An evaluation of theophylline dosing

Suggested by the Saudi national protocol for children with severe Asthma

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ABSTRACT

Objectives: To evaluate the impact of Saudi national protocol on the diagnosis and management of asthma for optimizing theophylline use in children with severe asthma. To also review theophylline clearance and provide guidelines for individualization of doses.

Methods: Theophylline level was estimated in blood samples of 66 children with severe asthma who were admitted to King Abdulaziz University Hospital during the period 1998-1999. The theophylline doses given to these patients was reviewed and patients were categorized into 2 groups: Group one had received doses recommended by Saudi national protocol ± 10%, group 2 had received doses <90% of that recommended by Saudi national protocol. The distribution of theophylline levels in blood samples of each group was estimated. Theophylline steady state level was used to estimate theophylline clearance using a standard pharmacokinetic equation.

Results: Out of the total samples from group one, 70% of theophylline levels were within therapeutic range, while only 10% of the total samples of group 2 were within therapeutic range. The mean theophylline clearance in children (1-8 years) was estimated as 0.092 ± 0.023 and was found significantly higher than the mean theophylline clearance (0.069 ± 0.014) which is observed in older children (9-13 years).

Conclusion: Saudi national protocol theophylline dose guidelines had a favorable impact on the optimization of theophylline use in children with severe asthma. Guidelines that ensure accurate adjustment of doses on individual basis in view of drug level were suggested.

Keywords: National protocol of asthma, therapeutic drug monitoring, theophylline, severe asthma in children, theophylline clearance.

Saudi Med J 2001; Vol. 22 (12): 1092-1095

Asthma is considered as one of the most common chronic illness of children in the Kingdom of Saudi Arabia. Community based studies showed a prevalence of 11.5%. The incidence among school children was found to be 10% in Riyadh, 13% in Jeddah and 17% in Qassim.[1] In 1995, the Saudi national protocol for the diagnosis and management of asthma (SNP) was established. A revised 2nd edition was adopted in 1997, which provided the criteria for diagnosis, assessment of severity and a stepwise approach for the pharmacotherapy of asthma. This protocol restricted the use of theophylline (TH) to treatment of acute asthma and provided the following guidelines for aminophylline (1mg=0.85mg of TH) dosage regimen. Loading dose 5-7mg/kg maintenance dose 1mg/kg/hr for children 1-9 years and 0.8mg/kg/hr for children >9-16 years. Monitoring TH blood level was also emphasized aiming at 10-15 μg/ml.[2] Theophylline a[1,3] dimethylxanthine is a bronchodilator which has a narrow therapeutic range and its pharmacokinetics show a marked inter and intra individual variability.[3-5] Recent studies have indicated that TH has anti-inflammatory effects. Also, it reduces both

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Received 14th March 2001. Accepted for publication in final form 7th July 2001.

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eosinophil survival rates in-vitro and eosinophil accumulation in bronchial tissues in patients with atopic asthma. It has also been shown to reduce T-cell proliferation and accumulation. Low doses of TH have been shown to reduce requirements for inhaled corticosteroid therapy in patients with asthma and may reduce the overall cost of treatment.[6] Theophylline has been included in the 1999 World Health Organization (WHO) essential drug list.[7] However, TH was considered as a 2nd or 3rd line therapy in the recent guidelines of National Institute of Health.[8] The aim of the present study is to evaluate the impact and optimization of the SNP on the use of TH and to review its clearance (CL) in Saudi children suffering from severe bronchial asthma.

Methods. ***Patients.*** The present study was conducted at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia Sixty-six children with severe asthma, admitted to the Pediatric Ward during the period October 1998 to July 1999 were enrolled in the study. Selection criterias were as follows: age 1-13 years having severe asthma at time of admission and receiving standard pharmacotherapy including TH. Patients having pneumonia, high fever, other chronic illness and liver impairment were excluded from this study. Severity of asthma was assessed according to the criteria proposed by the SNP.[2] All patients were confirmed as having severe asthma by the presence of a combination of the following: previous history of severe attacks or admission to the intensive care unit. Presence of severe dyspnea or decreased air movement, peak expiratory flow rate (for patients > 4 years) ≤ 50% with predicted values, PaO_2 < 60 Pa, $PaCO_2$ > 40 torr.

Patient management. All decisions were made by clinicians that are not aware of the study. Patients enrolled in the study received standard therapy during the first 24 hours: Oxygen to keep saturation over 95%, nebulized sulbutamol (2.5–5 mg in 2.5–5 cc saline) up to every 20 minutes, intravenous injection hydrocortisone (5-10mg/kg loading dose then 2.5-5 mg/kg every 6–8 hours), and aminophylline loading dose (5mg/kg by slow IV over 20 minutes) followed by maintenance dose (0.5 – 1mg/kg/hr) by continuous infusion which was kept constant using a mechanical pump.

Theophylline level determination. The average TH half-life in children is about 3 hours.[4,9] Thus when no loading dose is given the steady state (Css) blood concentration will be achieved after 5-6 half lives. However, when a loading dose is given and followed by a constant rate IV infusion maintenance dose, TH Css concentration can be attained within a few hours.[10] Nikiforidis et al[11] documented that pharmacokinetic parameters of TH could be estimated using TH concentration of samples taken during the first 8 hours after IV administration. To confirm this concept in the present study, 2 samples were taken from 5 patients, the first after 6-10 hours and the 2nd after 20-24 hours of starting infusion. Theophylline concentration in the first sample was found ± 10% of that in the 2nd sample in all patients. In view of these pharmacokinetic principles and our observation, all blood samples were taken within 6-10 hours of starting IV infusion and considered to represent TH Css concentration. Theophylline levels were analyzed by fluorescence polarization immunoassay (FPIA) method using the Abbott TDx analyzer. The coefficient of variation for the within-day and between-day variability was <5% for the concentration range 1-30 μg/ml. The drug therapeutic monitoring unit has joined efforts with the Abbot quality control program for drug analysis.

Audit of compliance to Saudi national protocol theophylline dose guidelines. To audit compliance of clinicians to SNP TH dose guidelines, TH doses, which had been given to each patient, were reviewed. Deviation of doses by > ±10% from the SNP TH recommended doses (calculated on the basis of age and body weight) were considered as non-compliant to these guidelines. Allowance of ± 10% was given as most clinicians usually round up doses upon their calculation for practical reasons. The patients were categorized into 2 groups: group one received the SNP TH recommended doses, group 2 received >10% lower doses. In order to present an accurate comparison of TH levels between the 2 groups, only the level of the first sample taken from each patient was considered. This was because clinicians usually change the dosage regimen in view of TH blood levels.

Estimation of mean theophylline clearance. Individual TH CL was estimated as follows CL (L/kg/hr)=Ko/Css[12] EQ one Ko=rate of constant IV infusion, (mg/kg/hr), Css=steady state TH concentration (mg/L). Mean TH CL was estimated in children classified into 2 age groups namely: one-8 years and 9-13 years to match the results of those reported in literatures.

Statistical analysis. Statistical analysis was performed using the Excel 7 and SPSS version 5 PC programs. Two-tailed T-test assuming unequal variance was used to compare mean values of TH CL. Chi square test was used to determine the significance of difference between percentages. Values of <0.05 were considered to be significant.

Results. ***Impact of compliance to Saudi national protocol dosing guidelines on theophylline level distribution.*** Out of 66 patients, 45 (68%) received TH doses as recommended by SNP. Twenty one patients (32%) received lower doses. Table 2 shows the impact of compliance to SNP dosing

Table 1 - Demographic characteristics of severe asthmatic children.

Age Range	Mean ± SD	Males n	%*	Females n	%*	Total n	%**
1-6	3.6 ± 1.65	25	(62.5)	15	(37.5)	40	(61)
7-13	9.8 ± 2.7	10	(38.5)	16	(61.5)	26	(39)
Total		**35**		**31**		**66**	

n=number, *=relative to the total number of patients of particular age group, **=relative to the total number of patients, SD=standard deviation

Table 2 - Theophylline level distribution in blood samples of patients who received theophylline in doses as recommended by Saudi national protocol (group 1) or sub-recommended doses (group 2).

TH Level ug/ml	Group 1 n	%*	Group 2 n	%*
Subtherapeutic				
<4	-	-	1	5
4-6	-	-	6	29
>6-8	4	9	5	24
>8-10	8	18	7	33
Sub total	12	27	19	90
Therapeutic				
>10-15	24	53	2	10
>15-20	7	16	-	-
Sub total	31	69	2	10
Toxic				
>20-25	2	4	-	-
Total	**45**		**21**	

TH=theophylline, n=number, *=relative to the total samples in each group

guidelines on TH level distribution. Blood samples from patients that received TH doses according to SNP guidelines group one showed a significantly higher percentage (70%) of levels within therapeutic range (10-20 μg/ml). About 18% of subtherapeutic levels were very close to the therapeutic range (8-10 μg/ml) and 4% of samples were potentially non-serious toxic levels (20-30 μg/ml). Concerning group 2 patients that received lower than recommended doses, only 10% of their samples were within therapeutic range, about 30% of levels were very close to therapeutic range but no toxic levels were observed.

Table 3 - Theophylline clearance in different age groups of severe asthmatic children.

Parameter	1st group 1-8 years n=47	2nd group 9-13 years n=19
Mean age ± SD	4.1 ± 2.2	10 ± 1.7
Mean TH CL ± SD	0.092* ± 0.023	0.069 ± 0.014
TH CL Range (min-max)	0.052 - 0.16	0.048 - 0.090
Median TH CL	0.089	0.068

n=number, TH=theophylline clearance, *=significantly higher than mean CL in the second group (p=0.043), SD=standard deviation

Mean theophylline clearance in different age groups. The mean TH CL in 2 age groups of severe asthmatic children is presented in Table 3. The 1-8 year age group showed a significantly higher mean TH CL (0.092 ± 0.023 L/kg/hr) compared to the older group 9-13 years. which showed a mean TH CL of 0.069 ± 0.014

Discussion. ***Impact of compliance to Saudi national protocol theophylline dosage guidleines on theophylline distribution.*** Good correlation between TH level and clinical response has been well established.[4] In the present study, the presence of about 32% of undermedicated patients reflected the over cautious behavior of some of our clinicians. Undermedication was considered the main reason for attaining subtherapeutic levels of TH (Table 2, group one). It is obvious that compliance to SNP guidelines had favorable impact on attaining TH levels within therapeutic range (70% of samples). However, the presence of about 27% and 4% samples in the sub-therapeutic and toxic ranges indicated that reliance on TH dose guidelines does not ensure that the therapeutic level is reached due to great interindividual variations of TH CL. Our results are similar to those reported by Cox et al[13] who estimated TH level distribution in blood samples from asthmatic children in pediatric hospitals as 70% therapeutic, 28% sub-therapeutic and 2% toxic. Therapeutic drug monitoring (TDM) of TH and the application of pharmacokinetic principles for dosage adjustment on an individual basis is essential for the following reasons: 1. Theophylline has a narrow therapeutic range, 2. Theophylline serum concentration is a major determinant of both efficacy and toxicity, 3. There is a large inter-patient variability in rate of TH elimination, 4. Serum concentration is affected by many factors that alter its pharmacokinetics including: Age, hepatic disease, viral infection, pneumonia, drug interaction.[4,14] A TH

level between 10-20 μg/ml has received general acceptance as providing optimal control of asthma symptoms in most patients.[5] In some recent studies, the TH therapeutic range was considered as 5-15 μg/ml[15] or as 8-20 μg /ml.[16] Recently, Holford[17] proposed that the target concentration strategy should replace the "misleading" conventional concept of therapeutic range.

Theophylline clearance in different age groups. Theophylline is eliminated principally by transformation in the liver to inactive metabolites. TH metabolism has been found to be age dependent. In infants it is slow due to immaturity of the hepatic microsomal enzymes and increases slowly during the first year of life. Younger children (1-9 years) have been reported to have higher clearance and shorter half-life compared to those from >9-16 years.[3,4] Eldesoky et al[18] estimated the mean TH CL in children (2-12 years, with a mean of 6.4 yrs ± 3.4) as 0.069 ± 0.012 L/hr/kg. Edward et al[5] estimated the mean TH CL as 0.086 and 0.072 L/kg/hr in children of 1-8 years and >9-12 years. In the present study, the younger age group (1-8 years), have significantly higher value of TH CL (0.092 ± 0.023 L/kg/hr) compared to the older group (9-13 yrs) (0.069 ± 0.014). These results are very close to those reported by Edward et al.[5] These results support the SNP dose guidelines that described higher TH doses for younger children (1-9 years) compared to doses described for older children (9–16 years).[2] It is worthy to remind that caution (lower doses) should be considered in all cases were TH CL is reduced such as status asthmaticus, fever, pneumonia, viral infection, impaired liver function or concurrent administration of drugs that inhibits TH CL.[4,19] Theophylline maintenance dose required to attain a certain target concentration (such as 12 μg/ml) can be estimated by multiplying the estimated individual TH CL x target Css level. This approach is simple but 2 criteria should be fulfilled to ensure its effectiveness: 1. Accuracy of the analytical results 2. Sampling for TH level determination must be at steady state.

In conclusion, SNP TH dose guidelines are very valuable for optimal initiation of TH therapy in severe asthmatic children. Therapeutic drug monitoring is essential to check the blood level and adjusting the maintenance dose on an individual basis to attain a certain target concentration. The following practical guidelines for dose adjustment are suggested. 1. Take blood sample for determination of TH level after 6–10 hours. 2. Estimate individual TH CL {infusion rate (mg/kg/hr) /blood level (mg/L)} 3. Adjust the maintenance dose, (new maintenance MD = Estimated individual TH CL x 12 (Css target TH level) d) take another sample after another 4-6 hours.

Acknowledgment. The authors greatly appreciate Biochemistry specialist Mr. Mohamed Khairul Alam for his continuous effort in determining theophylline level.

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