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Theophylline Toxicity in Thai Children

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SUMMARY Theophylline is a useful drug in the treatment of respiratory diseases with bronchospasm but it has very narrow safety margin. The study was carried out in 44 admitted Thai children with plasma theophylline levels > 20 μg/ml to determine the association between blood levels and symptoms of theophylline toxicity. The prevalence of theophylline toxicity (plasma theophylline level > 20 μg/ml) in Thai children is about 11%. Thirty-four percent of the patients who had theophylline levels less than 30 μg/ml and 78% of those who had levels more than 30 μg/ml had symptoms of theophylline toxicity. The symptoms were related to the gastrointestinal tract (34%), cardiovascular system (18.2%), neurological system (6.8%) and metabolism (54.5%). The possible causes of theophylline toxicity were respiratory tract infection, theophylline overdosage, interaction with other drugs, impairment of liver function, congenital heart disease and theophylline usage in neonates. Theophylline is still a useful drug but should be used with caution. Theophylline levels should be checked in every child who receives theophylline.

Theophylline is frequently prescribed for the treatment of respiratory diseases with bronchospasm. It has been used to prevent episodes of idiopathic apnea and bradycardia in prematurity.[1,2] Short-acting theophylline intravenously is useful in severe asthmatic exacerbation and long-acting theophylline is now used as a prophylactic agent in controlling symptoms of chronic asthma.[3-5] The safety margin of theophylline is very narrow. Maximal benefit with minimal risk of adverse effects is achieved when the peak plasma or serum concentration of theophylline is maintained between 10 and 20 μg/ml.[3,6,7] Theophylline toxic reactions including nausea, vomiting, headache, diarrhea, irritability and insomnia increase if the theophylline level exceeds 20 μg/ml.[8,9] At higher concentrations, there is a progressive increase in risk of toxic encephalopathy with hyperthermia, seizures, brain damage and death. Hyperglycemia, hypokalemia, hypertension and cardiac arrhythmia may also be observed at these higher levels.[8-13] The aim of this study is to determine the association between blood levels and symptoms of theophylline toxicity and the possible causes of theophylline toxicity in Thai children.

MATERIALS AND METHODS

The study was carried out in Thai children who were admitted to Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand over a five-year period (1993-1998) because of bronchospasm or apnea. All of them had plasma theophylline levels more than 20 μg/ml measured by using fluorescence polarization immunoassay method. The demographic and clinical data from their medical records were collected. The amount, route and pattern of theophylline usage were recorded. The signs and symptoms of theophylline toxicity were

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grouped according to the affected organ systems as follows: 1) cardiovascular system (heart rate, blood pressure and arrhythmias), 2) gastrointestinal system (nausea, vomiting, diarrhea and upper GI bleeding), 3) neurological system (seizure) and 4) metabolism (hyperglycemia, hyponatremia, hypokalemia, metabolic acidosis, hypercalcemia). All symptoms including cardiovascular, gastrointestinal, neurological and metabolic disturbances, determined in the analysis had occurred within two hours of the recorded plasma theophylline levels. Blood pressure, heart rate, blood electrolytes and liver function tests were compared with age-specific norms.[14,15] Body weight was compared with age-specific norms of Thai children.[16]

RESULTS

The total number of children who were admitted and checked for plasma theophylline levels were 569 cases. Among them, 63 (11%) of the cases had theophylline level higher than 20 μg/ml. Thirty-seven of the 63 cases had bronchospasm. Forty-four cases with complete data were evaluated. Male:female ratio was 1.8:1. The average age of the patients was 10 ± 3.4 months (6 days to 9 years) while the median was 6 months. Seventy percent of the cases (400/569) were below 6 months old. Sex and age distribution of Thai children with theophylline toxicity is shown in Fig 1. The clinical suspicion of theophylline toxicity was indicated in 18/44 cases (41%).

Fifty-two percent of the cases (256/569) were malnourished (weighed less than the 3rd percentile) when compared with norms of body weight at the same age. None of the cases weighed more than the 95th percentile. Eighty-four percent of the cases (478/569) had bronchospasm. Fourteen and 19% of the cases with bronchospasm had asthma and bronchopulmonary dysplasia as underlying diseases, respectively. More than 50% of the cases had respiratory tract infection and congenital heart disease. The diagnosis on admission of the cases is shown in Table 1. Plasma theophylline levels were 20-30 μg/ml in 80% of the cases. Only 0.5% had theophylline levels higher than 40 μg/ml. The distribution of plasma theophylline levels in children of various ages is shown in Fig 2. Routes of theophylline administration were continuous IV drip in 20 cases, slow IV push in 11 cases,

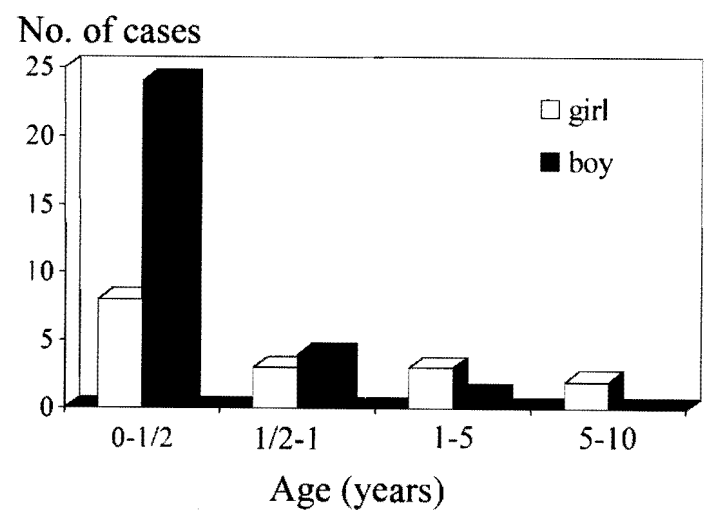

Fig. 1 Sex and age distribution of children with theophylline toxicity.

Table 1 The diagnosis on admission of the children with theophylline toxicity

Diagnosis	No. cases*
Bronchospasm	37
Asthma	5
Pneumonia	25
Bronchopulmonary dysplasia	7
Congenital heart diseases	23
Left to right shunt	14
Right to left shunt	9
Congestive heart failure	8
Others	7
Apnea of prematurity	4
Bronchiectasis	1
Diaphragmatic hernia	1
Stricture right main bronchus	1

*Some patients had more than one diagnosis

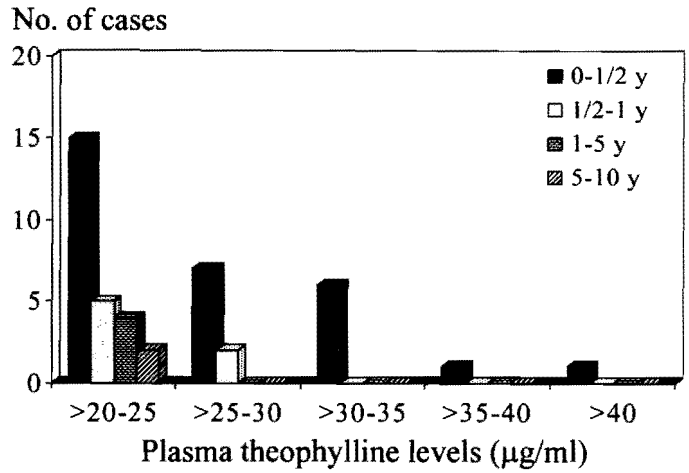

Fig. 2 Distribution of plasma theophylline levels in children with theophylline toxicity of various ages.

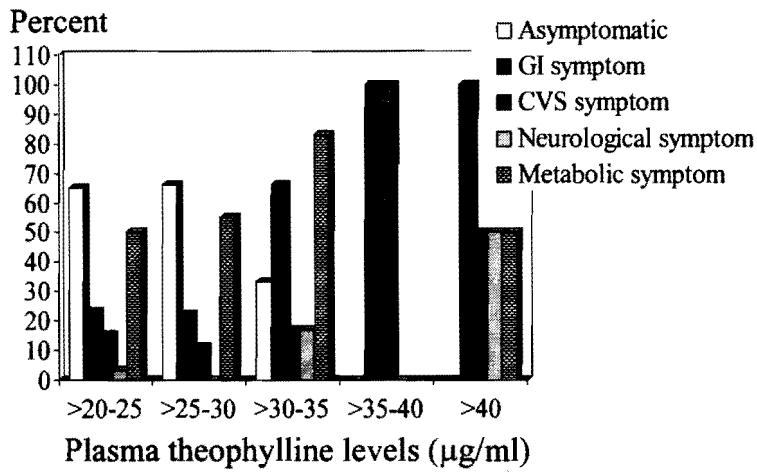

Fig. 3 Distribution of symptoms of theophylline toxicity in children with various plasma theophylline levels.

oral short-acting theophylline in 9 cases, sustained-release theophylline in 1 case and both continuous IV drip and oral short-acting form at the same time in 3 cases.

The symptoms of theophylline toxicity were found in 34% of patients with plasma theophylline level less than 30 μg/ml and 78% with a level higher than 30 μg/ml. All patients who had plasma theophylline levels higher than 35 μg/ml had symptoms from theophylline toxicity. Distribution of symptoms of theophylline toxicity in children with various plasma theophylline levels is shown in Fig 3 and Table 2. The percentages of cardiovascular, gastrointestinal and neurological symptoms increased when plasma theophylline levels increased. Gastrointestinal, cardiovascular, neurological and metabolic symptoms were found in 34, 18.2, 6.8 and 54.5% of the children with plasma theophylline levels more than 20 μg/ml. Gastrointestinal bleeding, arrhythmia and seizure could also be found in the children with theophylline levels less than 25 μg/ml. There was no case fatality. The two cases that had the plasma theophylline levels more than 40 μg/ml had nausea, vomiting and gastrointestinal bleeding. One of the cases had tachycardia and one had a seizure.

Possible causes of theophylline toxicity in Thai children from this study are shown in Table 3. Dose errors were found in 6 cases. One of them received a dose of 15 mg/kg/dose by intravenous drip and 3 of them were given oral theophylline at the same time as intravenous infusion. Two of the newborn infants received inappropriate doses and duration of theophylline therapy. The liver function was checked in only 12 patients and an abnormal SGOT and SGPT were found in 7 of them. There were 2 cases with a SGOT level higher than 1,500 U/l and one of them also had SGPT elevated to more than 1500 U/l. Drug interactions were detected in 12 cases. All of the cases with drug interactions received appropriate doses of theophylline. Six of them had abnormal liver function tests. The drugs that interacted with theophylline were cimetidine (8 cases), ranitidine (2 cases) and erythromycin (2 cases).

DISCUSSION

The use of theophylline, a 50-year-old drug has been debated because of its adverse effects and the introduction of new agents. Theophylline toxicity occurred in

Table 2 Distribution of symptoms of theophylline toxicity

Symptoms*	No. of cases	Plasma theophylline level (μg/ml)				
		> 20-25	> 25-30	> 30-35	> 35-40	> 40
GI						
Nausea, vomiting	13	5	1	4	1	2
GI bleeding	6	2	1	1	0	2
CVS						
Tachycardia	7	3	1	1	1	1
Arrhythmia	1	1	0	0	0	0
NS						
Seizure	3	1	0	1	0	1
Metabolic						
Hyperglycemia	15	6	2	5	0	2
Hyponatremia	8	7	0	0	0	1
Hypokalemia	6	4	1	1	0	0
Metabolic acidosis	4	2	2	0	0	0
Hypercalcemia	3	1	0	1	0	1

*More than one symptoms can be found in one cases

Table 3 Possible causes of theophylline toxicity in Thai children

Cause	Cases	
	N	%*
Dose error	6	13.6
Impaired liver function	7	58.3**
Drug interaction	12	27.3
Neonate: premature	7	15.9
full term	5	11.4
Congestive heart failure	8	18.2
Respiratory tract infection	25	56.8

*Total percent was more than 100 because the patients had more than one possible causes
**Liver function was obtained in only 12 cases

about 16% of the patients who received prescriptions for theophylline.[17] In this study, theophylline levels more than 20 μg/ml were found in 11% of the children who received theophylline therapy. Severe toxic effects from theophylline toxicity are quite rare in clinical practice.[17] The clinical suspicion of theophylline toxicity in Thai children was raised only in 41% of the cases who had a plasma theophylline > 20 μg/ml. Theophylline toxicity occurred more common in infants less than 6 months of age. A previous study showed that 16-24% of cases with theophylline toxicity were less than 1 year of age and 57-65% of them were below the age of 5.[18,19] Premature and full term neonates represented 27% of the cases in this study. The prevalence of theophylline toxicity is high in infants, neonates and prematures because of diminished theophylline clearance in very young children.[20-22] The dosage of theophylline should be adjusted for using in prematures and full term neonates.

A previous study showed that 29% of the cases who had theophylline levels of 25-50 μg/ml had no symptoms while all cases that had a level of > 50 μg/ml showed symptoms.[19] From this study, symptoms of theophylline toxicity were found in 34% of the children with plasma theophylline levels less than 30 μg/ml and in 78% with a level more than 30 μg/ml. All of the children who had plasma theophylline levels higher than 35 μg/ml had symptoms from theophylline toxicity. Cardiovascu-

lar, gastrointestinal and neurological symptoms from theophylline toxicity were directly related to increased plasma theophylline levels which was also shown in previous studies.[18,23] Nausea, vomiting and tachycardia were the most common clinical symptoms of theophylline toxicity. Gastrointestinal bleeding, arrhythmia and seizures could also be found in children with theophylline levels less than 25 μg/ml. Transient caffeine-like effects such as nausea, nervousness or insomnia commonly occur when initial doses of theophylline are too aggressive.[24] This problem is minimized by beginning with sufficiently low doses and increasing the dose slowly only if tolerated.[24] Metabolic imbalances were common in children who had theophylline levels higher than 20 μg/ml. A previous study showed that metabolic imbalances particularly hypokalemia were more common in patients with acute toxicity than in those with chronic toxicity.[17] Other metabolic and electrolyte abnormalities found include hypophosphatemia, hypomagnesemia, hypoglycemia and acidosis.[17] We found that clinical evidence of theophylline toxicity in children is quite variable and cannot be used as a screening method instead of plasma theophylline level. When the patients suffer from the symptoms mentioned above, theophylline toxicity should be excluded by determination of serum levels.

Dose errors were found in 6 cases and drug interactions with appropriate doses of theophylline were found in 12 cases. To prevent theophylline toxicity by dose error or drug interactions, doctors should carefully consider every drug used in any route before prescribing theophylline. Previous studies showed that there was no significant difference in frequency of symptoms between ingestion patterns.[18,25] In this study, there were 23 cases with congenital heart diseases. We expected that there would be an increased risk of arrhythmia in these patients but this was not observed. Seizures were found in 3 cases but were not severe and could be treated with benzodiazepines. A previous study showed that seizures was easily controlled in children with theophylline toxicity but quite difficult to control in adult.[26] Respiratory tract infection was found in more than half of the cases. A previous study showed that upper respiratory tract infections altered the theophylline metabolism by reduction of total body clearance of theophylline[17,27] so the dosage should be adjusted. The mechanism may be by a direct inhibitory effect of viruses or the effect of fever.[28]

The most common causes of excessive serum concentrations and severe toxic effect in children were patient, parent, or physician errors in dosing or in judgment. There was no case fatality in our study. Both cases were successfully treated and completely recovered without sequelae. Theophylline toxicity can be prevented by using appropriate dosage recommendations, paying careful attention to the patient's medical history, and monitoring plasma or serum theophylline concentrations more closely, especially in patients with intercurrent respiratory tract infections.

In conclusion, theophylline toxicity in Thai children is not uncommon. Theophylline should be used with caution especially in patients with reduced theophylline clearance, liver impairment, congenital heart diseases, respiratory tract infection or in neonates and premature babies. Drug interactions and overdosage are also the common causes. Symptoms of theophylline toxicity is directly correlated with increasing plasma theophylline level. Theophylline levels should be checked in the patients during increasing doses until it reaches the therapeutic level and then periodically checked when the patients have symptoms suggested theophylline toxicity or have precipitating factors that can increase the level such as upper respiratory tract infection and drug interaction. If there is any symptoms suspected of theophylline toxicity, the drug must be stopped and the level should be checked immediately.

REFERENCES

1. Bhatia J. Current options in the management of apnea of prematurity. Clin Pediatr 2000; 39:327-36.
2. Shannon DC, Gotay F, Stein IM, *et al.* Prevention of apnea and bradycardia in low-birth weight infants. Pediatrics 1975; 55:589-94.
3. Tomac N. Aminophylline in the treatment of bronchial asthma. Ann Allergy Asthma Immunol 1999; 83: 422-3.
4. Once-daily theophylline reduces serum eosinophil cationic protein and eosinophil levels in induced sputum of asthmatics. Int Arch Allergy Immunol 2000; 12: 123-8.
5. National Heart, Lung and Blood Institute, National Institutes of Health. Global initiative for Asthma NIH/NHLBI publication No 96-3659, Washington DC, NIH; 1998.
6. Weinberger M. The pharmacology and therapeutic use of Theophylline. J Allergy Clin Immunol 1984; 73: 525-40.
7. Neijens JH, Duiverman EJ, Graatsma BH, *et al.* Clinical and bronchodilating efficacy of controlled-release theophylline as a function of its serum concentrations in preschool children. J Pediatr 1985; 107: 811-5.
8. Handeles L, Bighley L, Richardson RH, *et al.* Frequent toxicity from IV aminophylline infusions in critically ill patients. Drug Intell Clin Pharmachol 1997; 11: 12-8.
9. Jacobs MH, Senior RM, Kessler G. Clinical experience with theophylline: relationships between dosage, serum concentration and toxicity. JAMA 1976; 235: 1983-6.

10. Helliwell M, Berry D. Theophylline poisoning in adults. Br Med J 1979; 2: 1114.
11. Miura T, Kimura K. Theophylline-induced convulsion in children with epilepsy. Pediatrics 2000; 105: 920.
12. Culberson CG, Langston JW, Herrick M. Aminophylline encephalopathy: a clinical electroencephalographic and neuropathological analysis. Tran Am Neurol Assoc 1979; 104: 224-6.
13. Hall KW, Dobson KE, Dalton JE, *et al.* Metabolic abnormalities associated with intentional theophylline overdose. Ann Intern Med 1984; 101: 457-62.
14. Horan MJ, Falkner B, Kimm SYS, *et al.* Report of the Second Task Force on Blood Pressure Control in children 1987. Pediatrics 1987; 79: 1-25.
15. Choukair MK. Blood chemistries/body fluids. In Siberry GK, Iannone R (eds). The Harriet Lane Handbook. 15th ed. St. Louis, Mosby, 2000; pp. 119-30.
16. Chavalittamrong B, Tantiwongse P. Height and weight of Thai children: update. J Med Assoc Thailand 1987; 70 (Suppl 1): 1-40.
17. Weinberger M, Hendeles L. Theophylline and phosphodiesterase inhibitors. In Middleton E Jr, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW. eds. Allergy: principles and practice. 5th ed. St Louis, Mosby, 1998; pp. 589-611.
18. Baker MD. Theophylline toxicity in children. J Pediatr 1986; 109: 538-42.
19. Powell EP, Reynolds SL, Rubenstein JS. Theophylline toxicity in children: a retrospective review. Pediatr Emerg Care 1993; 9: 129-33.
20. Nassif EG, Weinberger MM, Shannon D, *et al.* Theophylline deposition in infancy. J Pediatr 1981; 98: 158-61.
21. Du Preez MJ, Botha JH, Mc Fadyen ML, Holford NH. The pharmacokinetics of theophylline in premature neonate during the first few days after birth. Ther Drug Monit 1999; 21: 598-603.
22. Ellis EF, Koysooko R, Levy G. Pharmacokinetics of theophylline in children with asthma. Pediatrics 1976; 58: 542-7.
23. Gaudreault P, Wason S, Lovejoy F. Acute pediatric theophylline overdose: a summary of 28 cases. Pediatrics 1983; 102: 474-6.
24. Milavetz G, Aughan LM, Weinberger MM, *et al.* Evaluation of a scheme for establishing and maintaining dosage of theophylline in ambulatory patients with chronic asthma. J Pediatr 1986; 109: 351-4.
25. Paulocek RP, Rodvold KA. Evaluation of theophylline overdose and toxicities. Ann Emerg Med 1988; 17: 135-44.
26. Yarnell PR, Chu NS. Focal seizures and aminophylline. Neurology 1975; 25: 814-9.
27. Kraemer MJ, Furukawa CT, Koup JR, *et al.* Altered theophylline clearance during an influenza B outbreak. Pediatrics 1982; 69: 476-80.
28. Shilalukey K, Robieux I, Spino M, *et al.* Are current pediatric dose recommendations for intravenous theophylline appropriate? J Asthma 1993; 30: 109-21.