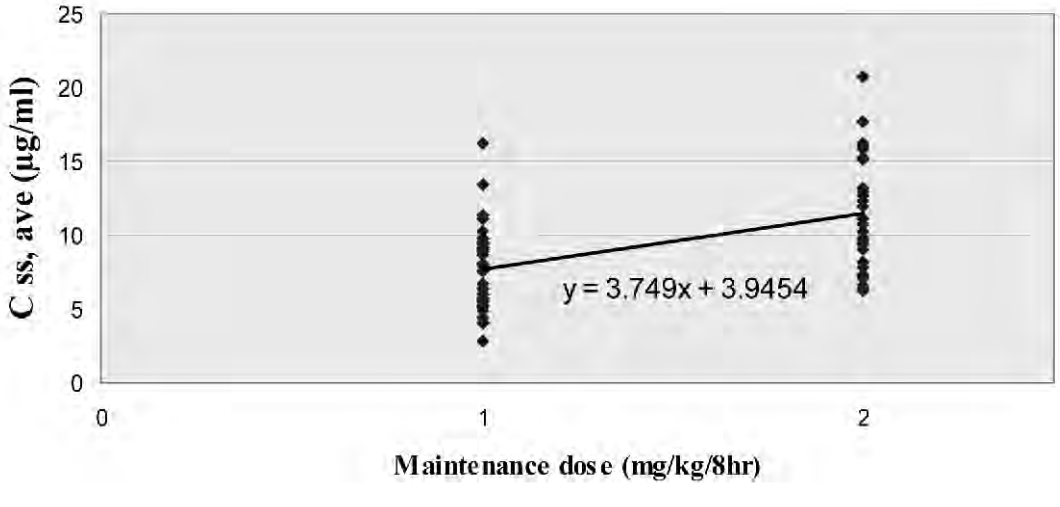

Figure 2. Point distribution of average steady-state serum concentration (Css, ave) of theophylline in premature neonates in two maintenance dosing groups (1 mg/kg versus 2 mg/kg; Q8h).

the drug nature, sampling times and that the multiple-dosing is being used in the study, the one-compartment open model was selected. At first, it was supposed that in the therapeutic range, we have linear pharmacokinetic.

From samples taken at trough level before the 11th dose, as mentioned, we have a trough level which can relate to the peak concentration by the formula:

$$Slope = \frac{\log Cp - \log Ct}{\tau} \quad (1)$$

Where, Slope, Cp, Ct, and τ, represent the slope of concentration-time curve, peak and trough concentrations and dosing interval, respectively.

On the other hand, we have:

$$Slope = \frac{-K}{2.303} \quad (2)$$

Where K is the drug elimination rate constant.

Also the following equation relates K to plasma half-life of the drug (t1/2):

$$K = \frac{0.693}{t_{1/2}} \quad (3)$$

Based on clinical pharmacokinetic population data, theophylline half-life in premature neonate can be taken as 30 hours [1]. Therefore, based on formula (3), the average K for these patients are obtained as 0.0231 h -1 and, then, based on relation (2), slope becomes -0.01. Negative sign of slope shows the declining trend of time–concentration curve between tenth and eleventh dose. Using the equation Cp for each patient can be calculated.

The following equation relates the C^{ave}_{ss} of a drug, the integral mean of the concentration of a drug at steady state, to the AUCτ of the drug, i.e., the area under plasma concentration-time curve of the drug in a dosing interval at steady state:

$$C^{ave}_{ss} = \frac{AUC_\tau}{\tau} \quad (4)$$

When half-life of a drug is long enough compared to the dosing interval, we can calculate AUCτ with the approximation of considering the trend curve connecting peak and trough as a straight line instead of an exponential trend, such that the geometry of AUCτ becomes a trapezoid (Figure 1):

$$AUC = (\frac{C_p + C_t}{2}) \times \tau \quad (5)$$

Therefore, having peak, trough and dosing interval known, AUCτ could be determined readily for each patient, which, in turn,

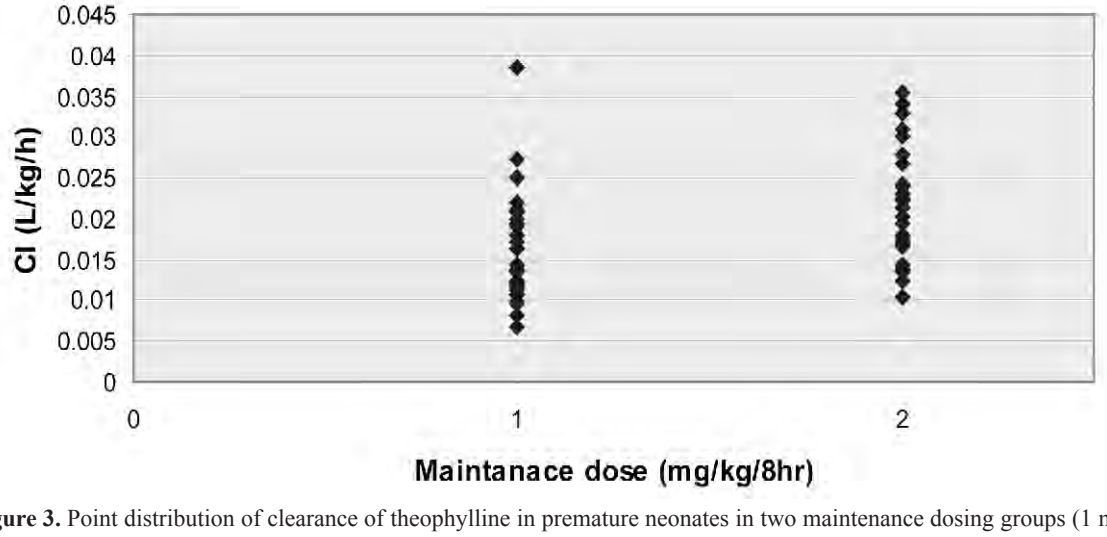

Figure 3. Point distribution of clearance of theophylline in premature neonates in two maintenance dosing groups (1 mg/kg versus 2 mg/kg; Q8h).

resulted in calculation of the individual C^{ave}_{ss}.

On the other hand, for a drug in steady state, we have:

$$C^{ave}_{ss} = \frac{F \times S \times MD}{Cl \times \tau} \quad (6)$$

Where, F is bioavaibility of the drug, S is the salt factor, MD is maintenance dose, and Cl is the total systemic clearance of theophylline. In IV administration, F equals to unity, S for aminophylline is 0.873, MD for group 1 of patients is 1 mg/kg and for group 2 of patients is 2 mg/kg, and τ is 8 h.

We calculated total systemic clearance (l/kg/h) of theophylline for each patient.

Finally, we calculated the volume of distribution of the drug in each patient having the formula:

$$V_d = \frac{Cl}{K} \quad (7)$$

Where, Vd is volume of distribution (l/kg) of theophylline, and K is the elimination rate constant of theophylline obtained from literature [1].

2.2. Statistical analysis

All the statistical comparisons were performed using the independent t test and the significance of correlation was judged by correlation (Pearson) test. All the tests were made by using "SPSS 15" software. The significance level throughout the study was taken as $p<0.05$.

3. Result

According to the criteria described earlier, 68 infants were eligible to be enrolled in this study. Of these patients, a total of 6 (8.8%) were excluded from the study due to the changes occurred in the dose of aminophylline before the eleventh dose. There was no significant difference between two groups in the baseline characteristics of the infants (gestational age, weight, and gender).

There was a significant difference in between two dosing levels ($p<0.001$) (7.69±2.92 µg/ml vs. 11.44±3.80 µg/ml) (Figure 2). Concentrations of these two dosing groups – that are related with a gradient line – is significant. Furthermore, the total clearance and volume of distribution are significantly different in two groups ($p<0.01$ for Cl and $p<0.01$ for Vd) (Figures 3 and 4).

The correlation between drug pharmacokinetic and individual personal characteristics, including gender, body weight, and gestational age was evaluated. No significant correlation

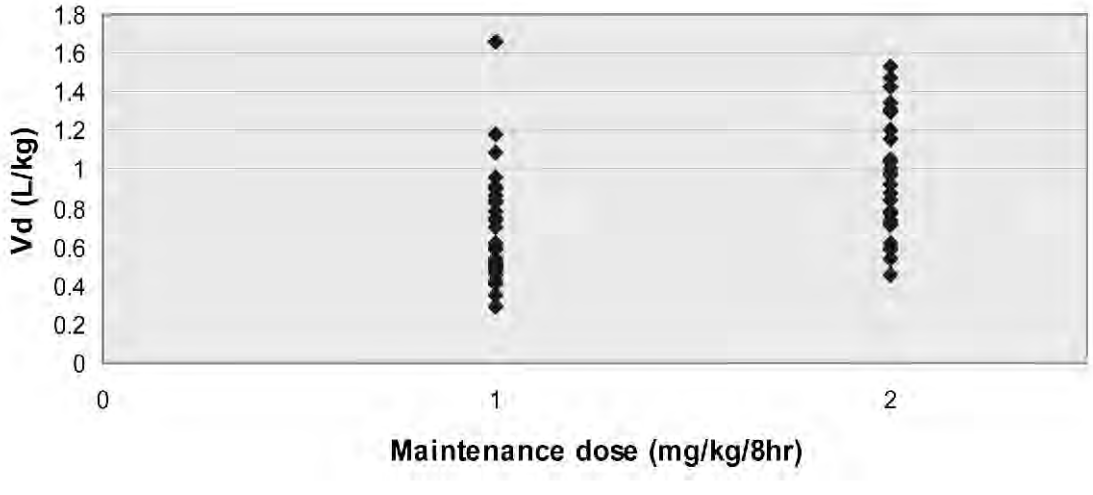

Figure 4. Point distribution of volume of distribution of theophylline in premature neonates in two maintenance dosing groups (1 mg/kg versus 2 mg/kg; Q8h).

could be found between the gender and C^{ave}_{ss} in different dosing levels (p>0.05 in both cases). The correlation between C^{ave}_{ss} and patient body weight was also not significant in dosing level 1, but it was significant in level 2 (Figures 5, 6).

The correlation between C^{ave}_{ss} and patients' gestational age was insignificant in dosing level 1, but it was significant in level 2 (Figures 7, 8). The effect of the patients' postnatal age (PNA) and the pharmacokinetic parameters was evaluated using C^{ave}_{ss} as the independent parameter measured in this study in two dosing levels. The correlation was insignificant in dose level 1, but it was significant in dose level 2 with a declining trend (Figures 9, 10).

It seems that there are two outlier points in this set with the PNAs obviously higher than the rest of the patients. We tried to ignore them and investigate the correlation. Statistical test showed that, upon this omission, no significant changes occurred in the final result.

Another parameter which seems to have a relation to theophylline pharmacokinetic parameters is post-conceptional age (PCA) which is the sum of gestational age and prenatal age. As shown in Figures 11 and 12, PCA affects drug serum concentration in a manner similar to PNA, i.e., significant effect only in 2 mg/kg dosing level with a decreasing trend.

4. Discussion

In this study, the main pharmacokinetic parameters of theophylline have been determined in a population of neonates suffering from premature apnea.

A standard, two-groups, open-label, parallel, multiple-dose, purpose-to-treat, multiple-drug design was used in this study for the evaluation of pharmacokinetic parameters of the apnic premature neonates upon administration of two different doses of 1 mg/kg and 2 mg/kg intermittent intravenous infusions during 20 min infusion periods with 8 h dosing intervals (τ). Generally, two time points are routinely measured in multiple dose studies in order to determine the pharmacokinetic parameters: peak and trough concentrations. Both of peak and trough serum concentrations are commonly used in clinical pharmacokinetic studies, but when there is any limitation in sampling, trough point is of a better reliance and applicability for pharmacokinetic evaluations as well as for therapeutic drug monitoring (TDM) purposes. Accordingly, as mentioned earlier, we could

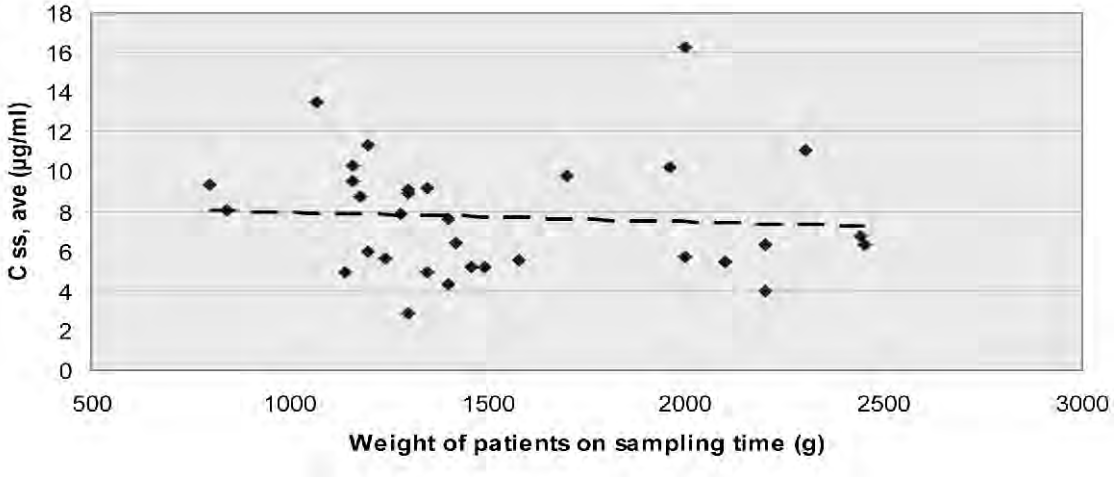

Figure 5. Correlation of body weight at sampling time and average theophylline serum concentration in premature neonates with 1 mg/kg Q8h (p=0.08). The dotted regression lines indicate non-significant relationship.

obtain only trough samples in the current study and, therefore, using a series of standard pharmacokinetic relations and population pharmacokinetic data from the literature, we calculated the pharmacokinetic parameters as mentioned in Materials and Methods.

4.1. Steady state serum concentration

As expected, a significant difference was found between average drug concentrations of two dosing groups in steady state ($p<0.05$; Figure 2). However, when drug administration rate grows two-times, the corresponding serum concentrations do not show proportional increase. Clearly, this observation indicates a type of non-linearity in drug pharmacokinetic in this population. We will discuss this issue further in clearance section as the non-linearity in drug concentrations routes back the unexpected differences in drug clearance in different doses.

4.2. Clearance

The total systemic clearance of theophylline in neonates included in this study showed a significant difference between two dosing groups ($p<0.05$) (Figure 3), which indicates the occurrence of non-linear pharmacokinetic in this population, as mentioned earlier. Jenne *et al*. have reported non-linear pharmacokinetic of theophylline in 83 children affected by obstructive lung disease receiving IV aminophylline, which is attributed to saturation of the drug elimination processes in the population studied [7]. In addition, Weinberger and Ginchansky reported in a study on 20 children with chronic asthma that patients receiving two-fold or greater IV aminophylline present a significantly lower drug clearance [8].

Interestingly, the above-mentioned reports on non-linearity of theophylline pharmacokinetic are different from the current study, as with the higher dosage rate we found a higher drug clearance indicated by a lower steady state serum concentration of the drug. Because of incomplete development of hepatic metabolizing enzyme systems in premature neonates, about 50% of the theophylline dose is excreted as unchanged drug via renal clearance [9]; therefore, upon saturation of the hepatic enzymes responsible for theophylline biotransformation, by increasing the dose, the drug elimination becomes more renal-dependent which acts more efficiently in theophylline elimination [10]. The other possible explanation for this result is that: because a large proportion of the drug is excreted unchanged in the urine in this group of patients, an increased diuretic effect of the

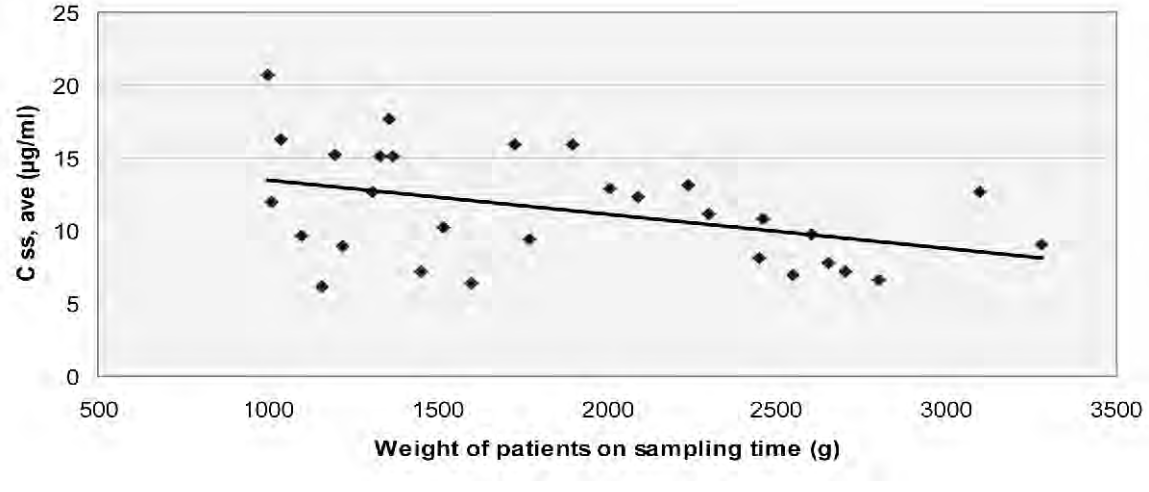

Figure 6. Correlation of body weight at sampling time and average theophylline serum concentration in premature neonates with 2 mg/kg Q8h (p=0.02). Significant relationships are represented by solid lines.

drug at larger doses increases the drug clearance with growing dosage rates [11].

4.3. Volume of distribution

The volume of distribution of theophylline, which is a parameter derived from clearance in our calculations differs significantly in the two dosing groups, as expected (Figure 4). Since we had to assume a fixed elimination rate constant in this study as a result of limitation in blood sampling, the situation in clearance is directly reflected in Vd. Therefore, no logical discussions can be made in this context.

In premature infants, apparent volume of distribution of theophylline is generally almost two-times higher than in adults (volume of distribution in adults is 0.3-0.7 l/kg, averaged 0.45 l/kg) [12]. Aranda *et al*. have suggested that volume of distribution in premature neonates is about 0.69 l/kg [13]. The volume of distribution of 0.91 l/kg for premature neonates was reported by Giacoia *et al*. [14]. Some other studies have calculated the theophylline Vd as 0.71 l/kg [3], 0.77 l/kg, and 0.76 l/kg [15]. Therefore, we can see high variations in results reported. The data obtained in the current study is similar to the results of Aranda *et al*. [13] for group 1, and to the results of Giacoia *et al*. [14] for group 2, i.e., the Vd values of 0.703±0.282 l/kg and 0.913±0.308 l/kg, for groups 1 and 2, respectively.

The higher volume of distribution of theophylline in premature neonates compared to those of children and adults can be described by two issues. First, neonates have a larger fraction of body water and, therefore, they have more exteracellular water in the first year of life, and it can be expected for water soluble drugs such as theophylline to have more volume of distribution in this period. Second, a lower protein binding capacity in premature neonates than in children and adults may account for this difference in Vd. The latter reason has also been established by a study on malnutritioned children. While theophylline Vd in normal children is 504.2 ml/kg, in under weight, marasmus and kwashiorkor children, it is 533.9, 677.5 and 724.6 ml/kg, respectively [16].

4.4. Weight

Another parameter that seems to have an effect on the average plasma concentration is patient's body weight. In our study, dose administration was based on the body weight, and the amount of drug that every patient received was in proportion with their weight.

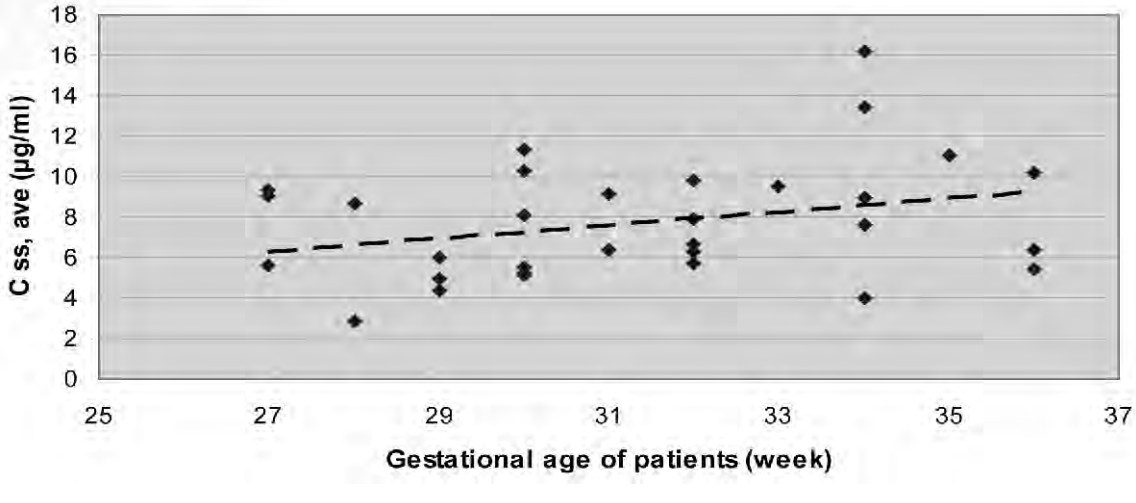

Figure 7. Correlation between gestational age and average theophylline serum concentration of premature neonates with 1 mg/kg Q8h (p=0.30).

Therefore, we expected that no relation between these two factors would exist in each group. However, based on our statistical test in the second dosage group, a significant reverse relationship exists between weight and theophylline serum concentration (Figure 6). This finding indicates some qualitative factors effective in this respect, i.e., something is happening with weight growth in neonates related to the drug disposition. This relationship is not significant in group 1 (Figure 5).

Gilman *et al*. have reported a non-significant correlation between body weight and theophylline clearance in premature neonates [17]. However, the result of a population pharmacokinetic study of theophylline in very premature Japanese infants with apnea by Fukuda *et al*., the effect of weight on theophylline clearance was confirmed [18].

4.5. Gestational age

Another characteristic that theoretically may have an effect on pharmacokinetic parameters is gestational age. To address this question, we noticed that the correlation between gestational age and pharmacokinetic parameters was insignificant in dose level 1 (Fig. 7), but it was significant in reverse direction in dose level 2 (Fig. 8). It is probable that the higher gestational age causes more maturation and decreased serum level in second group.

Maturation process occurs with age and newborns with higher gestational age automatically are more mature. In liver maturation, it is probable that cytochrome P-450 activity increases and drug metabolism or theophylline clearance increases with the increase of age. So, weight indirectly has an influence on serum concentration. In premature infants with greater weight, serum concentration is decreased and this logical behavior is seen in group two. There is no explanation in the scope of this study for the question why the dose group 1 does not show this correlation.

4.6. Correlation between patient postnatal age (PNA) and theophylline pharmacokinetic

Some researchers have changed their point of view into evaluation of the maturation process after birth in premature infants in terms of its effect on pharmacokinetic parameters. The clearance of theophylline in one infant determined at 20 and 48 weeks postnatal increased from 0.37 to 1.5 ml/kg/min, accordingly [19].

In 1976, Aranda *et al*. have reported no

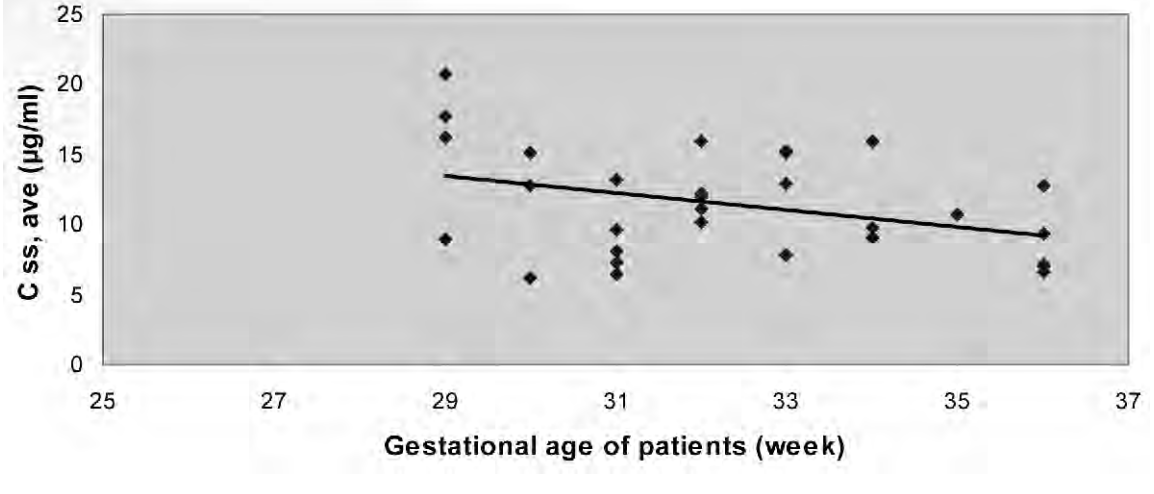

Figure 8. Correlation between gestational age and average theophylline serum concentration of premature neonates with 2 mg/kg Q8h (p=0.04). Significant relationships are represented by solid lines.

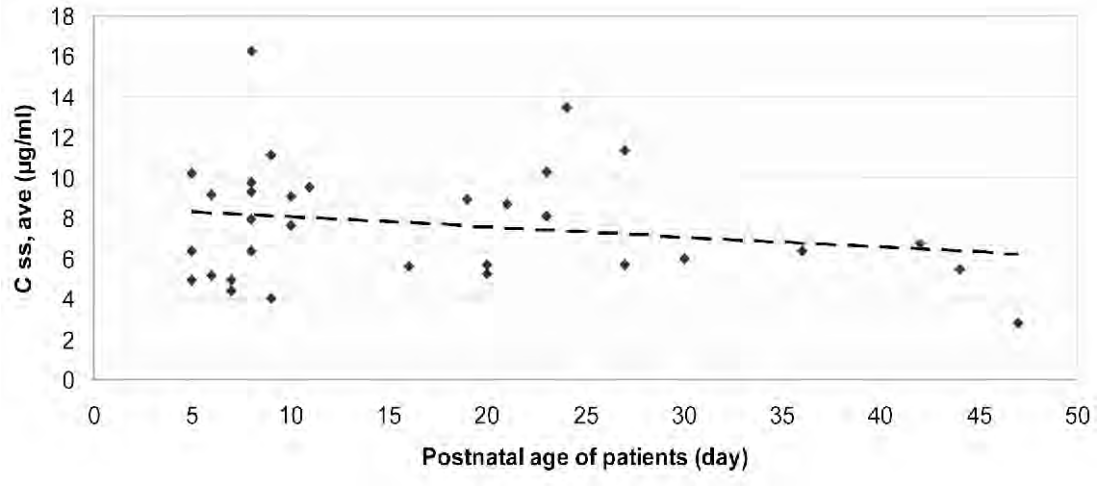

Figure 9. Correlation of postnatal age with average serum theophylline level of premature neonates with 1 mg/kg Q8h (p=0.24).

statistically significant correlation between theophylline half-life and postnatal age, gestational age or post-conceptional age in six premature infants [13]. In another study, a relatively shorter plasma half-life (19.8 h) and higher clearance (39 ml/kg/h) has been reported in older premature infants, which suggest dramatic changes in drug pharmacokinetic after the third week of postnatal life [20]. Giacoia *et al*. have performed a study of theophylline pharmacokinetic in eight premature neonates with apnea. They have proposed that baby clearance of theophylline appears to increase progressively with age [14]. Lönnerholm *et al*. have studied 17 preterm infants. In three of them repeated sampling have shown an increase in clearance of theophylline from 16.8±0.4 (mean ± SE) at a postnatal age of 6-11 days to 30.9±2.5 ml/kg/h at 64-69 days [21].

In the current study, serum levels of theophylline showed a significant reverse correlation with PNA in group 2, but not in group 1 (Figures 9 and 10). It means that in the former group, when postnatal age increases, theophylline serum concentration progressingly decreases which can be attributed to the progressive maturation

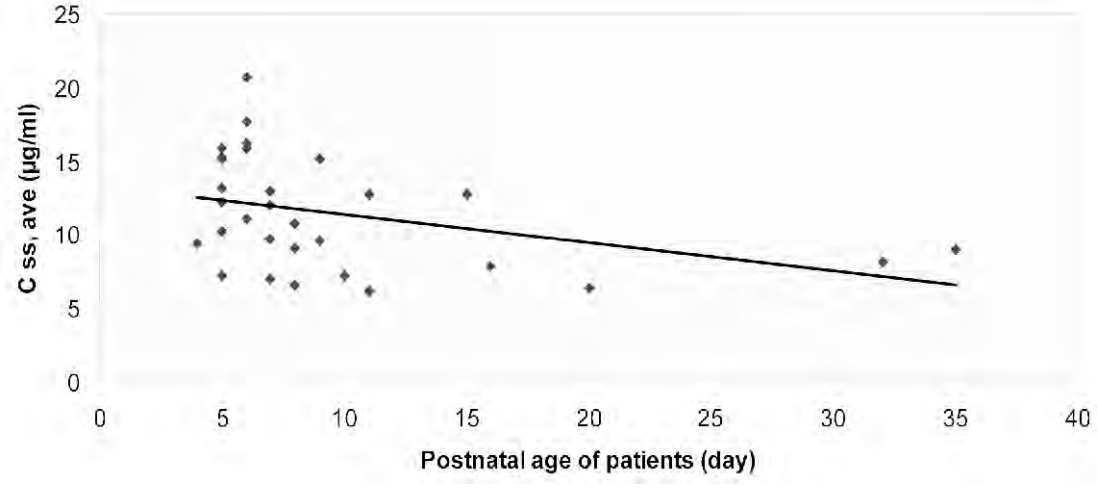

Figure 10. Correlation of postnatal age with average serum theophylline level of premature neonates with 2 mg/kg Q8h (p=0.04). Significant relationships are represented by solid lines.

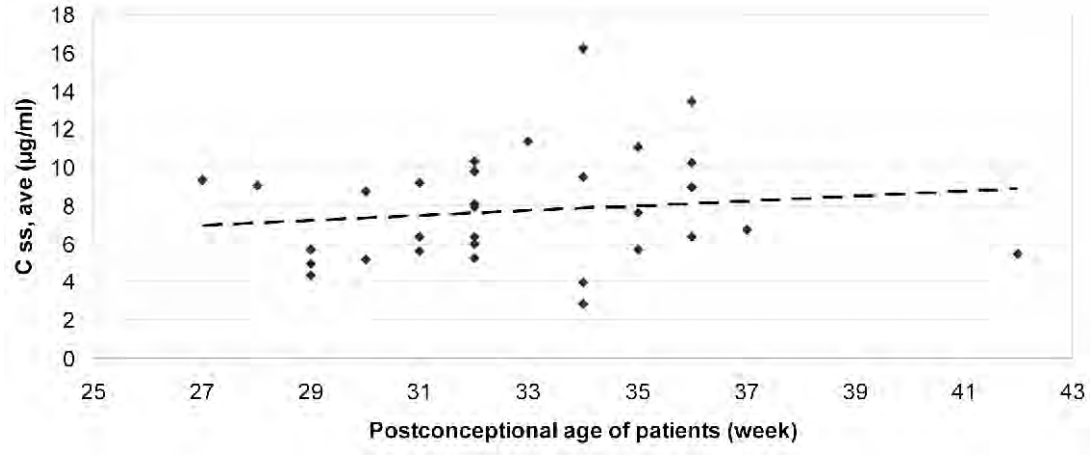

Figure 11. Correlation of post-conceptional age with average serum theophylline levels in premature neonates with 1 mg/kg Q8h (P = 0.43). No significant effect on the statistical inference.

occurred in drug elimination process. There is no logical explanation within the scope of this study for why this trend is not the case with the lower dose level.

4.7. Correlation between patient postconceptional age (PCA) and theophylline pharmacokinetic

PCA is another parameter of maturation being related quantitatively with drug pharmacokinetic. Kraus *et al*. have studied the maturation parameters on 52 infants. They studied theophylline clearance, serum caffeine-to-theophylline ratio and some other parameters as an indicator of maturation. Their findings indicated that post-conceptional age rather than postnatal age should be used as a maturational marker during theophylline therapy in infancy [22]. The result of this group is opposed to result of Dothey *et al.* [15] which preferred PNA instead of PCA.

Nonetheless, it can be clearly said that pharmacokinetic parameters of theophylline undergo substantial changes with neonatal age. However, in this study, the significant decreasing trend in drug serum level with

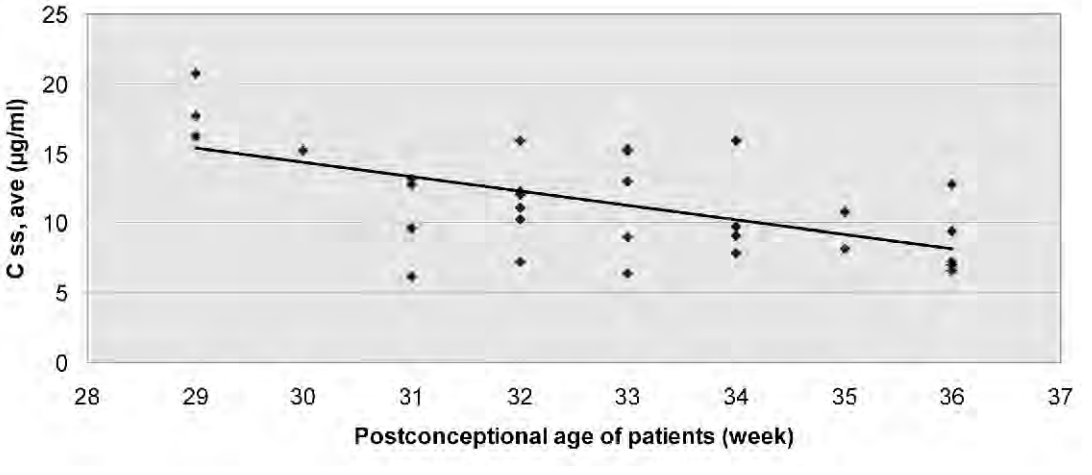

Figure 12. Correlation of post-conceptional age with average serum theophylline levels of premature neonates with 2 mg/kg Q8h (p=0.001). Significant relationships are represented by solid lines.

PCA was evident, again, only in group 2, with no explanation herewith (Figures 11 and 12).

A study on nine preterm infants (12 to 191 days old) has demonstrated that theophylline clearance correlate better with the post-natal age than with the post-conceptional age [15]. A strong correlation was obtained between log t1/2 and post-natal age. The correlation with the post-conceptional age was weaker. These investigators propose that the clearance of theophylline clearly increased during the first six months of life, whereas the t1/2 decreased with post-natal age. The lack of correlation between gestational age and changes in clearance or t1/2 was unexpected. The highly significant correlations between clearance, t1/2, and postnatal age suggest that the function of cytochrome P-450 is in a dormant stage during the intrauterine life and is induced rapidly after delivery. The impact of postnatal age is thus far more important than the gestational age. The correlations found between post-conceptional age and changes in clearance and t1/2 were initially puzzling. They also continue: the fact that the log t1/2 correlated better with the postnatal age than t1/2 itself suggest that the maturation of cytochrome P-450 probably follows a logarithmic process during the first six months of life and the present study will permit us to define age-specific dosage guidelines and to improve the efficacy and safety of theophylline treatment in the neonatal period [15].

Further studies are recommended in the way to develop non-invasive approaches, e.g. oral or rectal, for these patients. In this study, we encountered the limitation in blood sampling. It is suggested to find a way for having at least two, instead of one, blood samples for each patient. Our results, conclusions and recommendations are based on limited population as well as limited pharmacokinetic observations. Therefore, further studies are needed seriously to confirm the findings in a clinical scale.

5. Conclusion

According to theophylline serum concentrations, these two doses produce therapeutically safe and effective blood levels, but if higher doses become necessary, some problem may exist with potential toxicity based on pharmacokinetic data. Total systemic clearance of theophylline in patients receiving two doses, does not remain constant. It means that pharmacokinetic of theophylline in these neonates is somehow non-linear in this dosage range, showing negative deviation i.e. increased clearance and disproportionally increased Css.

Acknowledgement

We would like to thank Shiraz University of Medical Sciences for financial support of this study (grant no. 84-2746). This manuscript is relevant to the theses of Mohammad Moslehi.

References:

[1] Buaer LA. Theophylline. In: *Applied clinical pharmacokinetic*, 1st ed. McGraw-Hill, 2001; pp. 687-739.

[2] Murophy JE. Theophylline. In: *Clinical Pharmacokinetic*. 4th ed. ASHP, 2008; pp. 301-13.

[3] Jones RA, Baillie E. Dosage schedule for intravenous aminophylline in apnoea of prematurity; based on pharmacokinetic studies. *Arch Dis Child* 1979; 54: 190-3.

[4] Shannon DC, Gotay F, Stein IM, Rogers MC, Todres ID, Moylan FMB. Prevention of apnea and bradycardia I: low-birthweight infants. *Pediatrics* 1975; 55: 589-94.

[5] Lagercrantz H, Rane A, Tunell R. Plasma concentration-effect relationship of theophylline in treatment of apnea in preterm infants. *E J Clin Pharmacol* 1980; 18: 65-8.

[6] Pesce AJ, Rashkin M, Kotagal U. Standards of laboratory practice: theophylline and caffeine monitoring. *Clin Chem* 1998; 44: 1124-8.

[7] Jenne JW, Wyze E, Rood FS, Mac Donald FM. Pharmacokinetic of theophylline: application to adjustment of the clinical dose of aminophylline. *Clin Pharmacol Ther* 1972; 13: 349-60.

[8] Weinberger M, Ginchansky E. Dose-dependent kinetic of theophylline disposition in asthmatic children. *J Pediatr* 1977; 91: 820-4.

[9] Macnamary DG, Nixon GM, Anderson BJ. Methylxanthine for the treatment of apnea

associated with bronchiolitis and anesthesia. *Pediatr Anesthesia* 2004; 14: 541-550.

[10] Lowry JA, Jarrett RV, Wasserman G, Pettett G, Kauffman RE. Theophylline toxicokinetics in premature newborns. *Arch Pediatr Adolesc Med* 2001; 155: 934-9.

[11] Muttitt SC, Tierney AJ, Finer NN. The dose-respond of theophylline in the treatment of apnea of prematurity. *J Pediatr* 1988; 112: 115-21.

[12] McEvoy GK. *AHFS drug information essentials*. USA: American Society of Health-System Pharmacists, 2006; pp. 3554-78.

[13] Aranda JV, Sitar DS, Parsons WD, Loughnan PM, Neims AH. Pharmacokinetic aspects of theophylline in premature newborns. *N Eng J Med* 1976; 295: 413-6.

[14] Giacoia G, Jusko WJ, Menke J, Koup JR. Theophylline pharmacokinetic in premature infants with apnea. *J Pediatr* 1976; 89: 829-32.

[15] Dothey CI, Tserng KY, Kaw S, King KC. Maturational changes of theophylline pharmacokinetic in preterm ifants. *Clin Pharmacol Ther* 1989; 45: 461-8.

[16] Eriksson M, Paalzow L, Mariam TW. Pharmacokinetic of theophylline in Ethiopian children of differing nutritional status. *Eur J Clin Pharmacol* 1983; 24: 89-92.

[17] Gilman JT, Gal P, Levine RS, Hersh CB, Erkan NV. Factors influencing theophylline disposition in 179 newborns. *Ther Drug Monit* 1986; 8: 4-10.

[18] Fukuda T, Yukawa E, Kondo G, Maeda T, Shino T, Kondo Y, Imamura T, Irikura M, Irie T. Population pharmacokinetics of theophylline in very premature Japanese infants with apnea. *J Clin Phar Ther* 2005; 30: 591-6.

[19] Nassif EG, Weinberger MM, Shannon D, Guiang SF, Hendeles L, Jimenez D, Ekwo E. Theophylline disposition in infancy. *J Pediatr* 1981; 98: 158-61.

[20] Aranda JV, Turmen T, Sasyniuk Betty I. Pharmacokinetic of diuretics and methylxanthines in the neonates. *Eur J Clin Pharmacol* 1980; 18: 55-63.

[21] Lönnerholm G, Lindström B, Paalzow L, Sedin G. Plasma theophylline and caffeine and plasma clearance of theophylline during theophylline treatment in the first year of life. *Eur J Clin Pharmacol* 1983; 24: 371-4.

[22] Kraus DM, Fischer JH, Reitz SJ, Kecskes SA, Yeh TF, McCulloch KM, Tung EC, Cwik MJ. Alterations in theophylline metabolism during the first year of life. *Clin Pharmacol Ther* 1993; 54: 351-9.