

KINETICS OF THEOPHYLLINE IN APNEA OF PREMATURITY IN SMALL FOR GESTATIONAL AGE BABIES

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ABSTRACT

Objectives: To study the pharmacokinetics of theophylline and its correlations to pharmacodynamic effects in apnea of prematurity in small for gestational age babies. **Design:** Prospective case control study. Setting: Level III Neonatal Intensive Care Unit. **Subjects:** Ten small for gestational age (SGA) babies and 10 gestation matched appropriate for gestational age (AGA) babies with recurrent apnea of prematurity. **Methods:** All babies were investigated to exclude secondary causes of apnea. 5 mg/kg of aminophylline loading dose followed by 2 mg/kg as maintenance dose every 8 hourly intravenously was used. The trough and peak levels of theophylline were assessed on different days of therapy. Clinical monitoring was done for the efficacy and toxicity of the drug. Analysis was done using unpaired Student's 't' test and the correlation between plasma theophylline levels of different days was performed by using ANOVA. **Results:** The therapeutic drug levels were achieved within 24 hours in all babies. The SGA babies showed 25% higher drug levels as compared to AGA babies. The mean trough plasma theophylline levels ranged from 8.15 ± 1.59 to 12.37 ± 1.54 ug/ml in SGA babies while in AGA babies they ranged from 6.26 ± 1.93 to 9.96 ± 1.96 ug/ml in first 8 days of therapy. The mean peak levels in SGA babies ranged from 11.91 ± 1.84 to 17.13 ± 1.63 ug/ml and in AGA babies ranged from 8.17 ± 1.84 to 13.02 ± 1.48 ug/ml. Twenty per cent SGA and AGA babies each developed clinical toxicity though toxic drug levels were found in 50% SGA and 30% AGA babies. **Conclusion:** There is a need to modify dosage schedule for these babies.

Key words; Apnea of prematurity, Pharmacokinetics, Small for gestational age, Appropriate for gestational age, Theophylline.

APNEA of prematurity has been postulated to be a significant cause of brain damage in premature babies due to hypoxia following recurrent apneic episodes(1). Aminophylline forms the mainstay of medical therapy in these babies(2). The clearance of theophylline is decreased in newborns particularly prematures, compared to children and adults(3). In neonates the plasma protein

binding of the drugs is decreased and it is one of the important factors altering the pharmacokinetics of a drug. Preterm babies also exhibit decreased metabolism of the drug by the liver cytochrome P-450 monooxygenase system(4-7). SGA infants handle drugs differently than AGA babies due to different maturation of liver enzymes, having larger extracellular fluid

volumes, lower levels of plasma proteins, higher hematocrit values and relatively variable levels of free fatty acids(8-11). Presently, the dosage schedule followed for SGA babies is similar to the one used for AGA babies. In the developed countries, because of easy availability of drug monitoring facilities, the problem of suboptimal or over dosage is easily corrected and the dosage schedule is individualized. However, this is not possible in our country. Hence there is an urgent need to devise dosage schedule for our population, where a large proportion of babies are intrauterine growth retarded.

In view of this, the present study was carried out to evaluate the plasma theophylline concentrations and its correlations to pharmacodynamic effects in preterm small for gestational age babies during the first week of theophylline therapy.

Subjects and Methods

Ten preterm SGA babies (gestational age <35 weeks) whose birth weight was <10th centile for the gestation(12) with recurrent apneic spells due to 'apnea of prematurity' within first 2 weeks of life comprised the study cases. Ten gestation and postnatal age matched AGA babies with recurrent apnea constituted the control subjects.

Only babies born during the period July 1991 to June 1992 at Nehru Hospital of the Postgraduate Institute of Medical Education and Research, Chandigarh were included in the study. Informed consent was obtained from parents and the study design was approved by the Institute Ethics Committee. Gestational age was determined from the last menstrual period (LMP) and also assessed by modified Robinson and Farr's criteria(13-15).

Definitions

Apnea was defined as cessation of breathing for >20 seconds with or without bradycardia (heart rate <100/minute) and/or cyanosis. Apnea was considered recurrent when number of spells was more than 2 per hour.

Exclusion Criteria

Babies were excluded from the study if apnea was secondary to septicemia, pneumonia, meningitis, any thermal instability, metabolic disorders, intracranial pathology, impaired oxygenation, gastro-esophageal reflux and drugs. Also those who had asphyxia, cholestatic jaundice and were on certain drugs (phenobarbitone, dilantin, cimetidine, erythromycin and ciprofloxacin) known to alter the metabolism of theophylline were excluded.

Investigations

All babies were investigated with chest skiagram, blood gas analysis, complete work up for sepsis, hematocrit, blood glucose, serum calcium, serum electrolytes, record of temperature and cranial ultrasonography to exclude secondary causes of apnea. Estimation of total serum proteins by Biuret method(16) and total free fatty acids by the method of Dole(17) were done before starting them on aminophylline therapy.

Dosage Schedule

Babies with apneic attacks were administered 5 mg/kg of aminophylline as loading dose followed by 2 mg/kg every 8 hourly intravenously.

Sampling

0.5 ml of blood was drawn from an intravenous cannula in preheparinized tubes on days 1, 3, 5 and 7 before next due dose (TROUGH level, i.e., CSS_{min}) and

2 hours after the dose (PEAK level, i.e., CSS_{max}). Samples were centrifuged at 2500 rpm for 10 minutes, plasma separated and stored at $-20^{\circ}C$ until assayed for theophylline by HPLC technique(18).

Monitoring

While the baby was on aminophylline, monitoring was done for the number of apneic attacks, need for oxygen therapy and ventilatory support. Also a daily record was maintained during the study period for the: (a) toxic effects of the drug like tachycardia, feed intolerance, abdominal distension, diuresis, hyperexcitability and seizures; (b) electrolyte and metabolic abnormalities; and (c) serial cranial ultrasound for intraventricular hemorrhage.

Statistical Analysis

The data was analyzed using unpaired Student's 't' test. The correlation between plasma theophylline levels of different days was assessed by 'Analysis of Variance' (ANOVA).

Results

The 10 preterm SGA babies had gestational ages ranging from 28.1 to 33.1

weeks (mean \pm SD- 30.9 ± 1.77), birth weight from 740 to 1200 g (mean \pm SD- 1075.4 ± 158.50) and post conceptional age at the time of enrollment from 201 to 235 days (mean \pm SD- 220.1 ± 10.59). Amongst 10 preterm AGA babies, gestational ages ranged from 28 to 33.4 weeks (mean \pm SD- 31.0 ± 1.74), birth weight between 1250 to 1640 g (mean \pm SD- 1457.3 ± 126.02) and post conceptional age from 199 to 236 days (mean \pm SD- 219.4 ± 12.26). Both groups were matched for gestational age ($p > 0.05$) and post conceptional age ($p > 0.05$).

There was no significant difference ($p > 0.05$) in total serum protein, albumin and globulin levels amongst the two groups. However, free fatty acids were significantly higher in AGA babies compared to SGA babies ($p < 0.05$) (Table I).

The mean trough and peak plasma theophylline values achieved on day 1 itself were in therapeutic range and the values increased gradually over the next 7 days. There was no significant difference between day 1 to day 7 levels ($p > 0.05$) in both groups. There was a wide variation in plasma theophylline levels at all ages of estimation. SGA babies had statistically significant higher levels than AGA babies (Table II).

The area under the curve (AUC) for

TABLE I— Serum Protein and Free Fatty Acids (Mean \pm SD) in Small for Gestational Age and Appropriate for Gestational Age Babies.

Parameters	SGA Group (n=10)	AGA Group (n=10)	p value
Total serum protein (g/dl)	5.16 \pm 0.55	5.57 \pm 0.93	0.27
Serum albumin (g/dl)	2.66 \pm 0.35	3.01 \pm 0.49	0.069
Serum globulin (g/dl)	2.5 \pm 0.56	2.56 \pm 0.84	0.84
Free fatty acids (uEq/L)	654.0 \pm 368.46	978.4 \pm 248.54	0.033

trough plasma theophylline level was $72.15 \pm \text{SD } 26.89$ and $61.52 \pm \text{SD } 32.07$ whereas for peak plasma theophylline level it was $102.82 \pm \text{SD } 38.09$ and $82.67 \pm \text{SD } 38.28$ in both SGA and AGA babies, respectively ($p > 0.055$). Though the difference did not reach statistical significance, SGA babies had higher levels than AGA babies.

Theophylline was equally effective in both groups in treating apneic episodes. The mean duration of apnea was $2.00 \pm \text{SD } 1.33$ days (range 1 to 4) and $2.80 \pm \text{SD } 2.37$ days (range 1 to 8) in SGA and AGA babies, respectively ($p > 0.05$). There was recurrence of apnea in 3 babies in each group. Similarly duration of oxygen

therapy in SGA and AGA babies was $2.90 \pm \text{SD } 1.64$ days and $2.70 \pm \text{SD } 2.12$ days, respectively ($p > 0.05$). Two SGA babies and none of AGA babies required ventilatory support for the management of apnea.

Five babies in SGA group and 3 in AGA group had plasma levels of theophylline in toxic range (>20 (ig/ml). Out of these, 2 babies in each group also had simultaneous clinical evidence of toxicity. The mean time of onset of clinical toxicity in both groups was day 4 (range 3 to 5). The clinical manifestations were tachycardia, feed intolerance, abdominal distension and persistent hyperglycemia.

TABLE-II- Plasma Theophylline Levels on Various Days in Small for Gestational Age and Appropriate for Gestational Age Babies

Day	SGA Group (n=10)	AGA Group (n=10)	p value
Trough Levels			
D ₁	8.15 ± 1.59 (2.29-16.06)	6.26 ± 1.93 (2.65-15.38)	0.0292
D ₃	10.93 ± 1.66 (3.41-19.05)	8.26 ± 1.64 (4.62-20.64)	<0.001
D ₅	12.37 ± 1.54 (6.29-26.10)	9.55 ± 1.69 (4.40-22.23)	0.0019
D ₇	12.36 ± 1.93 (2.70-21.46)	9.96 ± 1.96 (5.44-17.20)	0.0118
Peak Levels			
D ₁	11.91 ± 1.84 (3.72-32.48)	8.17 ± 1.84 (3.12-18.91)	<0.001
D ₃	14.27 ± 1.43 (5.38-34.16)	11.29 ± 1.63 (5.14-23.00)	<0.001
D ₅	17.13 ± 1.63 (7.09-40.93)	12.94 ± 1.66 (6.00-29.13)	<0.001
D ₇	16.60 ± 1.73 (4.57-28.91)	13.02 ± 1.48 (7.55-22.80)	<0.001

The values ($\mu\text{g/ml}$) depicted are geometric means \pm SD and range.

Discussion

Apnea may be seen in up to 25% of preterm babies and is associated with significant morbidity and mortality(19). Theophylline has been the standard modality of treatment in apnea of prematurity. The pharmacokinetics of theophylline in preterm babies is different than term babies. The mean half life is 30 hours in preterm as compared to children (3½ hours) and adults (6 hours)(20). Factors that reduce the half life include phenobarbitone and phenytoin, while those that increase its half life include congestive cardiac failure, liver disease and drugs such as erythromycin, cimetidine and propranolol. In neonates 30-40% of circulating theophylline is bound to plasma protein and is metabolized mainly to caffeine (30%) in liver, small amount is converted to 1,3 dimethyl uric acid and the balance excreted unchanged by the kidneys. Preterms exhibit comparatively decreased metabolism of drug. In view of its longer half life, a loading intravenous dose is required to achieve quick therapeutic level. The subsequent maintenance dose is guided by serum theophylline concentration obtained after steady state is reached. The appropriate serum therapeutic level is 4-12 ug/ml for the treatment of idiopathic apnea(2).

The mean plasma theophylline levels in SGA babies were 25% higher than in AGA babies and the differences were statistically significant. The trend of higher values in SGA babies was apparent on day 1 and continued throughout the study period. The higher levels in SGA babies can be explained because of lower theophylline clearance, longer half life, higher apparent volume of distribution due to the larger extracellular fluid compartment, as well as immaturity of the liver enzymes particularly cytochrome P-450 monooxygenase

system and lower level of plasma proteins(4-7). In the present study, SGA babies had lower serum albumin levels as compared to AGA babies (*Table I*). The reduced plasma protein binding of drug may also be due to qualitative difference in the binding capacity of albumin(21,22). The lower level of free fatty acids in SGA babies may be due to utilization for glucose supply by neoglucogenesis(23,24).

In our study, all the babies in both the groups achieved a steady state following the initial loading dose and the first two maintenance doses given 8 hours apart. There was also no significant difference in mean trough or peak theophylline levels ($p > 0.05$) from day 1 to day 7 confirming the achievement of steady state. The mean trough and mean peak theophylline levels reached highest value on day 5 of the study and subsequently they came down slightly in the second week of life which suggests the postnatal maturation of renal and hepatic functions(25).

We found a significant correlation between plasma theophylline level and duration of apnea in both SGA and AGA babies. The complete disappearance of apneic spells within 2 days was directly related to the achievement of therapeutic concentrations of theophylline in these babies.

As many as 5 babies in SGA group had plasma theophylline levels in toxic range while in AGA group 3 babies had toxic levels. The simultaneous clinical evidence of toxicity was found in only 2 babies in each group. Since lesser number of SGA babies showed simultaneous clinical manifestation of toxicity, it could be due to better tolerance to higher level of theophylline. However, in view of the small sample size categorical conclusions in this context are difficult.

Based on the above findings, the

dosage schedule for these babies requires modification and a study with larger numbers and different dosage schedules needs to be undertaken.

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NOTES AND NEWS

FELLOWSHIPS IN THE FIELDS OF NEONATOLOGY IN AUSTRALIA

Vacancies are available for the posts of Registrar Level I to Level IV w.e.f. December 1997 onwards at the Neonatal Intensive Care Units of the following hospitals in Australia: (i) The Nepean Hospital, Penrith; (ii) The Royal Alexandra Hospital for Children, Camperdown; and (iii) Westmead Hospital, Westmead. The emoluments range from Australian \$ 40,000 to \$ 50,000 per annum. Candidates having experience in the field of assisted ventilation in newborn babies shall be preferred. It is mandatory to enclose a certificate confirming that the candidate has actually worked for a period of at least six months in one of the Level II Neonatal Units duly accredited by the National Neonatology Forum of India. The candidate should give the choice of the Center where he/she would prefer to be placed for assignment. The interested candidates are requested to send within the next four weeks their detailed curriculum vitae along with the names of the three referees to Dr. Meharban Singh, Professor and Head, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029.

PALS WORKSHOP AT KOTA ON 30th-31st MARCH/1996

This event will be held under auspices of IAP, Hadoti Branch and Department of Pediatrics, Kota Medical College, Kota. The registration is limited to 40 delegates on "First Come First Served" basis. The registration fee is Rs. 350/- only (Bank draft-IAP, Hadoti Branch, Kota). For further details contact: Dr. R. K. Gulati, Assistant Professor of Pediatrics, J.K. Loni Hospital, Kota. Tel: 0744-22232 (Res).