Lanterbine; Terbron; Terbuta; Tolbin†; Vida-Butaline; ***Hung.:*** Bricanyl; ***India:*** Bricanyl; ***Indon.:*** Astherin; Brasmatic; Bricasma; Forasma; Lasmalin; Nairet; Pulmobron; Relivan; Sedakter; Tabas; Terasma; Tismalin; Yarisma; ***Irl.:*** Bricanyl; ***Israel:*** Bricalin; Terbulin; ***Ital.:*** Bricanyl; ***Malaysia:*** Ataline; Bricanyl; Bucanil; Butaline; Butanil†; Terbron†; Terbulin†; Tolbin; ***Mex.:*** Bricanyl†; Tazikén†; Terbuken; ***Neth.:*** Bricanyl; Terbasmin; ***Norw.:*** Bricanyl; ***NZ:*** Bricanyl; ***Philipp.:*** Alloxygen; Astebron; Bricanyl; Bronchodam; Pulmonyl; Pulmoxcel; Terbulin; ***Port.:*** Bricanyl; ***S.Afr.:*** Bricanyl; ***Singapore:*** Ataline; Bricanyl; Bucanil†; Tolbin†; ***Spain:*** Tedipulmo; Terbasmin; ***Swed.:*** Bricanyl; ***Switz.:*** Bricanyl; ***Thai.:*** Asmaline; Asthmasian; Bricanyl; Broncholine; Bronchonyl; Bronco Asmo; Bucaril; Cencanyl; Med-Broncodil†; Proasma-T; Sulterline; Terbron†; Terbulin; Terbuno; Tolbin; Vacanyl†; ***Turk.:*** Bricanyl; ***UK:*** Bricanyl; Monovent†; ***USA:*** Brethine; Bricanyl†; ***Venez.:*** Bricanil†; Nortol†.

Multi-ingredient: ***Austria:*** Bricanyl comp; ***Braz.:*** Bricanyl Composto; ***Ger.:*** Bricanyl comp†; ***Hong Kong:*** Bricanyl Expectorant†; ***India:*** Ascoril +; Asmotone Plus; Bricarex; Bro-Zedex; Bronchosolvin; Cof QX; Grilinctus-BM; Mucaryl-AX†; Mucosol; Okaril Plus; Tergil; Tergil-T; Terpect; Terphylate; Terphylin; Theobric; Toscof; Tuspel Plus; ***Indon.:*** Bricasma Expectorant; Terasma Expectorant; ***Irl.:*** Bricanyl Expectorant; ***Mex.:*** Bricanyl EX; ***Philipp.:*** Bricanyl Expectorant; ***S.Afr.:*** Benylin Bronchospect; Bronchoped; Bronchospect†; ***Spain:*** Terbasmin Expectorante; ***Thai.:*** Bricanyl Expectorant†; Cofbron; Med-Broncodil Expectorant†; Terbosil†; Terbron Expectorant†; Tolbin.

Theobromine *(BAN)*

Santheose; Teobromiini; Teobromin; Teobromina; Teobrominas; Theobromin; Théobromine; Theobrominum. 3,7-Dihydro-3,7-dimethylpurine-2,6(1*H*)-dione; 3,7-Dimethylxanthine.

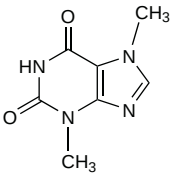
Теобромин

$C_7H_8N_4O_2$ = 180.2.

CAS — 83-67-0.

ATC — C03BD01; R03DA07.

ATC Vet — QC03BD01; QR03DA07.



Pharmacopoeias. In *Eur.* (see p.vii)

Ph. Eur. 6.2 (Theobromine). A white or almost white powder. Very slightly soluble in water and in dehydrated alcohol; slightly soluble in ammonia. It dissolves in dilute solutions of alkali hydroxides and in mineral acids.

Profile

Theobromine has the general properties of the other xanthines (see Theophylline, p.1140). It has a weaker activity than theophylline or caffeine and has practically no stimulant effect on the CNS. Large doses can cause nausea and vomiting. Theobromine has been used for its bronchodilating properties and in the treatment of cardiovascular disorders. Theobromine and calcium salicylate (theosalicin), theobromine and sodium acetate, and theobromine and sodium salicylate (themisalum, theobromsal) have all been used similarly to theobromine.

Theobromine is the chief xanthine in the beverage cocoa (p.2415). It is also present in chocolate and in small amounts in tea. Theobroma oil may contain up to 2% theobromine.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Asthma-Hilfe; ***Braz.:*** Urodonal†.

Theophylline *(BAN)*

Anhydrous Theophylline; Teofilin; Teofilina; Teofilinas; Teofillin; Teofillina; Teofylliini; Teofyllin; Theofylin; Théophylline; Theophyllinum. 3,7-Dihydro-1,3-dimethylpurine-2,6(1*H*)-dione; 1,3-Dimethylxanthine.

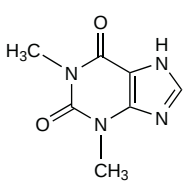
Теофиллин

$C_7H_8N_4O_2$ = 180.2.

CAS — 58-55-9.

ATC — R03DA04.

ATC Vet — QR03DA04.



Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

Ph. Eur. 6.2 (Theophylline). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

USP 31 (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

Theophylline Hydrate *(BANM)*

Teofilina monohidrato; Teofilinas monohidratas; Teofylliinimonohydraatti; Teofyllinmonohydrat; Theofylin monohydrát; Theophylline Monohydrate; Théophylline monohydratée; Theophyllinum monohydricum.

Теофиллина Гидрат

$C_7H_8N_4O_2,H_2O$ = 198.2.

CAS — 5967-84-0.

ATC — R03DA04.

ATC Vet — QR03DA04.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

Ph. Eur. 6.2 (Theophylline Monohydrate; Theophylline Hydrate BP 2008). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

USP 31 (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

Stability. Alcohol-free theophylline liquid repackaged in clear or amber polypropylene oral syringes could be stored at room temperature under continuous fluorescent lighting for at least 180 days without significant change in the concentration of theophylline.[1] However, it was recommended that solutions be protected from light because of the potential for discoloration.

Extemporaneous oral preparations of theophylline 5 mg/mL in commercial suspension vehicles were found[2] to be stable for up to 90 days in amber plastic bottles stored at 23° to 25°.

1. Johnson CE, Drabik BT. Stability of alcohol-free theophylline liquid repackaged in plastic oral syringes. *Am J Hosp Pharm* 1989; **46:** 980–1.
2. Johnson CE, *et al.* Stability of anhydrous theophylline in extemporaneously prepared alcohol-free oral suspensions. *Am J Health-Syst Pharm* 2005; **62:** 2518–20.

Adverse Effects

The adverse effects commonly encountered with theophylline and xanthine derivatives irrespective of the route, are gastrointestinal irritation and stimulation of the CNS. Serum concentrations of theophylline greater than 20 micrograms/mL (110 micromol/litre) are associated with an increased risk of adverse effects (but see below).

Theophylline may cause nausea, vomiting, abdominal pain, diarrhoea, and other gastrointestinal disturbances, insomnia, headache, anxiety, irritability, restlessness, tremor, and palpitations. Overdosage may also lead to agitation, diuresis and repeated vomiting (sometimes haematemesis) and consequent dehydration, cardiac arrhythmias including tachycardia, hypotension, electrolyte disturbances including profound hypokalaemia, hyperglycaemia, hypomagnesaemia, metabolic acidosis, rhabdomyolysis, convulsions, and death. Severe toxicity may not be preceded by milder symptoms. Convulsions, cardiac arrhythmias, severe hypotension, or cardiac arrest may follow rapid intravenous injection, and fatalities have been reported. The drug is too irritant for intramuscular use. Proctitis may follow repeated use of suppositories.

◊ Adverse effects are uncommon at serum-theophylline concentrations of 5 to 10 micrograms/mL but become more frequent at 15 micrograms/mL or above, and are greatly increased in frequency and severity at concentrations greater than 20 micrograms/mL.[1-3] The severity of toxicity is generally correlated with age, underlying disease, and serum-theophylline concentration, but a distinction has been made between acute and chronic theophylline intoxication; symptoms appear to occur at a lower theophylline concentration in chronic toxicity than after acute ingestion of large amounts.[1,2,4,5] Young infants and the elderly (over 60 years) appear to be at particular risk from chronic intoxication with theophylline.[6,7] Older patients with chronic intoxication may be at greater risk of major toxic effects, such as arrhythmias, seizures, and death, than those with acute intoxication.[5]

Common clinical manifestations of theophylline toxicity after overdosage of aminophylline or theophylline include nausea, vomiting, diarrhoea, agitation, tremor, hypertonicity, hyperventilation, supraventricular and ventricular arrhythmias, hypotension, and seizures. Metabolic disturbances such as hypokalaemia, hyperglycaemia, hypophosphataemia, hypercalcaemia, metabolic acidosis, and respiratory alkalosis often occur.[1-3] Other toxic effects reported include dementia,[8] toxic psychosis,[9] symptoms of acute pancreatitis,[10] rhabdomyolysis[11-13] with associated renal failure,[11] and acute compartment syndrome.[14]

Serious toxic symptoms may not be preceded by minor symptoms. In acute intoxication with sustained-release preparations the onset of major toxic symptoms may be delayed for up to 24 hours[1] and prolonged monitoring of such patients is required. Patients have recovered despite serum-theophylline concentrations in excess of 200 micrograms/mL[12,14] but fatalities have occurred with much lower serum concentrations.[10,15,16] Mortality in severe poisoning may be as high as 10%.

1. Dawson AH, Whyte IM. The assessment and treatment of theophylline poisoning. *Med J Aust* 1989; **151:** 689–93.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15:** 471–81.
3. Hardy CC, Smith J. Adverse reactions profile: theophylline and aminophylline. *Prescribers' J* 1997; **37:** 96–101.
4. Olson KR, *et al.* Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *Am J Emerg Med* 1985; **3:** 386–94.
5. Shannon M. Life-threatening events after theophylline overdose: a 10-year prospective analysis. *Arch Intern Med*1999; **159:** 989–94.
6. Shannon M, Lovejoy FH. Effect of acute versus chronic intoxication on clinical features of theophylline poisoning in children. *J Pediatr* 1992; **121:** 125–30.
7. Shannon M. Predictors of major toxicity after theophylline overdose. *Ann Intern Med* 1993; **119:** 1161–7.
8. Drummond I. Aminophylline toxicity in the elderly. *BMJ* 1982; **285:** 779–80.
9. Wasser WG, *et al.* Theophylline madness. *Ann Intern Med* 1981; **95:** 191.
10. Burgan THS, *et al.* Fatal overdose of theophylline simulating acute pancreatitis. *BMJ* 1982; **284:** 939–40.
11. Macdonald JB, *et al.* Rhabdomyolysis and acute renal failure after theophylline overdose. *Lancet* 1985; **i:** 932–3.
12. Rumpf KW, *et al.* Rhabdomyolysis after theophylline overdose. *Lancet* 1985; **i:** 1451–2.
13. Modi KB, *et al.* Theophylline poisoning and rhabdomyolysis. *Lancet* 1985; **ii:** 160–1.
14. Lloyd DM, *et al.* Acute compartment syndrome secondary to theophylline overdose. *Lancet* 1990; **ii:** 312.
15. Whyte KF, Addis GJ. Toxicity of salbutamol and theophylline together. *Lancet* 1983; **ii:** 618–19.
16. Davies RJ, Hawkey CJ. Fatal theophylline toxicity precipitated by in situ pulmonary artery thrombosis. *Postgrad Med J* 1989; **65:** 49–50.

Effects on carbohydrate metabolism. Hyperglycaemia is frequent in theophylline intoxication, and is thought to be secondary to theophylline-induced adrenal catecholamine release.[1,2] Whether the effects on blood glucose are significant at more modest serum concentrations of theophylline is unclear, although in 29 preterm infants, mean plasma-glucose concentrations were significantly higher after treatment with intravenous aminophylline and oral theophylline than in those not treated. Two of 15 treated infants developed clinically significant hyperglycaemia and glycosuria. It was recommended that plasma-glucose concentrations be monitored in preterm infants receiving theophylline.[3]

1. Kearney TE, *et al.* Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; **102:** 766–9.
2. Shannon M. Hypokalemia, hyperglycemia and plasma catecholamine activity after severe theophylline intoxication. *J Toxicol Clin Toxicol* 1994; **32:** 41–7.
3. Srinivasan G, *et al.* Plasma glucose changes in preterm infants during oral theophylline therapy. *J Pediatr* 1983; **103:** 473–6.

Effects on electrolytes. Hypokalaemia is a common metabolic disturbance in theophylline intoxication, but it has also been reported[1] in patients with plasma-theophylline concentrations within the therapeutic range. It is considered to be secondary to theophylline-induced adrenal catecholamine release, with cellular influx of potassium ions.[2] It is recommended[1] that plasma-potassium is monitored during intravenous theophylline therapy particularly if other drugs predisposing to hypokalaemia are also given (see also Interactions, below). Hypophosphataemia[1,3] and hyponatraemia[1] can also occur at therapeutic plasma-theophylline concentrations. Hypomagnesaemia[4] and hypercalcaemia[5] have occurred in theophylline overdose.

1. Zantvoort FA, *et al.* Theophylline and serum electrolytes. *Ann Intern Med* 1986; **104:** 134–5.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15:** 471–81.
3. Laaban J-P, *et al.* Hypophosphatemia complicating management of acute severe asthma. *Ann Intern Med* 1990; **112:** 68–9.
4. Hall KW, *et al.* Metabolic abnormalities associated with intentional theophylline overdose. *Ann Intern Med* 1984; **101:** 457–62.
5. McPherson ML, *et al.* Theophylline-induced hypercalcemia. *Ann Intern Med* 1986; **105:** 52–4.

Effects on the heart. ***ARRHYTHMIAS.*** Theophylline or aminophylline can precipitate sinus tachycardia and supraventricular and ventricular premature contractions at therapeutic serum-theophylline concentrations[1] and in overdose.[2,3] Multifocal atrial tachycardia has also been associated with both theophylline overdose[2] and serum-theophylline concentrations within the generally accepted therapeutic range of 10

to 20 micrograms/mL.[4] Use of theophylline with oral beta-adrenoceptor stimulants is associated with a significant increase in the mean heart rate.[5,6]

1. Josephson GW, *et al.* Cardiac dysrhythmias during the treatment of acute asthma: a comparison of two treatment regimens by a double blind protocol. *Chest* 1980; **78:** 429–35.
2. Greenberg A, *et al.* Severe theophylline toxicity: role of conservative measures, antiarrhythmic agents, and charcoal hemoperfusion. *Am J Med* 1984; **76:** 854–60.
3. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15:** 471–81.
4. Levine JH, *et al.* Multifocal atrial tachycardia: a toxic effect of theophylline. *Lancet* 1985; **i:** 12–14.
5. Coleman JJ, *et al.* Cardiac arrhythmias during the combined use of β-adrenergic agonist drugs and theophylline. *Chest* 1986; **90:** 45–51.
6. Conradson T-B, *et al.* Arrhythmogenicity from combined bronchodilator therapy in patients with obstructive lung disease and concomitant ischemic heart disease. *Chest* 1987; **91:** 5–9.

Effects on the kidneys. For a report of rhabdomyolysis-induced acute renal failure occurring after aminophylline overdose, see the general discussion on toxicity, above.

Effects on mental function. As mentioned in the general discussion on toxicityabove, theophylline toxicity has been associated with reports of dementia and toxic psychosis, as well as the more common adverse effects of anxiety and restlessness.

LEARNING AND BEHAVIOUR PROBLEMS. Several small studies[1-3] have suggested that theophylline may be associated with learning and behaviour problems in children, especially those with a low IQ. However, the FDA has concluded[4] that such studies provide insufficient evidence to support an adverse effect of theophylline on learning behaviour or school performance. Other studies have found no marked behavioural adverse effects that could be attributed to theophylline.[5,6] Additionally, academic achievement generally appeared to be unaffected by either asthma or by treatment with appropriate doses of theophylline.[7]

1. Furukawa CT, *et al.* Learning and behaviour problems associated with theophylline therapy. *Lancet* 1984; **i:** 621.
2. Springer C, *et al.* Clinical, physiologic, and psychologic comparison of treatment by cromolyn or theophylline in childhood asthma. *J Allergy Clin Immunol* 1985; **76:** 64–9.
3. Schlieper A, *et al.* Effect of therapeutic plasma concentrations of theophylline on behavior, cognitive processing, and affect in children with asthma. *J Pediatr* 1991; **118:** 449–55.
4. Anonymous. Theophylline and school performance. *FDA Drug Bull* 1988; **18:** 32–3.
5. Bender B, Milgrom H. Theophylline-induced behavior change in children: an objective evaluation of parents' perceptions. *JAMA* 1992; **267:** 2621–4.
6. Bender BG, *et al.* Neuropsychological behavioral changes in asthmatic children treated with beclomethasone dipropionate versus theophylline. *Pediatrics* 1998; **101:** 355–60.
7. Lindgren S, *et al.* Does asthma or treatment with theophylline limit children's academic performance? *N Engl J Med* 1992; **327:** 926–30.

Effects on the nervous system. ***CONVULSIONS.*** The risk of convulsions with acute theophylline toxicity is low at serum theophylline concentrations less than 60 micrograms/mL;[1] seizures are most likely in patients with peak concentrations above 100 micrograms/mL.[2] However, the risk of seizures is much greater after chronic overdosage;[1,2] seizure activity has been reported at serum concentrations just above or even within the therapeutic range.[3] Elderly patients or those with previous brain injury or neurological disease may be at increased risk,[2-4] although some have questioned the association.[1] The outcome of seizures appears to be variable: death and severe neurological deficit have occurred,[2,3] but other series have recorded recovery without serious morbidity.[4]

1. Paloucek FP, Rodvold KA. Evaluation of theophylline overdoses and toxicities. *Ann Emerg Med* 1988; **17:** 135–44.
2. Olson KR, *et al.* Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *Am J Emerg Med* 1985; **3:** 386–94.
3. Bahls FH, *et al.* Theophylline-associated seizures with "therapeutic" or low toxic serum concentrations: risk factors for serious outcome in adults. *Neurology* 1991; **41:** 1309–12.
4. Covelli HD, *et al.* Predisposing factors to apparent theophylline-induced seizures. *Ann Allergy* 1985; **54:** 411–15.

Effects on the skin. For reports of cutaneous reactions to theophylline and aminophylline, see under Hypersensitivity, below.

Effects on the urinary tract. Although diuresis is more commonly seen, urinary retention has been reported in male patients during therapy with aminophylline[1] or theophylline.[2]

1. Owens GR, Tannenbaum R. Theophylline-induced urinary retention. *Ann Intern Med* 1981; **94:** 212–13.
2. Prakash M, Washburne JD. Theophylline and urinary retention. *Ann Intern Med* 1981; **94:** 823.

Hypersensitivity. Hypersensitivity reactions have been reported after oral or intravenous doses of aminophylline. Reactions include erythematous rash with pruritus,[1,2] erythroderma,[2] and exfoliative dermatitis.[3] Aminophylline can produce both type I (immediate) and type IV (delayed) hypersensitivity reactions, the latter being due to the ethylenediamine component and can be confirmed by skin patch tests.[1-3] If hypersensitivity to ethylenediamine is confirmed it is recommended that aminophylline is avoided and treatment continued with theophylline or another theophylline salt.[1,3,4] Hypersensitivity reactions to theophylline have been reported rarely but type I reactions have occurred.[4] An erythematous, maculopapular rash has been reported[5] during treatment with a modified-release theophylline preparation, which did not occur when another modified-release theophylline product was given.

1. Hardy C, *et al.* Allergy to aminophylline. *BMJ* 1983; **286:** 2051–2.
2. Mohsenifar Z, *et al.* Two cases of allergy to aminophylline. *Ann Allergy* 1982; **49:** 281–2.
3. Nierenberg DW, Glazener FS. Aminophylline-induced exfoliative dermatitis: cause and implications. *West J Med* 1982; **137:** 328–31.
4. Gibb WRG. Delayed-type hypersensitivity to theophylline/aminophylline. *Lancet* 1985; **i:** 49.
5. Mendel S, *et al.* Dermatologic reaction to a sustained-release theophylline product. *Clin Pharm* 1985; **4:** 334–5.

Hyperuricaemia. In a study of 112 asthmatic patients receiving modified-release theophylline 200 to 400 mg 12-hourly, there was a significant correlation of serum-uric acid concentrations and serum-theophylline concentrations.[1] Gout has been reported in a woman receiving theophylline and aminophylline;[2] her serum-uric acid concentration was increased while receiving the xanthines, but subsequently fell when they were stopped, and rose again when treatment was resumed.

1. Morita Y, *et al.* Theophylline increases serum uric acid levels. *J Allergy Clin Immunol* 1984; **74:** 707–12.
2. Toda K, *et al.* Gout due to xanthine derivatives. *Br J Rheumatol* 1997; **36:** 1131–2.

Necrotising enterocolitis. Although there have been reports of neonatal necrotising enterocolitis associated with oral theophylline or aminophylline,[1,2] a study of 275 infants concluded that theophylline did not significantly contribute to its development.[3] It has been suggested that the high osmolality of liquid feeds and drugs including oral theophylline preparations may be involved in the aetiology of necrotising enterocolitis.[4]

1. Robinson MJ, *et al.* Xanthines and necrotising enterocolitis. *Arch Dis Child* 1980; **55:** 494–5.
2. Williams AJ. Xanthines and necrotising enterocolitis. *Arch Dis Child* 1980; **55:** 973–4.
3. Davis JM, *et al.* Role of theophylline in pathogenesis of necrotizing enterocolitis. *J Pediatr* 1986; **109:** 344–7.
4. Watkinson M, *et al.* Hyperosmolar preparations for neonates. *Pharm J* 1987; **241:** 488.

Withdrawal syndromes. Episodes of apnoea beginning 28 hours after birth and increasing in frequency and severity over the next 4 days occurred in a neonate whose mother had taken aminophylline and theophylline throughout pregnancy. Measurement of serum-theophylline concentration showed the increasing apnoea coincided with falling theophylline concentration. The infant's apnoea resolved on giving theophylline; treatment was stopped after 4 months.[1]

Worsening asthma control may occur when theophylline is withdrawn; there is some evidence of a rebound deterioration in lung function due to the development of tolerance.[2]

1. Horowitz DA, *et al.* Apnea associated with theophylline withdrawal in a term neonate. *Am J Dis Child* 1982; **136:** 73–4.
2. Bennett JA, *et al.* The airway effects of stopping regular oral theophylline in patients with asthma. *Br J Clin Pharmacol* 1998; **45:** 402–4.

Treatment of Adverse Effects

After theophylline or aminophylline overdosage, elimination may be enhanced by repeated oral doses of activated charcoal regardless of the route of overdose (see below). An osmotic laxative may also be considered. Treatment is symptomatic and supportive; ECG monitoring is recommended. Serum-theophylline concentrations should be monitored and if modified-release preparations have been taken monitoring should be prolonged. Metabolic abnormalities, particularly hypokalaemia, should be corrected; hypokalaemia may be so severe as to require intravenous infusion of potassium. In the non-asthmatic patient severe tachycardia, hypokalaemia, and hyperglycaemia may be reversed by a non-selective beta blocker (see also below). Patients with asthma or chronic obstructive pulmonary disease (COPD) who, after correction of hypokalaemia, have severe tachycardia, may be treated with intravenous verapamil. Alternatively direct current (DC) cardioversion may be considered. Ventricular arrhythmias causing haemodynamic compromise should also be treated with DC cardioversion. Isolated convulsions may be controlled by intravenous diazepam or a barbiturate; phenytoin may be less effective. In the most refractory cases general anaesthesia, and neuromuscular blockade, with ventilation, may be required.

Charcoal haemoperfusion or haemodialysis may be required.

◊ Reviews.

1. Dawson AH, Whyte IM. The assessment and treatment of theophylline poisoning. *Med J Aust* 1989; **151:** 689–93.
2. Skinner MH. Adverse reactions and interactions with theophylline. *Drug Safety* 1990; **5:** 275–85.
3. Minton NA, Henry JA. Treatment of theophylline overdose. *Am J Emerg Med* 1996; **14:** 606–12.

Activated charcoal. Multiple-dose oral activated charcoal is considered the cornerstone of treatment for theophylline and xanthine poisoning. It reduces the absorption of oral theophylline, and also enhances the elimination of theophylline from the body even after absorption or intravenous doses of xanthine. Aggressive antiemetic therapy may be required to allow use and retention of activated charcoal, since theophylline toxicity causes protracted vomiting. A cathartic such as sorbitol may be given with the activated charcoal to aid elimination of theophylline, but can cause fluid and electrolyte disturbances. For oral theophylline overdose the use of gastric lavage before oral activated charcoal may not be better than activated charcoal alone.

References.

1. Neuvonen PJ, *et al.* Comparison of activated charcoal and ipecac syrup in prevention of drug absorption. *Eur J Clin Pharmacol* 1983; **24:** 557–62.
2. Berlinger WG, *et al.* Enhancement of theophylline clearance by oral activated charcoal. *Clin Pharmacol Ther* 1983; **33:** 351–4.
3. Mahutte CK, *et al.* Increased serum theophylline clearance with orally administered activated charcoal. *Am Rev Respir Dis* 1983; **128:** 820–2.
4. Park GD, *et al.* Effects of size and frequency of oral doses of charcoal on theophylline clearance. *Clin Pharmacol Ther* 1983; **34:** 663–6.
5. Goldberg MJ, *et al.* The effect of sorbitol and activated charcoal on serum theophylline concentrations after slow-release theophylline. *Clin Pharmacol Ther* 1987; **41:** 108–11.
6. Al-Shareef AH, *et al.* The effects of charcoal and sorbitol (alone and in combination) on plasma theophylline concentrations after a sustained-release formulation. *Hum Exp Toxicol* 1990; **9:** 179–82.
7. Minton NA, *et al.* Prevention of drug absorption in simulated theophylline overdose. *Hum Exp Toxicol* 1995; **14:** 170–4.

Beta blockers. Infusion of propranolol after theophylline overdose in 2 patients was associated with improvement in hyperglycaemia, hypokalaemia, tachycardia, and hypotension. Beta-adrenergic blockade may therefore be of benefit in the management of the metabolic changes of theophylline poisoning, especially in the non-asthmatic patient.[1,2] However, in asthmatic patients, beta blockers should be reserved for those with severe hypokalaemia or cardiac arrhythmias when mechanical ventilation is available as beta blockers can cause bronchoconstriction.[1,2] Propranolol reduces the clearance of theophylline (see under Interactions, below) and it has been suggested that a non-interacting beta blocker may be more appropriate.[3] Esmolol has been used successfully to manage cardiovascular symptoms of overdosage.[4]

1. Kearney TE, *et al.* Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; **102:** 766–9.
2. Amin DN, Henry JA. Propranolol administration in theophylline overdose. *Lancet* 1985; **i:** 520–1.
3. Farrar KT, Dunn AM. Beta-blockers in treatment of theophylline overdose. *Lancet* 1985; **i:** 983.
4. Seneff M, *et al.* Acute theophylline toxicity and the use of esmolol to reverse cardiovascular instability. *Ann Emerg Med* 1990; **19:** 671–3.

Endoscopy. Absorption is delayed after overdosage with modified-release oral preparations of aminophylline or theophylline and may be further prolonged by the formation of tablet aggregates, or bezoars, in the stomach.[1-3] Of 11 patients admitted with overdosage, one vomited a bezoar, 2 had bezoars removed at gastroscopy, and in one a bezoar was found at necropsy.[3] If bezoar formation occurs gastric lavage and activated charcoal will have little if any effect and the patient may appear to stabilise before experiencing increasing serum-theophylline concentration and clinical deterioration;[1,2] fatalities have been reported.[1] Endoscopy should be considered in cases of modified-release theophylline overdosage in which clinical signs and serial concentration measurements suggest continuing drug absorption.[2]

1. Coupe M. Self-poisoning with sustained-release aminophylline: a mechanism for observed secondary rise in serum theophylline. *Hum Toxicol* 1986; **5:** 341–2.
2. Cereda J-M, *et al.* Endoscopic removal of pharmacobezoar of slow release theophylline. *BMJ* 1986; **293:** 1143.
3. Smith WDF. Endoscopic removal of a pharmacobezoar of slow release theophylline. *BMJ* 1987; **294:** 125.

Haemodialysis and haemoperfusion. Extracorporeal theophylline removal techniques after overdosage of aminophylline or theophylline have been reviewed.[1] Neither peritoneal dialysis nor exchange transfusion produced a significant increase in the total body clearance of theophylline, whereas haemodialysis could be expected to double clearance, and haemoperfusion results in four- to sixfold increases in clearance. Charcoal haemoperfusion should be considered if the plasma-theophylline concentration exceeds 100 micrograms/mL in an acute intoxication, or 60 micrograms/mL in chronic overdose (40 micrograms/mL if there is significant respiratory or heart failure, or liver disease) though plasma concentrations alone should not determine its use (see under Adverse Effects, above). If there is intractable vomiting, arrhythmias, or seizures charcoal haemoperfusion should be started without delay. In most patients a 4-hour haemoperfusion allows significant clinical improvement, but treatment should continue until plasma concentrations are below 15 micrograms/mL. Plasma concentrations should be followed at least every 4 hours for the first 12 hours post-perfusion, as rebound increases have been noted on terminating perfusion.

Haemodialysis may rarely be an alternative if haemoperfusion is not available, or in series with haemoperfusion if significant rhabdomyolysis is present. There has been a case report[2] of continuous venovenous haemofiltration used to treat severe theophylline toxicity.

1. Heath A, Knudsen K. Role of extracorporeal drug removal in acute theophylline poisoning: a review. *Med Toxicol* 1987; **2:** 294–308.
2. Henderson JH, *et al.* Continuous venovenous haemofiltration for the treatment of theophylline toxicity. *Thorax* 2001; **56:** 242–3.

Precautions

Theophylline or aminophylline should be given with caution to patients with peptic ulceration, porphyria, hyperthyroidism, hypertension, cardiac arrhythmias or other cardiovascular disease, or epilepsy, as these conditions may be exacerbated. They should also be given with caution to patients with heart failure, hepatic dysfunction, acute febrile illness, and to neonates and the elderly, since in all of these circumstances theophylline clearance may be decreased, resulting in increases in serum-theophylline concentrations and serum half-life. Conversely, smoking and alcohol consumption increase theophylline clearance. Many drugs interact with theophylline; for details see Interactions, below.

Intravenous injections of theophylline or aminophylline must be given very slowly to prevent dangerous CNS and cardiovascular adverse effects resulting from the direct stimulant effect.

Dosage requirements of theophylline vary widely between subjects; in view of the many factors affecting theophylline pharmacokinetics, serum concentration monitoring is necessary to ensure concentrations are within the therapeutic range.

Patients should not be transferred from one modified-release theophylline or aminophylline preparation to another without clinical assessment and the measurement of serum-theophylline concentrations because of bioavailability differences.

Acute febrile illness. A reduction in theophylline clearance has been noted in patients presenting with acute respiratory illness[1] and appears to be associated with the severity of the underlying pulmonary disease and the rate of change in the patient's condition.[2] Caution has been advised in giving theophylline to patients with chronic obstructive pulmonary disease with acute exacerbations, since these patients appear most likely to exhibit altered theophylline metabolism.[2]

Similarly, a decrease in theophylline clearance and an increase in the incidence of adverse effects has been reported during acute viral infections such as influenza in children receiving theophylline therapy for chronic asthma.[3,4] Another study in asthmatic children found that acute febrile illness accompanied by increased C-Reactive Protein (CRP) level may affect theophylline metabolism.[5] The authors postulated that cytokines released in the process of acute illness were responsible. Influenza vaccination has also been reported to reduce theophylline clearance (see under Interactions, below). The mechanism by which theophylline metabolism is reduced in these patients may be related to increased interferon production during the acute febrile response. A dosage reduction of one half has been recommended[6] in children receiving chronic theophylline therapy who are febrile for more than 24 hours. Further dose adjustments should be based on serum-theophylline concentrations until the patients have recovered from their acute illness and are restabilised on their usual dosage. However, conflicting results have been reported and in one controlled study RSV infection was found to have no significant effect on theophylline disposition in children.[7]

1. Vozeh S, *et al.* Changes in theophylline clearance during acute illness. *JAMA* 1978; **240:** 1882–4.
2. Richer M, Lam YWF. Hypoxia, arterial pH and theophylline disposition. *Clin Pharmacokinet* 1993; **25:** 283–99.
3. Chang KC, *et al.* Altered theophylline pharmacokinetics during acute respiratory viral illness. *Lancet* 1978; **i:** 1132–3.
4. Kraemer MJ, *et al.* Altered theophylline clearance during an influenza B outbreak. *Pediatrics* 1982; **69:** 476–80.
5. Yamaguchi A, *et al.* Higher incidence of elevated body temperature or increased C-reactive protein level in asthmatic children showing transient reduction of theophylline metabolism. *J Clin Pharmacol* 2000; **40:** 284–9.
6. American Academy of Pediatrics Committee on Drugs. Precautions concerning the use of theophylline. *Pediatrics* 1992; **89:** 781–3.
7. Muslow HA, *et al.* Lack of effect of respiratory syncytial virus infection on theophylline disposition in children. *J Pediatr* 1992; **121:** 466–71.

Age. For the effects of age on the metabolism and excretion of theophylline see under Pharmacokinetics, below. Dosage regimens for infants are discussed under Administration in Infants, in Uses and Administration, below.

Breast feeding. From one study of 3 women it was estimated that less than 1% of the total theophylline eliminated was found in breast milk.[1] Another study of 5 women estimated that a breast-fed infant would receive less than 10% of the maternal dose of theophylline.[2] These amounts were considered unlikely to cause toxicity, but it has been reported that irritability in one infant seemed to occur on the intermittent days when the mother took aminophylline. The American Academy of Pediatrics[3] states that theophylline is usually compatible with breast feeding, although it noted that irritability has been reported in infants whose mothers were receiving theophylline.

1. Stec GP, *et al.* Kinetics of theophylline transfer to breast milk. *Clin Pharmacol Ther* 1980; **28:** 404–8.
2. Yurchak AM, Jusko WJ. Theophylline secretion into breast milk. *Pediatrics* 1976; **57:** 518–20.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)

ECT. Patients receiving theophylline are at risk of prolonged seizures during ECT, and status epilepticus has been reported.[1,2] The ability of theophylline to prolong seizures has led to it being used as an adjunct in ECT.[3] Caffeine has been used similarly, see p.1118.

1. Peters SG, *et al.* Status epilepticus as a complication of concurrent electroconvulsive and theophylline therapy. *Mayo Clin Proc* 1984; **59:** 568–70.
2. Rasmussen KG, Zorumski CF. Electroconvulsive therapy in patients taking theophylline. *J Clin Psychiatry* 1993; **54:** 427–31.
3. Leentjens AFG, *et al.* Facilitation of ECT by intravenous administration of theophylline. *Convuls Ther* 1996; **12:** 232–7.

Porphyria. Theophylline has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. It has been recommended[1] that serum-theophylline concentrations are measured at monthly intervals throughout pregnancy and 1 and 4 weeks after delivery since the pharmacokinetics of theophylline may be altered. An increase in the volume of distribution of theophylline, a decrease in plasma-protein binding, and a continuing decrease in clearance throughout pregnancy have been noted in some patients, especially during the later part of pregnancy,[2-4] but other studies have noted an increase in theophylline clearance during pregnancy.[1,5] Some studies have found that after delivery there is a return of clearance values to those existing before pregnancy,[2] while others have not.[4]

In a study of 12 neonates whose mothers received various theophylline preparations throughout their pregnancies[6] maternal, cord, and neonatal heelstick theophylline concentrations ranged from 2.3 to 19.6 micrograms/mL. Transient jitteriness was seen in 2 neonates and tachycardia in one, at cord theophylline concentrations of 11.7 to 17 micrograms/mL. There were no instances of vomiting, seizure, arrhythmias, diarrhoea, or feeding disturbances, which had been reported previously.

1. Rubin PC. Prescribing in pregnancy: general principles. *BMJ* 1986; **293:** 1415–17.
2. Carter BL, *et al.* Theophylline clearance during pregnancy. *Obstet Gynecol* 1986; **68:** 555–9.
3. Frederiksen MC, *et al.* Theophylline pharmacokinetics in pregnancy. *Clin Pharmacol Ther* 1986; **40:** 321–8.
4. Gardner MJ, *et al.* Longitudinal effects of pregnancy on the pharmacokinetics of theophylline. *Eur J Clin Pharmacol* 1987; **31:** 289–95.
5. Romero R, *et al.* Pharmacokinetics of intravenous theophylline in pregnant patients at term. *Am J Perinatol* 1983; **1:** 31–5.
6. Labovitz E, Spector S. Placental theophylline transfer in pregnant asthmatics. *JAMA* 1982; **247:** 786–8.

Renal impairment. Theophylline is eliminated mainly by hepatic metabolism and usual doses of aminophylline or theophylline can be given to patients with renal impairment. In patients undergoing haemodialysis the clearance of theophylline is increased and its elimination half-life reduced; mean values of 84.8 and 83 mL/minute and 2.5 and 2.3 hours respectively have been reported.[1,2] Haemodialysis removes up to 40% of a dose of theophylline.[1] Peritoneal dialysis has little effect on the pharmacokinetics of theophylline removing about 3.2% of a dose.[1]

1. Lee C-SC, *et al.* Comparative pharmacokinetics of theophylline in peritoneal dialysis and hemodialysis. *J Clin Pharmacol* 1983; **23:** 274–80.
2. Anderson JR, *et al.* Effects of hemodialysis on theophylline kinetics. *J Clin Pharmacol* 1983; **23:** 428–32.

Smoking. Certain components of tobacco smoke, notably aromatic hydrocarbons, induce hepatic drug-metabolising enzymes and cigarette smoking has been reported[1-3] to increase theophylline clearance and shorten its elimination half-life. The effect of smoking may override factors that tend to decrease theophylline clearance, such as old age.[4] The duration of enzyme induction after stopping smoking is uncertain; theophylline clearance decreased by 38% after one week of abstinence from smoking in one study,[5] while others have found changes in clearance persisting for at least 3 months.[1] Tobacco chewing has also been reported to increase theophylline clearance,[6] but nicotine chewing gum appears to have no effect.[5]

1. Hunt SN, *et al.* Effect of smoking on theophylline disposition. *Clin Pharmacol Ther* 1976; **19:** 546–51.
2. Jusko WJ, *et al.* Enhanced biotransformation of theophylline in marihuana and tobacco smokers. *Clin Pharmacol Ther* 1978; **24:** 406–10.
3. Grygiel JJ, Birkett DJ. Cigarette smoking and theophylline clearance and metabolism. *Clin Pharmacol Ther* 1981; **30:** 491–6.
4. Cusack B, *et al.* Theophylline kinetics in relation to age: the importance of smoking. *Br J Clin Pharmacol* 1980; **10:** 109–14.
5. Lee BL, *et al.* Cigarette abstinence, nicotine gum, and theophylline disposition. *Ann Intern Med* 1987; **106:** 553–5.
6. Rockwood R, Henann N. Smokeless tobacco and theophylline clearance. *Drug Intell Clin Pharm* 1986; **20:** 624–5.

Interactions

The toxic effects of theophylline, aminophylline, and other xanthines are additive. Use with other xanthine medications should therefore be avoided; if intravenous aminophylline is to be given for acute bronchospasm in patients who have been taking maintenance theophylline therapy, serum-theophylline concentrations should be measured first and the initial dose reduced as appropriate (see Uses and Administration, below).

Theophylline clearance may be reduced by interaction with other drugs including allopurinol, some antiarrhythmics, cimetidine, disulfiram, fluvoxamine, interferon alfa, macrolide antibacterials and quinolones, oral contraceptives, tiabendazole, and viloxazine, and the dose of theophylline may need to be reduced. Phenytoin and some other antiepileptics, ritonavir, rifampicin, and sulfinpyrazone may increase theophylline clearance, and require an increase in dose or dosing frequency of theophylline.

Xanthines can potentiate hypokalaemia caused by hypoxia or associated with the use of $beta_2$-adrenoceptor stimulants ($beta_2$ agonists), corticosteroids, and diuretics. There is a risk of synergistic toxicity if theophylline is given with halothane or ketamine, and it may antagonise the effects of adenosine and of competitive neuromuscular blockers; lithium elimination may be enhanced with a consequent loss of effect. The interaction between theophylline and beta blockers is complex (see below) but use together tends to be avoided on pharmacological grounds since beta blockers produce bronchospasm.

◊ Theophylline is metabolised by several hepatic cytochrome P450 isoenzymes, of which the most important seems to be CYP1A2.[1] Numerous drugs affect the metabolic clearance of theophylline and aminophylline,[2] but the variability in theophylline pharmacokinetics makes the clinical significance of these interactions difficult to predict. Giving theophylline with drugs that inhibit its metabolism should be avoided but, if unavoidable, the dose of theophylline should be halved.[3] There is some evidence to suggest that less of a dose reduction is required in the presence of severe liver dysfunction,[4] aside from that already required by impaired hepatic metabolism, see Administration in Hepatic Impairment, below. Subsequent doses should be adjusted based on serum-theophylline monitoring.[3] Even when introducing medication for which no interaction is suspected, a check on the serum-theophylline concentration within 24 hours of beginning the new drug has been advised.[3]

Theophylline reduces liver plasma flow[5] and may therefore prolong the half-life and increase steady-state levels of hepatically eliminated drugs but it is claimed to have no effect on antipyrine clearance.[6]

1. Ha HR, *et al.* Metabolism of theophylline by cDNA-expressed human cytochromes P-450. *Br J Clin Pharmacol* 1995; **39:** 321–6.
2. Upton RA. Pharmacokinetic interactions between theophylline and other medication. *Clin Pharmacokinet* 1991; **20:** 66–80 (part I) and 135–50 (part II).
3. American Academy of Pediatrics Committee on Drugs. Precautions concerning the use of theophylline. *Pediatrics* 1992; **89:** 781–3.
4. Orlando R, *et al.* Liver dysfunction markedly decreases the inhibition of cytochrome P450 1A2-mediated theophylline metabolism by fluvoxamine. *Clin Pharmacol Ther* 2006; **79:** 489–99.
5. Onrot J, *et al.* Reduction of liver plasma flow by caffeine and theophylline. *Clin Pharmacol Ther* 1986; **40:** 506–10.
6. Døssing M, *et al.* Effect of theophylline and salbutamol on hepatic drug metabolism. *Hum Toxicol* 1989; **8:** 225–8.

Antiarrhythmics. An increase in serum-theophylline concentration from 93.2 to 194.2 micromol/litre with symptoms of tachycardia, nervousness, and tremors occurred in a patient 9 days after starting *amiodarone* therapy.[1] Elevated theophylline concentrations and/or decreased clearance have also been reported following addition of *mexiletine* to theophylline therapy.[2-6] Amiodarone and mexiletine probably interact with theophylline through inhibition of its hepatic metabolism. *Tocainide* has also been found to impair theophylline metabolism resulting in a reduction in theophylline clearance but the effect was substantially smaller than that of mexiletine.[7] In one patient stabilised on theophylline therapy, an increase in the plasma-theophylline concentration with subsequent toxicity was noted after starting treat-

ment with *propafenone*.[8] See also under Calcium-channel Blockers, below.

1. Soto J, *et al.* Possible theophylline-amiodarone interaction. *DICP Ann Pharmacother* 1990; **24:** 1115.
2. Stanley R, *et al.* Mexiletine-theophylline interaction. *Am J Med* 1989; **86:** 733–4.
3. Ueno K, *et al.* Interaction between theophylline and mexiletine. *DICP Ann Pharmacother* 1990; **24:** 471–2.
4. Hurwitz A, *et al.* Mexiletine effects on theophylline disposition. *Clin Pharmacol Ther* 1991; **50:** 299–307.
5. Loi C-M, *et al.* Inhibition of theophylline metabolism by mexiletine in young male and female nonsmokers. *Clin Pharmacol Ther* 1991; **49:** 571–80.
6. Ueno K, *et al.* Mechanism of interaction between theophylline and mexiletine. *DICP Ann Pharmacother* 1991; **25:** 727–30.
7. Loi C-M, *et al.* The effect of tocainide on theophylline metabolism. *Br J Clin Pharmacol* 1993; **35:** 437–40.
8. Lee BL, Dohrmann ML. Theophylline toxicity after propafenone treatment: evidence for drug interaction. *Clin Pharmacol Ther* 1992; **51:** 353–5.

Antibacterials. ***IMIPENEM.*** Seizures have been reported in 3 patients receiving theophylline who were given imipenem,[1] although serum concentrations of theophylline were not affected.

1. Semel JD, Allen N. Seizures in patients simultaneously receiving theophylline and imipenem or ciprofloxacin or metronidazole. *South Med J* 1991; **84:** 465–8.

ISONIAZID. Isoniazid inhibits oxidative enzymes in the liver and has been found to impair the elimination of theophylline. Both clearance and volume of distribution of theophylline were reduced with an increase in serum-theophylline concentrations in healthy subjects after 14 days of pretreatment with isoniazid[1] and theophylline toxicity has been reported[2] in a patient one month after adding theophylline to isoniazid therapy.

1. Samigun, *et al.* Lowering of theophylline clearance by isoniazid in slow and rapid acetylators. *Br J Clin Pharmacol* 1990; **29:** 570–3.
2. Torrent J, *et al.* Theophylline-isoniazid interaction. *DICP Ann Pharmacother* 1989; **23:** 143–5.

MACROLIDES. There are conflicting reports of the effect of *erythromycin* on the pharmacokinetics of theophylline. Significant decreases in the clearance of theophylline and prolonged elimination half-life have been reported[1-3] but other studies have found no interaction.[4,5] It has also been noted that the serum concentrations and bioavailability of erythromycin may be reduced by theophylline[6,7] (see also p.271). The clearance of theophylline is also markedly decreased by *troleandomycin*,[8-10] but there have been reports that for clinical purposes the pharmacokinetics of theophylline do not seem to be significantly altered by *dirithromycin*,[11-13] *josamycin*,[9,14] *midecamycin*,[10,15,16] *rokitamycin*,[17] *roxithromycin*,[18] or *spiramycin*.[19] *Clarithromycin* also seems unlikely to have a significant effect in most patients, but in a few theophylline dosage may need to be adjusted.[20,21] In one case report, serum-theophylline concentrations fell over a few days after the withdrawal of *azithromycin*.[22]

1. Zarowitz BJM, *et al.* Effect of erythromycin base on theophylline kinetics. *Clin Pharmacol Ther* 1981; **29:** 601–5.
2. Renton KW, *et al.* Depression of theophylline elimination by erythromycin. *Clin Pharmacol Ther* 1981; **30:** 422–6.
3. May DC, *et al.* The effects of erythromycin on theophylline elimination in normal males. *J Clin Pharmacol* 1982; **22:** 125–30.
4. Maddux MS, *et al.* The effect of erythromycin on theophylline pharmacokinetics at steady state. *Chest* 1982; **81:** 563–5.
5. Hildebrandt R, *et al.* Lack of clinically important interaction between erythromycin and theophylline. *Eur J Clin Pharmacol* 1984; **26:** 485–9.
6. Iliopoulou A, *et al.* Pharmacokinetic interaction between theophylline and erythromycin. *Br J Clin Pharmacol* 1982; **14:** 495–9.
7. Paulsen O, *et al.* The interaction of erythromycin with theophylline. *Eur J Clin Pharmacol* 1987; **32:** 493–8.
8. Weinberger M, *et al.* Inhibition of theophylline clearance by troleandomycin. *J Allergy Clin Immunol* 1977; **59:** 228–31.
9. Brazier JL, *et al.* Retard d'élimination de la théophylline dû à la troléandomycine: absence d'effet de la josamycine. *Therapie* 1980; **35:** 545–9.
10. Lavarenne J, *et al.* Influence d'un nouveau macrolide, la midécamycine, sur les taux sanguins de théophylline. *Therapie* 1981; **36:** 451–6.
11. Bachmann K, *et al.* Changes in the steady-state pharmacokinetics of theophylline during treatment with dirithromycin. *J Clin Pharmacol* 1990; **30:** 1001–5.
12. Bachmann K, *et al.* Steady-state pharmacokinetics of theophylline in COPD patients treated with dirithromycin. *J Clin Pharmacol* 1993; **33:** 861–5.
13. McConnell SA, *et al.* Lack of effect of dirithromycin on theophylline pharmacokinetics in healthy volunteers. *J Antimicrob Chemother* 1999; **43:** 733–6.
14. Ruff F, *et al.* Macrolide et théophylline: absence d'interaction josamycine-théophylline. *Nouv Presse Med* 1981; **10:** 175.
15. Principi N, *et al.* Effect of miocamycin on theophylline kinetics in children. *Eur J Clin Pharmacol* 1987; **31:** 701–4.
16. Couet W, *et al.* Lack of effect of ponsinomycin on the plasma pharmacokinetics of theophylline. *Eur J Clin Pharmacol* 1989; **37:** 101–4.
17. Ishioka T. Effect of a new macrolide antibiotic, 3′′-O-propionylleucomycin A (rokitamycin) on serum concentrations of theophylline and digoxin in the elderly. *Acta Ther* 1987; **13:** 17–24.
18. Saint-Salvi B, *et al.* A study of the interaction of roxithromycin with theophylline and carbamazine. *J Antimicrob Chemother* 1987; **20** (suppl B): 121–9.
19. Debruyne D, *et al.* Spiramycin has no effect on serum theophylline in asthmatic patients. *Eur J Clin Pharmacol* 1986; **30:** 505–7.
20. Bachand RT. Comparative study of clarithromycin and ampicillin in the treatment of patients with acute bacterial exacerbations of chronic bronchitis. *J Antimicrob Chemother* 1991; **27** (suppl A): 91–100.
21. Gillum JG, *et al.* Effect of combination therapy with ciprofloxacin and clarithromycin on theophylline pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother* 1996; **40:** 1715–16.
22. Pollak PT, Slayter KL. Reduced serum theophylline concentrations after discontinuation of azithromycin: evidence for an unusual interaction. *Pharmacotherapy* 1997; **17:** 827–9.

QUINOLONES. The fluoroquinolone antibacterials vary in their propensity to interact with theophylline. *Enoxacin* shows the most marked interaction and has been reported[1] to cause serious nausea and vomiting, tachycardia, and headaches, associated with unexpectedly high plasma-theophylline concentrations in patients with respiratory-tract infections. Studies,[2-5] mainly in healthy subjects, have found that enoxacin decreases theophylline clearance by up to 74%[3] with an increase in the elimination half-life and serum-theophylline concentration.

Ciprofloxacin[2,6-8] and *pefloxacin*[2] interact with theophylline to a lesser extent than enoxacin, decreasing theophylline clearance by about 30%. Eight clinically important interactions between ciprofloxacin and theophylline had been reported to the UK CSM[9] including 1 death. A ciprofloxacin-induced seizure has been reported[10] which may have been due to the combined inhibitory effects of the 2 drugs on GABA binding. It has been recommended that ciprofloxacin should not be used in patients treated with theophylline.[9]

Norfloxacin[4,11-13] and *ofloxacin*[4,11,14] have been reported to have minor effects on the pharmacokinetics of theophylline. Although their effects were usually considered not to be clinically significant, the US FDA had received 9 reports of theophylline toxicity associated with use with norfloxacin, including 1 death.[15] *Fleroxacin*,[16] *flumequine*,[17] *lomefloxacin*,[8,18,19] *moxifloxacin*,[20] and *rufloxacin*[21] have been reported to have no significant effect on the pharmacokinetics of theophylline in small studies in healthy subjects.

The mechanism of interaction involves a reduction in the metabolic clearance of theophylline due to inhibition of hepatic microsomal enzymes. However, the exact mechanism is unknown and it is difficult to predict which patients will be at risk. Extreme caution should be used when giving quinolones with theophylline, particularly in the elderly[15] and it may be advisable to use a non-interacting fluoroquinolone, although theophylline concentrations should still be monitored.

Of the non-fluorinated quinolones, *nalidixic acid*[2] has been reported not to affect theophylline clearance whereas *pipemidic acid* has markedly inhibited theophylline clearance.[19]

1. Wijnands WJA, *et al.* Enoxacin raises plasma theophylline concentrations. *Lancet* 1984; **ii:** 108–9.
2. Wijnands WJA, *et al.* The influence of quinolone derivatives on theophylline clearance. *Br J Clin Pharmacol* 1986; **22:** 677–83.
3. Beckmann J, *et al.* Enoxacin—a potent inhibitor of theophylline metabolism. *Eur J Clin Pharmacol* 1987; **33:** 227–30.
4. Sano M, *et al.* Inhibitory effect of enoxacin, ofloxacin and norfloxacin on renal excretion of theophylline in humans. *Eur J Clin Pharmacol* 1989; **36:** 323–4.
5. Koup JR, *et al.* Theophylline dosage adjustment during enoxacin coadministration. *Antimicrob Agents Chemother* 1990; **34:** 803–7.
6. Nix DE, *et al.* Effect of multiple dose oral ciprofloxacin on the pharmacokinetics of theophylline and indocyanine green. *J Antimicrob Chemother* 1987; **19:** 263–9.
7. Schwartz J, *et al.* Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. *Antimicrob Agents Chemother* 1988; **32:** 75–7.
8. Robson RA, *et al.* Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline. *Br J Clin Pharmacol* 1990; **29:** 491–3.
9. Bem JL, Mann RD. Danger of interaction between ciprofloxacin and theophylline. *BMJ* 1988; **296:** 1131.
10. Karki SD, *et al.* Seizure with ciprofloxacin and theophylline combined therapy. *DICP Ann Pharmacother* 1990; **24:** 595–6.
11. Sano M, *et al.* Comparative pharmacokinetics of theophylline following two fluoroquinolones co-administration. *Eur J Clin Pharmacol* 1987; **32:** 431–2.
12. Ho G, *et al.* Evaluation of the effect of norfloxacin on the pharmacokinetics of theophylline. *Clin Pharmacol Ther* 1988; **44:** 35–8.
13. Davis RL, *et al.* Effect of norfloxacin on theophylline metabolism. *Antimicrob Agents Chemother* 1989; **33:** 212–14.
14. Gregoire SL, *et al.* Inhibition of theophylline clearance by coadministered ofloxacin without alteration of theophylline effects. *Antimicrob Agents Chemother* 1987; **31:** 375–8.
15. Grasela TH, Dreis MW. An evaluation of the quinolone-theophylline interaction using the Food and Drug Administration spontaneous reporting system. *Arch Intern Med* 1992; **152:** 617–21.
16. Parent M, *et al.* Safety of fleroxacin coadministered with theophylline to young and elderly volunteers. *Antimicrob Agents Chemother* 1990; **34:** 1249–53.
17. Lacarelle B, *et al.* The quinolone, flumequine, has no effect on theophylline pharmacokinetics. *Eur J Clin Pharmacol* 1994; **46:** 477–8.
18. LeBel M, *et al.* Influence of lomefloxacin on the pharmacokinetics of theophylline. *Antimicrob Agents Chemother* 1990: **34:** 1254–6.
19. Staib AH, *et al.* Interaction of quinolones with the theophylline metabolism in man: investigations with lomefloxacin and pipemidic acid. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 289–93.
20. Stass H, Kubitza D. Lack of pharmacokinetic interaction between moxifloxacin, a novel 8-methoxyfluoroquinolone, and theophylline. *Clin Pharmacokinet* 2001; **40** (suppl 1): 63–70.
21. Kinzig-Schippers M, *et al.* Absence of effect of rufloxacin on theophylline pharmacokinetics in steady state. *Antimicrob Agents Chemother* 1998; **42:** 2359–64.

RIFAMPICIN. Rifampicin induces hepatic oxidative enzymes and a dose of 600 mg daily by mouth for 6 to 14 days has been shown to increase mean plasma-theophylline clearance by 25 to 82% due to enhancement of hepatic theophylline metabolism. This increase in clearance is sufficient to require dosage adjustment in some patients,[1-4] including children.[5]

1. Straughn AB, *et al.* Effect of rifampin on theophylline disposition. *Ther Drug Monit* 1984; **6:** 153–6.
2. Robson RA, *et al.* Theophylline-rifampicin interaction: non-selective induction of theophylline metabolic pathways. *Br J Clin Pharmacol* 1984; **18:** 445–8.
3. Boyce EG, *et al.* The effect of rifampin on theophylline kinetics. *J Clin Pharmacol* 1986; **26:** 696–9.
4. Adebayo GE, *et al.* Attenuation of rifampicin-induced theophylline metabolism by diltiazem/rifampicin coadministration in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 127–31.
5. Brocks DR, *et al.* Theophylline-rifampin interaction in a pediatric patient. *Clin Pharm* 1986; **5:** 602–4.

TETRACYCLINES. *Tetracycline* weakly inhibited theophylline clearance after 5 days of therapy in 5 non-smoking adults with chronic obstructive airways disease[1] and theophylline toxicity has been reported[2] in a patient given a 10-day course of tetracycline during theophylline therapy. *Doxycycline* has been reported not to have any significant effect on theophylline pharmacokinetics in healthy subjects.[3]

1. Gotz VP, Ryerson GG. Evaluation of tetracycline on theophylline disposition in patients with chronic obstructive airways disease. *Drug Intell Clin Pharm* 1986; **20:** 694–7.
2. McCormack JP, *et al.* Theophylline toxicity induced by tetracycline. *Clin Pharm* 1990; **9:** 546–9.
3. Jonkman JHG, *et al.* No influence of doxycycline on theophylline pharmacokinetics. *Ther Drug Monit* 1985; **7:** 92–4.

Antidepressants. Significantly reduced clearance and increased plasma concentrations of theophylline have been reported when given with *viloxazine*.[1,2] The dosage of theophylline should be decreased and its plasma concentrations monitored when viloxazine is also prescribed.[2] The interaction probably involves competition between the two drugs for hepatic microsomal enzymes.

Fluvoxamine has also been associated with a significant reduction in theophylline clearance[3,4] and theophylline toxicity has been described in patients when fluvoxamine was added to their therapy.[5,6] This interaction which is due to potent liver enzyme inhibition[7] has been the subject of a warning by the UK CSM[8] in which they issued the standard advice of avoiding the two drugs if at all possible and, where they could not be avoided, of giving half the dose of theophylline and monitoring plasma concentrations. A small study evaluating the effect of liver cirrhosis on the interaction between fluvoxamine and theophylline observed a decrease in fluvoxamine-induced inhibition of theophylline clearance as the severity of liver cirrhosis increased.[4] The authors suggest that theophylline may require less of a dose reduction in the presence of severe liver dysfunction, aside from that already required by impaired hepatic metabolism, see Administration in Hepatic Impairment, below.

St John's wort may have decreased theophylline concentrations and increased the theophylline dosage requirement in one case report.[9] However, a study[10] in 12 healthy subjects found that 15 days of treatment with St John's wort did not significantly change theophylline pharmacokinetics.

For a mention of the effect of theophylline on the renal clearance of *lithium*, see Xanthines, under Interactions of Lithium, p.405.

1. Thomson AH, *et al.* Theophylline toxicity following coadministration of viloxazine. *Ther Drug Monit* 1988; **10:** 359–60.
2. Perault MC, *et al.* A study of the interaction of viloxazine with theophylline. *Ther Drug Monit* 1989; **11:** 520–2.
3. Donaldson KM, *et al.* The effect [of] fluvoxamine at steady state on the pharmacokinetics of theophylline after a single dose in healthy male volunteers. *Br J Clin Pharmacol* 1994; **37:** 492P.
4. Orlando R, *et al.* Liver dysfunction markedly decreases the inhibition of cytochrome P450 1A2-mediated theophylline metabolism by fluvoxamine. *Clin Pharmacol Ther* 2006; **79:** 489–99.
5. Sperber AD. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. *Drug Safety* 1991; **6:** 460–2.
6. Thomson AH, *et al.* Interaction between fluvoxamine and theophylline. *Pharm J* 1992; **249:** 137.
7. Rasmussen BB, *et al.* Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 1995; **39:** 151–9.
8. Committee on Safety of Medicines/Medicines Control Agency. Fluvoxamine increases plasma theophylline levels. *Current Problems* 1994; **20:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 20/05/08)
9. Nebel A, *et al.* Potential metabolic interaction between St John's wort and theophylline. *Ann Pharmacother* 1999; **33:** 502.
10. Morimoto T, *et al.* Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 95–101.

Antiepileptics. *Phenytoin* markedly decreases the elimination half-life and increases the clearance of theophylline, probably due to hepatic enzyme induction, at therapeutic serum-phenytoin concentrations,[1-3] at subtherapeutic phenytoin concentrations,[2,4]

and even in heavy smokers.[2] A preliminary report suggested that the serum concentration of phenytoin may be decreased simultaneously,[5] perhaps due to enzyme induction by theophylline[5] or reduced phenytoin absorption.[6] The interaction has been reported to occur within 5 to 14 days of taking phenytoin and theophylline, and theophylline clearance has increased by up to 350%, and reductions in serum half-life have ranged from 25 to 70% of initial values.[3,4]

Carbamazepine has also been seen to increase theophylline elimination. In one patient, theophylline serum half-life was decreased by about 24 to 60%, and clearance was increased by about 35 to 100% when carbamazepine was given.[2] In an 11-year-old girl theophylline-serum half-life was almost halved with loss of asthma control after 3 weeks of concurrent carbamazepine therapy.[7] In turn, theophylline has been reported to reduce serum concentrations of carbamazepine—see p.475.

Although *phenobarbital* was not found to have a significant effect on the pharmacokinetics of a single dose of theophylline given intravenously,[8] enhanced theophylline clearance has been seen in patients after longer periods of treatment with phenobarbital.[9,10] The magnitude of the changes in theophylline elimination appears to be smaller with phenobarbital than phenytoin. *Pentobarbital* in high doses has also been reported to increase theophylline metabolism.[11] A more recent study[12] has also shown that therapeutic doses of pentobarbital (100 mg daily) increase plasma clearance of theophylline by a mean of 40%, although this was subject to marked interindividual variations. Renal clearance was not affected, suggesting hepatic enzyme induction as the probable mechanism.

1. Marquis J-F, *et al.* Phenytoin-theophylline interaction. *N Engl J Med* 1982; **307:** 1189–90.
2. Reed RC, Schwartz HJ. Phenytoin-theophylline-quinidine interaction. *N Engl J Med* 1983; **308:** 724–5.
3. Sklar SJ, Wagner JC. Enhanced theophylline clearance secondary to phenytoin therapy. *Drug Intell Clin Pharm* 1985; **19:** 34–6.
4. Miller M, *et al.* Influence of phenytoin on theophylline clearance. *Clin Pharmacol Ther* 1984; **35:** 666–9.
5. Taylor JW, *et al.* The interaction of phenytoin and theophylline. *Drug Intell Clin Pharm* 1980; **14:** 638.
6. Hendeles L, *et al.* Decreased oral phenytoin absorption following concurrent theophylline administration. *J Allergy Clin Immunol* 1979; **63:** 156.
7. Rosenberry KR, *et al.* Reduced theophylline half-life induced by carbamazepine therapy. *J Pediatr* 1983; **102:** 472–4.
8. Piafsky KM, *et al.* Effect of phenobarbital on the disposition of intravenous theophylline. *Clin Pharmacol Ther* 1977; **22:** 336–9.
9. Jusko WJ, *et al.* Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. *J Pharm Sci* 1979; **68:** 1358–66.
10. Saccar CL, *et al.* The effect of phenobarbital on theophylline disposition in children with asthma. *J Allergy Clin Immunol* 1985; **75:** 716–19.
11. Gibson GA, *et al.* Influence of high-dose phenobarbital on theophylline pharmacokinetics: a case report. *Ther Drug Monit* 1985; **7:** 181–4.
12. Dahlqvist R, *et al.* Induction of theophylline metabolism by pentobarbital. *Ther Drug Monit* 1989; **11:** 408–10.

Antifungals. There have been reports that *ketoconazole* does not appear significantly to alter the pharmacokinetics of theophylline.[1,2] The manufacturer of *fluconazole* has, however, stated that plasma clearance of theophylline may be decreased by fluconazole. A 16% reduction in theophylline clearance has been reported[3] after oral fluconazole but fluconazole was considered to have only a minor inhibitory effect on theophylline metabolism and theophylline disposition was not significantly affected. Theophylline metabolism has been inhibited to a similar degree by *terbinafine*.[4]

1. Brown MW, *et al.* Effect of ketoconazole on hepatic oxidative drug metabolism. *Clin Pharmacol Ther* 1985; **37:** 290–7.
2. Heusner JJ, *et al.* Effect of chronically administered ketoconazole on the elimination of theophylline in man. *Drug Intell Clin Pharm* 1987; **21:** 514–17.
3. Konishi H, *et al.* Effect of fluconazole on theophylline disposition in humans. *Eur J Clin Pharmacol* 1994; **46:** 309–12.
4. Trépanier EF, *et al.* Effect of terbinafine on theophylline pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother* 1998; **42:** 695–7.

Antigout drugs. *Allopurinol* 300 mg by mouth daily for 7 days was found to have no effect on the pharmacokinetics of theophylline after a single intravenous dose of aminophylline[1,2] or after oral theophylline given to steady state.[1] However, oral allopurinol 600 mg daily for 28 days has been found to inhibit the metabolism of theophylline,[3] increasing the mean half-life by 25% after 14 days and 29% after 28 days and there has been a report of allopurinol increasing peak plasma-theophylline concentrations by 38% in one patient within 2 days of use together.[4]

Probenecid has been reported[5] to have no effect on the hepatic metabolism or total body clearance of theophylline in a single-dose study in healthy subjects.

Sulfinpyrazone 800 mg daily for 7 days increased the total plasma clearance of theophylline by 22% in healthy subjects due to selective induction of certain cytochrome P450 isoenzymes.[6]

1. Grygiel JJ, *et al.* Effects of allopurinol on theophylline metabolism and clearance. *Clin Pharmacol Ther* 1979; **26:** 660–7.
2. Vozeh S, *et al.* Influence of allopurinol on theophylline disposition in adults. *Clin Pharmacol Ther* 1980; **27:** 194–7.
3. Manfredi RL, Vesell ES. Inhibition of theophylline metabolism by long-term allopurinol administration. *Clin Pharmacol Ther* 1981; **29:** 224–9.
4. Barry M, Feely J. Allopurinol influences aminophenazone elimination. *Clin Pharmacokinet* 1990; **19:** 167–9.
5. Chen TWD, Patton TF. Effect of probenecid on the pharmacokinetics of aminophylline. *Drug Intell Clin Pharm* 1983; **17:** 465–6.
6. Birkett DJ, *et al.* Evidence for a dual action of sulphinpyrazone on drug metabolism in man: theophylline-sulphinpyrazone interaction. *Br J Clin Pharmacol* 1983; **15:** 567–9.

Antineoplastics. There has been a report of increased clearance of theophylline in 3 patients given *aminoglutethimide*.[1]

The clearance of theophylline (given as theophylline, aminophylline, or choline theophyllinate) was reported to decrease by an average of 19% in 8 patients with severe corticosteroid-dependent asthma given low-dose weekly intramuscular injections of *methotrexate*.[2] A high degree of interpatient variability was seen. Three patients reported nausea; one of whom required a decrease in theophylline dose. The authors reported that the most likely explanation for the change in theophylline clearance was inhibition of microsomal enzyme activity.

For reference to a possible interaction between theophylline and *lomustine*, see Lomustine, p.741.

1. Lønning PE, *et al.* Effect of aminoglutethimide on antipyrine, theophylline, and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* 1984; **36:** 796–802.
2. Glynn-Barnhart AM, *et al.* Effect of low-dose methotrexate on the disposition of glucocorticoids and theophylline. *J Allergy Clin Immunol* 1991; **88:** 180–6.

Antivirals. A single injection of recombinant human *interferon alfa* reduced theophylline clearance by 33 to 81% in 8 of 9 subjects, resulting in a 1.5- to sixfold increase in the theophylline elimination half-life.[1] Injection of interferon alfa once daily for 3 days in 11 healthy subjects also reduced theophylline clearance and increased elimination half-life,[2] but the magnitude of the changes were of a similar order to normal intra-individual variation and the interaction was considered of minor clinical significance.

Licensed product information for *ritonavir* states that it substantially increases the clearance of theophylline; theophylline dosage may need to be increased to maintain efficacy.

There is evidence[3] that *aciclovir* inhibits theophylline metabolism, resulting in accumulation.

1. Williams SJ, *et al.* Inhibition of theophylline metabolism by interferon. *Lancet* 1987; **ii:** 939–41.
2. Jonkman JHG, *et al.* Effects of α-interferon on theophylline pharmacokinetics and metabolism. *Br J Clin Pharmacol* 1989; **27:** 795–802.
3. Maeda Y, *et al.* Inhibition of theophylline metabolism by aciclovir. *Biol Pharm Bull* 1996; **19:** 1591–5.

Benzodiazepines. For reference to the antagonism of benzodiazepine sedation by aminophylline, see Xanthines, under Interactions of Diazepam, p.992.

Beta blockers. *Propranolol* reduced theophylline clearance by 36% in healthy subjects given aminophylline intravenously. *Metoprolol* did not reduce clearance in the group as a whole, but a reduction was noted in some smokers whose theophylline clearance was initially high.[1] Propranolol is thought to exert a dose-dependent selective inhibitory effect on the separate cytochrome P450 isoenzymes involved in theophylline demethylation and 8-hydroxylation.[2] The less lipophilic beta blockers *atenolol*[3,4] and *nadolol*[4] had no significant effect on the pharmacokinetics of theophylline.

In general, however, beta blockers should be avoided in patients taking theophylline as they can dangerously exacerbate bronchospasm in patients with a history of asthma or chronic obstructive pulmonary disease.

1. Conrad KA, Nyman DW. Effects of metoprolol and propranolol on theophylline elimination. *Clin Pharmacol Ther* 1980; **28:** 463–7.
2. Miners JO, *et al.* Selectivity and dose-dependency of the inhibitory effect of propranolol on theophylline metabolism in man. *Br J Clin Pharmacol* 1985; **20:** 219–23.
3. Cerasa LA, *et al.* Lack of effect of atenolol on the pharmacokinetics of theophylline. *Br J Clin Pharmacol* 1988; **26:** 800–2.
4. Corsi CM, *et al.* Lack of effect of atenolol and nadolol on the metabolism of theophylline. *Br J Clin Pharmacol* 1990; **29:** 265–8.

Caffeine. Abstention from dietary methylxanthines by healthy subjects has resulted in faster elimination of theophylline.[1] While the addition of extra caffeine to the diet has been reported not to alter theophylline disposition,[2] some studies in healthy subjects have indicated that the ingestion of moderate amounts of caffeine (120 to 900 mg daily), which could be consumed by drinking several cups of coffee daily, can have a pronounced influence on the pharmacokinetics of theophylline.[3,4] In these latter studies the mean theophylline clearance was reduced by 23 and 29% with a corresponding increase in the elimination half-lives.

1. Monks TJ, *et al.* Influence of methylxanthine-containing foods on theophylline metabolism and kinetics. *Clin Pharmacol Ther* 1979; **26:** 513–24.
2. Monks TJ, *et al.* The effect of increased caffeine intake on the metabolism and pharmacokinetics of theophylline in man. *Biopharm Drug Dispos* 1981; **2:** 31–7.
3. Jonkman JHG, *et al.* The influence of caffeine on the steady-state pharmacokinetics of theophylline. *Clin Pharmacol Ther* 1991; **49:** 248–55.
4. Sato J, *et al.* Influence of usual intake of dietary caffeine on single-dose kinetics of theophylline in healthy human subjects. *Eur J Clin Pharmacol* 1993; **44:** 295–8.

Calcium-channel blockers. *Verapamil* has been reported[1] to decrease the clearance of theophylline by a mean of 14% in healthy subjects and although this was not considered to be clinically significant, symptoms of theophylline toxicity, associated with near doubling of the serum-theophylline concentration have occurred in a 76-year-old woman taking theophylline after 6 days of therapy with verapamil.[2] Studies in healthy subjects and asthmatic patients have produced conflicting results of the effect of *nifedipine* on the pharmacokinetics of theophylline. Reduced clearance[1] and an increase in the volume of distribution[3,4] of theophylline have been reported and both decreased[4] and increased[5] serum-theophylline concentrations; theophylline toxicity has been reported.[6,7] However, most studies have concluded that the effects of nifedipine are unlikely to be of clinical importance.[1,4,5,8]

Serum concentrations of theophylline have been reported to be increased by *diltiazem*[5] and reduced by *felodipine*;[9] neither of these effects were considered to be clinically significant.

1. Robson RA, *et al.* Selective inhibitory effects of nifedipine and verapamil on oxidative metabolism: effects on theophylline. *Br J Clin Pharmacol* 1988; **25:** 397–400.
2. Burnakis TG, *et al.* Increased serum theophylline concentrations secondary to oral verapamil. *Clin Pharm* 1983; **2:** 458–61.
3. Jackson SHD, *et al.* The interaction between iv theophylline and chronic oral dosing with slow release nifedipine in volunteers. *Br J Clin Pharmacol* 1986; **21:** 389–92.
4. Adebayo GI, Mabadeje AFB. Effect of nifedipine on antipyrine and theophylline disposition. *Biopharm Drug Dispos* 1990; **11:** 157–64.
5. Smith SR, *et al.* The influence of nifedipine and diltiazem on serum theophylline concentration-time profiles. *J Clin Pharm Ther* 1989; **14:** 403–8.
6. Parrillo SJ, Venditto M. Elevated theophylline blood levels from institution of nifedipine therapy. *Ann Emerg Med* 1984; **13:** 216–17.
7. Harrod CS. Theophylline toxicity and nifedipine. *Ann Intern Med* 1987; **106:** 480.
8. Spedini C, Lombardi C. Long-term treatment with oral nifedipine plus theophylline in the management of chronic bronchial asthma. *Eur J Clin Pharmacol* 1986; **31:** 105–6.
9. Bratel T, *et al.* Felodipine reduces the absorption of theophylline in man. *Eur J Clin Pharmacol* 1989; **36:** 481–5.

Cannabis. A search of the literature[1] revealed 2 studies, both published in the 1970s, that showed that marijuana smoking increased the clearance of theophylline.

1. Brown D. Influence on theophylline clearance. *Pharm J* 1994; **253:** 595.

Corticosteroids. In 3 patients with acute severe asthma given aminophylline intravenously, serum-theophylline concentrations rose rapidly from the therapeutic range to between 40 and 50 micrograms/mL when *hydrocortisone* was given intravenously.[1] In studies in healthy subjects, no significant changes in serum-theophylline concentrations were noted when hydrocortisone, *methylprednisolone*,[2] or *prednisone*[3] were given, although there was a trend towards increased theophylline clearance during corticosteroid therapy.[2,3] In preterm neonates, exposure to *betamethasone in utero* stimulated the hepatic metabolism of theophylline,[4,5] but did not affect dosage requirements.

The possibility that adverse effects such as hypokalaemia may be potentiated by use of theophylline with corticosteroids should be borne in mind.

1. Buchanan N, *et al.* Asthma—a possible interaction between hydrocortisone and theophylline. *S Afr Med J* 1979; 56: 1147–8.
2. Leavengood DC, *et al.* The effect of corticosteroids on theophylline metabolism. *Ann Allergy* 1983; **50:** 249–51.
3. Anderson JL, *et al.* Potential pharmacokinetic interaction between theophylline and prednisone. *Clin Pharm* 1984; **3:** 187–9.
4. Jager-Roman E, *et al.* Increased theophylline metabolism in premature infants after prenatal betamethasone administration. *Dev Pharmacol Ther* 1982; **5:** 127–35.
5. Baird-Lambert J, *et al.* Theophylline metabolism in preterm neonates during the first weeks of life. *Dev Pharmacol Ther* 1984; **7:** 239–44.

Disulfiram. In a study involving 20 recovering alcoholic patients, disulfiram decreased the plasma clearance and prolonged the elimination half-life of theophylline in a dose-dependent manner.[1] It was concluded that disulfiram exerts a dose-dependent inhibitory effect on the hepatic metabolism of theophylline and that, in order to minimise the risk of toxicity, the dosage of theophylline may need to be reduced by up to 50% if given together.

1. Loi C-M, *et al.* Dose-dependent inhibition of theophylline metabolism by disulfiram in recovering alcoholics. *Clin Pharmacol Ther* 1989; **45:** 476–86.

Diuretics. Although increased mean serum-theophylline concentrations were noted in 10 patients given continuous intravenous aminophylline infusions after intravenous injection of *furosemide*,[1] in 8 patients with chronic stable asthma, mean peak serum-theophylline concentrations were reduced from 12.14 micrograms/mL with placebo to 7.16 micrograms/mL when furosemide was given. Reduced concentrations were noted for up to 6 hours after furosemide.[2] Decreased theophylline concentrations were also noted in 4 neonates receiving oral or intravenous theophylline when given furosemide.[3] Serum-theophylline concentrations returned to normal when furosemide and theophylline were given more than 2 hours apart.

The possibility that adverse effects such as hypokalaemia may be potentiated if theophylline is given with diuretics should be borne in mind.

1. Conlon PF, *et al.* Effect of intravenous furosemide on serum theophylline concentration. *Am J Hosp Pharm* 1981; **38:** 1345–7.
2. Carpentiere G, *et al.* Furosemide and theophylline. *Ann Intern Med* 1985; **103:** 957.
3. Toback JW, Gilman ME. Theophylline-furosemide inactivation. *Pediatrics* 1983; **71:** 140–1.

Gastrointestinal drugs. Oral *antacids* do not appear to affect the total absorption of theophylline from the gut.[1-5] However, some studies have shown a reduction in the rate of absorption from both immediate-[1] and modified-release theophylline preparations[2] after antacids. Also an increase in peak serum-theophylline concentrations has been noted with certain modified-release formulations.[3]

Cimetidine inhibits the oxidative metabolism of theophylline reducing its clearance by 20 to 35% and prolonging its serum half-life;[6-8] toxic effects have been reported.[6] It has been recommended that the dose of aminophylline should be reduced by about one-third if given with cimetidine.[6] This inhibition of theophylline metabolism may be enhanced by liver disease,[9] but there is wide interindividual variation. The reduction in clearance may be greater in smokers.[10] Studies have suggested that *ranitidine* does not significantly inhibit theophylline metabolism,[11-14] even at very high doses.[15] However, there have been occasional reports of theophylline toxicity after use with ranitidine.[16-18] *Famotidine*[19] has also been reported to not alter theophylline disposition but one small study found a significant decrease in theophylline clearance in some patients with chronic obstructive pulmonary disease.[20]

Omeprazole, *lansoprazole*, and *pantoprazole* generally have insignificant or no effect on theophylline clearance.[21,22] In CYP2C19 poor metabolisers there may be an increase in omeprazole concentrations and subsequent induction of CYP1A, a major enzyme of theophylline metabolism. A pharmacokinetic study[23] of this induction in 5 poor metabolisers given omeprazole did find a trend towards an increase in theophylline clearance.

1. Arnold LA, *et al.* Effect of an antacid on gastrointestinal absorption of theophylline. *Am J Hosp Pharm* 1979; **36:** 1059–62.
2. Shargel L, *et al.* Effect of antacid on bioavailability of theophylline from rapid and timed-release drug products. *J Pharm Sci* 1981; **70:** 599–602.
3. Darzentas LJ, *et al.* Effect of antacid on bioavailability of a sustained-release theophylline preparation. *Drug Intell Clin Pharm* 1983; **17:** 555–7.
4. Myhre KI, Walstad RA. The influence of antacid on the absorption of two different sustained-release formulations of theophylline. *Br J Clin Pharmacol* 1983; **15:** 683–7.
5. Muir JF, *et al.* Lack of effect of magnesium-aluminium hydroxide on the absorption of theophylline given as a pH-dependent sustained-release preparation. *Eur J Clin Pharmacol* 1993; **44:** 85–8.
6. Bauman JH, *et al.* Cimetidine-theophylline interaction: report of four patients. *Ann Allergy* 1982; **48:** 100–102.
7. Vestal RE, *et al.* Cimetidine inhibits theophylline clearance in patients with chronic obstructive pulmonary disease: a study using stable isotope methodology during multiple oral dose administration. *Br J Clin Pharmacol* 1983; **15:** 411–18.
8. Roberts RK, *et al.* Cimetidine-theophylline interaction in patients with chronic obstructive airways disease. *Med J Aust* 1984; **140:** 279–80.
9. Gugler R, *et al.* The inhibition of drug metabolism by cimetidine in patients with liver cirrhosis. *Klin Wochenschr* 1984; **62:** 1126–31.
10. Grygiel JJ, *et al.* Differential effects of cimetidine on theophylline metabolic pathways. *Eur J Clin Pharmacol* 1984; **26:** 335–40.
11. Breen KJ, *et al.* Effects of cimetidine and ranitidine on hepatic drug metabolism. *Clin Pharmacol Ther* 1982; **31:** 297–300.
12. Seggev JS, *et al.* No evidence for interaction between ranitidine and theophylline. *Arch Intern Med* 1987; **147:** 179–80.
13. Adebayo GI. Effects of equimolar doses of cimetidine and ranitidine on theophylline elimination. *Biopharm Drug Dispos* 1989; **10:** 77–85.
14. Boehning W. Effect of cimetidine and ranitidine on plasma theophylline in patients with chronic obstructive airways disease treated with theophylline and corticosteroids. *Eur J Clin Pharmacol* 1990; **38:** 43–5.
15. Kelly HW, *et al.* Ranitidine at very large doses does not inhibit theophylline elimination. *Clin Pharmacol Ther* 1986; **39:** 577–81.
16. Fernandes E, Melewicz FM. Ranitidine and theophylline. *Ann Intern Med* 1984; **100:** 459.
17. Gardner ME, Sikorski GW. Ranitidine and theophylline. *Ann Intern Med* 1985; **102:** 559.
18. Hegman GW, Gilbert RP. Ranitidine-theophylline interaction—fact or fiction? *DICP Ann Pharmacother* 1991; **25:** 21–5.
19. Chremos AN, *et al.* Famotidine does not interfere with the disposition of theophylline in man: comparison to cimetidine. *Clin Pharmacol Ther* 1986; **39:** 187.
20. Dal Negro R, *et al.* Famotidine and theophylline pharmacokinetics: an unexpected cimetidine-like interaction in patients with chronic obstructive pulmonary disease. *Clin Pharmacokinet* 1993; **24:** 255–8.
21. Kokufu T, *et al.* Effects of lansoprazole on pharmacokinetics and metabolism of theophylline. *Eur J Clin Pharmacol* 1995; **48:** 391–5.
22. Dilger K, *et al.* Lack of drug interaction between omeprazole, lansoprazole, pantoprazole and theophylline. *Br J Clin Pharmacol* 1999; **48:** 438–44.
23. Cavuto NJ, *et al.* Effect of omeprazole on theophylline clearance in poor metabolizers of omeprazole. *Clin Pharmacol Ther* 1995; **57:** 215.

General anaesthetics. There have been several reports[1,2] of increased cardiotoxicity when patients taking theophylline were anaesthetised with *halothane*. There was also an early report of seizures and tachycardia attributed to an interaction between theophylline and *ketamine*.[3]

1. Barton MD. Anesthetic problems with aspirin-intolerant patients. *Anesth Analg* 1975; **54:** 376–80.
2. Richards W, *et al.* Cardiac arrest associated with halothane anesthesia in a patient receiving theophylline. *Ann Allergy* 1988; **61:** 83–4.
3. Hirschman CA, *et al.* Ketamine-aminophylline-induced decrease in seizure threshold. *Anesthesiology* 1982; **56:** 464–7.

Leukotriene inhibitors and antagonists. *Zileuton* prolongs the half-life and reduces the clearance of theophylline;[1] dosage of theophylline should be reduced to avoid toxicity when both drugs are given together, and plasma-theophylline concentrations should be monitored. Use of *zafirlukast* with theophylline decreased zafirlukast plasma concentrations but had no effect on theophylline plasma concentrations in clinical trials. However, toxic serum-theophylline concentrations occurred in one patient when zafirlukast was added to therapy, and recurred on rechallenge.[2] A dose of *montelukast* 10 mg daily did not affect the pharmacokinetics of theophylline, but doses of 200 mg and 600 mg daily reduced the maximum plasma concentration, area under the concentration-time curve, and elimination half-life of theophylline.[3]

1. Granneman GR, *et al.* Effect of zileuton on theophylline pharmacokinetics. *Clin Pharmacokinet* 1995; **29** (suppl 2): 77–83.
2. Katial RK, *et al.* A drug interaction between zafirlukast and theophylline. *Arch Intern Med* 1998; **158:** 1713–15.
3. Malmstrom K, *et al.* Effect of montelukast on single-dose theophylline pharmacokinetics. *Am J Ther* 1998; **5:** 189–95.

Methoxsalen. In a single-dose pharmacokinetic study in 3 healthy subjects, the rate of elimination of theophylline was decreased after a single oral dose of methoxsalen, while urinary excretion of unchanged theophylline increased.[1] Methoxsalen probably inhibits the metabolism of cytochrome P450 isoenzyme CYP1A2,[2] and it has been suggested that theophylline dose reductions are likely to be required when used with systemic methoxsalen but seem unlikely to be necessary with topical PUVA therapy.

1. Apseloff G, *et al.* Inhibition and induction of theophylline metabolism by 8-methoxypsoralen: in vivo study in rats and humans. *Drug Metab Dispos* 1990; **18:** 298–303.
2. Tantcheva-Poór I, *et al.* Liver cytochrome P450 CYP1A2 is markedly inhibited by systemic but not by bath PUVA in dermatological patients. *Br J Dermatol* 2001; **144:** 1127–32.

Neuromuscular blockers. For reference to resistance to neuromuscular block with pancuronium in patients receiving aminophylline, see Xanthines, p.1905.

Oral contraceptives. Oral contraceptives have been reported to decrease the clearance of theophylline by about 30%, and serum concentrations may be increased,[1-3] due to the inhibitory effects of oral contraceptives on hepatic P450 isoenzymes.

1. Tornatore KM, *et al.* Effect of chronic oral contraceptive steroids on theophylline disposition. *Eur J Clin Pharmacol* 1982; **23:** 129–34.
2. Gardner MJ, *et al.* Effects of tobacco smoking and oral contraceptive use on theophylline disposition. *Br J Clin Pharmacol* 1983; **16:** 271–80.
3. Roberts RK, *et al.* Oral contraceptive steroids impair the elimination of theophylline. *J Lab Clin Med* 1983; **101:** 821–5.

Sympathomimetics. The effect of beta-adrenoceptor agonists on the pharmacokinetics of theophylline is unclear. Whereas some studies have found that *orciprenaline*[1] or *terbutaline*[2] had no effect on theophylline disposition, others have shown an increase in theophylline clearance after *isoprenaline*[3,4] or *terbutaline*.[5,6]

Use of theophylline with beta-adrenoceptor agonists can potentiate adverse effects including hypokalaemia,[7,8] hyperglycaemia,[7] tachycardia,[7,8] hypertension,[7] and tremor.[9] Of 9 patients reported to the UK CSM with hypokalaemia during such combined therapy, 4 had clinical sequelae of cardiorespiratory arrest, intestinal pseudo-obstruction, or confusion. Monitoring of serum-potassium concentrations was recommended in patients with severe asthma given both beta-adrenoceptor agonists and xanthine derivatives.[10]

The possibility of an interaction with *phenylpropanolamine* should also be borne in mind, as it has been shown to reduce the clearance of theophylline significantly.[11]

1. Conrad KA, Woodworth JR. Orciprenaline does not alter theophylline elimination. *Br J Clin Pharmacol* 1981; **12:** 756–7.
2. Snidow J, *et al.* Acute effects of short-term subcutaneous terbutaline on theophylline disposition. *Eur J Clin Pharmacol* 1987; **32:** 191–3.
3. Hemstreet MP, *et al.* Effect of intravenous isoproterenol on theophylline kinetics. *J Allergy Clin Immunol* 1982; **69:** 360–4.
4. Griffith JA, Kozloski GD. Isoproterenol-theophylline interaction: possible potentiation by other drugs. *Clin Pharm* 1990; **9:** 54–7.
5. Danziger Y, *et al.* Reduction of serum theophylline levels by terbutaline in children with asthma. *Clin Pharmacol Ther* 1985; **37:** 469–71.
6. Garty M, *et al.* Increased theophylline clearance in asthmatic patients due to terbutaline. *Eur J Clin Pharmacol* 1989; **36:** 25–8.
7. Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. *Br J Clin Pharmacol* 1986; **21:** 451–3.
8. Whyte KF, *et al.* Salbutamol induced hypokalaemia: the effect of theophylline alone and in combination with adrenaline. *Br J Clin Pharmacol* 1988; **25:** 571–8.
9. van der Vet APH, *et al.* Pharmacodynamics (lungfunction tests, tremor measurements and cAMP determinations) of a single dose of 0.5 mg terbutaline subcutaneously during sustained-release theophylline medication in patients with asthmatic bronchitis. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 569–73.
10. Committee on Safety of Medicines. β agonists, xanthines and hypokalaemia. *Current Problems 28* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 20/05/08)
11. Wilson HA, *et al.* Phenylpropanolamine significantly reduces the clearance of theophylline. *Am Rev Respir Dis* 1991; **143:** A629.

Tacrine. Results of a study in healthy subjects indicated that tacrine reduced theophylline clearance by about 50% and increased plasma-theophylline concentrations. Competitive inhibition by tacrine of theophylline metabolism was proposed.[1]

1. deVries TM, *et al.* Effect of multiple-dose tacrine administration on single-dose pharmacokinetics of digoxin, diazepam, and theophylline. *Pharm Res* 1993; **10** (suppl): S333.

Tiabendazole. Tiabendazole has been reported[1,2] to increase serum-theophylline concentrations and to decrease theophylline clearance. It has been recommended[2] that theophylline dosage should be reduced by 50% when tiabendazole therapy is started.

1. Sugar AM, *et al.* Possible thiabendazole-induced theophylline toxicity. *Am Rev Respir Dis* 1980; **122:** 501–3.
2. Lew G, *et al.* Theophylline-thiabendazole drug interaction. *Clin Pharm* 1989; **8:** 225–7.

Ticlopidine. Theophylline elimination half-life was increased and plasma clearance was decreased in 10 healthy subjects after the use of ticlopidine 500 mg daily by mouth for 10 days.[1]

1. Colli A, *et al.* Ticlopidine-theophylline interaction. *Clin Pharmacol Ther* 1987; **41:** 358–62.

Vaccines. Transient inhibition of the hepatic metabolism of theophylline, possibly secondary to interferon production, resulting in increased theophylline serum half-life and concentration has been reported after BCG vaccination[1] and influenza vaccination.[2,3] Other studies have not been able to confirm the interaction with influenza vaccine.[4-7] The differing findings are probably due to differences in vaccine; modern purified subvirion vaccines which do not induce interferon production do not appear to alter theophylline metabolism.[8,9]

1. Gray JD, *et al.* Depression of theophylline elimination following BCG vaccination. *Br J Clin Pharmacol* 1983; **16:** 735–7.
2. Renton KW, *et al.* Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1980; **123:** 288–90.
3. Walker S, *et al.* Serum theophylline levels after influenza vaccination. *Can Med Assoc J* 1981; **125:** 243–4.
4. Goldstein RS, *et al.* Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1982; **126:** 470.
5. Fischer RG, *et al.* Influence of trivalent influenza vaccine on serum theophylline levels. *Can Med Assoc J* 1982; **126:** 1312–13.
6. Britton L, Ruben FL. Serum theophylline levels after influenza vaccination. *Can Med Assoc J* 1982; **126:** 1375.
7. Patriarca PA, *et al.* Influenza vaccination and warfarin or theophylline toxicity in nursing-home residents. *N Engl J Med* 1983; **308:** 1601–2.
8. Stults BM, Hashisaki PA. Influenza vaccination and theophylline pharmacokinetics in patients with chronic obstructive lung disease. *West J Med* 1983; **139:** 651–4.
9. Winstanley PA, *et al.* Lack of effect of highly purified subunit influenza vaccination on theophylline metabolism. *Br J Clin Pharmacol* 1985; **20:** 47–53.

Pharmacokinetics

Theophylline is rapidly and completely absorbed from liquid preparations, capsules, and uncoated tablets; the rate, but not the extent, of absorption is decreased by food, and food may also affect theophylline clearance. Peak serum-theophylline concentrations occur 1 to 2 hours after ingestion of liquid preparations, capsules, and uncoated tablets. Modified-release preparations exhibit considerable variability in their absorption characteristics and in the effect of food. They are generally not considered to be interchangeable; if a patient needs to be transferred from one such preparation to another then the dose should be retitrated. Rectal absorption is rapid from enemas, but may be slow and erratic from suppositories. Absorption after intramuscular injection is slow and incomplete.

Theophylline is about 40 to 60% bound to plasma proteins, but in neonates, or adults with liver disease, binding is reduced. Optimum therapeutic serum concentrations for bronchodilatation are generally considered to range from 10 to 20 micrograms/mL (55 to 110 micromol/litre) although some consider a lower range appropriate (see Therapeutic Drug Monitoring, below).

Theophylline is metabolised in the liver to 1,3-dimethyluric acid, 1-methyluric acid (via the intermediate 1-methylxanthine), and 3-methylxanthine. Demethylation to 3-methylxanthine (and possibly to 1-methylxanthine) is catalysed by the cytochrome P450 isoenzyme CYP1A2; hydroxylation to 1, 3-dimethyluric

acid is catalysed by CYP2E1 and CYP3A3. Both the demethylation and hydroxylation pathways of theophylline metabolism are capacity-limited, resulting in non-linear elimination. The metabolites are excreted in the urine. In adults, about 10% of a dose of theophylline is excreted unchanged in the urine, but in neonates around 50% is excreted unchanged, and a large proportion is excreted as caffeine. Considerable interindividual differences in the rate of hepatic metabolism of theophylline result in large variations in clearance, serum concentrations, and half-lives. Hepatic metabolism is further affected by factors such as age, smoking, disease, diet, and drug interactions. The serum half-life of theophylline in an otherwise healthy, non-smoking asthmatic adult is 7 to 9 hours, in children 3 to 5 hours, in cigarette smokers 4 to 5 hours, in neonates and premature infants 20 to 30 hours, and in elderly non-smokers 10 hours. The serum half-life of theophylline may be increased in patients with heart failure or liver disease. Steady state is usually achieved within 48 hours with a consistent dosing schedule.

Theophylline crosses the placenta; it is also distributed into breast milk.

Absorption. ***FOOD.*** Food has substantial but variable effects on the absorption of theophylline from modified-release formulations but it is difficult to predict whether a particular formulation will be affected.[1] Some formulations are not affected by the presence of food but for others increases or decreases in the rate and/or extent of absorption have been reported. The composition and fluid content of the food appears to be important and a rapid release of theophylline ('dose-dumping') has occurred with some formulations after a meal, especially one with a high fat content.

A diet high in protein and low in carbohydrate has been reported to increase theophylline clearance, and a low-protein, high-carbohydrate diet to decrease theophylline clearance.[2-6] The consumption of methylxanthines, particularly caffeine, in the diet may decrease theophylline clearance (see Caffeine, under Interactions, above).

1. Jonkman JHG. Food interactions with sustained-release theophylline preparations: a review. *Clin Pharmacokinet* 1989; **16:** 162–79.
2. Kappas A, *et al.* Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. *Clin Pharmacol Ther* 1976; **20:** 643–53.
3. Feldman CH, *et al.* Effect of dietary protein and carbohydrate on theophylline metabolism in children. *Pediatrics* 1980; **66:** 956–62.
4. Feldman CH, *et al.* Interaction between nutrition and theophylline metabolism in children. *Ther Drug Monit* 1982; **4:** 69–76.
5. Juan D, *et al.* Effects of dietary protein on theophylline pharmacokinetics and caffeine and aminopyrine breath tests. *Clin Pharmacol Ther* 1986; **40:** 187–94.
6. Juan D, *et al.* Impairment of theophylline clearance by a hypocaloric low-protein diet in chronic obstructive pulmonary disease. *Ther Drug Monit* 1990; **12:** 111–14.

Metabolism and excretion. ***AGE.*** From about 1 year of age until adolescence, children have a rapid theophylline clearance.[1] Premature infants and those under 1 year of age have a slower clearance[2,3] due to immature metabolic pathways.[3-5] In neonates the capacity of hepatic cytochrome P450 enzymes is much reduced compared with older children and adults, and *N*-demethylation and oxidation reactions play a minor role in the metabolism of theophylline.[4-6] Neonates are, however, capable of methylating theophylline at the N7 position to form caffeine, which is present at about one-third the concentration of theophylline at steady state.[5,6] The proportion of theophylline excreted unchanged is also increased in premature neonates and decreases with age as hepatic enzyme systems develop.[6] More rapid clearance on the first day of life in premature neonates has been reported.[7]

Some studies have found a progressive decline in clearance throughout adult years[8] whereas others have not.[9] Similarly, some studies have noted a decreased clearance in the elderly[10,11] but others have found no significant change.[12,13]

1. Zaske DE, *et al.* Oral aminophylline therapy: increased dosage requirements in children. *JAMA* 1977; **237:** 1453–5.
2. Aranda JV, *et al.* Pharmacokinetic aspects of theophylline in premature newborns. *N Engl J Med* 1976; **295:** 413–16.
3. Kraus DM, *et al.* Alterations in theophylline metabolism during the first year of life. *Clin Pharmacol Ther* 1993; **54:** 351–9.
4. Grygiel JJ, Birkett DJ. Effect of age on patterns of theophylline metabolism. *Clin Pharmacol Ther* 1980; **28:** 456–62.
5. Tserng K-Y, *et al.* Theophylline metabolism in premature infants. *Clin Pharmacol Ther* 1981; **29:** 594–600.
6. Tserng K-Y, *et al.* Developmental aspects of theophylline metabolism in premature infants. *Clin Pharmacol Ther* 1983; **33:** 522–8.
7. Stile IL, *et al.* Pharmacokinetics of theophylline in premature infants on the first day of life. *Clin Ther* 1986; **8:** 336–41.
8. Randolph WC, *et al.* The effect of age on theophylline clearance in normal subjects. *Br J Clin Pharmacol* 1986; **22:** 603–5.
9. Wiffen JK, *et al.* Does theophylline clearance alter within the adult age range? *Br J Clin Pharmacol* 1984; **17:** 219P.
10. Antal EJ, *et al.* Theophylline pharmacokinetics in advanced age. *Br J Clin Pharmacol* 1981; **12:** 637–45.
11. Jackson SHD, *et al.* The relationship between theophylline clearance and age in adult life. *Eur J Clin Pharmacol* 1989; **36:** 29–34.
12. Bauer LA, Blouin RA. Influence of age on theophylline clearance in patients with chronic obstructive pulmonary disease. *Clin Pharmacokinet* 1981; **6:** 469–74.
13. Fox RW, *et al.* Theophylline kinetics in a geriatric group. *Clin Pharmacol Ther* 1983; **34:** 60–7.

ELIMINATION KINETICS. There is evidence that the elimination of theophylline is dose-dependent and that at high serum concentrations, a small change in dose of a theophylline preparation could cause a disproportionate increase in serum-theophylline concentration, due to a reduction in clearance.[1-3] However, it is not clear that this effect is clinically significant when serum-theophylline concentrations are within the therapeutic range.[4-8] It has also been suggested that repeated oral dosing of theophylline might result in a decrease of clearance compared with pre-treatment values.[9]

1. Weinberger M, Ginchansky E. Dose-dependent kinetics of theophylline disposition in asthmatic children. *J Pediatr* 1977; **91:** 820–4.
2. Tang-Liu DD-S, *et al.* Nonlinear theophylline elimination. *Clin Pharmacol Ther* 1982; **31:** 358–69.
3. Butcher MA, *et al.* Dose-dependent pharmacokinetics with single daily dose slow release theophylline in patients with chronic lung disease. *Br J Clin Pharmacol* 1982; **13:** 241–3.
4. Koëter GH, *et al.* Pharmacokinetics of sustained release theophylline in low and high multidose regimens. *Br J Clin Pharmacol* 1981; **12:** 647–51.
5. Rovei V, *et al.* Pharmacokinetics of theophylline: a dose-range study. *Br J Clin Pharmacol* 1982; **14:** 769–78.
6. Gundert-Remy U, *et al.* Non-linear elimination processes of theophylline. *Eur J Clin Pharmacol* 1983; **24:** 71–8.
7. Brown PJ, *et al.* Lack of dose dependent kinetics of theophylline. *Eur J Clin Pharmacol* 1983; **24:** 525–7.
8. Milavetz G, *et al.* Dose dependency for absorption and elimination rates of theophylline: implications for studies of bioavailability. *Pharmacotherapy* 1984; **4:** 216–20.
9. Efthimiou H, *et al.* Influence of chronic dosing on theophylline clearance. *Br J Clin Pharmacol* 1984; **17:** 525–30.

GENDER. A higher theophylline clearance and shorter elimination half-life has been reported in healthy premenopausal women than in healthy men, probably due to sex-related differences in hepatic metabolism.[1] Changes in the pharmacokinetics of theophylline in women have also been reported according to the stage of the menstrual cycle;[2,3] another study[4] found no changes.

1. Nafziger AN, Bertino JS. Sex-related differences in theophylline pharmacokinetics. *Eur J Clin Pharmacol* 1989; **37:** 97–100.
2. Brguerolle B, *et al.* Influence of the menstrual cycle on theophylline pharmacokinetics in asthmatics. *Eur J Clin Pharmacol* 1990; **39:** 59–61.
3. Nagata K, *et al.* Increased theophylline metabolism in the menstrual phase of healthy women. *J Allergy Clin Immunol* 1997; **100:** 39–43.
4. Matsuki S, *et al.* Pharmacokinetic changes of theophylline and amikacin through the menstrual cycle in healthy women. *J Clin Pharmacol* 1999; **39:** 1256–62.

Pregnancy and breast feeding. For mention of the pharmacokinetics of theophylline during pregnancy and breast feeding, see under Precautions, above.

Protein binding. Albumin is the major plasma binding protein for theophylline, binding is pH-dependent, and the percentage of theophylline bound at physiological pH is reported to range from about 35 to 45%.[1,2] Some studies have found the plasma protein binding of theophylline to be concentration dependent,[3] but others have not confirmed this.[1,4] Protein binding has been reported to be slightly but significantly higher in patients with bronchial asthma than in healthy controls.[5] Reduced protein binding occurs in patients with hypoalbuminaemia;[6,7] it has also been found in obese subjects[8] (possibly due to elevated concentrations of free fatty acids, which can displace theophylline from binding sites).

1. Buss D, *et al.* Determinants of the plasma protein binding of theophylline in health. *Br J Clin Pharmacol* 1983; **15:** 399–405.
2. Brørs O, *et al.* Binding of theophylline in human serum determined by ultrafiltration and equilibrium dialysis. *Br J Clin Pharmacol* 1983; **15:** 393–7.
3. Gundert-Remy U, Hildebrandt R. Binding of theophylline and its metabolites to human plasma proteins. *Br J Clin Pharmacol* 1983; **16:** 573–4.
4. Buss DC, *et al.* Protein binding of theophylline. *Br J Clin Pharmacol* 1985; **19:** 529–31.
5. Trnavská Z. Theophylline protein binding. *Arzneimittelforschung* 1990; **40:** 166–9.
6. Leopold D, *et al.* The ex vivo plasma protein binding of theophylline in renal disease. *Br J Clin Pharmacol* 1985; **19:** 823–5.
7. Connelly TJ, *et al.* Characterization of theophylline binding to serum proteins in pregnant and nonpregnant women. *Clin Pharmacol Ther* 1990; **47:** 68–72.
8. Shum L, Jusko WJ. Effects of obesity and ancillary variables (dialysis time, drug, albumin, and fatty acid concentrations) on theophylline serum protein binding. *Biopharm Drug Dispos* 1989; **10:** 549–62.

Therapeutic drug monitoring. Dosage requirements of theophylline preparations vary widely between subjects and even vary with time in individuals, since serum-theophylline concentrations are influenced by factors including disease states, other drugs, diet, smoking, and age. Serious toxicity is related to serum concentration and may not be preceded by minor symptoms. For these reasons it is recommended that serum-theophylline concentrations should be monitored.

The generally accepted optimal serum concentration is between 10 and 20 micrograms/mL,[1-4] but this should be regarded as a guide and not a rigid barrier and clinical decisions should never be based solely on the serum concentration.[1] The therapeutic range in the treatment of neonatal apnoea is usually considered to be 5 to 15 micrograms/mL although some babies may respond at lower concentrations.[5] Some now consider that this is a more appropriate range in asthma (except perhaps acute severe asthma).[6] It has been suggested that pulmonary function tests provide a better guide in long-term therapy with theophylline.[7]

Serum-theophylline concentrations were originally measured by spectrophotometry but this is subject to considerable interference from other drugs. High performance liquid chromatography is now the method of choice when extreme accuracy is important and the enzyme multiplied immunoassay technique (EMIT) has become popular because of its rapidity and adaptability to processing large batches.[2] Devices are also available that provide serum-theophylline measurements within several minutes using monoclonal antibody technology.[2,8]

The use of salivary concentrations for monitoring theophylline dosage requirements has been tried, because it is noninvasive, but poor correlations between salivary- and serum-theophylline concentrations mean it has not gained general usage.

1. Hampson JP. The theophylline "therapeutic window"—fact or fallacy? *Pharm J* 1988; **241:** 722–4.
2. Bierman CW, Williams PV. Therapeutic monitoring of theophylline: rationale and current status. *Clin Pharmacokinet* 1989; **17:** 377–84.
3. Holford N, *et al.* Theophylline target concentration in severe airways obstruction—10 or 20 mg/L. A randomised concentration-controlled trial. *Clin Pharmacokinet* 1993; **25:** 495–505.
4. Pesce AJ, *et al.* Standards of laboratory practice: theophylline and caffeine monitoring. *Clin Chem* 1998; **44:** 1124–8.
5. Edwards C. Theophylline and caffeine. *Pharm J* 1986; **237:** 128–9.
6. Hardy CC, Smith J. Adverse reactions profile: theophylline and aminophylline. *Prescribers' J* 1997; **37:** 96–101.
7. Ashutosh K, *et al.* Use of serum theophylline level as a guide to optimum therapy in patients with chronic obstructive lung disease. *J Clin Pharmacol* 1990; **30:** 324–9.
8. Clifton GD, *et al.* Accuracy and time requirements for use of three rapid theophylline assay methods. *Clin Pharm* 1988; **7:** 462–6.

Uses and Administration

Theophylline is a xanthine (p.1108) and relaxes bronchial smooth muscle, relieves bronchospasm, and has a stimulant effect on respiration. It stimulates the myocardium and CNS, decreases peripheral resistance and venous pressure, and causes diuresis. It is still not clear how theophylline exerts these effects. Inhibition of phosphodiesterase with a resulting increase in intracellular cyclic adenosine monophosphate (cyclic AMP) occurs, and may play a role. Other proposed mechanisms of action include adenosine receptor antagonism, prostaglandin antagonism, and effects on intracellular calcium. In addition, theophylline may also have an anti-inflammatory effect.

Theophylline is used as a bronchodilator in the management of reversible airways obstruction, such as in asthma. Although selective beta$_2$ adrenoceptor stimulants (beta$_2$ agonists) such as salbutamol are generally the preferred bronchodilators for initial treatment, theophylline is commonly used as an adjunct to beta$_2$ agonist and corticosteroid therapy in patients requiring an additional bronchodilating effect. Some patients with chronic obstructive pulmonary disease also have a beneficial response to theophylline therapy. Theophylline is also used to relieve apnoea in neonates. It was formerly used as an adjunct in the treatment of heart failure, and may occasionally have a role in patients with this condition who are also suffering from obstructive airways disease.

Theophylline may be given in the anhydrous form or as the hydrate. Doses of theophylline are usually expressed as anhydrous theophylline; theophylline hydrate 1.1 mg is equivalent to about 1 mg of theophylline.

The pharmacokinetics of theophylline may be altered by factors including age, smoking, disease, diet, and drug interactions (see above under Precautions, Interactions, and Pharmacokinetics). Theophylline doses should therefore be adjusted for each individual patient

according to clinical response, adverse effects, and serum-theophylline concentrations.

- Optimum **therapeutic serum concentrations** of theophylline are traditionally considered to range from 10 to 20 micrograms/mL (55 to 110 micromoles/litre) and toxic effects are more common above 20 micrograms/mL. A range of 5 to 15 micrograms/mL may be effective, and associated with fewer adverse effects.

For long-term use, once a maintenance dose has been established, monitoring of serum-theophylline concentrations at 6- to 12-monthly intervals has been recommended.

In the management of **acute severe bronchospasm**, theophylline may be given by *intravenous infusion* where available, though usually aminophylline is preferred (see p.1114). (Anhydrous theophylline 1 mg is equivalent to about 1.18 mg anhydrous aminophylline or 1.28 mg aminophylline hydrate.)

- In patients who have not received theophylline, aminophylline, or other xanthine-containing medications in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes followed by a suggested maintenance dose of 400 to 600 micrograms/kg per hour. Lower doses should be used in the elderly and those with cor pulmonale, heart failure, or liver disease; smokers may require a higher maintenance dose. Dosage should be calculated in terms of lean or ideal body-weight.
- Intravenous theophylline therapy is best avoided in patients already taking theophylline, aminophylline, or other xanthine-containing medication but, if considered necessary, serum-theophylline concentrations should be measured to determine a loading dose. Loading doses are based on the expectation that each 500 micrograms of theophylline/kg of lean body-weight will result in an increase of serum-theophylline concentration of 1 microgram/mL.

In the treatment of **acute bronchospasm** that has not required intravenous therapy, theophylline has been given *orally* in conventional dosage forms; modified-release preparations are not suitable.

- In adults not currently taking theophylline or xanthine-containing products a suggested loading dose is 5 mg/kg, to produce an average peak serum concentration of 10 micrograms/mL. Doses should again be reduced in the elderly and those with cor pulmonale, heart failure, or liver disease; smokers may require a higher maintenance dose.

In the long-term management of **chronic bronchospasm**, theophylline may be given orally in doses ranging from 300 to 1000 mg daily in divided doses as conventional tablets, capsules, liquid preparations, or modified-release preparations. For conventional dosage forms the divided doses are generally given every 6 to 8 hours. However, modified-release preparations are more commonly used as they reduce adverse effects and the need for frequent dosing, especially in patients with a rapid theophylline clearance.

- A usual dose of modified-release theophylline is 175 to 500 mg every 12 hours, though the bioavailability of different modified-release theophylline preparations may not be comparable and retitration of dosage is required if the patient is changed from one modified-release preparation to another. Larger doses may be given in either the evening or the morning to achieve optimum therapeutic effect when symptoms are most severe. Modified-release preparations which are given once daily are also available; usual doses are 400 or 600 mg daily.
- Initially, low doses of theophylline should be given and they should be gradually adjusted according to clinical response and serum-theophylline measurements. In the USA a preferred approach to initial dosage titration in adults may be to begin with 300 mg daily, in divided doses, for 3 days; if well tolerated, the total daily dose is increased to 400 mg for 3 days, and then, if tolerated and required, to 600 mg. For doses of theophylline used in children, see Administration in Children, below.

Intramuscular injection and dosage by suppository are not recommended due to severe local irritation and slow unreliable absorption.

Theophylline is an ingredient of some preparations promoted for coughs.

There are topical cosmetic preparations containing theophylline derivatives, particularly aminophylline, that have been promoted for the local reduction of body fat (p.1115).

Theophylline monoethanolamine (theophylline olamine), theophylline calcium salicylate, theophylline and sodium acetate (theophylline sodium acetate), theophylline sodium glycinate (theophylline sodium aminoacetate), theophylline calcium glycinate, and theophylline glycinate have all been used similarly to theophylline.

◊ General references.

1. Vasallo R, Lipsky JJ. Theophylline: recent advances in the understanding of its mode of action and uses in clinical practice. *Mayo Clin Proc* 1998; **73:** 346–54.

Administration. Various methods have been proposed for estimating theophylline pharmacokinetic parameters to enable optimisation of initial dosage but none should be substituted for the subsequent determination of serum-theophylline concentrations and clearance at steady state.[1-3]

It was noted in 1997 that dosage requirements for theophylline had declined relative to those of historical controls, apparently due to a downward shift in theophylline clearance in the US population (perhaps due to environmental changes, such as a decrease in exposure to tobacco smoke).[4] It was suggested that earlier dosage guidelines for theophylline needed to be revised in the light of these data, so that the initial oral dose did not exceed 300 mg daily—for an approach to initial dosage titration consonant with this view, see Uses and Administration, above.

1. Erdman SM, *et al.* An updated comparison of drug dosing methods part II: theophylline. *Clin Pharmacokinet* 1991; **20:** 280–92.
2. Hogue SL, Phelps SJ. Evaluation of three theophylline dosing equations for use in infants up to one year of age. *J Pediatr* 1993; **123:** 651–6.
3. Lee TC, *et al.* Theophylline population pharmacokinetics from routine monitoring data in very premature infants with apnoea. *Br J Clin Pharmacol* 1996; **41:** 191–200.
4. Asmus MJ, *et al.* Apparent decrease in population clearance of theophylline: implications for dosage. *Clin Pharmacol Ther* 1997; **62:** 483–9.

Administration in children. In the management of **acute severe bronchospasm** in children, theophylline may be given by *intravenous infusion* where available, although aminophylline is preferred (see p.1115). In children who have not had theophylline, aminophylline or other xanthine-containing medicine in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes. Initial maintenance doses are designed to achieve a serum-theophylline concentration of 10 micrograms/mL. The following doses, based on lean or ideal body-weight, have been suggested:

- 1 to 9 years of age, 0.8 to 1 mg/kg per hour
- 9 to 12 years of age, 0.7 to 0.77 mg/kg per hour

Serum-theophylline concentrations should be used to guide further dose adjustments. See Administration in Infants, below for doses used in children under 1 year of age. Children 12 years of age and over can receive similar doses to adults, see Uses and Administration, above.

If intravenous theophylline therapy is considered necessary in children who are already being given theophylline, aminophylline or other xanthine-containing medicine, serum-theophylline concentrations should be measured to determine a loading dose. Loading doses are based on the expectation that each 500 micrograms of theophylline/kg of lean body-weight will result in a 1-microgram/mL increase in serum-theophylline concentration.

In the treatment of **acute bronchospasm** that has not required intravenous therapy, theophylline has been given *orally* using immediate-release preparations to children aged 1 year old and above, using doses similar to those used in adults, see Uses and Administration, above. For doses used in children under 1 year of age, see Administration in Infants, below.

Oral modified-release preparations of theophylline are given to children from 6 months of age in the long-term management of **chronic bronchospasm**. Dose and dosage frequency depend on the preparation being used, and licensed product information should be consulted; different formulations are not considered interchangeable.

ADMINISTRATION IN INFANTS. Theophylline clearance is reduced in premature neonates and infants under 1 year of age due to an immature hepatic microsomal enzyme system (see under Metabolism and Excretion in Pharmacokinetics, above). Postconceptional age may have a slight influence on theophylline clearance but postnatal age is thought to be more significant.[1]

Theophylline dosage guidelines for infants under 1 year of age were issued by the FDA[2] in 1985, but a number of clinicians considered that higher doses might be necessary.[1,3,4] Subsequent guidelines for *oral* theophylline,[5] issued in 1995, suggested a modified regimen: premature infants should be given initial doses of 1 mg/kg every 12 hours if less than 24 days postnatal age, or 1.5 mg/kg every 12 hours if more than 24 days; in full-term infants up to 1 year of age initial daily dosage (to be given in 3 or 4 divided doses) could be calculated on the basis of the equation:

$$\text{Daily dose (mg/kg)} = (0.2 \times \text{age in weeks}) + 5.0$$

Subsequent dosage should be adjusted based on steady-state serum-theophylline concentrations, which might take as long as 5 days to be achieved in premature neonates if a loading dose is not used.[5] The recommended serum concentrations were 5 to 10 micrograms/mL in neonates and 10 to 15 micrograms/mL in older infants. If a loading dose is considered necessary, 5 mg/kg (or 1 mg/kg for each 2 micrograms/mL increase in serum-theophylline concentration in those already being given theophylline) has been suggested.

Other equations and models of population pharmacokinetics have been proposed for the calculation of appropriate theophylline doses in neonates.[6-8]

Theophylline may be given by *intravenous infusion*, where available, in the management of **acute severe bronchospasm** in infants, although aminophylline is preferred (see p.1115). In infants who have not had theophylline, aminophylline or other xanthine-containing medicine in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes. In neonates the following initial maintenance doses have been suggested by the *American Hospital Formulary Service* to achieve a serum-theophylline concentration of 7.5 micrograms/mL :

- neonate, postnatal age 24 days or less, 1 mg/kg every 12 hours
- neonate, postnatal age over 24 days, 1.5 mg/kg every 12 hours

To achieve a serum-theophylline concentration of 10 micrograms/mL the following initial maintenance doses have been suggested by the *Canadian Pharmacists Association*:

- neonate, 170 micrograms/kg per hour
- 6 weeks to 6 months of age, 430 micrograms/kg per hour
- 6 months to 1 year of age, 500 to 600 micrograms/kg per hour

Serum-theophylline concentrations should be used to guide further dose adjustments.

Theophylline may be given prophylactically to reduce some of the adverse renal consequences of perinatal asphyxia (see below).

Theophylline has been used in **neonatal apnoea**, although caffeine is preferred. See Neonatal Apnoea, under Caffeine p.1118.

1. Gilman JT, Gal P. Inadequacy of FDA dosing guidelines for theophylline use in neonates. *Drug Intell Clin Pharm* 1986; **20:** 481–4.
2. Anonymous. Use of theophylline in infants. *FDA Drug Bull* 1985; **15:** 16–17.
3. Murphy JE, *et al.* New FDA guidelines for theophylline dosing in infants. *Clin Pharm* 1986; **5:** 16.
4. Kriter KE, Blanchard J. Management of apnea in infants. *Clin Pharm* 1989; **8:** 577–87.
5. Hendeles L, *et al.* Revised FDA labeling guideline for theophylline oral dosage forms. *Pharmacotherapy* 1995; **15:** 409–27.
6. Hogue SL, Phelps SJ. Evaluation of three theophylline dosing equations for use in infants up to one year of age. *J Pediatr* 1993; **123:** 651–6.
7. Lee TC, *et al.* Theophylline population pharmacokinetics from routine monitoring data in very premature infants with apnoea. *Br J Clin Pharmacol* 1996; **41:** 191–200.
8. Gagnon AJ. Aminophylline dosing in the treatment of apnea of prematurity—a commentary. *Pharmacotherapy* 1996; **16:** 317–18.

Administration in hepatic impairment. Theophylline clearance is reduced by 50% or more in patients with hepatic insufficiency such as cirrhosis, acute hepatitis, or cholestasis. Careful attention to dose reduction and frequent monitoring of serum-theophylline concentrations are required.

Asthma. Theophylline and its derivatives may be used in the treatment of chronic asthma (p.1108) as an adjunct to $beta_2$ agonists and corticosteroid therapy when an additional bronchodilator is indicated. Modified-release preparations can be useful in the control of nocturnal asthma.

Evidence suggests[1,2] that adding low-dose oral theophylline to inhaled corticosteroids is as effective as increasing the dose of corticosteroid in patients with moderate asthma and persistent symptoms. A systematic review[3] of studies that compared theophylline with long-acting $beta_2$ agonists found that they were both effective for control of nocturnal asthma, but that long-acting $beta_2$ agonists may be more effective in reducing asthma symptoms, including night waking and the need for rescue medication, and are associated with fewer adverse effects.

The use of xanthines in acute asthma attacks is more controversial. UK guidelines permit the use of intravenous aminophylline in patients with severe or life-threatening acute asthma unrespon-

sive to maximal doses of bronchodilators and oral corticosteroids, (a point supported in children[4] but not in adults[5] by systematic review) whereas US guidelines do not consider xanthines have any benefit over the optimal use of beta agonists and consequently do not recommend their use (see p.1108).

1. Wang Y, *et al.* Comparison of inhaled corticosteroid combined with theophylline and double-dose inhaled corticosteroid in moderate to severe asthma. *Respirology* 2005; **10:** 189–95.
2. Lim S, *et al.* Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax* 2000; **55:** 837–41.
3. Tee AKH, *et al.* Long acting beta-agonists versus theophylline for maintenance treatment of asthma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 19/03/08).
4. Mitra A, *et al.* Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 19/03/08).
5. Parameswaran K, *et al.* Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).

Cardiac arrhythmias. Theophylline has been tried in various bradyarrhythmias, usually when other treatment has failed or is contra-indicated.[1-6] It appears to be of little value in bradyasystolic cardiac arrest.[7,8]

1. Viskin S, *et al.* Aminophylline for bradyasystolic cardiac arrest refractory to atropine and epinephrine. *Ann Intern Med* 1993; **118:** 279–81.
2. Sra JS, *et al.* Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. *N Engl J Med* 1993; **328:** 1085–90.
3. Bertolet BD, *et al.* Theophylline for the treatment of atrioventricular block after myocardial infarction. *Ann Intern Med* 1995; **123:** 509–11.
4. Alboni P, *et al.* Effects of permanent pacemaker and oral theophylline in sick sinus syndrome: the THEOPACE study: a randomized controlled trial. *Circulation* 1997; **96:** 260–6.
5. Ling CA, Crouch MA. Theophylline for chronic symptomatic bradycardia in the elderly. *Ann Pharmacother* 1998; **32:** 837–9.
6. Cawley MJ, *et al.* Intravenous theophylline — an alternative to temporary pacing in the management of bradycardia secondary to AV nodal block. *Ann Pharmacother* 2001; **35:** 303–7.
7. Abu-Laban RB, *et al.* Aminophylline in bradyasystolic cardiac arrest: a randomised placebo-controlled trial. *Lancet* 2006; **367:** 1577–84.
8. Hayward E, *et al.* Aminophylline in bradyasystolic cardiac arrest. *Emerg Med J* 2007; **24:** 582–3.

Cheyne-Stokes respiration. Oral theophylline considerably reduced Cheyne-Stokes respiration (periodic breathing) and episodes of central apnoea in 2 studies in patients with stable heart failure and left ventricular systolic dysfunction.[1,2] This was associated with an improvement in arterial-oxygen saturation during sleep. One study[1] observed no significant change in cardiac function, although pulmonary function did improve. Theophylline was also effective in a patient with Cheyne-Stokes respiration possibly related to diabetic autonomic neuropathy[3] (the use of the term Cheyne-Stokes respiration to describe this patient's respiratory disorder has been questioned[4,5]).

1. Javaheri S, *et al.* Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med* 1996; **335:** 562–7.
2. Hu K, *et al.* The effect of theophylline on sleep-disordered breathing in patients with stable chronic congestive heart failure. *Chin Med J* 2003; **116:** 1711–16.
3. Pesek CA, *et al.* Theophylline therapy for near-fatal Cheyne-Stokes respiration: a case report. *Ann Intern Med* 1999; **130:** 427–30.
4. Sin DD, Bradley TD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; **131:** 713.
5. Geigel EJ, Chediak AD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; **131:** 713–14.

Chronic obstructive pulmonary disease. In the treatment of chronic obstructive pulmonary disease (p.1112), the bronchodilators of first choice are usually either an antimuscarinic such as ipratropium bromide, or a $beta_2$ agonist such as salbutamol, given by inhalation. However the addition of an oral xanthine such as theophylline may be of value in some patients to maximise respiratory function and for its positive cardiac inotropic effects.

A systematic review[1] of studies comparing oral theophylline with placebo in patients with moderate to severe chronic obstructive pulmonary disease (COPD), found that theophylline treatment improved lung function, ventilatory capacity, and arterial blood gas tensions. A decrease in thoracic gas entrapment and hyperinflation, and an increase in respiratory muscle function and diaphragmatic strength could be responsible for the improvement in symptoms. Improvements in arterial blood gas tensions may result from an increased tidal volume caused by either a direct positive inotropic effect on the respiratory muscles, or a central stimulatory action, or both. The authors concluded that theophylline produced an improvement in lung function similar to that reported for long acting $beta_2$ agonists in COPD patients, and that with close monitoring beneficial effects may be obtained from theophylline therapy in those patients who remain symptomatic from COPD despite first-line bronchodilator therapy. Theophylline has been reported to exert an inhibitory effect on airway inflammation in COPD, particularly at plasma concentrations below 10 micrograms/mL.[2] It has also been suggested that low-dose theophylline may restore corticosteroid responsiveness in COPD patients, but further research is required to assess its role.

1. Ram FSF, *et al.* Oral theophylline for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 19/03/08).
2. Barnes PJ. Theophylline for COPD. *Thorax* 2006; **61:** 742–4.

Contrast nephropathy. For mention of theophylline as a potential protectant against kidney damage induced by iodinated contrast media, see Effects on the Kidneys, under Amidotrizoic Acid, p.1476.

ECT. For mention of the use of theophylline as an adjunct to electroconvulsive therapy, see under Precautions, above.

Erythrocytosis. When pharmacological treatment is required for secondary erythrocytosis (p.1198), current UK guidelines[1,2] recommend an ACE inhibitor or an angiotensin II receptor antagonist as the usual drugs of first choice. Although theophylline appears to be less effective than an ACE inhibitor in post-transplantation erythrocytosis[3] an oral daily dose of 8 mg/kg has produced beneficial effects.[4,5] Theophylline may be of use given either alone or with an ACE inhibitor in those who fail to respond to first-line therapy. Theophylline treatment may also reduce erythrocytosis associated with chronic obstructive pulmonary disease.[6]

1. McMullin MF, *et al.* General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130:** 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 19/03/08)
2. McMullin MF, *et al.* National Cancer Research Institute, Myeloproliferative Disorder Subgroup. British Committee for Standards in Haematology. Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis. *Br J Haematol* 2007; **138:** 821–2. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_amendment_07.pdf (accessed 19/03/08)
3. Ok E, *et al.* Comparison of the effects of enalapril and theophylline on polycythemia after renal transplantation. *Transplantation* 1995; **59:** 1623–45.
4. Bakris GL, *et al.* Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. *N Engl J Med* 1990; **323:** 86–90.
5. Ilan Y, *et al.* Erythrocytosis after renal transplantation: the response to theophylline treatment. *Transplantation* 1994; **57:** 661–4.
6. Oren R, *et al.* Effect of theophylline on erythrocytosis in chronic obstructive pulmonary disease. *Arch Intern Med* 1997; **157:** 1474–8.

Methotrexate neurotoxicity. For reference to the use of aminophylline or theophylline to relieve the acute neurotoxicity of methotrexate, see Other Drugs, under Treatment of Adverse Effects, p.747.

Perinatal asphyxia. Perinatal asphyxia frequently results in damage to the kidneys;[1] vasomotor nephropathy or acute renal failure may develop as a result of decreased perfusion to the kidneys.[2] Theophylline has been studied for the prevention of renal dysfunction associated with perinatal asphyxia in both term and preterm neonates.[1-3] Beneficial effects have been observed after early use of intravenous theophylline, including significant decreases in serum creatinine[1-3] and urinary β2-microglobulin (an indicator of tubular performance),[1,3] and a significant increase in creatinine clearance.[1-3] A single dose of 8 mg/kg theophylline, by slow intravenous injection in the first hour of life, was given to neonates at term.[1,3] Lower doses were used for preterm neonates; 1 mg/kg daily for 3 consecutive days.[2]

1. Bhat MA, *et al.* Theophylline for renal function in term neonates with perinatal asphyxia: a randomised, placebo-controlled trial. *J Pediatr* 2006; **149:** 180–4.
2. Cattarelli D, *et al.* A randomised, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 2006; **91:** F80–F84.
3. Jenik AG, *et al.* A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. *Pediatrics* 2000; **105:** e45. Also available at: http://pediatrics.aappublications.org/cgi/content/full/105/4/e45 (accessed 19/03/08)

Preparations

BP 2008: Prolonged-release Theophylline Tablets;
USP 31: Theophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution; Theophylline Capsules; Theophylline Extended-release Capsules; Theophylline in Dextrose Injection; Theophylline Oral Solution; Theophylline Sodium Glycinate Elixir; Theophylline Sodium Glycinate Tablets; Theophylline Tablets; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aminofilin†; Asmabiol†; Crisasma; Drilyna; Nefoben; Teodosis; Teosona; Teosona Sol; Theo-Dur†; ***Austral.:*** Nuelin; ***Austria:*** Aerodyne†; Afonilum; Euphyllin; Respicur; Theoplus; Theospirex; Unifyl; ***Belg.:*** Euphyllin; Theo-2; Theolair; Xanthium; ***Braz.:*** Bermacia†; Codrinan; Talofilina; Teofilab; Teolong; Teophyl; Teoston; ***Canad.:*** Apo-Theo; Novo-Theophyl; Quibron-T†; Theo-Dur†; Theolair; Uniphyl; ***Chile:*** Elixine; ***Cz.:*** Afonilum; Euphyllin; Euphylong†; Spophyllin; Teotard†; Theo-Dur†; Theophyllard†; Theoplus; Uni-Dur†; Unilair†; ***Denm.:*** Nuelin; Pulmo-Timelets; Theo-Dur; UniXan; Uno-Lin†; ***Fin.:*** Euphyllin†; Nuelin; Retafyllin; Theo-Dur†; Theofol; ***Fr.:*** Euphylline; Theostat; Xanthium†; ***Ger.:*** Aerobin; Afonilum; Afonilum novo; afpred-THEO; Bronchoparat; Bronchoretard; Contiphyllin; Cronasma†; duraphyllin; Euphylong; Pulmidur†; Pulmo-Timelets; Solosin; Theo; Theolair†; Tromphyllin; Unilair; Uniphyllin; ***Gr.:*** Aberten; Mediphyllin Chrono; Novaphylline†; Theo-Bros; Theo-Dur; Theoplus; Uniphyllin; ***Hong Kong:*** CP-Theo; Euphylong; Novo-Theophyl†; Nuelin; Slo-Theo; Theo-Dur†; Theotrim; ***Hung.:*** Egifilin; Euphylong; Retafyllin; Theophtard; Theospirex; ***India:*** Phylobid; Phyloday; Theo PA; Theobid; Theoday; Theoped; Unicontin; ***Indon.:*** Bronchophylin; Brondilex; Bronsolvan; Euphyllin; Quibron-T; Retaphyl; Theobron; ***Irl.:*** Nuelin; Slo-Phyllin; Uniphyllin Continus; Zepholin; ***Israel:*** Glyphyllin; Theotard; Theotrim; ***Ital.:*** Aminomal; Diffumal; Euphyllina; Frivent; Paidomal; Respicur; Tefamin; Theo-24; Theo-Dur; Theolair; ***Jpn:*** Theodur; Theolong; ***Malaysia:*** Apo-Theo; Nuelin; Numalin†; Retafyllin; Theolin†; ***Mex.:*** Apoteoprol†; Elixofilina; Fluidasa; Pharmafil; Slo-Bid†; Teolong†; Uni-Dur†; ***Neth.:*** Euphylong; Theolair; ***Norw.:*** Nuelin; Theo-Dur; ***NZ:*** Nuelin; ***Philipp.:*** Asmasolon; Brondil (Reformulated); Nuelin; Phenedrine; Theo-Dur; ***Pol.:*** Afonilum; Euphyllin; Theoplus; Theospirex; Theovent; ***Port.:*** Eufilina; Lepobron†; Teonibsa†; Teovent†; Unicontin; ***Rus.:*** Teotard (Теотард); ***S.Afr.:*** Alcophyllin; Chronophyllin†; Euphyllin; Microphyllin; Nuelin; Pulmophyllin; Theoplus; Uniphyl; ***Singapore:*** Apo-Theo; Nuelin; Retafyllin†; Theolin; Theoplus†; Xanthium†; ***Spain:*** Chantaline†; Elixifilin; Eufilina; Histafilin; Pulmeno; Teolixir; Teromol; Theo Max†; Theo-Dur; Theolair; Theoplus; Unilong†; Vent Retard†; ***Swed.:*** Euphylong†; Theo-Dur; ***Switz.:*** Euphyllin; Sodip-phylline†; Theolair; Unifyl; ***Thai.:*** Aerobin†; Almarion; Asmasolon; Bronoday; Franol; Med-Phylline†; Nuelin; Retafyllin; Temaco; Theotrim; Xanthium; ***Turk.:*** Bronkolin; Pirasmin; Talotren; Teobag; Teokap; Teosel; Theo-Dur; Xanthium; ***UAE:*** Theophar; ***UK:*** Nuelin; Slo-Phyllin; Uniphyllin Continus; ***USA:*** Accurbron; Aerolate; Aquaphyllin†; Asmalix; Elixomin†; Elixophyllin; Quibron-T†; Respbid†; Slo-Bid; Slo-Phyllin; Sustaire†; T-Phyl; Theo-24; Theo-X†; Theochron; Theoclear†; Theolair; Theovent†; Uniphyl; ***Venez.:*** Nuelin; Teobid.

Multi-ingredient: ***Arg.:*** Airbronal†; Bronkasma†; Dexa Aminofilin; Dexa Teosona; Fatigan Bronquial†; Inastmol†; Sedacris; ***Austria:*** Ambredin; Asthma 23 D; ***Braz.:*** Abacateirol†; Alergotox†; Asmatiron†; Bronquitos; Endotussin; Franol; Marax; ***Canad.:*** ratio-Theo-Bronc; ***Cz.:*** Oxantil; ***Fin.:*** Theofol Comp; ***Fr.:*** Hypnasmine†; ***Ger.:*** Broncho-Euphyllin; ***Gr.:*** Gulamyl; ***India:*** Alergin; Asmapax; Asthmino†; Broncofol-P†; Broncofol†; Dericip; Dericip Plus; Deriphyllin; Etyofil†; Marax; Tergil-T; Theo-Asthalin; Theobric; ***Indon.:*** Asmadex; Asmano; Asmasolon; Asthma Soho; Neo Napacin; Prinasma; Teosal; Theochodil; Tusapres; ***Irl.:*** Franol Expectorant†; ***Malaysia:*** Asthma; Brondal†; Grenin†; Theophylline Expectorant; ***Mex.:*** Aminoefedrison; ***Philipp.:*** Mucophylline; ***Pol.:*** Baladex; ***Port.:*** Cosmaxil†; Prelus†; ***S.Afr.:*** Actophlem; Alcophyllex; Diatussin; Metaxol; Solphyllex; Solphyllin; Theophen; Theophen Comp; ***Spain:*** Novofilin†; Teolixir Compositum; ***Thai.:*** Almasal; Asiabron; Bronchil; Brondil; Mila-Asma; Polyphed; Qualiton; ***UK:*** Do-Do ChestEze; Franol Plus†; Franol†; ***USA:*** Elixophyllin-GG; Elixophyllin-KI; Glyceryl-T; Hydrophed; Marax; Neoasma; Quadrinal; Quibron†; Slo-Phyllin GG†; Tedrigen; Theodrine; Theomax DF; ***Venez.:*** Marax†; Metilfedrin†; Metoxifilin; Teofedril†.

Tiotropium Bromide *(BAN, rINN)*

Ba-679; Ba-679BR; Bromuro de tiotropio; Tiotropii bromidum; Tiotropium, bromure de; Tiotropyum Bromür. 6β,7β-Epoxy-3β-hydroxy-8-methyl-1α*H*,5α*H*-tropanium bromide di-2-thienylglycolate.

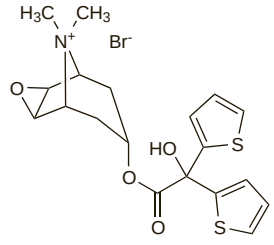
Тиотропия Бромид

$C_{19}H_{22}BrNO_4S_2$ = 472.4.

CAS — 186691-13-4 (tiotropium); 139404-48-1 (anhydrous tiotropium bromide or tiotropium bromide hydrate); 136310-93-5 (anhydrous tiotropium bromide); 411207-31-3 (tiotropium bromide monohydrate).

ATC — R03BB04.

ATC Vet — QR03BB04.



Adverse Effects and Precautions

As for Ipratropium Bromide (p.1124).

Pharyngitis, sinusitis, rhinitis, and epistaxis have also been reported after inhalation.

Patients with moderate to severe renal impairment (creatinine clearance 50 mL/minute or less) should be closely monitored as tiotropium bromide is mainly excreted by the kidneys.

Effects on the cerebrovascular system. In March 2008 the FDA reported[1] that the manufacturer of tiotropium bromide (*Boehringer Ingelheim*) had informed them that they had identified a possible increased risk of stroke in patients taking tiotropium bromide. From pooled analysis of 29 clinical studies in patients with chronic obstructive pulmonary disease preliminary estimates of the risk of stroke were 8 per 1000 patients treated for