Clinical Pharmacology Update
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Theophylline and its interactions[1]

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Drug-drug interactions and drug-disease interactions can substantially affect the elimination/metabolism of theophylline resulting in the potential for undertreatment or serious theophylline toxicity. Macrolide antibiotics, including troleandomycin and erythromycin, cimetidine, and allopurinol, have the capability of decreasing theophylline clearance with resulting increased serum levels, while phenytoin increases theophylline clearance. Drug-disease interactions of theophylline with cirrhosis, congestive heart failure, chronic obstructive pulmonary disease, and acute infections result in impaired clearance with increased serum levels and the potential for serious theophylline toxicity. Other factors, including smoking, which cause a marked increase in clearance, and diet, also play a role. In these situations, serum theophylline monitoring is advised.

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Theophylline (and its ethylenediamine salt, aminophylline) is an important and fundamental treatment for acute and chronic bronchospasm associated with a variety of illnesses, although its mechanism of action is still poorly understood. Its usefulness was demonstrated more than 60 years ago,[1] and guidelines for its administration, including a description of several now well-recognized adverse effects, were subsequently reported in 1937.[2] It has a low therapeutic index, a poor correlation between dose and effects, and a potential for serious toxicity. Its administration frequently has resulted in adverse effects. Theophylline-induced seizures, for example, are resistant to usual forms of treatment and can be associated with a 50% mortality.[3] With improved understanding of the factors important in optimal dosing, including therapeutic drug monitoring, the frequency of adverse effects can be minimized while achieving optimal bronchodilatation.[4]

Evaluation of adverse drug reactions (and drug-disease interactions) is difficult[5]; this is also true in the case of theophylline. Associated diseases and concomitant drug therapy can affect the disposition of theophylline resulting in the potential for overdosing and, less frequently, underdosing. Some reviews have included suggestions for alterations in theophylline dosing based, in some instances, on sparse information, extrapolation of data from children to adults (which may or may not be appropriate because of age-related differences in pharmacokinetics), studies of short-term drug administration, or drug doses infrequently used in clinical practice. This article will review some of the interactions believed to

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be of practical importance and clinical significance in prescribing theophylline.

Theophylline disposition

Although many factors can affect the pharmacokinetics of theophylline resulting in many interindividual variations,[6] its essential pharmacokinetic features are outlined in *Table 1*; for convenience, the numbers are rounded off and averages given.

The amount of theophylline per tablet and extent of absorption varies with the preparation, although sustained-release anhydrous theophylline preparations are essentially completely absorbed.[7] Aminophylline is the ethylenediamine salt of theophylline and contains 80% theophylline. Protein binding ranges from 53% to 65% and may vary with age and underlying disease.[6] Theophylline is eliminated primarily by liver metabolism via parallel zero-order and first-order pathways to several well-recognized metabolites[8] using the mixed-function oxidase system; the activity of this system is inducible by administration of certain drugs[9] and environmental chemicals.[10] There is evidence that the elimination of theophylline follows, at least in part, nonlinear zero-order elimination kinetics.[11] The hepatic extraction ratio for theophylline is low (about 0.1); therefore, its elimination is not likely to be dependent on changes in hepatic blood flow.

Drug-drug interactions

Several medications can substantially alter the disposition of theophylline and serve as a potential source of variation in theophylline disposition (*Table 2*). Concomitant drug therapy, therefore, has the potential for causing significant increase or decrease in theophylline blood levels and clinical response.

Antibiotics

Antibiotics may be prescribed for treatment of acute respiratory infections in asthmatic patients who are taking theophylline to control chronic bronchospasm. The macrolide antibiotics troleandomycin and erythromycin can alter theophylline elimination, although the mechanisms are as yet unclear. The clearance of theophylline decreased by 50% when troleandomycin was concomitantly administered in a series of patients including 1 in whom theophylline-associated seizures developed.[12] Based on these findings, it has been recommended that in this situation the dose of theophylline be reduced by 50%. This impaired clearance explains, at least in part, the previously reported benefit of this infrequently prescribed antibiotic in controlling symptoms of asthma.[13] Erythromycin is one of the more commonly prescribed antibiotics for outpatient therapy.[14] Although initially controversial, it now appears that giving enough erythromycin (1 g daily) long enough (a week or more) reduces the clearance of theophylline by about 25%.[15] This effect is less than that of troleandomycin, but is large enough to be clinically significant. How long this altered clearance continues after discontinuing erythromycin is unknown. The effect of co-administration of other antibiotics with theophylline is less clear. In one study in which short-term administration of erythromycin showed no significant change in theophylline disposition, a similar lack of change was noted for tetracycline and cephalexin[16]; it is not clear what effects long-term dosing may have had. Although ampicillin has been reported to have no effect on the half-life of theophylline in infants and young children,[17] (a group that characteristically eliminates theophylline rapidly), extrapolation of these results to adults must be viewed with caution. Little or no data are otherwise available concerning these interactions in adults. In summary, macrolide antibiotics have been shown to alter the elimination of theophylline in adults, but data regarding interactions with other antibiotics is sparse and inconclusive. The dose of theophylline may need to be reduced by 50% in the case of concomitant administration of troleandomycin and 25% in the case of erythromycin. Serum theophylline levels may be a helpful guide, particularly when co-administering less well-studied antibiotics.

H_2-receptor antagonists

As theophylline can cause several gastrointestinal symptoms, cimetidine may be prescribed for treatment. Cimetidine has been found to impair elimination of a wide variety of drugs.[18] In clinically useful dosages, the impairment of elimination occurs independently of its H_2-receptor antagonism properties, probably acting as an inhibitor of the mixed-function oxidase system.[19] A

study of healthy, normal volunteers revealed that cimetidine in usual doses for eight days prolonged the elimination half-life of theophylline by 64%, and clearance diminished by 30%, although there was wide interpatient variation.[20]

The effects of cimetidine versus ranitidine on theophylline disposition have also been studied.[21] Cimetidine in a dose of 1,200 mg daily, again, had profound effects, increasing the half-life of theophylline from 5.7 to 9.2 hours with a 36% decrease in theophylline clearance. Ranitidine (300 mg daily), however, did not alter theophylline disposition. Although further study may be required, based on current information, if an H_2-receptor antagonist is indicated for a patient on chronic theophylline therapy, ranitidine should be prescribed.

Table 1. Pharmacokinetic profile of theophylline

Bioavailability	96% (some 100%)
Urinary excretion	10%
% Protein bound	50%
Clearance	0.70 mL/min/kg
Hepatic extraction ratio	0.1
Volume of distribution	0.50 L/kg
Elimination half-life	3–9 hr (6)
Effective concentration	10–20 μg/mL
Potentially toxic concentration	>20 μg/mL
Routes of elimination	
Renal	10%
Metabolic	90%
Active metabolite	3-Methylxanthine

Table 2. Drugs affecting theophylline disposition

Drug	Potential effect on theophylline level
Macrolide antibiotics	↑
Erythromycin	
Troleandomycin	
Cimetidine*	↑
Phenytoin	↓
Allopurinol	↑
Phenobarbital	? Significance
Propranolol	↑
Influenza vaccine	↑

* But not ranitidine.

Phenytoin

Phenytoin is a well-known inducer of hepatic mixed-function oxidases and could, therefore, affect the clearance of theophylline. In an elegant study, it was found that phenytoin (300 mg daily) increased the clearance of theophylline by about 60% with a 50% decrease in elimination half-life.[22] Similar results were obtained in a follow-up study, which also examined urinary excretion of theophylline metabolites.[23] Based on these findings, it is apparent that adding phenytoin to a patient's regimen of theophylline may cause theophylline levels to fall below optimal concentrations. If co-administration of phenytoin is necessary, the dose of theophylline should be increased by 50% or more with careful monitoring of theophylline levels.

The above drug-drug interactions are generally accepted as causing clinically significant changes in theophylline disposition. Many other interactions have been described, although their clinical significance has not been substantiated or is of uncertain importance.

Allopurinol

As the elimination of theophylline may proceed in part via xanthine oxidase, allopurinol could conceivably affect theophylline elimination. Short-term administration of allopurinol (300 mg daily) was found to have no effect on theophylline clearance.[24] Doses twice that commonly used (600 mg daily for 14 days) decreased theophylline clearance by 21%.[25]

Barbiturates

Phenobarbital is also a potent microsomal mixed-function oxidase inducer and has been combined with theophylline in combination tablets. The use of such combination tablets has been correctly criticized for several reasons, including lack of flexibility in dosing regimens, and of equal importance, ineffectiveness of such added ingredients. The use of such combination tablets for chronic asthma treatment should be abandoned.[7]

Whether or not phenobarbital can affect theophylline disposition has been a matter of controversy. It appears, however, that phenobarbital in doses of 90 mg daily (as might be used to treat seizure disorders) can increase theophylline clearance and, as a result, lower theophylline levels.[26]

Beta blockers

It is most unlikely that beta blockers would be used in a patient with asthma because of their ability to precipitate bronchospasm in susceptible patients. Propranolol, however, has been shown to reduce theophylline clearance, especially in patients whose clearance has been previously enhanced by cigarette smoking.[27]

Halothane

When surgery is required for a patient on maintenance theophylline, special precautions may be necessary. The arrhythmogenic effect of theophylline may be potentiated when halothane anesthesia is used, resulting in potentially serious ventricular arrhythmias.[28]

Drug-disease interactions

Associated diseases can also, in certain instances, profoundly affect the elimination of theophylline (*Table 3*). Generally, these drug-disease interactions cause alterations in theophylline elimination, presumably because of impairment in the ability of the liver to metabolize theophylline.

Cirrhosis

Marked alterations in theophylline disposition have been shown to occur in patients with cirrhosis. For example, in a study of adult patients with alcoholic cirrhosis, the mean half-life of theophylline increased more than threefold (6.7 hours in controls versus 25.6 hours in cirrhotics).[29] In another study, which examined multiple determinants in theophylline elimination, liver disease was found to be the most important determinant in altering theophylline clearance in patients more than 40 years old.[30] A fourfold increase in the elimination half-life (from a mean of 6.0 hours in controls to 28.8 hours in cirrhotics) and a corresponding decrease in clearance (63.0 mL/kg/hr in normals and 18.8 mL/kg/hr in cirrhotics) was found in another study, which also pointed out that these changes were most prominent in biopsy-proved cirrhosis as opposed to cirrhosis suspected on clinical grounds.[31] Acute hepatitis can also cause similar changes but to a lesser degree.[32]

Heart failure

Bronchospasm may be a notable feature in patients with congestive heart failure and, in particular, acute pulmonary edema; intravenous aminophylline may afford some relief in conjunction with other conventional medications. However, in this setting also, theophylline elimination may be unpredictable, resulting in potential toxicity. In a study reviewing theophylline disposition in acutely ill patients, theophylline clearance was reduced by 43% in patients with congestive heart failure[33]; usual maintenance doses of aminophylline would, therefore, cause potentially toxic levels. Just as important, as the signs of congestive heart failure cleared, theophylline clearance increased. The severity of congestive heart failure may play an important role; those with mild symptoms may show little or no change in theophylline clearance, whereas those with moderate or severe findings may have marked changes.[30] The patient with acute pulmonary edema is even more difficult to evaluate for theophylline dosing. One study showed not only reduced elimination of theophylline by a factor of three, but also a 20-fold variation in clearance and half-life.[34] Again, monitoring serum theophylline levels is, therefore, mandatory if optimal dosing in this common setting is to be achieved. The implications of these studies are clear. Infusion rates of maintenance theophylline and oral-dosing regimens for patients with congestive heart failure should be reduced by about 40%.[33] In this situation, and in pulmonary edema in particular, serum theophylline level monitoring is essential not only because of marked alterations in elimination, but also because of large interindividual variations.

Age

As a drug eliminated primarily by metabolism, one might infer that as the ability of the liver to metabolize drugs declines with age,[35] the elimination of theophylline would also decline; several studies have shown this to be the case. In evaluating several factors that may alter theophylline disposition, advancing age correlated with decreasing theophylline clearance.[30] When clearance of unbound theophylline was measured in a group of elderly patients, significant decreases were found.[36] However, not all studies have confirmed this variation.[37,38] The geriatric patient may, in fact, be more at risk from adverse reactions to theophylline due to associated diseases that affect theophylline disposition rather than the effects of age on drug elimination. It is im-

portant to evaluate patients on an individual basis and consider all factors that may alter drug disposition.

Fever

Acute infectious illness and fever have been reported to diminish theophylline elimination.[39,40] However, these brief reports have not been confirmed, and in one report,[41] the patients were children; extrapolating these results to adults may or may not be applicable. Based on a study[33] showing that pneumonia in adults decreases theophylline elimination, it was recommended that the dose of maintenance aminophylline be reduced by a factor of 40%. Influenza vaccination has been reported to cause a substantial increase in theophylline half-life.[42]

Chronic obstructive pulmonary disease

Theophylline may benefit patients with chronic obstructive pulmonary disease (COPD), not only because of its bronchodilating effects, but also because it diminishes diaphragmatic fatigue and improves contractility.[43] In a study that examined the disposition of theophylline in acutely ill patients, the clearance of theophylline was reduced to about 80% of normal in patients with severe airways obstruction.[30]

Other interactions (*Table 4*)

Smoking

Cigarette smoke contains certain polycyclic hydrocarbons, which are potent inducers of drug-oxidizing systems involved in the metabolism of theophylline.[10] Studies have shown that smokers eliminate theophylline more rapidly with clearance rates increasing more than twofold.[44] This increased clearance is further enhanced by smoking marijuana.[45] Based on such studies, it has been recommended that in these situations the theophylline maintenance dose be increased by a factor of 1.6.[33]

Dietary factors

A diet containing twice daily portions of charcoal-broiled beef for five days decreased theophylline half-life by more than 20%[46]; presumably this occurs also by inducing drug-oxidizing ability of the liver by polycyclic hydrocarbons formed as food is cooked over charcoal.[47] Proportions of protein and carbohydrates in the diet may also alter theophylline disposition. A high-protein, low-carbohydrate diet may cause a decline in theophylline half-life, whereas a low-protein, high-carbohydrate diet may produce an opposite effect.[48] Dietary methylxanthines, the main one of which is caffeine, compete with theophylline for the same drug-metabolizing systems. One study has shown, for example, that the half-life of theophylline declined to a slight but significant degree after a one-week period on a xanthine-free diet.[49] Taking a new once-a-day theophylline preparation with a diet high in fat content may cause potentially toxic symptoms.[7] These dietary factors may explain some interindividual variations in theophylline disposition. Considered alone, however, it is unlikely that they substantially affect the elimination of theophylline in patients on a day-to-day basis.

Table 3. Diseases and conditions affecting theophylline disposition

Disease or condition	Potential effect on theophylline level
Hepatic disease	↑
Congestive heart failure (acute pulmonary edema)	↑
Old age	?
COPD	↑
Respiratory infections	↑

COPD = chronic obstructive pulmonary disease.

Table 4. Other factors affecting theophylline disposition

Factor	Potential effect on theophylline level
Cigarette smoking	↓
Marijuana smoking	↓
Charcoal-broiled foods	↓
High protein diet	↓
Dietary methylxanthines	↑
Genetic factors	?

Table 5. Modifications of theophylline maintenance dose[33, 52]

Associated disease or factor	Dose factor
Nonsmoker	1.0
Smoker	1.6
Congestive heart failure	0.4
Pneumonia	0.4
Cirrhosis	0.4
Severe airways obstruction	0.8

Genetic variation

In order to explain interindividual differences in theophylline kinetics, the question has been raised as to whether there may be some genetic basis for these perturbations. Genetic factors probably are not significant, although an inherited trait for prolonged theophylline elimination has been reported in one family.[50] No association has been found with known pharmacogenetic variations such as those associated with the metabolism of debrisoquine and sparteine.[51]

Discussion

When prescribing and estimating dosages of medications, it is assumed that the patient receiving such medications will absorb, distribute, and eliminate the medications in a fashion similar to those from whom standard dosing regimens have been derived. However, large intersubject and intrasubject variation in drug disposition may occur. As this review indicates, multiple factors can affect the disposition of theophylline, some of which cause substantial variations resulting in the potential for serious toxicity; others are of lesser clinical importance, but can explain some interindividual variations in theophylline disposition.

Several important points should be kept in mind when prescribing theophylline or administering aminophylline. Included are the interactions with macrolide antibiotics, cimetidine, and allopurinol, all of which interfere with theophylline elimination with a potential for increased serum levels. Since phenytoin increases elimination, the dose of theophylline should be increased; conversely, if phenytoin is discontinued the dose of theophylline should be decreased.

Impaired hepatic elimination caused by liver disease, congestive heart failure, or old age have the potential for significantly increased serum levels and for serious toxicity. Smoking, conversely, increases elimination and can, therefore, result in underdosing.

Given all these variables, how can theophylline be safely prescribed in complex clinical situations? Powell et al[33] has proposed a scheme, taking all these factors into account, and this has been further elaborated by Mungal[52] (*Table 5*). Maintenance doses of aminophylline or theophylline should be increased by a factor of 1.6 for smokers. For patients with congestive heart failure or pneumonia, the dose should be reduced by a factor of 0.4. In the presence of severe COPD, it should be reduced by a factor of 0.8 and for cirrhotics by 0.4. For example, a 70-kg patient might ordinarily, after an appropriate loading dose, receive 40 mg/hr as maintenance infusion of aminophylline (70 kg × 0.6 mg/kg/hr = 42 mg/hr or 40 mg/hr). If such a patient also has severe COPD and pneumonia, the initial maintenance infusion should be decreased to 13 mg/hr [40 mg/hr × 0.8 (for severe COPD) × 0.4 (for pneumonia) = 12.8 or 13 mg/hr]. Although these sorts of calculations and guidelines are based on reasonable estimates, monitoring theophylline levels is essential for optimal therapy.

When prescribing a drug such as theophylline with its low therapeutic index and poor correlation between dose and effect, the many factors that affect its disposition must be considered; monitoring theophylline levels is mandatory in these situations. No one person can keep in mind all the factors that potentially cause underdosing or overdosing for all drugs used on a daily basis, many times in complex clinical situations. When questions arise or circumstances occur in which alterations in theophylline disposition may result in underdosing or overdosing, reference should be made to drug information resources and the use of theophylline drug levels.

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References

1. Hirsch S. Klinischer und experimenteller Beitrag zur krampflösenden Wirkung der Purinderivate. Klin Wochenschr 1922; **1**:615–618.
2. Herrmann G, Aynesworth MB. Successful treatment of persistent extreme dyspnea "status asthmaticus"; use of theophylline ethylene diamine (aminophylline, USP) intravenously. J Lab Clin Med 1937; **23**:135–148.
3. Zwillich CW, Sutton FD Jr, Neff TA, Cohn WM, Matthay

RA, Weinberger MM. Theophylline-induced seizures in adults, correlation with serum concentrations. Ann Intern Med 1975; **82:**784–787.
4. Jacobs MH, Senior RM. Kessler G. Clinical experience with theophylline: relationships between dosage, serum concentration and toxicity. JAMA 1976; **235:**1983–1986.
5. Blanc S, Leuenberger P, Berger JP, Brooke EM, Schelling JL. Judgements of trained observers on adverse drug reactions. Clin Pharmacol Ther 1979; **25:**493–498.
6. Ogilvie RI. Clinical pharmacokinetics of theophylline. Clin Pharmacokinet 1978; **3:**267–293.
7. Hendeles L, Iafrate RP, Weinberger M. A clinical and pharmacokinetic basis for the selection and use of slow release theophylline products. Clin Pharmacokinet 1984; **9:**95–135.
8. Jenne JW, Nagasawa HT, Thompson RD. Relationship of urinary metabolites of theophylline to serum theophylline levels. Clin Pharmacol Ther 1976; **19:**375–381.
9. Goldberg DM. The expanding role of microsomal enzyme induction and its implications for clinical chemistry. Clin Chem 1980; **26:**691–699.
10. Conney AH, Burns JJ. Metabolic interactions among environmental chemicals and drugs. Science 1972; **178:**576–586.
11. Tang-Liu DD-S, Williams RL, Riegelman S. Nonlinear theophylline elimination. Clin Pharmacol Ther 1982; **31:**358–369.
12. Weinberger M, Hudgel D, Spector S, Chidsey C. Inhibition of theophylline clearance by troleandomycin. J Allergy Clin Immunol 1977; **59:**228–231.
13. Zeiger RS, Schatz M, Sperling W, Simon RA, Stevenson DD. Efficacy of troleandomycin in outpatients with severe, corticosteroid-dependent asthma. J Allergy Clin Immunol 1980; **66:**438–446.
14. Baum C, Kennedy DL, Forbes MB, Jones JK. Drug use and expenditures in 1982. JAMA 1985; **253:**382–386.
15. Prince RA, Wing DS, Weinberger MM, Hendeles LS, Riegelman S. Effect of erythromycin on theophylline kinetics. J Allergy Clin Immunol 1981; **68:**427–431.
16. Pfeifer HJ, Greenblatt DJ, Friedman P. Effects of three antibiotics on theophylline kinetics. Clin Pharmacol Ther 1979; **26:**36–40.
17. Kadlec GJ, Ha LT, Jarboe CH, Richards D, Karibo JM. Effect of ampicillin on theophylline half-life in infants and young children. South Med J 1978; **71:**1584.
18. Bauman JH, Kimelblatt BJ. Cimetidine as an inhibitor of drug metabolism: therapeutic implications and review of the literature. Drug Intell Clin Pharm 1982; **16:**380–386.
19. Breen KJ, Bury R, Desmond PV, et al. Effects of cimetidine and ranitidine on hepatic drug metabolism. Clin Pharmacol Ther 1982; **31:**297–300.
20. Reitberg DP, Bernhard H, Schentag JJ. Alteration of theophylline clearance and half-life by cimetidine in normal volunteers. Ann Intern Med 1981; **95:**582–585.
21. Powell JR, Rogers JF, Wargin WA, Cross RE, Eshelman FN. Inhibition of theophylline clearance by cimetidine but not ranitidine. Arch Intern Med 1984; **144:**484–486.
22. Marquis J-F, Carruthers SG, Spence JD, Brownstone YS, Toogood JH. Phenytoin-theophylline interaction. N Engl J Med 1982; **307:**1189–1190.
23. Miller M, Cosgriff J, Kwong T, Morken DA. Influence of phenytoin on theophylline clearance. Clin Pharmacol Ther 1984; **35:**666–669.
24. Grygiel JJ, Wing LMH, Farkas J, Birkett DJ. Effects of allopurinol on theophylline metabolism and clearance. Clin Pharmacol Ther 1979; **26:**660–667.
25. Manfredi RL, Vesell ES. Inhibition of theophylline metabolism by long-term allopurinol administration. Clin Pharmacol Ther 1981; **29:**224–229.
26. Landay RA, Gonzalez MA, Taylor JC. Effect of phenobarbital on theophylline disposition. J Allergy Clin Immunol 1978; **62:**27–29.
27. Conrad KA, Nyman DW. Effects of metoprolol and propranolol on theophylline elimination. Clin Pharmacol Ther 1980; **28:**463–467.
28. Roizen MF, Stevens WC. Multiform ventricular tachycardia due to interaction of aminophylline and halothane. Anesth Analg (Cleve) 1978; **57:**738–741.
29. Piafsky KM, Sitar DS, Rangno RE, Ogilvie RI. Theophylline disposition in patients with hepatic cirrhosis. N Engl J Med 1977; **296:**1495–1497.
30. Jusko WJ, Gardner MJ, Mangione A, Schentag JJ, Koup JR, Vance JW. Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. J Pharm Sci 1979; **68:**1358–1366.
31. Mangione A, Imhoff TE, Lee RV, Shum LY, Jusko WJ. Pharmacokinetics of theophylline in hepatic disease. Chest 1978; **73:**616–622.
32. Staib AH, Schuppan D, Lissner R, Zilly W, von Bomhard G, Richter E. Pharmacokinetics and metabolism of theophylline in patients with liver diseases. Int J Clin Pharmacol Ther Toxicol 1980; **18:**500–502.
33. Powell JR, Vozeh S, Hopewell P, Costello J, Sheiner LB, Riegelman S. Theophylline disposition in acutely ill hospitalized patients. Am Rev Resp Dis 1978; **118:**229–238.
34. Piafsky KM, Sitar DS, Rangno RE, Ogilvie RI. Theophylline kinetics in acute pulmonary edema. Clin Pharmacol Ther 1977; **21:**310–316.
35. Greenblatt DJ, Sellers EM, Shader RI. Drug disposition in old age. N Engl J Med 1982; **306:**1081–1088.
36. Antal EJ, Kramer PA, Mercik SA, Chapron DJ, Lawson IR. Theophylline pharmacokinetics in advanced age. Br J Clin Pharmacol 1981; **12:**637–645.
37. Cusack B, Kelly JG, Lavan J, Noel J, O'Malley K. Theophylline kinetics in relation to age: the importance of smoking. Br J Clin Pharmacol 1980; **10:**109–114.
38. Fox RW, Samaan S, Bukantz SC, Lockey RF. Theophylline kinetics in a geriatric group. Clin Pharmacol Ther 1983; **34:**60–67.
39. Clark CJ, Boyd G. Theophylline pharmacokinetics during respiratory viral infection (letter). Lancet 1979; **1:**492.
40. Anolik R, Kolski GB, Schaible DH, Ratner J. Transient alteration of theophylline half-life: possible association with herpes simplex infection. Ann Allergy 1982; **49:**109–111.
41. Chang KC, Lauer BA, Bell TD, Chai H. Altered theophylline pharmacokinetics during acute respiratory viral illness. Lancet 1978; **1:**1132–1133.
42. Renton KW, Gray JD, Hall RI. Decreased elimination of theophylline after influenza vaccination. Can Med Assoc J 1980; **123:**288–290.
43. Murciano D, Aubier M, Lecocguic Y, Pariente R. Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. N Engl J Med 1984; **311:**349–353.
44. Hunt SN, Jusko WJ, Yurchak AM. Effect of smoking on theophylline disposition. Clin Pharmacol Ther 1976; **19:**546–551.
45. Jusko WJ, Schentag JJ, Clark JH, Garner M, Yurchak

AM. Enhanced biotransformation of theophylline in marihuana and tobacco smokers. Clin Pharmacol Ther 1978; **24:**406–410.
46. Kappas A, Alvares AP, Anderson KE, et al. Effect of charcoal-broiled beef on antipyrine and theophylline metabolism. Clin Pharmacol Ther 1978; **23:**445–450.
47. Conney AH, Pantuck EJ, Hsiao K-C, et al. Enhanced phenacetin metabolism in human subjects fed charcoal-broiled beef. Clin Pharmacol Ther 1976; **20:**633–642.
48. Kappas A, Anderson KE, Conney AH, Alvares AP. Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. Clin Pharmacol Ther 1976; **20:**643–653.
49. Monks TJ, Caldwell J, Smith RL. Influence of methylxanthine-containing foods on theophylline metabolism and kinetics. Clin Pharmacol Ther 1979; **26:**513–524.
50. Miller M, Opheim KE, Raisys VA, Motulsky AG. Theophylline metabolism: variation and genetics. Clin Pharmacol Ther 1984; **35:**170–182.
51. Dahlqvist R, Bertilsson L, Birkett DJ, Eichelbaum M, Säwe J, Sjöqvist F. Theophylline metabolism in relation to antipyrine, debrisoquine, and sparteine metabolism. Clin Pharmacol Ther 1984; **35:**815–821.
52. Mungall D. Theophylline. [In] Mungall D, ed. Applied Clinical Pharmacokinetics. New York, Raven Press, 1983, pp 127–152.