

associated with IgE-mediated release of histamine which can be inhibited with antihistamines. *Delayed cold urticaria* is a rare disease consisting of a painful induration occurring 12 to 24 hours after local cold exposure.

The treatment of urticaria induced by physical agents should be based primarily on removal of the cause. As with patients with other types of urticaria, these patients should be advised to minimize their exposure to alcohol, heat, acetylsalicylic acid, exertion and emotional stress. Topical agents and corticosteroids as well as attempts to desensitize patients with allergens are of no help in these situations. Appropriate sun screens may be of value in patients with solar urticaria, and antihistamines, including cyproheptadine and hydroxyzine, are of particular value in patients with dermatographia, cholinergic urticaria or cold urticaria.

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**Factors That Influence Theophylline Metabolism**

MANY ALLERGISTS in the United States consider theophylline to be the initial bronchodilator of choice. Serum levels of theophylline of 7 to 20  $\mu\text{g}$  per ml are generally accepted as therapeutic. Although symptoms of toxicity may occur when the level of theophylline in the serum is in the therapeutic range, toxicity is generally associated with levels in excess of 20  $\mu\text{g}$  per ml. It is incumbent on the physician using this valuable but potentially toxic drug to appreciate the number of factors that influence its biotransformation and clearance.

*Body Weight*

The apparent volume of distribution for theophylline is reduced in obese patients. When calculating dosage, one must use a patient's ideal weight to avoid toxicity.

*Age*

The dosage of theophylline required for children less than 1 year of age varies greatly. In this group, monitoring of serum levels of theophylline may be required to avoid problems with toxicity.

Children 1 to 8 years of age have average plasma clearance values above those noted for adults. The recommended oral dose for this group varies from 16 to 24 mg per kg of body weight per day. For those between 9 and 16 years of age, the recommended oral dose is 16 to 20 mg, and for adults it is 9.6 to 19 mg per kg of body weight per day.

*Diet*

Dietary methylxanthines, particularly caffeine, have been shown to interfere with theophylline elimination in normal persons. A decrease in theophylline elimination has also been noted in patients on high carbohydrate-low protein diets while a high protein-low carbohydrate diet increases theophylline elimination. Charcoal-broiled foods with a high polycyclic carbon content may increase the rate of theophylline biotransformation.

*Diseases Altering Theophylline Metabolism*

Theophylline clearance is affected by a variety of diseases involving the cardiorespiratory systems and the liver. These include congestive heart failure, acute pulmonary edema, chronic obstructive pulmonary disease, pneumonia, and cirrhosis and other hepatic diseases. Reduction in the dose of theophylline administered to these patients and careful monitoring of serum theophylline levels is required for proper management. Acute febrile illness has also been reported as a cause of transient increase in serum theophylline levels.

*Smoking*

In cigarette and marijuana smokers, there is a faster plasma theophylline clearance and a shorter half-life than in nonsmokers. Jusko and co-workers have shown that an additive increase in theophylline clearance occurs in those who smoke both substances.

An approximate reduction of 50 percent in theophylline clearance has been reported in patients who were receiving troleandomycin (250 mg four times daily). A similar but less pronounced effect due to erythromycin has been reported recently and appears due to reduced clearance and consequent prolonged half-life of theophylline. A reduction in theophylline dose is necessary for patients already receiving high-dose treatment when erythromycin or troleandomycin is coadministered. The possibility of other, as yet unrecognized, drug interactions with theophylline must be appreciated. If symptoms suggestive

of theophylline toxicity occur, a careful review of medications being administered should be made and the theophylline kinetics studied.

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**Gastroesophageal Reflux and Asthma**

RESPIRATORY MANIFESTATIONS of gastroesophageal (GE) reflux are increasingly being reported. In children and infants, reflux has been associated with bronchiolitis, pneumonitis and failure to thrive, while in adults bronchitis, laryngitis, bronchiectasis, atelectasis, fibrosis, pneumonia and intractable asthma are reported complications. The theories proposed to explain how GE reflux may cause or exacerbate asthma are: (1) microaspiration of gastric contents resulting in an exudative mucosal reaction, (2) vagal reflex arc from the esophagus to the lungs causing bronchoconstriction and (3) nonspecific irritant effect of microaspirates on a hyperactive bronchial airway.

The principal support of GE reflux-inducing asthma has come from reports of an increased association between hiatus hernia and asthma, and improvement of the respiratory systems following medical or surgical antireflux procedures. Unequivocal evidence that microaspiration occurs

is lacking, but a recent study using a radioisotope technique showed gastropulmonary aspiration in two patients. Airway resistance increases after intraesophageal acid instillation in some asthma patients, in agreement with the vagal reflex arc theory.

GE reflux can be detected by techniques ranging from routine upper gastrointestinal series to more sensitive methods of cineradiography, esophagoscopy with biopsy, acid probe pH determination, acid perfusion study, esophageal manometry and isotope scintiscanning. University agreement on the criteria for diagnosing reflux is lacking. Further studies are needed to delineate the exact role of GE reflux in the pathophysiology of certain respiratory diseases. Until then clinicians should consider the diagnosis of GE reflux particularly in patients with recurrent pneumonitis or nocturnal asthma who also have gastrointestinal distress. Treatment is directed against factors that tend to decrease lower esophageal pressure, including smoking, the use of drugs such as theophylline, and the presence of anatomic abnormalities.

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