Precautions Concerning the Use of Theophylline

Committee on Drugs

Theophylline is commonly prescribed for pediatric patients with asthma, other forms of reactive airway disease, and apnea of prematurity.1-3 This statement is to remind physicians of the necessity to reduce the dosage of theophylline and to monitor the patient’s serum concentration to prevent increased risk of toxicity when the drug is administered in the presence of acute febrile illness or in combination with certain medications.

The serum concentration of theophylline must be maintained within a relatively narrow range to achieve optimal therapeutic benefit while avoiding toxic side effects. While patients with milder airway disease may benefit from serum concentrations less than 10 mg/L, the greatest likelihood of obtaining maximal bronchodilatation with reasonable safety is achieved with peak serum concentrations between 10 mg/L to 20 mg/L.4-7 Serum concentrations of 6 mg/L to 12 mg/L are recommended when treating patients for apnea.8 Doses required to maintain theophylline concentrations within these ranges vary greatly due to large individual differences in theophylline metabolism.8-14

Undesirable side effects, including headaches, dizziness, nervousness, insomnia, anorexia, nausea, vomiting, and epigastric pain have been associated with serum theophylline concentrations which exceed the recommended therapeutic range.15-19

Concentrations greater than 30 mg/L carry an increased risk of more serious side effects, including hypokalemia, cardiac dysrhythmia, and seizures.18-22 Although seizures are uncommon at concentrations less than 40 mg/L,15,17 there is not a strong correlation between serum concentration and risk of seizures. Seizures have occurred in patients with serum concentrations less than 20 mg/L,17 in contrast, individuals have tolerated serum levels greater than 120 mg/L with no seizure activity.19 Typically, seizures are preceded by other side effects such as insomnia, irritability, nausea, and vomiting. However, in rare instances seizures may be the first manifestation of theophylline toxicity displayed by a patient. Seizures associated with theophylline toxicity may be refractory to anticonvulsant therapy, and a high incidence of severe residual neurologic deficits and death has been reported among patients with this problem.20

Theophylline metabolism may be inhibited during acute viral illness or with concurrent administration of certain drugs.23-28 Because metabolism by the liver is responsible for 90% of theophylline elimination, this inhibition may increase serum theophylline concentrations as much as twofold unless a commensurate dose reduction is instituted.29 The resulting rise in concentration may increase the risk of toxicity.

Theophylline accumulation to toxic levels in association with influenza virus26,27 and respiratory syncytial virus28 infections has been reported in pediatric patients previously stabilized on a specific dose. There is evidence that the acute febrile response per se may be more important in reducing drug metabolism than the specific etiologic agent. For example, the clearance of antipyrine, a drug metabolized by the liver, is reduced in the presence of etiocholanolone-induced noninfectious fever29 as well as fever associated with bacterial pneumonia.31 The mechanism by which drug metabolism is reduced may be related due to increased interferon production which occurs during the acute febrile response. Fever is considered the most practical clinical indication for reducing theophylline dose and for close monitoring of serum concentration since fever may be associated more closely with reduced theophylline clearance than the specific etiologic agent, and diagnosis of a specific viral etiology early in the illness rarely is feasible.

It is recommended that the dose be reduced by one half in children receiving chronic theophylline therapy who are febrile for more than 24 hours.7,32 Further dose adjustments should be based on serum concentration monitoring until the patients have recovered from their acute illnesses and are restabilized on their usual doses. Alternatively, the physician may consider treating the asthmatic patient with other bronchodilators and discontinuing theophylline.

Another area of concern for patients receiving theophylline relates to drug-drug interactions.23-25 Two drugs that are commonly prescribed for pediatric patients which are known to interfere with theophylline metabolism are erythromycin33-40 and cimetidine.41-44 Additional drugs which are known to interfere with theophylline metabolism are listed in the Table.23-25 These drugs should be avoided in patients who are receiving chronic theophylline therapy. If concurrent use is absolutely necessary, the dose of theophylline should be decreased by one half and subsequently adjusted based on serum concentration monitoring. In addition, it is advisable to check serum theophylline concentrations within 24 hours after starting any new concurrently administered medica-

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

TABLE. Drugs Reported to Inhibit Metabolism of Theophylline\(^{1,3,4}\) (Listed in Alphabetical Order by Generic Name)

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<th>Drug</th>
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<tr>
<td>Allopurinol</td>
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<td>Cimetidine</td>
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<td>Ciprofloxacin</td>
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<td>Diltiazem</td>
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<td>Disulfiram</td>
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<td>Enoxacin</td>
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<td>Idroclamide</td>
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Summary and Recommendations

1. Theophylline continues to be an important adjunct in the management of reactive airway diseases and central apnea in pediatric patients.
2. Theophylline metabolism may be reduced in the presence of acute febrile illnesses and certain concurrently administered medications which inhibit theophylline metabolism, thereby increasing the risk of toxicity if the dose is not reduced.
3. The dose of theophylline should be reduced by one half in patients who are febrile for longer than 24 hours. Further dose adjustments should be based on serum concentration monitoring until the patients have recovered from their acute illness and are restabilized on their usual dosages.
4. The concurrent administration of drugs which interfere with theophylline metabolism (Table) should be avoided. If concurrent use is necessary, the dose of theophylline should be decreased by one half and subsequently adjusted based on serum concentration monitoring.
5. It is advisable to check the serum theophylline concentration within 24 hours after beginning any new concurrently administered medication for which there is no specific information regarding interactions with theophylline.

Committee on Drugs, 1991 to 1992
Ralph E. Kaufman, MD, Chairman
William Banner, Jr, MD
Cheston Berlin, Jr, MD
Jeffrey L. Blumer, MD, PhD
Richard L. Gorman, MD
George H. Lambert, MD
Geraldine S. Wilson, MD

Liaison Representatives
Donald R. Bennett MD, PhD, American Medical Association
Jose F. Cordero, MD, MPH, Centers for Disease Control
Paul G. Tomich, MD, American College of Obstetricians and Gynecologists
Sam A. Licata, MD, Canadian Paediatric Society
Paul Kaufman, MD, Pharmaceutical Manufacturers' Association
Gloria Troendle, MD, Food and Drug Administration
Sumner J. Yaife, MD, National Institutes of Health
AAP Section Liaison
Charles J. Coté, MD, Section on Anesthesiology
Consultants
Mary Ellen Mortensen, MD
Wayne Snodgrass, MD, PhD
Anthony R. Temple, MD
Stanley J. Szefler, MD
Miles M. Weinberger, MD
AAP Section Consultant
David G. Tinkelman, MD
Chairman, Section on Allergy and Immunology

References
32. Weinberger M. *Managing Asthma.* Baltimore, MD: Williams & Wilkins; 1990:89
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