renal impairment (see below). It is unsuitable for the relief of acute bronchospasm or in patients with unstable respiratory disease.

Effects on the heart. A prescription event monitoring study found an excess risk of non-fatal heart failure in elderly patients receiving bambuterol, particularly in the first month of treatment.[1] See also under Salbutamol, p.1131.

1. Martin RM, *et al.* Risk of non-fatal cardiac failure and ischaemic heart disease with long acting β agonists. *Thorax* 1998; **53:** 558–62.

Interactions

As for Salbutamol, p.1132. Bambuterol inhibits plasma cholinesterases and can prolong the action of drugs such as suxamethonium (see Sympathomimetics, under Suxamethonium, p.1912) that are inactivated by these enzymes.

Pharmacokinetics

Nearly 20% of a dose of bambuterol is absorbed from the gastrointestinal tract after oral doses. It is slowly metabolised in the body to its active metabolite, terbutaline; peak terbutaline concentrations are reported to occur about 4 to 7 hours after a dose of bambuterol as tablets. The slow rate at which metabolism occurs determines the prolonged duration of action of bambuterol of at least 24 hours. Hydrolysis of bambuterol is catalysed by plasma cholinesterase; however, bambuterol also inhibits plasma cholinesterase and therefore partly inhibits its own metabolism. For the metabolism and excretion of terbutaline, see p.1139.

◊ References.

1. Sitar DS. Clinical pharmacokinetics of bambuterol. *Clin Pharmacokinet* 1996; **31:** 246–56.
2. Nyberg L, *et al.* Pharmacokinetics of bambuterol in healthy subjects. *Br J Clin Pharmacol* 1998; **45:** 471–8.
3. Bang U, *et al.* Pharmacokinetics of bambuterol in subjects homozygous for the atypical gene for plasma cholinesterase. *Br J Clin Pharmacol* 1998; **45:** 479–84.
4. Ahlström H, *et al.* Pharmacokinetics of bambuterol during oral administration to asthmatic children. *Br J Clin Pharmacol* 1999; **48:** 299–308.
5. Rosenborg J, *et al.* Pharmacokinetics of bambuterol during oral administration of plain tablets and solution to healthy adults. *Br J Clin Pharmacol* 2000; **49:** 199–206.

Uses and Administration

Bambuterol is an inactive prodrug of terbutaline (p.1138), a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has similar actions to those of salbutamol (p.1133) except that it has a more prolonged duration of action (at least 24 hours). Bambuterol hydrochloride is used as a long-acting bronchodilator for persistent reversible airways obstruction in conditions such as asthma (p.1108). The usual dose is 10 to 20 mg orally once daily at bedtime. Doses may need to be reduced in renal impairment (see below).

Administration in renal impairment. Licensed product information recommends that the initial dose of bambuterol hydrochloride should be halved in patients with renal impairment (glomerular filtration rate less than 50 mL/minute). Further doses should be adjusted according to response.

Asthma. References.

1. Fugleholm AM, *et al.* Therapeutic equivalence between bambuterol, 10 mg once daily, and terbutaline controlled release, 5 mg twice daily, in mild to moderate asthma. *Eur Respir J* 1993; **6:** 1474–8.
2. Gunn SD, *et al.* Comparison of the efficacy, tolerability and patient acceptability of once-daily bambuterol tablets against twice-daily controlled release salbutamol in nocturnal asthma. *Eur J Clin Pharmacol* 1995; **48:** 23–8.
3. Zarkovic JP, *et al.* The Bambuterol Multicentre Study Group. One-year safety study with bambuterol once daily and terbutaline three times daily in 2-12-year-old children with asthma. *Pediatr Pulmonol* 2000; **29:** 424–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Bambec; ***Braz.:*** Bambec; ***Cz.:*** Bambec†; ***Denm.:*** Bambec; ***Fr.:*** Oxeol; ***Ger.:*** Bambec; ***Hong Kong:*** Bambec†; ***Hung.:*** Bambec†; ***India:*** Bambudil; ***Ital.:*** Bambec†; ***Malaysia:*** Bambec†; ***Norw.:*** Bambec; ***NZ:*** Bambec; ***Philipp.:*** Bambec; ***Singapore:*** Bambec; ***Spain:*** Bambec; ***Swed.:*** Bambec; ***Thai.:*** Bambec; ***UK:*** Bambec.

Multi-ingredient: ***India:*** Montair Plus.

Bamifylline Hydrochloride *(BANM, USAN, rINNM)*

AC-3810; Bamifylline, Chlorhydrate de; Bamifyllini Hydrochloridum; BAX-2739Z; 8102-CB; CB-8102; Hidrocloruro de bamifilina. 8-Benzyl-7-[2-(*N*-ethyl-*N*-2-hydroxyethylamino)ethyl]theophylline hydrochloride.

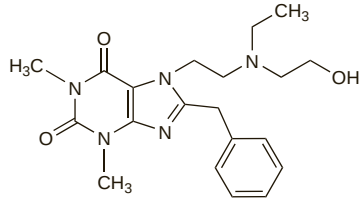
Бамифиллина Гидрохлорид

$C_{20}H_{27}N_5O_3,HCl$ = 421.9.

CAS — 2016-63-9 (bamifylline); 20684-06-4 (bamifylline hydrochloride).

ATC — R03DA08.

ATC Vet — QR03DA08.



(bamifylline)

Profile

Bamifylline hydrochloride is a theophylline derivative (p.1140) that is used for its bronchodilator properties in reversible airways obstruction. It is not converted to theophylline in the body. It is given in usual oral doses of 600 or 900 mg daily in 2 or 3 divided doses. It is also given rectally as suppositories, and by slow intravenous infusion.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Trentadil; ***Braz.:*** Bamifix; ***Fr.:*** Trentadil; ***Ital.:*** Airest†; Bamifix; Bamixol†; Briofil.

Bitolterol Mesilate *(BANM, rINNM)* ⊗

Bitoltérol, Mésilate de; Bitolterol Mesylate *(USAN)*; Bitolteroli Mesilas; Mesilato de bitolterol; Win-32784. 4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-*o*-phenylene di-*p*-toluate methanesulphonate.

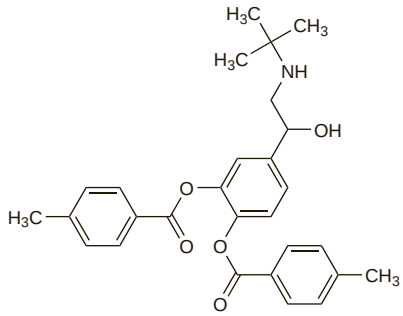
Битолтерола Мезилат

$C_{28}H_{31}NO_5,CH_4O_3S$ = 557.7.

CAS — 30392-40-6 (bitolterol); 30392-41-7 (bitolterol mesilate).

ATC — R03AC17.

ATC Vet — QR03AC17.



(bitolterol)

Profile

Bitolterol is an inactive prodrug that is hydrolysed in the body to colterol, a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has similar properties to those of salbutamol (p.1131).

It has been used as a bronchodilator in the management of diseases with reversible airways obstruction such as asthma (p.1108) or in some patients with chronic obstructive pulmonary disease (p.1112); inhalation results in the rapid onset of bronchodilatation (2 to 4 minutes) with a duration of action of 5 or more hours.

Bitolterol has been given by inhalation via a metered-dose aerosol supplying 370 micrograms of bitolterol mesilate per inhalation. For the *relief* of bronchospasm the usual adult dose is 2 inhalations (740 micrograms) followed by a third inhalation (370 micrograms) if required. For the *prevention* of bronchospasm the usual adult dose is 2 inhalations (740 micrograms) every 8 hours. Maximum doses have been stated to be 3 inhalations (1110 micrograms) every 6 hours or 2 inhalations (740 micrograms) every 4 hours. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, bitolterol indicates deterioration of asthma control and the need for review of therapy.

Alternatively, a 0.2% inhalation solution of bitolterol mesilate has been given by nebulisation. Using *continuous flow* nebulisation, the usual adult dose is from 1.5 to 3.5 mg three or four times daily as required, to a maximum daily dose of 14 mg. Using *intermittent flow* nebulisation, the usual adult dose is 0.5 to 2 mg three or four times daily as required, up to a maximum daily dose of 8 mg. In all cases dosage intervals should be greater than or equal to 4 hours.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Tornalate.

Bufylline *(BAN)*

Ambuphylline *(USAN)*; Bufilina; Theophylline-aminoisobutanol. 2-Amino-2-methylpropan-1-ol theophyllinate.

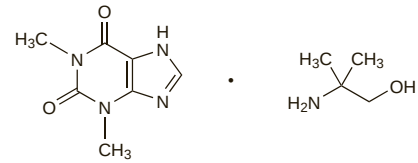
Буфиллин

$C_{11}H_{19}N_5O_3$ = 269.3.

CAS — 5634-34-4.

ATC — R03DA10.

ATC Vet — QR03DA10.



Profile

Bufylline is a theophylline derivative (p.1140) that has been used for its bronchodilator effects as an ingredient of preparations promoted for coughs and other respiratory-tract disorders. The ethiodide has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Broncolex†; EMS Expectorante; Revenil; Revenil Dospan; Revenil Expectorante; ***S.Afr.:*** Nethaprin Dospan; Nethaprin Expectorant.

Caffeine *(BAN)*

Anhydrous Caffeine; Cafeína; Caféine; Coffeinum; Guaranine; Kofeiini; Kofein; Kofeina; Kofeinas; Koffein; Methyltheobromine; Théine. 1,3,7-Trimethylpurine-2,6(3*H*,1*H*)-dione; 1,3,7-Trimethylxanthine; 7-Methyltheophylline.

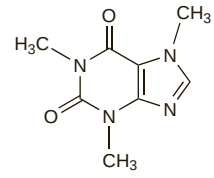
Кофеин

$C_8H_{10}N_4O_2$ = 194.2.

CAS — 58-08-2.

ATC — N06BC01.

ATC Vet — QN06BC01.



NOTE. Compounded preparations of caffeine may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 6.2 (Caffeine). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 31 (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Caffeine Citrate *(BANM)*

Cafeína, citrato de; Citrated Caffeine; Coffeinum Citricum.

Кофеина Цитрат

$C_8H_{10}N_4O_2,C_6H_8O_7$ = 386.3.

CAS — 69-22-7.

ATC — N06BC01.

ATC Vet — QN06BC01.

Caffeine Hydrate *(BANM)*

Cafeína monohidrato; Caféine monohydratée; Caffeine Monohydrate; Coffeinum monohydricum; Kofeiinimonohydraatti; Kofein monohydrát; Kofeinas monohidratas; Koffein-monohidrát; Koffeinmonohydrat.

Кофеин Моногидрат

$C_8H_{10}N_4O_2,H_2O$ = 212.2.
CAS — 5743-12-4.
ATC — N06BC01.
ATC Vet — QN06BC01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 6.2 (Caffeine Monohydrate; Caffeine Hydrate BP 2008). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 31 (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Stability. References to the stability of caffeine and caffeine citrate.

1. Eisenberg MG, Kang N. Stability of citrated caffeine solutions for injectable and enteral use. *Am J Hosp Pharm* 1984; **41:** 2405–6.
2. Nahata MC, *et al.* Stability of caffeine injection in intravenous admixtures and parenteral nutrition solutions. *DICP Ann Pharmacother* 1989; **23:** 466–7.
3. Hopkin C, *et al.* Stability study of caffeine citrate. *Br J Pharm Pract* 1990; **12:** 133.
4. Donnelly RF, Tirona RG. Stability of citrated caffeine injectable solution in glass vials. *Am J Hosp Pharm* 1994; **51:** 512–14.
5. Fraser BD. Stability of caffeine citrate injection in polypropylene syringes at room temperature. *Am J Health-Syst Pharm* 1997; **54:** 1106, 1108.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p.1140.

Tolerance occurs rapidly to the stimulating effects of caffeine; physical signs of withdrawal including irritability, restlessness, lethargy, and headache may occur if intake is stopped abruptly.

◊ General references.

1. Wills S. Drugs and substance misuse: caffeine. *Pharm J* 1994; **252:** 822–4.
2. Fredholm BB, *et al.* Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 1999; **51:** 83–133.

Breast feeding. Studies examining the transfer of caffeine into breast milk after oral doses of 35 to 336 mg of caffeine have recorded peak maternal plasma concentrations of 2.4 to 4.7 micrograms/mL, peak maternal saliva concentrations of 1.2 to 9.2 micrograms/mL, and peak breast-milk concentrations of 1.4 to 7.2 micrograms/mL. At these concentrations in breast milk, the calculated daily caffeine ingestion by breast-fed infants ranged from 1.3 to 3.1 mg, which was not thought to present a hazard, although irritability and a poor sleeping pattern have been reported.[1-4]

The American Academy of Pediatrics[5] states that caffeine is excreted slowly by the infant and may be associated with irritability and poor sleeping pattern when ingested by breast-feeding mothers. However, no effects occur with moderate intake of caffeinated beverages (2 to 3 cups daily) and caffeine is usually compatible with breast feeding.

1. Tyrala EE, Dodson WE. Caffeine secretion into breast milk. *Arch Dis Child* 1979; **54:** 787–800.
2. Hildebrandt R, *et al.* Transfer of caffeine to breast milk. *Br J Clin Pharmacol* 1983; **15:** 612P.
3. Sagraves R, *et al.* Pharmacokinetics of caffeine in human breast milk after a single oral dose of caffeine. *Drug Intell Clin Pharm* 1984; **18:** 507.
4. Berlin CM, *et al.* Disposition of dietary caffeine in milk, saliva, and plasma of lactating women. *Pediatrics* 1984; **73:** 59–63.
5. 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)

Effects on the cardiovascular system. An increased caffeine intake has been associated with an increase in daytime blood pressure.[1] The study, in 82 healthy, normotensive adolescents, suggested that caffeine consumption may be a factor contributing to essential hypertension in young people.

High dose caffeine (25 mg/kg) used as a loading dose in the prevention and treatment of neonatal apnoea (see p.1118) resulted in a marked reduction of cerebral and intestinal blood flow velocity in preterm infants;[2] no changes were noted in left ventricular output, blood pressure, or heart rate. The authors attributed the effect on blood flow velocity to vasoconstriction, and suggested a smaller caffeine loading dose, repeated several hours later. A later study, also in preterm infants, which examined the effect of a divided loading dose of caffeine (12.5 mg/kg repeated after 4 hours), found that cerebral blood flow velocity was decreased after the second dose; intestinal blood flow velocity and left ventricular output remained unchanged.[3] The authors concluded that the 20% reduction in cerebral blood flow velocity observed was probably not meaningful for infants with adequate cerebral oxygen supply; however, an infant's ability to respond to hypoxaemia by vasodilatation may be compromised.

For a discussion of the effects of caffeine-containing beverages on cardiovascular risk factors, see p.2415.

1. Savoca MR, *et al.* Association of ambulatory blood pressure and dietary caffeine in adolescents. *Am J Hypertens* 2005; **18:** 116–20.
2. Hoecker C, *et al.* Caffeine impairs cerebral and intestinal blood flow velocity in preterm infants. *Pediatrics* 2002; **109:** 784–7.
3. Hoecker C, *et al.* Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006; **91:** F61–F64.

Effects on mental function. A report of 6 cases of excessive daytime sleepiness associated with high caffeine intake.[1]

1. Regestein QR. Pathologic sleepiness induced by caffeine. *Am J Med* 1989; **87:** 586–8.

Headache. Headache is a recognised symptom of caffeine withdrawal and even subjects who drink moderate amounts of coffee can develop headaches lasting 1 to 6 days when switched to a decaffeinated brand.[1] It has also been suggested that postoperative headache could be attributed to caffeine withdrawal as fasting patients are required to abstain from drinking tea or coffee before surgical procedures. Several studies[2-4] have found a positive association between postoperative headache and daily caffeine consumption, although there have also been negative findings.[5] A prospective study suggested that a prophylactic intravenous dose of caffeine on the day of surgery reduced the likelihood of postoperative headache in patients at risk of caffeine withdrawal.[6]

In a case-control study,[7] investigating the possible association of dietary and medicinal caffeine use with chronic daily headache (CDH), caffeine was found to be a modest risk factor for CDH onset, regardless of headache type. Patients suffering from CDH were more likely overall to have been high caffeine consumers before the onset of CDH; no association was found with current caffeine consumption.

1. van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. *BMJ* 1990; **300:** 1558–9.
2. Galletly DC, *et al.* Does caffeine withdrawal contribute to postanaesthetic morbidity? *Lancet* 1989; **i:** 1335.
3. Weber JG, *et al.* Perioperative ingestion of caffeine and postoperative headache. *Mayo Clin Proc* 1993; **68:** 842–5.
4. Nikolajsen L, *et al.* Effect of previous frequency of headache, duration of fasting and caffeine abstinence on perioperative headache. *Br J Anaesth* 1994; **72:** 295–7.
5. Verhoeff FH, Millar JM. Does caffeine contribute to postoperative morbidity? *Lancet* 1990; **336:** 632.
6. Weber JG, *et al.* Prophylactic intravenous administration of caffeine and recovery after ambulatory surgical procedures. *Mayo Clin Proc* 1997; **72:** 621–6.
7. Scher AI, *et al.* Caffeine as a risk factor for chronic daily headache: a population-based study. *Neurology* 2004; **63:** 2022–7.

Overdosage. Reports and reviews of caffeine toxicity.

1. Zimmerman PM, *et al.* Caffeine intoxication: a near fatality. *Ann Emerg Med* 1985; **14:** 1227–9.
2. Dalvi RR. Acute and chronic toxicity of caffeine: a review. *Vet Hum Toxicol* 1986; **28:** 144–50.
3. Rivenes SM, *et al.* Intentional caffeine poisoning in an infant. *Pediatrics* 1997; **99:** 736–8.
4. Anderson BJ, *et al.* Caffeine overdose in a premature infant: clinical course and pharmacokinetics. *Anaesth Intensive Care* 1999; **27:** 307–11.
5. Ergenekon E, *et al.* Caffeine intoxication in a premature neonate. *Paediatr Anaesth* 2001; **11:** 737–9.
6. Holstege CP, *et al.* Massive caffeine overdose requiring vasopressin infusion and hemodialysis. *J Toxicol Clin Toxicol* 2003; **41:** 1003–7.

Pregnancy. In the USA, the FDA has advised pregnant women to limit their intake of caffeine and caffeine-containing beverages to a minimum, but this recommendation was based largely on *animal* studies and the effect of caffeine on the human fetus and fetal loss during pregnancy is controversial.[1] Although some studies found no evidence that moderate caffeine use increased the risk of spontaneous abortion,[2,3] others have reported conflicting results.[4,5] There is some evidence for an effect on fetal growth, but again it is not clear that this applies generally: a prospective population-based study in the UK found that a decreased birth-weight with increased caffeine intake was only significant in smokers.[6] The authors of this study concurred that a reduction in caffeine intake during pregnancy would be prudent, together with stopping smoking. An association between high maternal caffeine intake during pregnancy and an increased risk of the sudden infant death syndrome has also been reported,[7] although another study found no such association.[8]

1. Eskenazi B. Caffeine during pregnancy: grounds for concern? *JAMA* 1993; **270;** 2973–4.
2. Mills JL, *et al.* Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *JAMA* 1993; **269:** 593–7.
3. Klebanoff MA, *et al.* Maternal serum paraxanthine, a caffeine metabolite, and the risk of spontaneous abortion. *N Engl J Med* 1999; **341:** 1639–44.
4. Infante-Rivard C, *et al.* Fetal loss associated with caffeine intake before and during pregnancy. *JAMA* 1993; **270:** 2940–3.
5. Cnattingius S, *et al.* Caffeine intake and the risk of first-trimester spontaneous abortion. *N Engl J Med* 2000; **343:** 1839–45.
6. Cook DG, *et al.* Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study. *BMJ* 1996; **313:** 1358–62.
7. Ford RPK, *et al.* Heavy caffeine intake in pregnancy and sudden infant death syndrome. *Arch Dis Child* 1998; **78:** 9–13.
8. Alm B, *et al.* Caffeine and alcohol as risk factors for sudden infant death syndrome. *Arch Dis Child* 1999; **81:** 107–11.

Interactions

Like theophylline (see p.1142) caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isoenzyme CYP1A2, and is subject to numerous interactions with other drugs and substances which enhance or reduce its metabolic clearance.

◊ Reviews.

1. Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin Pharmacokinet* 2000; **39:** 127–53.

Alcohol. In a study of 8 healthy subjects given an oral dose of alcohol of 2.2 mL/kg, caffeine 150 mg by mouth did not antagonise the central effects of alcohol and, instead, a synergistic interaction occurred which further increased reaction time. The common practice of drinking coffee after drinking alcohol in order to sober up is not supported by these results.[1] Another study[2] found that some antagonism of the central effects of alcohol was produced by caffeine, although there was no reversal of subjective sensations of drunkenness; however the dose of caffeine in this study (400 mg) was considerably higher.

1. Oborne DJ, Rogers Y. Interactions of alcohol and caffeine on human reaction time. *Aviat Space Environ Med* 1983; **54:** 528–34.
2. Azcona O, *et al.* Evaluation of the central effects of alcohol and caffeine interaction. *Br J Clin Pharmacol* 1995; **40:** 393–400.

Antiarrhythmics. In 7 healthy subjects and 5 patients with cardiac arrhythmias, *mexiletine* in a single dose of 200 mg and a dose of 600 mg daily respectively, reduced the elimination of caffeine by 30 to 50%.[1] *Lidocaine*, *flecainide*, and *tocainide* had no effect on caffeine elimination in healthy subjects.[1]

1. Joeres R, Richter E. Mexiletine and caffeine elimination. *N Engl J Med* 1987; **317:** 117.

Antibacterials. Caffeine elimination half-life has been reported to be increased and clearance decreased when given with *ciprofloxacin*,[1-3] *enoxacin*,[2,3] and *pipemidic acid*,[2,3] whereas *lomefloxacin*,[4] *norfloxacin*,[2,3] and *ofloxacin*[2,3] had little or no effect on these parameters. Enoxacin had the greatest inhibitory effect on caffeine clearance.[2,3]

1. Healy DP, *et al.* Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1989; **33:** 474–8.
2. Harder S, *et al.* Ciprofloxacin-caffeine: a drug interaction established using in vivo and in vitro investigations. *Am J Med* 1989; **87** (suppl 5A): 89–91S.
3. Barnett G, *et al.* Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition. *Eur J Clin Pharmacol* 1990; **39:** 63–9.
4. Healy DP, *et al.* Lack of interaction between lomefloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1991; **35:** 660–4.

Antidepressants. Fluvoxamine has been reported to significantly reduce the clearance and prolong the elimination half-life of caffeine.[1] The clinical importance of this interaction, attributed to inhibition of cytochrome P450 isoenzyme CYP1A2 by fluvoxamine, remains to be established.

1. Culm-Merdek KE, *et al.* Fluvoxamine impairs single-dose caffeine clearance without altering caffeine pharmacodynamics. *Br J Clin Pharmacol* 2005; **60:** 486–93.

Antiepileptics. The mean clearance of caffeine was increased and its half-life decreased in epileptic patients taking *phenytoin* compared with healthy controls, resulting in lower plasma-caffeine concentrations. Treatment with *carbamazepine* or *valproic acid* had no effect on the pharmacokinetics of caffeine.[1]

1. Wietholtz H, *et al.* Effects of phenytoin, carbamazepine, and valproic acid on caffeine metabolism. *Eur J Clin Pharmacol* 1989; **36:** 401–6.

Antifungals. In a single-dose study in healthy subjects, *terbinafine* 500 mg by mouth decreased the clearance and increased the elimination half-life of caffeine 3 mg/kg given intravenously. *Ketoconazole* 400 mg by mouth did not prolong the elimination of caffeine to a significant extent.[1]

1. Wahlländer A, Paumgartner G. Effect of ketoconazole and terbinafine on the pharmacokinetics of caffeine in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 279–83.

Antigout drugs. In a study in 2 healthy subjects, the plasma half-life of caffeine was essentially unchanged by 7 days of treatment with *allopurinol* 300 mg or 600 mg daily by mouth. However, allopurinol caused a specific, dose-dependent inhibition of the conversion of 1-methylxanthine to 1-methyluric acid.[1]

1. Grant DM, *et al.* Effect of allopurinol on caffeine disposition in man. *Br J Clin Pharmacol* 1986; **21:** 454–8.