CHAPTER 20

THEOPHYLLINE

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Theophylline is a bronchial smooth muscle relaxant used in the treatment of asthma and other respiratory diseases. There are various proposed mechanisms of action of theophylline, including phosphodiesterase inhibition, adenosine receptor antagonism, histone deacetylase activation, apoptosis of inflammatory cells (e.g., neutrophils and T cells), and increased interleukin secretion.[1] As methylxanthines, theophylline and caffeine are also used to treat apnea, bradycardia, and weaning from the ventilator in neonates.[2,3] The use of theophylline has decreased considerably over the past 25 yr due to the development and use of more effective treatments, particularly for asthma in children and adults. However, theophylline still continues to have a role when patients fail to respond to preferred agents such as inhaled corticosteroids and long-acting beta agonists for chronic management. Additionally, aminophylline is used as an tertiary alternative in cases of failed response to inhaled beta2-agonists and systemic corticosteroids for status asthmaticus.[4-7] A series of Cochrane Collaborative reviews established that theophylline:

- is an effective preventive treatment for childhood asthma, although less effective and with a higher side-effect profile than inhaled corticsteroids[8];
- should not be used in the treatment of exacerbations of chronic obstructive pulmonary disease (COPD)[5]; improves lung function and levels of oxygen and carbon dioxide in the blood of patients with COPD, who prefer it over placebo despite side effects[6];
- is useful in extubating small preterm infants (<1000 g) in their first week of life[9]; and,
- has similar effects to caffeine for treating apnea in preterm infants, but has a narrower therapeutic range and shorter half-life and is thus potentially less useful once caffeine can be administered.[10]

Although some evidence from the Cochrane Collaborative demonstrates its use in the chronic management of childhood asthma, theophylline is not a preferred treatment for asthma for all ages.[5,8] In fact, according to the National Asthma Education and Prevention Program, sustained-release theophylline (immediate release is not recommended) is considered a nonpreferred, alternative adjunctive maintenance treatment for asthma in older children (>5 yr) and adults.[3,5] Additionally, methylxanthines such as aminophylline are not preferred alternative agents for treatment of asthma exacerbations compared to intravenous (IV) magnesium sulfate due to increased adverse effects and potential longer length of stay and time for symptom improvement.[5,11] Data comparing efficacy and safety of aminophylline compared to IV beta2-agonists remain limited and do not provide evidence of an additive effect to acute therapy such as inhaled beta2-agonists.[11,13]

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS[14]

The following dose recommendations are suggested to achieve theophylline concentrations of 5–10 mg/L in the neonate and approximately 10 mg/L in all other patient populations. Dosage adjustment should be based on an assessment of serum concentration and the patient's clinical status. For example, a concentration of 10 mg/L may be considered within normal limits; however, if a patient remains symptomatic, dosage increases may still be necessary to reach concentrations up to 15 mg/L for effect. Also noteworthy is that additional care is advised in individualizing dosing for neonates due to greater potential for toxicity secondary to age-dependent pharmacokinetic differences in metabolism and

clearance (CL). Caution is required when dosing patients who are unhealthy (e.g., critically ill), who smoke, or who are on other medications known to alter theophylline CL (see drug–drug interactions and drug–disease state or condition interactions sections).

Loading dose[5,14]

The suggested loading dose of theophylline for patients without a history of theophylline use is 5 mg/kg/dose (~6 mg/kg/dose of aminophylline). If the patient has been receiving theophylline, it is advisable to first measure a concentration and then base the loading dose on the difference needed to achieve a desired concentration change. Generally, an increase of approximately 1 mg/L in concentration will occur with every 0.5 mg/kg/dose of theophylline in a loading dose, based on ideal body weight (IBW). This generalization is based on a V of 0.5 L/kg; however, note that V varies based on age, with reported ranges of 0.3–0.7 L/kg. Only rapid or immediate-release products should be used for oral loading doses, and IV doses are generally given over 20–30 min. The National Asthma Education and Prevention Program stated that in the emergency department "theophylline/aminophylline is not recommended because it appears to provide no additional benefit to optimal inhaled beta2-agonist therapy and may increase adverse effects."[5] Thus, at least for the emergency treatment of asthma, loading doses would not be warranted. The use of IV aminophylline has been noted in the critical care setting for management of acute asthma when conventional, preferred agents (i.e., inhaled short-acting beta2-agonist and systemic corticosteroid) and primary alternatives (i.e., magnesium sulfate) fail to provide sufficient response.[5,7,11]

Maintenance dose[14–16]

All doses in **Table 20-1** are expressed in terms of anhydrous theophylline and should be converted to the proper dosage if aminophylline or another salt form is administered. The doses suggested represent the recommended starting and usual maximum dose. Further dosing should be individualized based on the patient's therapeutic response and measured steady state theophylline concentration. A patient's theophylline CL can be calculated from a properly measured concentration and dosing history, and a patient-specific dose can then be determined based on the actual CL.

DOSAGE FORM AVAILABILITY[14,19]

Theophylline products are available in different salt forms and different delivery forms (IV, oral liquids including syrups and elixirs, regular-release tablets and capsules, suppositories, and extended- and sustained-release tablets and capsules). When converting from one product to another, both theophylline salt (S) equivalence (**Table 20-2)** and bioavailability (**Table 20-3**) should be considered.

GENERAL PHARMACOKINETIC INFORMATION

Absorption

The bioavailability of theophylline depends on its formulation and route of administration.[14,19-21] With few exceptions, the bioavailability for most theophylline products is quite good (90% to 100%). The absorption of theophylline can be delayed by intake of food; however, the extent of absorption is unchanged.[14] When a patient is changed from IV to oral therapy, the maintenance infusion should be stopped and oral therapy should begin immediately.[21] Table 20-3 provides the bioavailability percent [fraction (F) of dose] that is theophylline and comments for various products.

Distribution

Theophylline is not distributed into fatty tissue; therefore, for obese patients, IBW should be used in the calculation of doses. **Table 20-4** provides the population volumes of distribution for various age groups. Theophylline has been reported to distribute in the saliva with reports of saliva concentrations ranging from 50% to 100% of serum concentrations.[14,22] Correlation of salivary and serum theophylline