Optimization of Theophylline Use in Management of Bronchial Asthma and Neonatal Apnea

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Introduction

Bronchial asthma (BA) is a reversible inflammatory condition of the airway with hyper responsiveness to a variety of stimuli, characterized by airway smooth – muscle constriction and may associate with edema, and obstruction of airways by secretions. *(Shapiro, 1992; Woolcock, 1993)*, and an increase in the incidence and prevalence of asthma worldwide *(Levy and Hilton 1992; Fleming et al.,1987)*. A community based studies in Saudi children showed a prevalence of 11.5%. Incidence among school children in Jeddah is about 13% and 17% in Qassim *(Al Frayh, 1990)*. BA is recognized as a significant health problem leading to high mortality and morbidity *(Buist & Vollmer, 1990; Weiss & Wagner, 1990)*, attributed to the lack of sufficient anti-inflammatory therapy and over reliance on bronchodilator and symptomatic therapy (*Garrett et al.,1995*). Some countries established natural guidelines since 1989, adopting an international consensus report in 1992 lead to the more recent global strategy initiated by World Health Organization (WHO) in 1993, emphasizing that asthma requires specific anti-inflammatory therapy. In 1995,a Saudi National Protocol (SNP) for management of asthma was established, classifying the severity of asthma into four steps based on clinical grounds and objective measures including peak expiratory flow rate (PEF), and the the continuous preventive treatment, while apnea, is a pause in breathing that has one or more of the following characteristics: lasts for more than 15-20 seconds, associated with the baby's colour changing to pale, purplish or blue, associated

with bradycardia < 100 beats/min, (Finer et al.,1992). Incidence and severity of apnea are inversely related to gestational age, although there is considerable variation. 50% of less than 1.5 kg birth weight (bwt) of infants requires pharmacologic intervention or ventilatory support for recurrent prolonged apneic episodes. The peak incidence occurs between 5 and 7 days postnatal age *(Dennis & Mayock, 2000)*. Three mechanisms of apnea of prematurity are considered: central apnea, obstructive apnea , and mixed apnea *(Barrington and Finer, 1991)*.

Apnea of prematurity is by far the most common cause of apnea in a premature infant, but it is necessary to initially investigate and rule out the following etiological disorders (*Miller & Martin, 1992)* infection, temperature regulation, gastrointestinal, neurological, drugs, metabolic, cardiovascular, hematological, and pulmonary disorders. Apnea if untreated may lead to ischemia and eventually leukomalacia *(Koons et al., 1993; Miller & Martin, 1992)*, which is a failure of the mechanisms that protect cerebral blood flow.

Methods

84 files of asthmatic children admitted to Pediatric Ward at KAUH during the period of January 1996 – December 1999 for retrospective (76 files) and January 2000–June 2001 for prospective (9 files) were reviewed and patients were selected. 50 preterm neonates enrolled in the study were admitted to Neonatal Intensive Care Unit (NICU) at Maternity and Children's Hospital Al Mosaidia, Jeddah, Saudi Arabia during the period 1998-2000.

Pharmacotherapy of apnea: TH was given in the form of aminophylline (250 mg/10ml) by slow I.V over 10 mins, drawn by a tuberculine syringe and

transferred to a 5mls syringe, diluted to a total of a 5mls with saline. LD of 4-6 mg/kg, MD of 0.53 mg/kg/12h.

Management of convulsion (8 patients), 20 mg/kg of phenobarbital (PBL) was given I.V, followed by 5 mg/kg/day. For management of gastrointestinal bleeding (19 patients) cimetidine was given I.V. in a dose of 5mg/kg/12h. Both drugs were given at least 7 days. Most patients received one or more antibiotics.

Selection Criteria:

Astham: 1) Age: 1-13 yr, 2) diagnosed as having severe asthma by the presence of a combination of the followings: previous history of severe attacks or admission to ICU. Presence of dyspnea or decreased air movement, PEFR (for patients >4 years) ≤50% with predicted values, PaO_2 <60 torr, $PaCO_2$>40 torr., 3) received standard therapy, and 4) patient has no other Chronic illness. Chronic illness like pneumonia, high fever, liver impairment were excluded because their medication induce liver enzyme which interfere with the PK of theophylline (TH).

Neonatal apnea: 1) preterm <34 weeks gestational age (GA), 2). Received TH for management of apnea of prematurity, 3). TH was started within the 1st month afterbirth. Exclusion criteria were preterm with congenital abnormalities, cholestatic jaundice, and those who suffered birth asphyxia.

Data Collection:_ Data related to TH dosing time of sampling are available in the request form kept in Drug Monitoring Unit (DMU) archives. The following data *were completed from the* patient's medical file: demographic, family history, frequency & severity of attacks, triggering factors, assessment of response,

results of laboratory investigations, pulmonary function tests, clinical investigations, vital signs monitoring and adverse effects due to TH or other medications.

Sample collection of apnea: TH Css level in preterm to be approximately attained after 5-6 days of repeated administration *(Brazier et al., 1979)*. Two blood samples were collected from each patient for determination of TH level, the 1st sample was taken 1hr. post LD, and the 2nd on the 6th day half-way between doses. In all cases, 1ml was drawn into a plain tube, immediately centrifuged to separate the serum, and kept at 4^0C until analysis within 2 days.

Estimation of PK parameters of apnea: The 50 preterm neonates who received TH were subdivided into three groups according to the concomitantly taken drugs, group 1: (8 patients) received PBL, group 2: (19 patients) received cimetidine, group 3: (23 patients) received neither PBL nor cimetidine.

PK analysis was performed using the conventional PK equations (6)

Apparent volume of distribution (V_d) was determined by:

V_d (L/kg) = (LD x 0.8) / C_1 ..... Eq1

C_1= TH level (mg/L) determined 1h post LD.

0.8: salt factor to convert aminophylline dose to TH equivalent.

The clearance (CL) was estimated by:

CL (L/Kg/hr) = (MD x 0.8) / (C_{ss} x τ) Eq2

C_{ss}: TH level (mg/L) determined half way between doses at steady state, τ: dosing interval (hr).

\Elimination rate constant (Ke) was determined by:

Ke (hr^{-1}) = CL / V_d Eq3

Half life ($t_{0.5}$) was determined by:

$T_{0.5}$ (hr) = 0.693/Ke Eq4

TH level determination of Asthma and Neonatal apnea: TH levels were analyzed by Fluorescence Polarization Immuno Assay (FPIA) method, using Abbot TDx analyzer. The assay was conducted according to the manufacturers' protocol and two c ontrols (low, 5mg/ml and high, 25mg/ml) were run with each carousel of serum samples. The coefficient of variation for within day and between-day precision is <5% for concentration range (1-30ug/ml)

Samples taken 6 hrs after starting maintenance dose (MD) was considered steady state (Css) and used for the evaluation of dose guidelines proposed in SNP and Pharmacokinetic (PK) analysis.

Auditing compliance with SNP dosage guidelines: Allowance of ±10% was given as most clinicians usually round up doses upon their calculation. The patients were categorized into two groups; group I: received the SNP TH recommended doses, group II: received >10% lower doses, only the TH levels of the 1st samples taken at Css were considered.

Estimation of mean TH Clearance (CL) for asthmatic patients: Patients were classified into two groups: 1-8 yrs and 9-13 yrs. Individual TH CL was estimated using the following equation.

CL (L/kg/hr) = infusion rate (mg/kg/hr) / Salt factor ÷ Css TH level (mg/L)

Statistical analysis was performed using Excel 7 and Sigma Statistics version 2. Values of $p<0.05$ were considered to be significant.

Prospective Study of Asthma: In view of results obtained from the

retrospective study, clinicians were instructed by DMU to provide all severe asthmatic children enrolled in the study a pharmacotherapy as suggested by SNP 2nd version 1997 as follows:

LD: 6mg/kg by slow I.V. infused over 30 minutes.

MD: to be started after 1 hr of LD.

The clinical response was assessed using the following measures: PEFR, respiratory rate, ausculation, dyspnea, accessory muscles, pulsus paradoxes, and O_2 saturation. TH level determination, TH CL estimation, laboratory investigations, and statistical analysis were done as in retrospective.

Results

TH clearance, data of retrospective (76) and prospective (9) patients were pooled to provide a conclusive result. Severe asthma among the younger age group (1-5 yr) was significantly higher than that in other age group (>5-9 yr & >9-13). From the family history,71.8% have positive family history of asthma. The younger age group showed higher incidence of anemia, leucocytosis and eiosinophylia among female compared to males (69% vs. 46%)

Table 1: TH level distribution in blood samples of patients received theophylline in doses as recommended by SNP (group I) or sub- recommended doses (group II)

TH LEVEL µg/ml	GROUP I dosing according to SNP		GROUP II dosing lower than SNP	
	No.	%*	No.	%*
Subtherapeutic				

<4	1	2.439	1	4.167
4 – 6	4	9.756	**8**	33.333
>6 – 8	4	9.756	3	12.500
>8 – 10	8	19.512	7	29.167
Sub total	**17**	**41.463**	**19**	**79.167**
Therapeutic				
>10 – 15	18	43.902	4	16.667
>15 – 20	5	12.195	1	4.167
Sub total	**23**	**56.097**	**5**	**20.833**
Toxic				
>20 – 25	**1**	4.44		
Total	**41**		**24**	

* % Relative to the total samples in each group.
** significantly higher p<0.001

Prospective evaluation of TH dosing guidelines: 9 children received TH dosing according to SNP guidelines. All patients were samples at Css. 8 patients have TH level within therapeutic (10-20ug/ml) and one patient only have a TH level of 9ug/ml.

Mean TH CL in different age groups: The 1-8 year age group showed a significantly higher mean TH CL (0.094 ± 0.023 L/kg/hr) compared to the older group 9-13 years, which showed a mean TH CL of 0.072 ± 0.017.

Table 2: THCL in Different Age Groups of Severe Asthmatic Children

PARAMETER	1st Group 1 – 8 YR N= 29	2nd Group 9 – 13 YR N= 10
Mean age ± SD	4.420 ± 2.047	9.900 ± 1.524
Mean THCL ± SD	0.092* ± 0.023	0.072 ± 0.017
TH CL Range (min – max)	0.064 – 0.161	0.037 – 0.094
Median TH CL	0.089	

* significantly higher than mean CL in the 2nd group (p=0.006)

Table 3: Characteristics of preterm neonates classified according to concomitantly administered drugs

Parameter	Gr. 1 Phenobarbital	Gr 2 Cimetidine	Gr. 3 Other patients*	(Gr. 2 + Gr 3)
No. of patients	8	19	23	42
Gender (n) M/F	3/5	12/7	13/10	25/17
Ethnic origin (n)				

African/Asian	2/6	3/16	5/18	8/34
Gestational Age (wk)				
Range	27 – 33	28 – 33	27 – 33	27 – 33
Mean ± SD	29.25[a] ± 2.43	30.79[a] ±1.27	29.65[a] ±1.70	30.17 ± 1.60
Birth weight(kg)				
Range	0.88 – 1.93	1 – 2.30	0.88 – 1.64	0.88 – 2.3
Mean ± SD	1.19[b] ± 0.41	1.40[b] ± 0.32	1.29[b] ± 0.21	1.34 ± 0.26
Apgar score				
1 min = Mean ± SD	5.56[c] ±2.23	6.20[c] ±2.05	6.45[c] ±2.30	6.00 ± 2.15
5 mins =Mean ±SD	6.65[d] ±2.17	7.45[d] ±2.22	7.85[d] ±2.13	8.21 ± 1.08
Antibiotics (n)				
Gentamycin	6	13	14	27
Vancomycin	3	3	8	11
Amikacin	2	3	10	13
Claforan	8	11	8	19

*received neither phenobarbital nor cimetidine

a:(P=0.043), b: (P=0.047), c (P=0.617), d: (p=0.407) using one way anova. Tukey test showed no significant difference among means of all parameters.

Table 4– Effect of concomitantly administrated drugs on PK parameters of TH in preterm neonates.

PK parameters		Phenobarbital N=8	Cimetidine N=19	No interfering drugs N= 23	P value
V_d	Mean ± SD	0.884 ± 0.173	0.733 ± 0.194	0.793 ± 0.295	P>0.05
	Range	0.675-1.179	0.427 – 1.030	0.306 – 1.395	
	95% conf. Interval	0.764 – 1.004	0.646 – 0820	0.672 – 0.914	
	Coeff. Of variation%	19.570	24.467	37.200	
CL	Mean ± SD	0.036* ± 0.017	0.019 ± 0.007	0.018 ± 0.005	P=0.02
	Range	0.017-0.067	0.010 – 0.035	0.008 – 0.026	
	95% conf. Interval	0.024 – 0.048	0.016 – 0.022	0.016 – 0.020	
	Coeff. Of variation%	47.222	36.842	27.778	
Ke	Mean ± SD	0.042 ± 0.023	0.027 ± 0.012	0.026 ± 0.012	P=>0.05
	Range	0.023 – 0.092	0.013 – 0.062	0.012 – 0.055	
	95% conf. Interval	0.026 – 0.058	0.022 – 0.032	0.021 – 0.031	
	Coeff. Of variation%	54.762	44.444	46.154	
$t_{0.5}$	Mean ± SD	20.076 ± 8.180	29.591 ± 11.300	31.623 ± 12.890	P=0.01
	Range	7.567 – 30.603	11.139 – 52.321	12.603 – 59.945	
	95% conf. Interval	14.408 – 25.745	24.488 – 34.610	26.355 – 36.891	
	Coeff. Of variation%	40.745	38.187	40.761	

Table 5: Mean PK parameters of TH in preterm neonates excluding patients that received Phenobarbital (n = 42)

Parameter	Mean ± SD	Range	Coefficient of variation%	95 % confidence interval
V_d	0.766 ± 0.25	0.306 – 1.395	32.2	0.737 –0.815
CL	0.0186 ± 0.006	0.008 –0.035	31.6	0.018 –0.019
Ke	0.027 ± 0.011	0.012 – 0.062	41.5	0.025 –0.029
$T_{0.5}$	30.68 ± 12.1	11.140 – 59.95	39.5	28.813 –32.546

*GA range: 27 – 33 wks, mean: 31.2 ± 1.6, Bwt range: 0.88 – 2.3 kg. mean 1.34 ± 0.27

Table 6 – PK parameters of TH in preterm neonates classified according to their demographic characteristics. (excluding those received Phenobarbital)

	Pk Values (Mean ± SD)			
GA (wk)	**V_d**	**CL**	**Ke**	**$T_{0.5}$**
GA 1 (n =12)				

Range	27 - 29	0.801 ± 0.288	0.018 ±0.001	0.026 ± 0.010	31.625 ± 13.561
Mean ± SD	28 ± 0.426				
GA 11 (n =30)					
Range	30 – 33	0.751 ± 0.241	0.019 ±0.006	0.027 ± 0.012	30.296 ± 11.687
Mean ± SD	31.033± 0.927				
Bwt (Kg)					
Bwt I (n=5)					
Range	0.88 – 1	0.688 ±0.303	0.016 ±0.006	0.026 ±0.101	31.437 ± 14.231
Mean ± SD	0.974 ± 0.053				
Bwt II (n=31)					
Range	1 – 1.5	0.767 ±0.245	0.018 ±0.006	0.026 ± 0.009	29.926 ± 10.847
Mean ± SD	1.311 ± 0.135				
Bwt III (n=6)					
Range	1.5 – 2.3	0.818 ± .282	0.019 ±0.006	0.027 ± 0.018	33.919 ±17.75
Mean ± SD	1.815 ± 0.270				

Table 7 – Relationship between aminophylline maintenance dose (MD) mg/kg/12h and TH level distribution at Css (n=24)

MD	Total Samples[a]	TH level (ug/ml) <6		6-12		>12-15	
		N	%[b]	N	%	N	%
>.5-1.0	14	12	85.7	2	4.3	-	-
1.1-1.5	18	11	61.1	7	38.9	-	-
1.6-2.0	5	1	20	4	80©	-	-
2.1-3.0	4	-	-	2	50	2	50
3.1-3.5	1	-	-	-	-	1	100
Total	*42*	*24*	*57.14*	*15*	*35.71*	*3*	*7.1*

(a) number of samples or patients are the same
(b) relative to the total number of samples within each patient group received certain MD.
© significantly high (p<0-0.1)

Discussion

Good correlation between TH level and clinical response has been well established *(Milgrom H., 1993)* 32% of the total patients, 79% received lower TH doses than recommended by SNP, reflecting over cautious behavior of some of our clinicians. Undermedication was considered the main reason for attaining subtherapeutic levels. Compliance to SNP guidelines had favorable mpact on attaining TH levels within therapeutic range. Presence of minimal percentage of subtherapeutic level and toxic ranges indicated that reliance on TH dose guidelines does not ensure the attainment of level due to great inter-individual

variations of TH CL. Our results are similar to those reported by (*Cox et al.,1993).* Therapeutic Drug Monitoring (TDM) of TH and the application of PK principles for dosage adjustments on individual basis. In the present study, the younger age group (1-8 yrs), have significantly higher value of TH CL as 0.094 ± 0.023 L/kg/hr compared to the older group (9-13 yrs) 0.072 ± 0.017. These results are very close to those reported by *Edward et al., 1992, and* they support the SNP dose guidelines that described higher TH for younger children of 1-9 years, compared to doses described for older group of 9-16 years *(Al Rayes et al., 1995).* It is worth mentioning that caution should be considered in all cases were TH CL s reduced by status asthmaticus, fever, pneumonia, viral infection, impaired liver function or concurrent administration of drugs that inhibits TH CL *(Milgrom, 1993; Behrman et al., 2002*). Metabolic and renal clearance of TH is markedly reduces in neonates and showed variable absorption after oral administration *(Baird-Lambert e .al., 1984).*

In view of our findings, all patients excluding those receiving PBL were combined in one group that represent the subject of all coming discussions. The mean values ± SD of TH PK parameters were as follows: (V_d): 0.77 ± 0.25 L/kg, (Ke): 0.027 ± 0.011 h^{-1}, (CL): 0.019 ± 0.006 K/kg/h, ($T_{0.5}$): 30.7 ± 12.1. Our results are comparable with some reported values. The following values for V_d were reported: 0.77 (*Gilman et al.,1986),* 0.91 *(Riechert et al. 1981*), 0.86 *(Micali et al.,. 1993),* and 0.71 (*Jones & Baillie, 1979*). The reported values for TH CL were: 0.024 (*Brazier et al., 1979);* 0.0188 *(Haimann et al., 1982);* 0.028 (*Riechert et al., 1981).*

Conclusion and Recommendation

This study supports and encourages the use of SNP dose guidelines

for initial infusion rates of TH to achieve an initial concentration of 10 ug/ml. Final dosage adjustment should be guided by TH serum level measurement during the 1st 6hr after I.V. TH administration.

LD: 6 mg/kg by slow I.V injection over 30 minutes

MD: 1-8 yrs = 0.9 mg/kg/hr, 9-13 yrs = 0.7 mg/kg/hr.

For dose adjustment purposes, TDM unit should be consulted.

Table 8: Suggested optimal Aminophylline maintenance dose mg/kg/12h to attain certain TH level ug/ml.

Target TH Css level	6	7	8	9	10	11	12
MD	1.7	2	2.2	2.9	2.8	3.1	3.4

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تحقيق الاستخدام المثالي للأدوية ذات المجال العلاجي الضيق في المرضى السعوديين : الثيوفلين لعلاج الربو القصبي لدى الأطفال وخمول التنفس لدى الأطفال حديثي الولادة

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المستخلص : يعتبر الربو القصبي من أكثر الأمراض المزمنة شيوعاً في المملكة العربية السعودية، وقد أظهرت إحدى الدراسات أن نسبة انتشار المرض في الأطفال ١١,٥% وقد وضعت وزارة الصحة البرنامج الوطني السعودي لتشخيص وعلاج الربو القصبي. والذي قيد استخدام عقار الثيوفلين على الحالات الحادة وأكد على أهمية متابعة تركيزه في الدم للمحافظة على تركيز (١٠-١٥ مكجم/مل).

وقد أجريت الدراسة على ٨٥ طفلاً (١-١٢ سنة) يعانون من الربو القصبي الحاد الذين تم تنويمهم بالمستشفي الجامعي بقسم الأطفال (٧-١٠ أيام) وتم متابعتهم إكلينيكياً مع إجراء الفحوصات المخبرية المختلفة وإعطاء العقار بالحقن الوريدي المستمر.

كما أن خمول التنفس من المشاكل الصحية الشائعة عند الأطفال المبتسرين ويعد عقار الثيوفلين من الأدوية التي لها الأولوية لمعالجة هذه المشكلة ولكنه يعاني من المجال العلاجي الضيق بالإضافة إلى التفاوت الكبير في معاملات حركية الدواء.

وقد أجريت الدراسة على ٥٠ طفلاً مبتسراً (عمر الحمل ٢٦-٣٣ أسبوع) يعانون من خمول التنفس وقد تلقوا جميعاً جرعة ابتدائية من الثيوفلين وقدرها ٣-٦ مجم/كجم تبعها جرعات داعمة ٥-٢ مجم/كجم كل ١٢ ساعة، وتلقى ٨ مرضى عقار الفينوباربيتال بينما تلقى ١٩ مريضاً عقار السيمتدين لمدة أسبوع على الأقل.

أخذت عينات دم لتحليل مستوى تركيز العقار من كل مريض الأولى بعد ساعة من الجرعة الابتدائية والثانية في اليوم الخامس (عند مرحلة البنات) وقد قدر تركيز العقار بواسطة التحليل بجهاز "TDxanalyzer".

وقد استهدفت هذه الدراسة تعيين بعض معاملات حركية الدواء للثيوفلين واستخدامها لوضع إرشادات لتحقيق الاستخدام الأمثل لهذا العقار في الأطفال المصابين بالربو القصبي الحاد والأطفال حديثي الولادة المصابين بخمول التنفس.

وفيما يلي موجز لأهم النتائج التي تم التوصل إليها:

١. تبين أن ٣٣% من المرضى تلقوا جرعات أقل من المنصوص عليها في البرنامج السعودي و ٣٤% من العينات أخذت في أوقات غير صحيحة مما تسبب في وجود نسبة عالية من العينات في المستوى دون العلاجي.
٢. تم اقتراح طريقة عملية لتعديل الجرعات بما يلائم كل حالة في ضوء نتائج تحليل الدواء.

وقد لوحظ أن الأطفال عمر (١-٥ سنوات) أكثر عرضه للإصابة بالربو القصبي الحاد وأن نسبة الذكور أعلى من نسبة الإناث في هذه الفئة (٣ :٢) تبين أن معامل تصفية العقار يعتمد على العمر مع وجود اختلافات واضحة بين الأفراد (١-٥ سنوات) ٠,٠٩٤± ٠,٠٣٧، (٥-٩سنوات) : ٠,٠٨٩±٠,٠١٧، (٩-١٣) سنة ٠,٠٨٣±٠,٠٣٥ لتر/كجم/ساعة ومن ثم تم تحديد المجال العلاجي للثيوفلين (٩-١٥ مكجم/ ملم) في حالات الربو القصبي الحاد عند الأطفال.

كما تبين من دراسة خمول التنفس عند المبتسرين أن عقار الفينوباربيتال أدى إلى زيادة معدل تصفية العقار "clearance" وقلل في فترة نصف العمر "life-half" بينما لم يؤثر عقار السيمتدين على أيّ من هذه المعاملات.

كما لوحظ وجود اختلاف كبير بين المرضى في هذه المعاملات وبناء على هذه النتائج مع الأخذ بالاعتبارات العملية فإن الدراسة توصي بنظام الجرعات التالي للتيوفلين لعلاج خمول التنفس خلال الشهر الأول من العمر جرعة ابتدائية ٦-٧ ملجم/كجم، يليه جرعة داعمة ١,٥-٢ ملجم/كجم كل ١٢ ساعة. كما تم وضع طريقة عملية لتعديل الجرعات في ضوء نتائج قياس الدواء في الدم حتى يتم تعديل الجرعات بما يلائم النمو أو وجود تفاعلات دوائية.