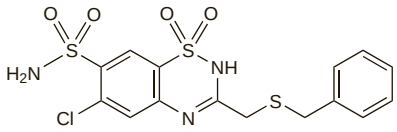
Benzthiazide *(BAN, rINN)* ⊗

Benzthiazidum; Benztiazida; P-1393. 3-Benzylthiomethyl-6-chloro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Бензтиазид

$C_{15}H_{14}ClN_3O_4S_3$ = 431.9.

CAS — 91-33-8.



Profile

Benzthiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p.1307). It is used for oedema, including that associated with heart failure (p.1165), and has also been used for hypertension (p.1171). It has been given alone but is often given with triamterene. The usual initial oral dose for oedema is 75 mg daily, although higher doses have been given. The dose is reduced for maintenance; intermittent dosing may be adequate.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Exna†.

Multi-ingredient: ***India:*** Ditide; ***Switz.:*** Dyrenium compositum; ***UK:*** Dytide.

Bepridil Hydrochloride *(BANM, USAN, rINNM)*

Bepridiilihydrokloridi; Bépridil, Chlorhydrate de; Bepridilhydroklorid; Bepridili Hydrochloridum; CERM-1978; Hidrocloruro de bepridil; Org-5730. *N*-Benzyl-*N*-(3-isobutoxy-2-pyrrolidin-1-ylpropyl)aniline hydrochloride monohydrate.

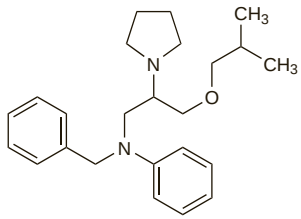
Бепридила Гидрохлорид

$C_{24}H_{34}N_2O,HCl,H_2O$ = 421.0.

CAS — 64706-54-3 (bepridil); 49571-04-2 (bepridil); 64616-81-5 (anhydrous bepridil hydrochloride); 74764-40-2 (bepridil hydrochloride monohydrate).

ATC — C08EA02.

ATC Vet — QC08EA02.



(bepridil)

Profile

Bepridil is a calcium-channel blocker (p.1154). It has similar properties to nifedipine (p.1350) but reduces the heart rate and does not usually cause reflex tachycardia. It also has antiarrhythmic activity. It is not related chemically to other calcium-channel blockers such as diltiazem, nifedipine, or verapamil.

Bepridil is used as the hydrochloride in the management of angina pectoris (p.1157). Ventricular arrhythmias, including torsade de pointes, and agranulocytosis have been associated with bepridil and, as a result, it is usually reserved for patients who have not responded adequately to other anti-anginal drugs. The usual initial dose is 200 mg of bepridil hydrochloride orally once daily. Provided that prolongation of the QT interval has not occurred after 2 to 4 weeks, the dose may be increased, if necessary, to a maximum of 300 mg once daily. Elderly patients and those with hepatic or renal impairment may be given an initial dose of 100 mg once daily; in exceptional circumstances this may be increased to a maximum of 200 mg once daily.

◊ References.

1. Hollingshead LM, *et al.* Bepridil: a review of its pharmacological properties and therapeutic use in stable angina pectoris. *Drugs* 1992; **44:** 835–57.
2. Awni WM, *et al.* Pharmacokinetics of bepridil and two of its metabolites in patients with end-stage renal disease. *J Clin Pharmacol* 1995; **35:** 379–83.

Porphyria. Bepridil is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Unicordium; ***USA:*** Vascor†.

Beraprost Sodium *(USAN, rINNM)*

Beraprost sódico; Béraprost Sodique; ML-1129; ML-1229 (beraprost); Natrii Beraprostum; TRK-100. Sodium (±)-(1*R*,2*R*,3a*S*,8b*S*)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1*H*-cyclopenta[*b*]benzofuran-5-butyrate.

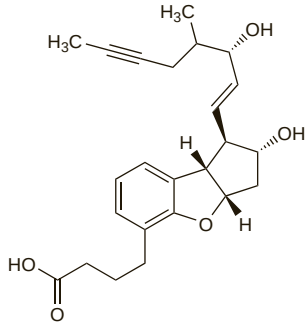
Натрий Берапрост

$C_{24}H_{29}NaO_5$ = 420.5.

CAS — 88430-50-6 (beraprost); 88475-69-8 (beraprost sodium).

ATC — B01AC19.

ATC Vet — QB01AC19.



(beraprost)

Profile

Beraprost is a synthetic analogue of epoprostenol (prostacyclin) that causes vasodilatation and prevents platelet aggregation. It is given orally as the sodium salt in the management of pulmonary hypertension (p.1179) and peripheral vascular disease (p.1178).

In primary pulmonary hypertension, beraprost sodium is given in an initial dose of 60 micrograms daily in three divided doses; this may be increased gradually if necessary to 180 micrograms daily in three or four divided doses. For peripheral vascular disease a dose of 120 micrograms daily in three divided doses is used.

Adverse effects of beraprost include headache, flushing, nausea, diarrhoea, and increased liver enzyme, bilirubin, and triglyceride concentrations.

Cardiovascular disorders. References to the use of beraprost for pulmonary hypertension or intermittent claudication;[1-7] results of studies for the latter indication have been conflicting. It has been tried with sildenafil in patients with pulmonary hypertension.[8]

1. Nagaya N, *et al.* Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. *J Am Coll Cardiol* 1999; **34:** 1188–92.
2. Lievre M, *et al.* Oral beraprost sodium, a prostaglandin I analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. *Circulation* 2000; **102:** 426–31.
3. Melian EB, Goa KL. Beraprost: a review of its pharmacology and therapeutic efficacy in the treatment of peripheral arterial disease and pulmonary arterial hypertension. *Drugs* 2002; **62:** 107–33.
4. Galiè N, *et al.* Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002; **39:** 1496–1502.
5. Mohler ER, *et al.* Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I analogue: a double-blinded, randomized, controlled trial. *J Am Coll Cardiol* 2003; **41:** 1679–86.
6. Barst RJ, *et al.* Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003; **41:** 2119–25.
7. Hashiguchi M, *et al.* Studies on the effectiveness and safety of cilostazol, beraprost sodium, prostaglandin E1 for the treatment of intermittent claudication. *Yakugaku Zasshi* 2004; **124:** 321–32.
8. Ikeda D, *et al.* Addition of oral sildenafil to beraprost is a safe and effective therapeutic option for patients with pulmonary hypertension. *J Cardiovasc Pharmacol* 2005; **45:** 286–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Dorner; ***Jpn:*** Dorner; ***Philipp.:*** Dorner; ***Thai.:*** Dorner.

Beta Blockers ⊗

β-Bloqueantes.

Бета-блокаторы

Beta blockers (beta-adrenoceptor blocking drugs or antagonists) are competitive antagonists of catecholamines at beta-adrenergic receptors in a wide range of tissues. Although they have broadly similar properties they differ in their affinity for $beta_1$ or $beta_2$ receptor subtypes, intrinsic sympathomimetic activity, membrane-stabilising activity, blockade of alpha-adrenergic receptors, and pharmacokinetic properties including differences in lipid solubility (see Table 4, below, for some of these characteristics). These differences may affect the choice of drug in specific situations.

Table 4. Characteristics of beta blockers.

Beta blocker	$Beta_1$ selectivity	ISA*	MSA**	Vasodilator activity
Acebutolol	+	+	+	0
Alprenolol	0	+	0	0
Atenolol	+	0	0	0
Betaxolol	+	0	0	0
Bisoprolol	+	0	0	0
Carteolol	0	+	0	0
Carvedilol	0	0	0	+
Celiprolol	+	+	–	+
Esmolol	+	0	0	0
Labetalol	0	0	0	+
Levobunolol	0	0	0	0
Metipranolol	0	0	0	0
Metoprolol	+	0	0	0
Nadolol	0	0	0	0
Nebivolol	+	0	0	+
Oxprenolol	0	+	+	0
Penbutolol	0	0	0	0
Pindolol	0	++	0	0
Propranolol	0	0	++	0
Sotalol	0	0	0	0
Timolol	0	0	0	0

0 = absent or low; + = moderate; ++ = high; – = no information

* ISA = Intrinsic sympathomimetic activity

** MSA = Membrane-stabilising activity

Adverse Effects

Beta blockers are generally well tolerated and most adverse effects are mild and transient. Reactions may be more severe after intravenous than oral doses; ocular use has also been associated with systemic adverse effects. The most frequent and serious adverse effects are related to their beta-adrenergic blocking activity. Among the most serious adverse effects are heart failure, heart block, and bronchospasm. Troublesome subjective effects include fatigue and coldness of the extremities; when beta blockers are used for long-term treatment of asymptomatic diseases such as hypertension, such effects may be an important determinant of patient compliance.

Cardiovascular effects include bradycardia and hypotension; heart failure or heart block may be precipitated or worsened in patients with underlying cardiac disorders. Abrupt withdrawal of beta blockers may exacerbate angina and may lead to sudden death. (For further details on withdrawal of beta blockers, see Precautions, below.)

Bronchospasm, shortness of breath, and dyspnoea may be precipitated, particularly in patients with a history of obstructive airways disease, due to blockade of $beta_2$ receptors in bronchial smooth muscle. Drugs with selectivity for $beta_1$ receptors or with intrinsic sympathomimetic activity at $beta_2$ receptors may be less likely to induce bronchospasm (but see Precautions, below). Pneumonitis, pulmonary fibrosis, and pleurisy have also been reported.

CNS effects include headache, depression, dizziness, hallucinations, confusion, amnesia, and sleep disturbances including nightmares. Coma and convulsions have been reported after beta-blocker overdosage. Beta blockers that are lipid soluble are more likely to enter the brain and would be expected to be associated with a higher incidence of CNS adverse effects, although this is not proven.

Fatigue is a common adverse-effect of beta blockers. Paraesthesia, arthralgia, and myopathies, including muscle cramps, have been reported. Reduced peripheral circulation can produce coldness of the extremities and may exacerbate peripheral vascular disease such as Raynaud's syndrome.

Adverse gastrointestinal effects include nausea and vomiting, diarrhoea, constipation, and abdominal cramping.

Beta blockers interfere with carbohydrate and lipid metabolism and can produce hypoglycaemia, hyperglycaemia, and changes in blood concentrations of triglycerides and cholesterol (see below for further details).

Skin rash, pruritus, exacerbation of psoriasis, excess sweating, and reversible alopecia have occurred with use of beta blockers.

Decreased tear production, blurred vision, conjunctivitis, and soreness are among the ocular symptoms that have been reported. Adverse effects specific to ocular use are also discussed below.

Haematological reactions include nonthrombocytopenic purpura, thrombocytopenia, and rarely agranulocytosis. Transient eosinophilia can occur.

An asymptomatic increase in antinuclear antibodies has occurred with many beta blockers; SLE has also been reported. Other adverse effects reported with some beta blockers include dry mouth, raised liver enzymes, male impotence, sclerosing peritonitis, and retroperitoneal fibrosis.

Carcinogenicity. An apparent excess of deaths from cancer was noted in elderly men, but not women, given atenolol during a study of antihypertensive therapy.[1] However, 2 subsequent studies found no evidence of a link between atenolol and cancer.[2,3]

1. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992; **304:** 405–12.
2. Fletcher AE, *et al.* Cancer mortality and atenolol treatment. *BMJ* 1993; **306:** 622–3.
3. Hole DJ, *et al.* Incidence of and mortality from cancer in hypertensive patients. *BMJ* 1993; **306:** 609–11.

Effects on bones and joints. Adverse effects on the bones and joints have occurred in patients receiving beta blockers. Five cases of arthralgia associated with the use of metoprolol had been reported to the FDA;[1] there had also been 6 reports of similar symptoms with propranolol, and 1 with atenolol. A case of polymyalgia rheumatica-like syndrome has also been reported.[2]

However, epidemiological studies have also suggested that beta blockers may increase bone mineral density[3] and reduce the risk of fractures,[3,4] although another study[5] could not confirm this effect.

1. Sills JM, Bosco L. Arthralgia associated with β-adrenergic blockade. *JAMA* 1986; **255:** 198–9.
2. Snyder S. Metoprolol-induced polymyalgia-like syndrome. *Ann Intern Med* 1991; **114:** 96–7.
3. Pasco JA, *et al.* β-Adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. *J Bone Miner Res* 2004; **19:** 19–24.
4. Schlienger RG, *et al.* Use of β-blockers and risk of fractures. *JAMA* 2004; **292:** 1326–32.
5. Reid IR, *et al.* β-Blocker use, BMD, and fractures in the study of osteoporotic fractures. *J Bone Miner Res* 2005; **20:** 613–18.

Effects on the breast. A 54-year-old woman developed breast pain and swelling a few weeks after starting atenolol for hypertension;[1] it resolved when the atenolol was stopped.

1. Kelleher JA. Atenolol-induced breast pain in a woman with hypertension. *Ann Pharmacother* 2006; **40:** 990–2.

Effects on carbohydrate metabolism. The sympathetic nervous system is involved in the control of carbohydrate metabolism and beta blockers can interfere with carbohydrate and insulin regulation; both hypoglycaemia and hyperglycaemia have been reported in patients with no history of diabetes, as well as in patients with types 1 or 2 diabetes mellitus.

Beta blockers cause hypoglycaemia in non-diabetics, possibly by increasing peripheral glucose uptake through increased insulin sensitivity.[1] Those most at risk include fasting or nutritionally-compromised patients, haemodialysis patients, neonates after maternal treatment with beta blockers, and patients with liver disease;[1] those undertaking vigorous exercise[2] and children may also be at risk. Glucose metabolism is controlled by the action of catecholamines at the $beta_2$ receptor, and therefore cardioselective beta blockers are less likely to cause hypoglycaemia than their non-cardioselective counterparts;[1] however, hypoglycaemia was reported[3] in a non-diabetic patient given the cardioselective beta blocker metoprolol pre-operatively for cardiovascular protection.

Traditionally beta blockers have been considered unsafe in diabetics because of reports that they may precipitate and prolong hypoglycaemia, an effect that was first seen in the 1960s in adult type 1 diabetics taking propranolol; however, in a long-term study[4] in type 2 diabetics, there was no difference in the incidence of hypoglycaemia in patients receiving captopril or the cardioselective beta blocker atenolol, and both significantly improved outcome. A case-control study[5] and a review[6] of the use of beta blockers in diabetic patients both concluded that the incidence of hypoglycaemia was not increased and that beta blockers were appropriate therapy for diabetics. Nonetheless, beta blockers may mask the adrenaline-mediated symptoms of hypoglycaemia such as tachycardia and tremor, and non-cardioselective beta blockers may delay recovery in patients given glucose for hypoglycaemia;[6] cardioselective beta blockers are less likely to mask the signs of hypoglycaemia and are therefore preferred in diabetics.[7]

Both cardioselective and non-cardioselective beta blockers may increase fasting blood glucose concentrations in non-diabetic hypertensive patients,[8,9] and epidemiological studies have shown that the risk of developing diabetes mellitus is increased by beta blockers.[10-12] The mechanism is possibly through inhibition of pancreatic insulin release,[1,13] although it has been suggested that hypertensive patients are predisposed to diabetes mellitus and beta blockers act as a precipitating factor;[10,14] changes in bodyweight in some of the studies may also have confounded the results.[6] Hyperglycaemia can also occur in diabetic patients treated with beta blockers;[14] however, the established benefits generally outweigh the risk.

Although the adverse effects of beta blockers on carbohydrate metabolism are well-established, there is some evidence that the newer, vasodilating beta blockers, such as carvedilol[15,16] and nebivolol,[17,18] may have beneficial effects on insulin resistance or glucose control, and weight gain may be less with carvedilol.[19] New onset diabetes was also more likely to occur with metoprolol than carvedilol in a study on patients with heart failure.[20]

1. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.
2. Holm G, *et al.* Severe hypoglycaemia during physical exercise and treatment with beta-blockers. *BMJ* 1981; **282:** 1360.
3. Brown DR, Brown MJ. Hypoglycemia associated with preoperative metoprolol administration. *Anesth Analg* 2004; **99:** 1427–8.
4. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998; **317:** 713–20.
5. Thamer M, *et al.* Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 1999; **21:** 1387–1400.
6. Sawicki PT, Siebenhofer A. Betablocker treatment in diabetes mellitus. *J Intern Med* 2001; **250:** 11–17.
7. The Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.
8. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Propranolol or hydrochlorothiazide alone for the initial treatment of hypertension IV: effect on plasma glucose and glucose tolerance. *Hypertension* 1985; **7:** 1008–16.
9. Pollare T, *et al.* Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *BMJ* 1989; **298:** 1152–7.
10. Samuelsson O, *et al.* Diabetes mellitus in treated hypertension: incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial in Göteborg, Sweden. *J Hum Hypertens* 1994; **8:** 257–63.
11. Gress TW, *et al.* Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000; **342:** 905–12.
12. Taylor EN, *et al.* Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care* 2006; **29:** 1065–70.
13. Luna B, Feinglos MN. Drug-induced hyperglycemia. *JAMA* 2001; **286:** 1945–8.
14. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part 1). *Drugs* 1990; **40:** 6–18.
15. Bakris GL, *et al.* Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004; **292:** 2227–36. Correction. *ibid.*; 2583.
16. Giugliano D, *et al.* Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension: a randomized, controlled trial. *Ann Intern Med* 1997; **126:** 955–9.
17. Celik T, *et al.* Comparative effects of nebivolol and metoprolol on oxidative stress, insulin resistance, plasma adiponectin and soluble P-selectin levels in hypertensive patients. *J Hypertens* 2006; **24:** 591–6.
18. Poirier L, *et al.* Effects of nebivolol and atenolol on insulin sensitivity and haemodynamics in hypertensive patients. *J Hypertens* 2001; **19:** 1429–35.
19. Messerli FH, *et al.* Body weight changes with beta-blocker use: results from GEMINI. *Am J Med* 2007; **120:** 610–15.
20. Torp-Pedersen C, *et al.* Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007; **93:** 968–73.

Effects on the circulation. Hypotension is a recognised adverse effect of beta blockers, and severe reactions have been reported. Near-fatal shock occurred[1] in an elderly patient with chronic bronchitis and angina pectoris within 40 minutes of taking acebutolol 400 mg. Hypotension, leading to a rise in serum creatinine indicative of kidney ischaemia, occurred[2] in 2 women after a single oral dose of atenolol 100 mg or 2 oral doses of atenolol 50 mg; both had presented with severe hypertension, hyponatraemia, hypokalaemia, and high renin activity. Renal artery thrombosis believed to be due to the hypotensive effect of atenolol was reported[3] in a 70-year-old man with a history of circulatory and cardiac disorders. He had received atenolol 100 mg for treatment of moderate hypertension.

Beta blockers have been tried in neurally mediated hypotension (see Hypotension under Uses, below), but this may be hazardous: a 27-year-old man had[4] ten episodes of syncope with severe bradycardia after taking atenolol for recurrent vasovagal syncope; episodes ceased on stopping the atenolol. The authors suggested that the atenolol aggravated the vasovagal syncope, and recommended careful monitoring of patients given beta blockers for this condition.

1. Tirlapur VG, *et al.* Shock syndrome after acebutolol. *Br J Clin Pract* 1986; **40:** 33–4.
2. Kholeif M, Isles C. Profound hypotension after atenolol in severe hypertension. *BMJ* 1989; **298:** 161–2.
3. Shaw AB, Gopalka SK. Renal artery thrombosis caused by antihypertensive treatment. *BMJ* 1982; **285:** 1617.
4. Wang C-C, *et al.* Worsening of vasovagal syncope after beta-blocker therapy. *Chest* 1994; **106:** 963–5.

Effects on the gastrointestinal tract. Sclerosing peritonitis was noted as part of the 'oculomucocutaneous syndrome' that occurred with practolol. However, while both sclerosing peritonitis and retroperitoneal fibrosis have also been reported with a number of other beta blockers, including atenolol,[1,2] metoprolol,[3,4] oxprenolol,[5] propranolol,[6] sotalol,[7] and timolol,[8,9] a review[10] of 100 cases of retroperitoneal fibrosis concluded that beta blockers could not be considered as the cause.

Abdominal pain and bloody diarrhoea were reported[11] in a patient the day after treatment was started with propranolol; symptoms were attributed to splanchnic vasoconstriction caused by the drug, which may have exacerbated pre-existing mesenteric ischaemia.

1. Nielsen BV, Pedersen KG. Sclerosing peritonitis associated with atenolol. *BMJ* 1985; **290:** 518.
2. Johnson JN, McFarland J. Retroperitoneal fibrosis associated with atenolol. *BMJ* 1980; **280:** 864.
3. Thompson J, Julian DG. Retroperitoneal fibrosis associated with metoprolol. *BMJ* 1982; **284:** 83–4.
4. Clark CV, Terris R. Sclerosing peritonitis associated with metoprolol. *Lancet* 1983; **i:** 937.
5. McCluskey DR, *et al.* Oxprenolol and retroperitoneal fibrosis. *BMJ* 1980; **281:** 1459–60.
6. Pierce JR, *et al.* Propranolol and retroperitoneal fibrosis. *Ann Intern Med* 1981; **95:** 244.
7. Laakso M, *et al.* Retroperitoneal fibrosis associated with sotalol. *BMJ* 1982; **285:** 1085–6.
8. Baxter-Smith DC, *et al.* Sclerosing peritonitis in patient on timolol. *Lancet* 1978; **ii:** 149.
9. Rimmer E, *et al.* Retroperitoneal fibrosis associated with timolol. *Lancet* 1983; **i:** 300.

10. Pryor JP, *et al.* Do beta-adrenoceptor blocking drugs cause retroperitoneal fibrosis? *BMJ* 1983; **287:** 639–41.
11. Köksal AŞ, *et al.* Propranolol-exacerbated mesenteric ischemia in a patient with hyperthyroidism. *Ann Pharmacother* 2005; **39:** 559–62.

Effects on lipid metabolism. The adrenergic system is involved in the control of lipid metabolism and beta blockers may therefore have effects on plasma-lipid concentrations. In general, beta blocker therapy results in increased concentrations of very-low-density lipoprotein and triglycerides, a reduction in high-density lipoprotein, and no change in low-density lipoprotein.[1] These effects may be less pronounced with beta$_1$ cardioselective drugs, beta blockers with intrinsic sympathomimetic activity, and beta blockers that also block alpha-adrenergic receptors. For example, pindolol,[2,3] a beta blocker with intrinsic sympathomimetic activity, and arotinolol[4] and carvedilol,[5] which possess alpha-adrenergic blocking properties, are reported to have no adverse effects on plasma-lipid concentrations, although acute pancreatitis due to severe hypertriglyceridaemia has been reported[6] in a patient treated with metoprolol followed by atenolol. However, the effects on lipid concentrations are generally fairly small, and a review of the subject[7] concluded that there was little or no evidence that such effects negated the beneficial effects of beta blockers on cardiovascular outcomes.

1. Krone W, Nägele H. Effects of antihypertensives on plasma lipids and lipoprotein metabolism. *Am Heart J* 1988; **116:** 1729–34.
2. Hunter Hypertension Research Group. Effects of pindolol, or a pindolol/clopamide combination preparation, on plasma lipid levels in essential hypertension. *Med J Aust* 1989; **150:** 646–52.
3. Terént A, *et al.* Long-term effect of pindolol on lipids and lipoproteins in men with newly diagnosed hypertension. *Eur J Clin Pharmacol* 1989; **36:** 347–50.
4. Sasaki J, *et al.* Effects of arotinolol on serum lipid and apolipoprotein levels in patients with mild essential hypertension. *Clin Ther* 1989; **11:** 580–3.
5. Sharp RP, *et al.* Impact of carvedilol on the serum lipid profile. *Ann Pharmacother* 2008; **42:** 564–71.
6. Durrington PN, Cairns SA. Acute pancreatitis: a complication of beta-blockade. *BMJ* 1982; **284:** 1016.
7. Weir MR, Moser M. Diuretics and β-blockers: is there a risk for dyslipidemia? *Am Heart J* 2000; **139:** 174–84.

Effects on mental state. Beta blockers can cross the blood-brain barrier and there are numerous reports of adverse psychiatric effects. Theoretically this is more likely with lipophilic drugs (such as propranolol, timolol, and metoprolol) but there have also been reports of psychosis[1] and delirium[2] with atenolol.

Although beta blockers have been associated with depression,[3] the risk may not be as high as has sometimes been suggested; a review[4] of randomised studies in myocardial infarction, heart failure, or hypertension, which included over 35 000 patients, found no significant increase in the risk of depression in those taking beta blockers.

1. Viadero JJ, *et al.* Acute psychotic behavior associated with atenolol. *Am J Psychiatry* 1983; **140:** 1382.
2. Arber N, *et al.* Delirium induced by atenolol. *BMJ* 1988; **297:** 1048.
3. Parker WA. Propranolol-induced depression and psychosis. *Clin Pharm* 1985; **4:** 214–18.
4. Ko DT, *et al.* β-Blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002; **288:** 351–7.

Effects after ophthalmic use. Ophthalmic use of beta blockers may produce ocular irritation (including hypersensitivity), blepharitis, keratitis, decreased corneal sensitivity, visual disturbances, diplopia, photophobia, and ptosis. Uveitis has been reported with metipranolol eye drops.[1] Iris depigmentation has occurred[2] after the use of topical levobunolol. Older patients using topical beta blockers may be at greater risk of decreased corneal sensitivity or corneal anaesthesia with the consequent risk of keratitis.[3]

Systemic absorption may occur after the use of beta blockers in eye drops. Excess drug can drain into the lachrymal ducts to be absorbed through the nasal mucosa. Absorption also occurs via the ophthalmic and facial veins. After such absorption the beta blocker reaches the systemic circulation without undergoing first-pass hepatic metabolism.

The main systemic effects associated with topical ocular use of beta blockers are on the pulmonary, cardiovascular, and central nervous systems.[4,5]

Both cardioselective and non-cardioselective topical beta blockers have been shown to cause pulmonary effects, and these can occur in patients without a history of obstructive airways disease.[6] Reported events include acute pulmonary oedema associated with use of metipranolol eye drops,[7] and wheezing after a single dose of topical levobunolol, which developed into severe respiratory distress requiring hospitalisation after a second dose.[8] Myocardial infarction has been reported[9] shortly after a single dose of betaxolol eye drops; the patient was also taking atenolol and indapamide for hypertension. Systemic effects have also been reported in patients using timolol eye drops, including depression and bradycardia, with a rise in blood pressure and neurological signs of stroke after rapid withdrawal of the drops,[10] syncope and falls,[11] and severe nausea and vomiting, which resolved within a few days of withdrawal but recurred on rechallenge.[12] A number of cases of alopecia associated with ocular use of beta blockers have also been reported.[13]

1. Akingbehin T, Villada JR. Metipranolol-associated granulomatous anterior uveitis. *Br J Ophthalmol* 1991; **75:** 519–23.
2. Doyle E, Liu C. A case of acquired iris depigmentation as a possible complication of levobunolol eye drops. *Br J Ophthalmol* 1999; **83:** 1405–6.
3. Weissman SS, Asbell PA. Effects of topical timolol (0.5%) and betaxolol (0.5%) on corneal sensitivity. *Br J Ophthalmol* 1990; **74:** 409–12.
4. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
5. Vander Zanden JA, *et al.* Systemic adverse effects of ophthalmic β-blockers. *Ann Pharmacother* 2001; **35:** 1633–7.
6. Kirwan JF, *et al.* Do selective topical β antagonists for glaucoma have respiratory side effects? *Br J Ophthalmol* 2004; **88:** 196–8.
7. Johns MD, Ponte CD. Acute pulmonary edema associated with ocular metipranolol use. *Ann Pharmacother* 1995; **29:** 370–3.
8. Stubbs GM. Betagan drops. *Med J Aust* 1994; **161:** 576.
9. Chamberlain TJ. Myocardial infarction after ophthalmic betaxolol. *N Engl J Med* 1989; **321:** 1342.
10. Rao MR, *et al.* Systemic hazards of ocular timolol. *Br J Hosp Med* 1993; **50:** 553.
11. Müller ME, *et al.* Syncope and falls due to timolol eye drops. *BMJ* 2006; **332:** 960–1.
12. Wolfhagen FHJ, *et al.* Severe nausea and vomiting with timolol eye drops. *Lancet* 1998; **352:** 373.
13. Fraunfelder FT, *et al.* Alopecia possibly secondary to topical ophthalmic β-blockers. *JAMA* 1990; **263:** 1493–4.

Hypersensitivity. For the suggestion that beta blockers may exacerbate anaphylactic reactions, see under Precautions, below.

Overdosage. Many cases of beta-blocker overdosage[1] are uneventful, but some patients develop severe and occasionally fatal cardiovascular depression. Effects can include bradycardia, cardiac conduction block, hypotension, heart failure, and cardiogenic shock. Convulsions, coma, respiratory depression, and bronchoconstriction can also occur, although infrequently. Most reports of serious toxic reactions after overdosage concern beta blockers with significant membrane-stabilising activity, such as propranolol or oxprenolol, which may have quinidine-like effects (see p.1383). Overdosage of beta blockers with intrinsic sympathomimetic activity may present with tachycardia and hypertension. Overdosage of sotalol, a beta blocker with class II and III antiarrhythmic properties, usually presents as ventricular tachyarrhythmia.

1. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and β-blocker toxicity. *Toxicol Rev* 2004; **23:** 223–38.

Treatment of Adverse Effects

Beta blockers are generally well tolerated and adverse effects usually respond to a reduction in dose. In overdosage, use of activated charcoal or gastric lavage should be considered if the patient presents within 1 hour of ingestion. Mild hypotension may respond to intravenous fluids. If hypotension continues, intravenous glucagon should be given; sympathomimetics may be used as an alternative or given with glucagon. Isoprenaline has been the sympathomimetic of choice since it acts mainly at beta receptors, but other sympathomimetics are often used; very high doses may be required (see below). Atropine may be given intravenously for bradycardia; sympathomimetics or a cardiac pacemaker may also be required. Beta$_2$ agonists or xanthines may be given for bronchospasm; hypoglycaemia may respond to glucose or glucagon. Haemodialysis may be of benefit for severe overdosage with renally excreted beta blockers, but is usually unnecessary.

Overdosage. Atropine, glucagon, and sympathomimetics are the mainstay of treatment for severe beta blocker overdosage (see above). Very high doses of sympathomimetics have been used in some patients; a woman[1] who had taken acebutolol, labetalol, and trimipramine required isoprenaline at a rate of 1660 micrograms/minute and dopamine at a rate of 200 micrograms/kg per minute to maintain her blood pressure. However, standard therapy is not effective in all patients and alternatives have been tried.

The phosphodiesterase inhibitor enoximone has been used successfully in patients resistant to standard treatment,[2,3] and a dramatic response to calcium chloride has been reported in a patient with electromechanical dissociation after propranolol overdosage.[4] It has been suggested[5,6] that high doses of insulin given with glucose (hyperinsulinaemia/euglycaemia therapy) may be of benefit, although there is no clinical evidence to support this. There has also been a report[7] of the successful use of sodium bicarbonate in a patient with cardiac arrest after overdosage with multiple drugs, including propranolol; it was suggested that the increased sodium load counteracted the sodium-channel blocking effect of propranolol.

1. Lewis M, *et al.* Survival following massive overdose of adrenergic blocking agents (acebutolol and labetalol). *Eur Heart J* 1983; **4:** 328–32.
2. Hoeper MM, Boeker KHW. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; **335:** 1538.
3. Sandroni C, *et al.* Enoximone in cardiac arrest caused by propranolol: two case reports. *Acta Anaesthesiol Scand* 2006; **50:** 759–61.
4. Brimacombe JR, *et al.* Propranolol overdose—a dramatic response to calcium chloride. *Med J Aust* 1991; **155:** 267–8.
5. Shepherd G. Treatment of poisoning caused by β-adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm* 2006; **63:** 1828–35.
6. Mégarbane B, *et al.* The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and β-blocker poisoning. *Toxicol Rev* 2004; **23:** 215–22.
7. Shanker UR, *et al.* Sodium bicarbonate to treat massive β blocker overdose. *Emerg Med J* 2003; **20:** 393.

Precautions

Beta blockers should not be given to patients with bronchospasm or asthma or to those with a history of obstructive airways disease. This contra-indication generally applies even to those beta blockers considered to be cardioselective. However, cardioselective beta blockers may be used with extreme caution when there is no alternative treatment (see Obstructive Airways Disease, below). Other contra-indications include metabolic acidosis, cardiogenic shock, hypotension, severe peripheral arterial disease, sinus bradycardia, and second- or third-degree AV block; caution should be observed in first-degree block. Although beta blockers are used in the management of heart failure, they should not be given to patients with uncontrolled heart failure and treatment should be begun with great care, starting with a low dose and cautiously titrating upwards. Patients with phaeochromocytoma should not be given beta blockers without alpha-adrenoceptor blocking therapy as well.

Beta blockers may mask the symptoms of hyperthyroidism and of hypoglycaemia. They may unmask myasthenia gravis. Psoriasis may be aggravated. Beta blockers may increase the number of attacks of chest pain in patients with Prinzmetal's angina; this occurs especially with non-cardioselective beta blockers, which should be avoided. Beta blockers increase sensitivity to allergens and also the severity of anaphylactoid reactions; patients with a history of anaphylaxis to an antigen may be more reactive to repeated challenge with the antigen while taking beta blockers (see Hypersensitivity, below).

Abrupt withdrawal of beta blockers has sometimes resulted in angina, myocardial infarction, ventricular arrhythmias, and death. Patients on long-term treatment with a beta blocker should have their medication stopped gradually over a period of 1 to 2 weeks. In patients undergoing surgery, beta blockers may reduce the risk of arrhythmias but increase the risk of hypotension; the decision to withdraw or continue therapy depends on individual patient risk—see Cardiovascular Risk Reduction, below. If beta blockers are withdrawn, this should take place at least 24 to 48 hours before surgery; if they are continued, atropine may be given to counter increases in vagal tone and anaesthetics causing myocardial depression, such as ether, cyclopropane, and trichloroethylene, are best avoided. It is of the greatest importance that the anaesthetist is aware that beta blockers are being taken.

Use of beta blockers in pregnancy shortly before delivery has occasionally resulted in bradycardia and other adverse effects such as hypoglycaemia and hypotension in the neonate. Many beta blockers are distributed into breast milk.

Similar precautions apply when beta blockers are used as eye drops since systemic absorption can occur.

Contact lenses. Beta blockers may reduce tear flow, leading to irritation of the eye in wearers of contact lenses and potentially to the dehydration of soft lenses.[1]

1. McGuire T. Drugs interfering with contact lenses. *Aust J Hosp Pharm* 1987; **17:** 55–6.

Hypersensitivity. Anaphylactic reactions to stings and other antigens may be potentiated by beta blockers[1-3] and the risk of serious reactions may be increased. In addition, beta blockers may antagonise the effects of adrenaline in the management of anaphylaxis (see Interactions under Sympathomimetics, p.1408). Particular caution is necessary when beta blockers are used in patients with a history of anaphylaxis.[3]

1. Hannaway PJ, Hopper GDK. Severe anaphylaxis and drug-induced beta-blockade. *N Engl J Med* 1983; **308:** 1536.
2. Pedersen DL. Hymenoptera stings and beta-blockers. *Lancet* 1989; **ii:** 619.
3. Lang DM. Anaphylactoid and anaphylactic reactions: hazards of β-blockers. *Drug Safety* 1995; **12:** 299–304.

Obstructive airways disease. Beta blockers may precipitate bronchospasm and are generally contra-indicated in patients with obstructive airways disease.[1,2] However, systematic reviews have suggested that short-term use of cardioselective beta blockers does not produce adverse respiratory effects in patients with mild to moderate asthma[3] or chronic obstructive pulmonary disease.[4] The reviewers concluded that, given the established benefits of beta blockers in cardiovascular disorders, they should not be withheld in such patients, although patients should be carefully monitored since long-term effects were less clear. A retrospective study[5] found that use of beta blockers increased the rate of hospitalisations and emergency department visits in patients with asthma, but not in those with non-asthmatic chronic obstructive pulmonary disease, suggesting that the benefits and risks need to be assessed for each patient individually. Another study[6] found that patients with acute exacerbations of chronic obstructive pulmonary disease who were given beta blockers had lower mortality than those who were not.

1. Committee on Safety of Medicines/Medicines Control Agency. Reminder: beta-blockers contraindicated in asthma. *Current Problems* 1996; **22:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 10/01/08)
2. The Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.
3. Salpeter S, *et al.* Cardioselective beta-blockers for reversible airway disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 10/01/08).
4. Salpeter S, *et al.* Cardioselective beta-blockers for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 10/01/08).
5. Brooks TWA, *et al.* Rates of hospitalizations and emergency department visits in patients with asthma and chronic obstructive pulmonary disease taking β-blockers. *Pharmacotherapy* 2007; **27:** 684–90.
6. Dransfield MT, *et al.* Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; **63:** 301–5.

Pregnancy. Many beta blockers cross the placenta, and giving them to pregnant women shortly before delivery may result in neonatal adrenergic blockade, with symptoms of bradycardia, hypoglycaemia or hypotension. Furthermore, the treatment of maternal hypertension with beta blockers, particularly atenolol, in early pregnancy or for a long duration has been associated with growth retardation of the fetus.[1-3] However, beta blockers are recommended therapy for maternal conditions such as hypertension, pre-eclampsia, cardiac arrhythmias, and ischaemic heart disease;[4,5] cardioselective agents with no effect on uterine contraction are preferred.[5]

1. Butters L, *et al.* Atenolol in essential hypertension during pregnancy. *BMJ* 1990; **301:** 587–9.
2. Lydakis C, *et al.* Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 1999; **12:** 541–7.
3. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 10/01/08).
4. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003; **24:** 761–81.
5. Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.

Withdrawal. The abrupt withdrawal of beta blockers may lead to rebound hypertension or overshoot hypertension where the patient's blood pressure is higher than before treatment. Angina can be exacerbated, myocardial infarction induced, and fatalities have occurred.[1,2]

1. Houston MC, Hodge R. Beta-adrenergic blocker withdrawal syndromes in hypertension and other cardiovascular diseases. *Am Heart J* 1988; **116:** 515–23.
2. Psaty BM, *et al.* The relative risk of incident coronary heart disease associated with recently stopping the use of β-blockers. *JAMA* 1990; **263:** 1653–7.

Interactions

Both pharmacodynamic and pharmacokinetic interactions have been reported with beta blockers. **Pharmacodynamic** interactions may occur with drugs whose actions enhance or antagonise the various effects of beta blockers at $beta_1$ and $beta_2$ receptors, including their antihypertensive effect, cardiodepressant effect, effect on carbohydrate metabolism, or effect on bronchial $beta_2$ receptors. The characteristics of the individual beta blocker must therefore be borne in mind when considering likely interactions; for more details on the characteristics of different beta blockers, see Uses and Administration, below.

Drugs that enhance the antihypertensive effects of beta blockers, such as ACE inhibitors, calcium-channel blockers, and clonidine may be useful in controlling hypertension (but see Antihypertensives, below). Drugs that cause hypotension such as aldesleukin and general anaesthetics also enhance the antihypertensive effects of beta blockers while other drugs, for example NSAIDs, antagonise the antihypertensive effects.

Use of beta blockers with other cardiac depressants such as antiarrhythmics and rate-limiting calcium-channel blockers can precipitate bradycardia and heart block; the combination of intravenous verapamil and beta blockers should especially be avoided. Sotalol is particularly prone to interactions with other drugs affecting cardiac conduction (see p.1398). Beta blockers may potentiate bradycardia due to digoxin.

The interaction between beta blockers and sympathomimetics is complex and depends on the selectivity of both drugs (see under Sympathomimetics, p.1408). Patients taking beta blockers may have an exaggerated hypertensive response to adrenaline, caused by unopposed alpha-mediated vasoconstriction, while the bronchodilator effects are inhibited; the response to adrenaline given for anaphylaxis may also be reduced in patients on long-term treatment with beta blockers.

In diabetic patients beta blockers can reduce the response to insulin and oral hypoglycaemics through their effects on pancreatic beta receptors (see Effects on Carbohydrate Metabolism, above).

Pharmacokinetic interactions occur with drugs that alter the absorption or metabolism of beta blockers. Although these interactions may alter the beta blocker plasma concentration, they are not usually clinically significant since there is little association between plasma concentrations and therapeutic effect or toxicity and there are wide interindividual differences in steady-state plasma concentrations of beta blockers.

Drugs that reduce absorption include aluminium salts (but see also Antacids, below) and bile-acid binding resins such as colestyramine.

Metabolism of some beta blockers can be increased by drugs such as barbiturates and rifampicin and decreased with drugs such as cimetidine, erythromycin, fluvoxamine, and hydralazine. Drugs that alter hepatic blood flow also affect metabolism of some beta blockers. For example, cimetidine and hydralazine decrease hepatic blood flow and this contributes to the decreased hepatic clearance seen with these drugs. Drugs that influence hepatic metabolism affect beta blockers that are extensively metabolised, such as labetalol, propranolol, and timolol, while beta blockers that are excreted largely unchanged, for example atenolol and nadolol, are unaffected.

Since systemic absorption can occur after ocular use of beta blockers the possibility of similar interactions should be considered.

◊ General references.

1. McDevitt DG. Interactions that matter: 12. β-adrenoceptor antagonists. *Prescribers' J* 1988; **28:** 25–30.
2. Blaufarb I, *et al.* β-Blockers: drug interactions of clinical significance. *Drug Safety* 1995; **13:** 359–70.
3. Brodde OE, Kroemer HK. Drug-drug interactions of beta-adrenoceptor blockers. *Arzneimittelforschung* 2003; **53:** 814–22.

Antacids. Bioavailability of metoprolol was increased when given with an antacid containing aluminium and magnesium salts, but the bioavailability of atenolol was reduced. Variable results on bioavailability of propranolol have been reported when aluminium hydroxide was given with propranolol.[1]

1. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18:** 210–19.

Antiarrhythmics. Use of beta blockers with antiarrhythmic drugs and other drugs affecting cardiac conduction can precipitate bradycardia and heart block.

Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after starting beta-blocker therapy in patients receiving *amiodarone*.[1] Amiodarone was found to increase plasma-metoprolol concentrations in patients with cardiac arrhythmias, probably through inhibition of the cytochrome P450 isoenzyme CYP2D6 by the metabolite desethylamiodarone.[2] However, an analysis[3] of the CAMIAT and EMIAT studies in patients after myocardial infarction found that patients taking amiodarone and beta blockers had better outcomes than patients on one, or neither, drug, suggesting that any interaction may not always be detrimental. Use of *flecainide* with propranolol produced additive negative inotropic effects on the heart and increased serum concentrations of both drugs.[4] In a pharmacokinetic study in 12 healthy males, giving *propafenone* with propranolol resulted in increases in serum-propranolol concentrations but only modest enhancement of beta-blocking activity.[5] An increase in serum-metoprolol concentration has been reported after use of propafenone with metoprolol.[6] The metabolism of metoprolol may be decreased by *quinidine*.[7] Both quinidine and beta blockers have a negative inotropic action on the heart; bradycardia[8] and hypotension[9] have occurred in patients given quinidine with beta blockers.

For a report of reduced clearance of *disopyramide* by atenolol, see p.1270.

The interactions of sotalol are discussed on p.1398.

1. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; **17:** 130–40.
2. Fukumoto K, *et al.* Effect of amiodarone on the serum concentration/dose ratio of metoprolol in patients with cardiac arrhythmia. *Drug Metab Pharmacokinet* 2006; **21:** 501–5.
3. Boutitie F, *et al.* Amiodarone interaction with β-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. *Circulation* 1999; **99:** 2268–75.
4. Holtzman JL, *et al.* The pharmacodynamic and pharmacokinetic interaction of flecainide acetate with propranolol: effects on cardiac function and drug clearance. *Eur J Clin Pharmacol* 1987; **33:** 97–9.
5. Kowey PR, *et al.* Interaction between propranolol and propafenone in healthy volunteers. *J Clin Pharmacol* 1989; **29:** 512–17.
6. Wagner F, *et al.* Drug interaction between propafenone and metoprolol. *Br J Clin Pharmacol* 1987; **24:** 213–20.
7. Leemann T, *et al.* Single-dose quinidine treatment inhibits metoprolol oxidation in extensive metabolizers. *Eur J Clin Pharmacol* 1986; **29:** 739–41.
8. Dinai Y, *et al.* Bradycardia induced by interaction between quinidine and ophthalmic timolol. *Ann Intern Med* 1985; **103:** 890–1.
9. Loon NR, *et al.* Orthostatic hypotension due to quinidine and propranolol. *Am J Med* 1986; **81:** 1101–4.

Antibacterials. Serum-atenolol concentrations in 6 healthy subjects were reduced by a 1-g oral dose of *ampicillin*.[1] Plasma concentrations of propranolol,[2] metoprolol,[3] celiprolol,[4] and bisoprolol[5] may be reduced by *rifampicin*. Licensed product information for *telithromycin* states that it causes increased plasma concentrations of metoprolol.

1. Schäfer-Korting M, *et al.* Atenolol interaction with aspirin, allopurinol, and ampicillin. *Clin Pharmacol Ther* 1983; **33:** 283–8.
2. Shaheen O, *et al.* Influence of debrisoquin phenotype on the inducibility of propranolol metabolism. *Clin Pharmacol Ther* 1989; **45:** 439–43.
3. Bennett PN, *et al.* Effect of rifampicin on metoprolol and antipyrine kinetics. *Br J Clin Pharmacol* 1982; **13:** 387–91.
4. Lilja JJ, *et al.* Rifampicin reduces plasma concentrations of celiprolol. *Eur J Clin Pharmacol* 2004; **59:** 819–24.
5. Kirch W, *et al.* Interaction of bisoprolol with cimetidine and rifampicin. *Eur J Clin Pharmacol* 1986; **31:** 59–62.

Anticoagulants. For the effect of beta blockers on the pharmacokinetics of some oral anticoagulants, see p.1430.

Antidepressants. Bradycardia and heart block, occurring shortly after starting *fluoxetine* therapy, have been reported in patients receiving metoprolol[1] and propranolol.[2] Possible mechanisms include impaired conduction through the AV node and inhibition by fluoxetine of the oxidative metabolism of beta blockers. Use of fluoxetine also increased the plasma concentration of carvedilol in patients with heart failure but no clinical effects were noted.[3]

Fluvoxamine inhibits oxidative metabolism, and increased plasma concentrations of propranolol have been noted in patients receiving fluvoxamine.

1. Walley T, *et al.* Interaction of metoprolol and fluoxetine. *Lancet* 1993; **341:** 967–8.
2. Drake WM, Gordon GD. Heart block in a patient on propranolol and fluoxetine. *Lancet* 1994; **343:** 425–6.
3. Graff DW, *et al.* Effect of fluoxetine on carvedilol pharmacokinetics, CYP2D6 activity, and autonomic balance in heart failure patients. *J Clin Pharmacol* 2001; **41:** 97–106.

Antihypertensives. An enhanced antihypertensive effect is seen when other antihypertensives are given with beta blockers. However, some combinations should be avoided (see Calcium-channel Blockers, below). Beta blockers can potentiate the severe orthostatic hypotension that may follow the initial dose of alpha blockers such as prazosin and can exacerbate rebound hypertension after withdrawal of clonidine treatment (see Precautions, p.1247).

Antimalarials. Antimalarials such as *halofantrine*, *mefloquine*, and *quinine* can cause cardiac conduction defects and caution is necessary if they are used with beta blockers. Cardiopulmonary arrest has occurred after a single dose of mefloquine in a patient taking propranolol.[1]

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32:** 13–14.

Antimigraine drugs. For the effect of propranolol on *rizatriptan*, see p.625.

See also under Ergotamine Tartrate, p.621, for further interactions with drugs used in the treatment of migraine.

Anxiolytics and antipsychotics. Plasma concentrations of some beta blockers may be reduced by *barbiturates*.[1-3] Increased plasma-propranolol concentrations and bioavailability, and reduced metabolism, have been reported in healthy subjects also given *chlorpromazine*.[4]

See p.990 for the effect of beta blockers on the pharmacokinetics of some *benzodiazepines*.

1. Sotaniemi EA, *et al.* Plasma clearance of propranolol and sotalol and hepatic drug-metabolizing enzyme activity. *Clin Pharmacol Ther* 1979; **26:** 153–61.
2. Haglund K, *et al.* Influence of pentobarbital on metoprolol plasma levels. *Clin Pharmacol Ther* 1979; **26:** 326–9.
3. Seideman P, *et al.* Decreased plasma concentrations and clinical effects of alprenolol during combined treatment with pentobarbitone in hypertension. *Br J Clin Pharmacol* 1987; **23:** 267–71.
4. Vestal RE, *et al.* Inhibition of propranolol metabolism by chlorpromazine. *Clin Pharmacol Ther* 1979; **25:** 19–24.

Calcium-channel blockers. Use of calcium-channel blockers with beta blockers has resulted in hypotension, bradycardia, conduction defects, and heart failure.[1]

Beta blockers should be avoided if possible with rate-limiting calcium-channel blockers such as *verapamil* (see p.1422) and *diltiazem*. Although they are reportedly safe with dihydropyridines such as *nifedipine*,[2] heart failure and severe hypotension have been reported (see under Nifedipine, p.1353). Reported pharmacokinetic interactions include increased plasma concentrations of propranolol and of metoprolol with concurrent use of diltiazem[3] or verapamil,[1] and increased plasma concentrations of propranolol with *nicardipine*.[4]

1. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic and genetic considerations. *Clin Pharmacokinet* 1990; **18:** 295–317.
2. Reid JL. First-line and combination treatment for hypertension. *Am J Med* 1989; **86** (suppl 4A): 2–5.
3. Tateishi T, *et al.* Effect of diltiazem on the pharmacokinetics of propranolol, metoprolol and atenolol. *Eur J Clin Pharmacol* 1989; **36:** 67–70.
4. Schoors DF, *et al.* Influence of nicardipine on the pharmacokinetics and pharmacodynamics of propranolol in healthy volunteers. *Br J Clin Pharmacol* 1990; **29:** 497–501.

Cardiac glycosides. For reference to an interaction between beta blockers and *digoxin*, see p.1262.

Ciclosporin. For the effect of carvedilol on plasma-ciclosporin concentrations, see p.1827.

Ergot derivatives. *Nicergoline* enhanced the cardiac depressant action of propranolol in healthy subjects.[1]

For reports of enhanced vasoconstrictor action in patients taking *ergot alkaloids* and beta blockers, see p.621.

1. Boismare F, *et al.* Potentiation by an alpha-adrenolytic agent, nicergoline, of the cardiac effects of propranolol. *Methods Find Exp Clin Pharmacol* 1983; **5:** 83–8.

Food. Studies in healthy subjects found that *grapefruit juice* greatly reduced the plasma concentration of celiprolol[1] and talinolol,[2] but had much less effect on acebutolol.[3] An effect on gastrointestinal absorption was suggested as the mechanism.[1,2] Studies with *orange juice* have found a similar effect on celiprolol[4] and, to a lesser extent, atenolol.[5]

1. Lilja JJ, *et al.* Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. *Clin Pharmacol Ther* 2003; **73:** 192–8.
2. Schwarz UI, *et al.* Grapefruit juice ingestion significantly reduces talinolol bioavailability. *Clin Pharmacol Ther* 2005; **77:** 291–301.
3. Lilja JJ, *et al.* Effects of grapefruit juice on the pharmacokinetics of acebutolol. *Br J Clin Pharmacol* 2005; **60:** 659–63.
4. Lilja JJ, *et al.* Orange juice substantially reduces the bioavailability of the beta-adrenergic-blocking agent celiprolol. *Clin Pharmacol Ther* 2004; **75:** 184–90.
5. Lilja JJ, *et al.* Effects of orange juice on the pharmacokinetics of atenolol. *Eur J Clin Pharmacol* 2005; **61** 337–40.

General anaesthetics. Beta blockers are usually continued perioperatively although the anaesthetist must be informed of their use (see Precautions, above). However, the hypotensive effects of beta blockers may be potentiated by general anaesthetics, and anaesthetics that cause myocardial depression, such as *ether, cyclopropane,* and *trichloroethylene* should preferably be avoided.

Histamine H_2-antagonists. Plasma concentrations of propranolol and metoprolol may be increased by *cimetidine*;[1] pharmacokinetic studies indicate that cimetidine exerts its effect by reducing hepatic blood flow and impairing beta blocker metabolism. Cimetidine has been reported to increase the bioavailability of labetalol,[1] and to increase the systemic effects of timolol eye drops.[2]

1. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.
2. Ishii Y, *et al.* Drug interaction between cimetidine and timolol ophthalmic solution: effect on heart rate and intraocular pressure in healthy Japanese volunteers. *J Clin Pharmacol* 2000; **40:** 193–9.

Local anaesthetics. For details of the effect of beta blockers in reducing the clearance of *bupivacaine*, see p.1855, and of *lidocaine*, see p.1863. For the effects of propranolol with *cocaine*, see p.1860.

Neuromuscular blockers. For the effects of beta blockers on neuromuscular blockers, see under Atracurium, p.1904.

NSAIDs. The antihypertensive effect of beta blockers may be impaired by some NSAIDs, possibly due to their inhibition of renal synthesis of vasodilating prostaglandins. This interaction probably occurs with all beta blockers but may not occur with all NSAIDs. For example, *sulindac* appears to affect blood pressure control less than *indometacin*.[1]

A randomised study[2] in 12 healthy subjects found that *celecoxib* significantly inhibited the metabolism of metoprolol by the cytochrome P450 isoenzyme CYP2D6.

1. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic and genetic considerations. *Clin Pharmacokinet* 1990; **18:** 295–317.
2. Werner U, *et al.* Celecoxib inhibits metabolism of cytochrome P450 2D6 substrate metoprolol in humans. *Clin Pharmacol Ther* 2003; **74:** 130–7.

Opioid analgesics. Bioavailability of propranolol and metoprolol was increased in subjects given *dextropropoxyphene*;[1] dextropropoxyphene is an inhibitor of the cytochrome P450 isoenzyme CYP2D6 and was reported[2] to increase serum concentrations of metoprolol, a CYP2D6 substrate, in a patient given both drugs, resulting in bradycardia. Intravenous *morphine* may increase serum concentrations of esmolol.[3]

1. Lundborg P, *et al.* The effect of propoxyphene pretreatment on the disposition of metoprolol and propranolol. *Clin Pharmacol Ther* 1981; **29:** 263–4.
2. Marraffa JM, *et al.* Profound metoprolol-induced bradycardia precipitated by acetaminophen-propoxyphene. *Clin Pharmacol Ther* 2006; **79:** 282–6.
3. Lowenthal DT, *et al.* Clinical pharmacology, pharmacodynamics and interactions with esmolol. *Am J Cardiol* 1985; **56:** 14F–17F.

Oral contraceptives. Plasma-metoprolol concentrations were increased in some women taking oral contraceptives.[1]

1. Kendall MJ, *et al.* Metoprolol pharmacokinetics and the oral contraceptive pill. *Br J Clin Pharmacol* 1982; **14:** 120–2.

Parasympathomimetics. For the effect of beta blockers on the response to *anticholinesterases*, see p.632.

Thyroid drugs. For a discussion of thyroid status and its effect on plasma-propranolol concentrations and the effects of propranolol on *thyroid hormone* metabolism, see p.2172.

Xanthines. For details of reduced *theophylline* clearance in patients receiving some beta blockers, see p.1144.

Pharmacokinetics

Beta blockers differ widely in their pharmacokinetic properties. Differences in lipid solubility contribute to these varying pharmacokinetic properties.

Beta blockers with high lipid solubility (lipophilic beta blockers) include alprenolol and propranolol.

Hydrophilic beta blockers, such as atenolol and nadolol, have low lipid solubility and when compared with lipophilic beta blockers generally:

- tend to be less readily absorbed from the gastrointestinal tract
- are less extensively metabolised
- have low plasma-protein binding
- have relatively long plasma half-lives
- cross the blood-brain barrier less readily

Beta blockers cross the placenta and most are known to distribute into breast milk.

There is no clear correlation between plasma concentrations of beta blockers and therapeutic activity, especially when the beta blocker undergoes metabolism to active metabolites.

Uses and Administration

Beta blockers are competitive antagonists of the effects of catecholamines at beta-adrenergic receptor sites. The different types of adrenergic receptor are described under the Actions and Uses of Sympathomimetics (see p.1408). Blockade of beta receptors has the following effects:

- $beta_1$ blockade mainly affects the heart, reducing heart rate, myocardial contractility, and rate of conduction of impulses through the conducting system (class II antiarrhythmic effect, see p.1153). It also leads to suppression of adrenergic-induced renin release and lipolysis
- $beta_2$ blockade leads to increased bronchial resistance and inhibition of catecholamine-induced glucose metabolism; there may also be an effect on heart rate. $Beta_2$ blockade also appears to be the main mechanism for the reduction in intra-ocular pressure associated with beta blockers
- the role of $beta_3$ blockade is not clear

Beta blockers differ in their affinity for the subtypes of beta receptor, as well as in their actions at other receptors and ancillary properties (see Table 4, p.1225). The cardiovascular effects of beta blockers relate to their action at $beta_1$ receptors, and all clinically used beta blockers are $beta_1$ antagonists. Propranolol and other nonselective beta blockers also have antagonist effects at $beta_2$ receptors, and this may be responsible for many of their adverse effects. Beta blockers with a higher affinity for $beta_1$ than $beta_2$ receptors, such as atenolol and metoprolol, cause fewer noncardiovascular effects and are described as cardioselective or second generation. However, selectivity is relative and, as doses are increased, activity at $beta_2$ receptors becomes clinically important. Beta blockers with additional properties such as vasodilatation have been described as third generation, and include carvedilol, celiprolol, and nebivolol.

Beta blockers such as acebutolol, celiprolol, oxprenolol, and pindolol also possess intrinsic (partial) sympathomimetic activity in that they activate beta receptors in the absence of catecholamines and are therefore partial agonists. Beta blockers with intrinsic sympathomimetic activity produce less resting bradycardia than beta blockers without.

At high blood concentrations, propranolol and some other beta blockers also possess a membrane-stabilising effect. This effect may not be evident at therapeutic doses but may be important in overdose. The non-cardioselective beta blocker sotalol also has class III antiarrhythmic activity.

Beta blockers that cause vasodilatation may do so by a number of mechanisms: carvedilol and labetalol block $alpha_1$ receptors; celiprolol has $beta_2$ agonist effects; and nebivolol has a direct action on the endothelium, possibly involving nitric oxide release.

Beta blockers are used in the treatment of hypertension (p.1171), angina pectoris (p.1157), cardiac arrhythmias (p.1160), and myocardial infarction (p.1175) and also have a role in heart failure (below). They are also used to control symptoms of sympathetic overactivity in the management of alcohol withdrawal (p.1626), in anxiety disorders (below), in hyperthyroidism (p.2165), and in tremor (below). Beta blockers are used in the prophylaxis of migraine (below) and of variceal bleeding associated with portal hypertension (p.2346). They are also used, with an alpha blocker, in the initial management of phaeochromocytoma (below). Some beta blockers are used as eye drops in the management of glaucoma and ocular hypertension (below).

Choice of beta blocker. The selection of a specific beta blocker for an individual patient depends on the condition being treated and patient characteristics such as liver and kidney function or existing disease such as diabetes. Patient tolerance also varies for different beta blockers. The characteristics of the beta blocker, for example, $beta_1$ selectivity and intrinsic sympathomimetic activity may also influence selection, as may additional pharmacological properties such as vasodilator activity. Although the clinical significance of these differences has been debated, only certain beta blockers have a proven benefit in some conditions (for example, heart failure) and this will also influence choice.

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1. Anonymous. Which beta-blocker? *Med Lett Drugs Ther* 2001; **43:** 9–11.
2. Brown MJ. A rational basis for selection among drugs of the same class. *Heart* 2003; **89:** 687–94.

Anxiety disorders. Beta blockers have been used in patients with various anxiety disorders,[1] including generalised anxiety disorder (p.952), panic disorder (p.952), and performance anxiety[1] (see under Phobic Disorders, p.953). However, their benefits do not appear to be particularly great and they are probably most useful in reducing symptoms such as tremor or palpitations that are mediated through beta stimulation. Improvement usually occurs within 1 to 2 hours with relatively low doses of beta blockers (propranolol 40 mg, oxprenolol 40 to 80 mg, nadolol 40 mg). Some patients require higher doses and longer periods of treatment for a beneficial effect.

1. Tyrer P. Current status of β-blocking drugs in the treatment of anxiety disorders. *Drugs* 1988; **36:** 773–83.

Burns. Beta blockers have been tried in major burn injury (p.1578) to attenuate the hypermetabolism and marked catabolism that may result. A study[1] in children with severe burns found that oral propranolol reduced energy expenditure and muscle-protein catabolism, suggesting beta blockers could have an anabolic effect.

1. Herndon DN, *et al.* Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001; **345:** 1223–9.

Cardiomyopathy. See Heart Failure, below.

Cardiovascular risk reduction. Beta blockers have established benefits in patients with *ischaemic heart disease*,[1] and long-term therapy with beta blockers has an important role in reducing cardiovascular risk in patients with angina pectoris (p.1157), and particularly in patients who have had a myocardial infarction (p.1175). They have also been used to reduce ischaemia and cardiac events in patients undergoing surgery, but their benefits in this situation are less clear.

Perioperative use of beta blockers is controversial (see Precautions, above); they reduce the risk of ischaemia and arrhythmias, but increase the risk of hypotension, and they have often been stopped pre-operatively to enable better control of blood pressure during surgery. However, there is some evidence that continuing or starting beta blockers perioperatively may be of benefit in patients at risk of cardiovascular events, although not all studies have come to the same conclusions. A systematic review[2] of studies with beta blockers suggested a reduction in myocardial ischaemia, non-fatal myocardial infarction, and mortality from cardiovascular causes in patients at high cardiovascular risk undergoing major noncardiac surgery, and a retrospective study[3] also suggested that perioperative beta blockers reduced in-hospital mortality in high-risk patients, although there was no benefit (and possible harm) in low-risk patients. However, another systematic review and meta-analysis[4] concluded that, while the evidence for the use of beta blockers was encouraging, it was too unreliable for definitive conclusions to be drawn. More recent studies[5,6] using perioperative metoprolol have found no benefit, and a further large study[7] found fewer cardiac events but a higher risk of stroke and death in patients given metoprolol. The conflicting conclusions may relate to the wide range of protocols used in the beta blocker studies, whether patients were already taking beta blockers, and the different selection criteria used for the reviews and analyses. Recognising these limitations, consensus guidelines for non-cardiac surgery in the USA recommend[8] that beta blockers should be continued perioperatively in patients receiving them for accepted indications, and that patients undergoing vascular surgery who are at high risk of cardiovascular events (confirmed by pre-operative testing) should have beta blockers started; in patients at lower risk, use of beta blockers may be considered, but there is less evidence of benefit. It is not clear which beta blockers should be preferred, but a retrospective study[9] found that patients who took atenolol pre- and postoperatively had a lower risk of events than patients who took metoprolol.

Beta blockers may also have benefits in patients undergoing cardiac surgery. Observational studies have found that prior[10] or pre-operative[11] use of beta blockers reduces ischaemic complications, while perioperative[12] and postoperative[13] beta blockers have been shown to reduce the risk of atrial fibrillation, although one study found[14] that the effects on atrial fibrillation only applied to patients already taking beta blockers pre-operatively.

Although beta blockers effectively lower blood pressure, they do not reduce cardiovascular events to the same extent as some other antihypertensives and may not be first choice for *hypertension* (p.1171).[15,16]

1. Ellison KE, Gandhi G. Optimising the use of β-adrenoceptor antagonists in coronary artery disease. *Drugs* 2005; **65:** 787–97.
2. Auerbach AD, Goldman L. β-Blockers and reduction of cardiac events in noncardiac surgery: scientific review. *JAMA* 2002; **287:** 1435–44.
3. Lindenauer PK, *et al.* Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005; **353:** 349–61.
4. Devereaux PJ, *et al.* How strong is the evidence for the use of perioperative β blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005; **331:** 313–16.
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13. Coleman CI, *et al.* Impact of prophylactic postoperative β-blockade on post-cardiothoracic surgery length of stay and atrial fibrillation. *Ann Pharmacother* 2004; **38:** 2012–16.
14. Crystal E, *et al.* Metoprolol prophylaxis against postoperative atrial fibrillation increases length of hospital stay in patients not on pre-operative beta blockers: the beta blocker length of stay (BLOS) trial. *Heart* 2004; **90:** 941–2.
15. Lindholm LH, *et al.* Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; **366:** 1545–53.
16. Wiysonge CS, *et al.* Beta-blockers for hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 12/06/08).

Extrapyramidal disorders. Beta blockers (in low doses) have been suggested for the management of antipsychotic-induced akathisia although evidence of benefit is limited (see under Chlorpromazine, p.971).

Glaucoma and ocular hypertension. Topical beta blockers are often the drugs of first choice for the initial treatment and maintenance of open-angle glaucoma and other chronic glaucomas (p.1873). They are believed to inhibit beta receptors in the ciliary epithelium and reduce the secretion of aqueous humour. Clinical studies have established that betaxolol, carteolol, levobunolol, metipranolol, and timolol are effective, generally reducing intra-ocular pressure to a similar extent,[1-5] although a meta-analysis suggested that timolol might be slightly more effective than betaxolol in lowering intra-ocular pressure.[6] The possibility of systemic effects after topical use needs to be borne in mind (see Effects after Ophthalmic Use, above), especially in the elderly.[7]

Beta blockers have also been used for prophylaxis of postoperative ocular hypertension.[8,9]

1. LeBlanc RP, *et al.* Timolol: long-term Canadian Multicentre Study. *Can J Ophthalmol* 1985; **20:** 128–30.
2. Stewart RH, *et al.* Betaxolol vs timolol: a six-month double-blind comparison. *Arch Ophthalmol* 1986; **104:** 46–8.
3. Geyer O, *et al.* Levobunolol compared with timolol: a four-year study. *Br J Ophthalmol* 1988; **72:** 892–6.
4. Krieglstein GK, *et al.* Levobunolol and metipranolol: comparative ocular hypotensive efficacy, safety, and comfort. *Br J Ophthalmol* 1987; **71:** 250–3.
5. Scoville B, *et al.* A double-masked comparison of carteolol and timolol in ocular hypertension. *Am J Ophthalmol* 1988; **105:** 150–4.
6. van der Valk R, *et al.* Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. *Ophthalmology* 2005; **112:** 1177–85.
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Heart failure. Beta blockers have negative inotropic properties and have in the past been contra-indicated in patients with heart failure (p.1165). However, there is increasing evidence that they are in fact of benefit since persistent activation of the sympathetic nervous system appears to be associated with disease progression. Reviews,[1-3] meta-analyses,[4,5] and long-term studies[6,7] have confirmed that the beta blockers bisoprolol, carvedilol, and metoprolol all improve mortality in patients with chronic heart failure, and another study[8] has shown benefit with nebivolol in elderly patients. A further meta-analysis[9] found that fewer patients were withdrawn from treatment with beta blockers than placebo, suggesting that the benefits outweigh their adverse effects. Subgroup analysis[10] of one of the large studies also confirmed that metoprolol was well tolerated and of benefit in diabetics, despite potential effects on diabetic control (see Effects on Carbohydrate Metabolism under Adverse Effects, above). Beta blockers have also improved functional status in patients with chronic heart failure.[11] Beta blockers are therefore now recommended, as part of standard therapy, given with ACE inhibitors and diuretics, in all patients with clinically stable heart failure due to left ventricular systolic dysfunction where there are no contra-indications; the benefit in patients with preserved left ventricular function is less clear, although the empirical use of beta blockers to reduce heart rate and improve myocardial ischaemia has been suggested.[12]

The benefit of beta blockers in heart failure may not be a class effect, and in general only those with an established benefit should be used. Not all beta blockers have been studied in heart failure, but there is also evidence that some are ineffective; a study[13] with bucindolol was stopped early because no mortality benefit was found. For those that have been shown to improve mortality, it is not clear if they are all equally effective.[14] A meta-analysis[15] has suggested that vasodilating beta blockers such as carvedilol have a greater effect on overall mortality than those that do not produce vasodilatation, and a large study[16] comparing carvedilol with metoprolol also found a greater mortality reduction with carvedilol, although the equivalence of the doses used in the study has been questioned.[17] The optimum dose is also unclear; many patients are unable to tolerate the target doses used in clinical studies, but an analysis[18] of a study with metoprolol suggested that the mortality benefit was equal in those receiving low or high doses.

Beta blockers may also be of value in some patients with heart failure due to cardiomyopathy (p.1163). A number of beta blockers have provided symptomatic benefit in idiopathic dilated cardiomyopathy, and the heart failure studies that showed a mortality benefit included patients with dilated cardiomyopathy. In hypertrophic cardiomyopathy, beta blockers may be of value for symptomatic management to curtail tachycardia, reduce anginal pain, and prevent syncope.

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15. Bonet S, *et al.* β-Adrenergic blocking agents in heart failure: benefits of vasodilating and nonvasodilating agents according to patients' characteristics: a meta-analysis of clinical trials. *Arch Intern Med* 2000; **160:** 621–7.
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17. Dargie HJ. β-Blockers in heart failure. *Lancet* 2003; **362:** 2–3.
18. Wikstrand J, *et al.* Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol* 2002; **40:** 491–8.

Hypotension. Beta blockers have a hypotensive effect and are usually used to reduce blood pressure in patients with hypertension, or occasionally to produce controlled hypotension during surgery. Paradoxically, however, they may be used in the management of neurally mediated hypotension in patients who require drug therapy (see p.1174), although there is limited evidence to support their use, and adverse effects may be a concern. Beta blockers with partial agonist activity have been used in orthostatic hypotension due to autonomic failure (p.1530) but are potentially dangerous.

Migraine and tension type headache. Beta blockers (usually propranolol or metoprolol) are considered[1] by many to be the drugs of choice in patients requiring prophylactic treatment for migraine (p.616). Their mechanism of action in this disorder is not fully understood. Other beta blockers reported to be effective include atenolol, nadolol, and timolol; those with intrinsic sympathomimetic activity may not be effective.

Beta blockers may sometimes also be of benefit in patients with chronic tension-type headache (p.617).

Propranolol has been tried in the treatment of children with abdominal migraine (see under Pizotifen, p.624).

1. Limmroth V, Michel MC. The prevention of migraine: a critical review with special emphasis on β-adrenoceptor blockers. *Br J Clin Pharmacol* 2001; **52:** 237–43.

Peripheral vascular disease. Beta blockers may cause coldness of the extremities and have been reported to induce secondary Raynaud's syndrome. However, they may be of some help in the management of erythromelalgia (see under Vasospastic Arterial Disorders on p.1188).

Phaeochromocytoma. Beta blockers are used, with an alpha blocker, in the initial management of phaeochromocytoma (p.1179). Beta blockers reduce the responses to the beta-adrenoceptor stimulating effects of adrenaline. Treatment must be started with the alpha blocker and only when alpha blockade is successfully established can tachycardia be controlled by the cautious use of a beta blocker. A β_1-selective blocker is preferred so that peripheral β_2-mediated vasodilatation is unaffected. In most cases modest doses are sufficient although higher doses may be required for a tumour that is mainly adrenaline-secreting.

Tetanus. Autonomic overactivity, usually due to excessive catecholamine release, may occur as a complication of tetanus and is usually controlled with sedation (see p.1901). Beta blockers have also been used but may produce severe hypertension and are therefore not usually recommended. Labetalol has both alpha- and beta-blocking properties and intravenous labetalol has been used successfully to control the cardiovascular effects of tetanus,[1] although it has not been shown to offer any advantage over propranolol in this situation. Esmolol, a short-acting beta blocker, has also been used.[2]

1. Domenighetti GM, *et al.* Hyperadrenergic syndrome in severe tetanus: extreme rise in catecholamines responsive to labetalol. *BMJ* 1984; **288:** 1483–4.
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Tetralogy of Fallot. For the use of beta blockers in the management of tetralogy of Fallot, see under Uses of Propranolol, p.1381.

Tremor. Tremor is a rhythmical oscillation of part of the body caused by involuntary contraction of opposing muscles. It may occur during action, maintenance of posture, or at rest, and varies in frequency and amplitude. Resting tremor is associated mainly with parkinsonism (p.791), whereas action tremor, which includes postural tremor and kinetic tremor, occurs in a wide variety of disorders. Treatment of the underlying disorder may remove the tremor. Drugs such as bronchodilators, tricyclic antidepressants, lithium, and caffeine may induce tremor; withdrawal of the causative drug usually alleviates the tremor. However, tremor often has no known underlying cause. Such tremor is referred to as **essential tremor** or benign essential tremor; it is usually postural and tends to affect the hands, head, voice, and sometimes the legs and trunk. It is exacerbated by emotional stress and anxiety. Essential tremor may appear at any age and is a lifelong condition that may progress with increasing age. In many cases there is a family history of the disorder (familial essential tremor).

Mild cases of essential tremor may not require regular drug treatment. Single doses of a beta blocker or a benzodiazepine may be useful in acute circumstances to control exacerbations provoked by stress. A single dose of propranolol usually produces a maximum effect after 1 to 2 hours and the effect may persist for several hours. Small amounts of alcohol may also provide effective temporary relief of essential tremor, although its regular use is obviously discouraged.

For more severe cases of essential tremor long-term drug treatment may be required (and may also be tried in other forms of tremor).[1-5] A beta blocker (usually a non-cardioselective beta blocker such as propranolol) is often the first drug used. Up to 70% of people have been reported to respond, although the average tremor reduction is only about 50 to 60%. The beneficial effect appears to be mainly due to blockade of peripheral $beta_2$ receptors on extrafusal muscle fibres and muscle spindles, although there may also be a CNS effect. Adverse effects may be troublesome on long-term use. Primidone may also be tried[6] although there may be a high incidence of acute adverse reactions after initial doses. Concern has been expressed that patients may become tolerant to these drugs given long-term. However, 3 small studies found a reduced response on long-term therapy in only a few patients.[7-9] Local injection of botulinum A toxin has been tried in refractory essential tremor. Benzodiazepines, and antimuscarinic or dopaminergic antiparkinsonian drugs may be effective in some forms of tremor.[1] Other drugs that have shown some benefit include gabapentin and topiramate.[1-4,10] Many other drugs have been tried, but there is little evidence to support their use.[10] In very severe disabling cases, surgery (thalamotomy or deep brain stimulation) may have to be considered.

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2. Louis ED. Essential tremor. *N Engl J Med* 2001; **345:** 887–91.
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6. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986; **36:** 121–4.
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Betaxolol Hydrochloride

(BANM, USAN, rINNM) ⊗

ALO-1401-02; Betaksolol Hidroklorür; Betaksololihydrokloridi; Betaksololio hidrochloridas; Bétaxolol, chlorhydrate de; Betaxolol-hidroklorid; Betaxolol-hydrochlorid; Betaxololhydroklorid; Betaxololi hydrochloridum; Hidrocloruro de betaxolol; SL-75212-10. 1-{4-[2-(Cyclopropylmethoxy)ethyl]phenoxy}-3-isopropylaminopropan-2-ol hydrochloride.

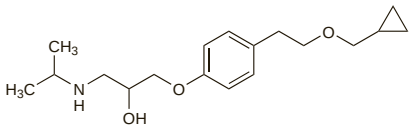
Бетаксолола Гидрохлорид

$C_{18}H_{29}NO_3$,HCl = 343.9.

CAS — 63659-18-7 (betaxolol); 63659-19-8 (betaxolol hydrochloride).

ATC — C07AB05; S01ED02.

ATC Vet — QC07AB05; QS01ED02.



(betaxolol)

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

Ph. Eur. 6.2 (Betaxolol Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in dichloromethane. Protect from light.

USP 31 (Betaxolol Hydrochloride). A white crystalline powder. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol. pH of a 2% solution in water is between 4.5 and 6.5. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Betaxolol is completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism, resulting in a high oral bioavailability of about 90%. It has high lipid solubility. Betaxolol is about 50% bound to plasma proteins. It crosses the placenta and is distributed into breast milk where higher concentrations have been achieved than in maternal blood. The plasma elimination half-life of betaxolol ranges from 14 to 22 hours. The primary route of elimination is via hepatic metabolism and urinary excretion; only about 15% is excreted in the urine as unchanged drug.

Pregnancy and breast feeding. The pharmacokinetics of betaxolol were investigated in the perinatal period in 28 pregnant hypertensive patients receiving doses of 10 to 40 mg daily.[1] Pharmacokinetic values were similar to those seen in non-pregnant patients. Umbilical-cord concentrations were similar to maternal blood concentrations and showed a negative correlation between concentration in cord blood and timing of the last dose of betaxolol. Thus the betaxolol concentration in neonates can be considerably reduced by stopping maternal drug use 16 to 18 hours before birth. The blood-betaxolol half-life in the neonates ranged from 14.8 to 38.5 hours. The mean apparent half-life in infants with gestational age less than 36 weeks was about 32% higher than in full-term neonates. Betaxolol concentrations in milk and/or colostrum were determined in 3 mothers. In all samples the milk-to-blood ratio was greater than 2.

1. Morselli PL, *et al.* Placental transfer and perinatal pharmacokinetics of betaxolol. *Eur J Clin Pharmacol* 1990; **38:** 477–83.

Uses and Administration

Betaxolol is a cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and to have little membrane-stabilising activity.

Betaxolol is used as the hydrochloride in the management of hypertension (p.1171), angina pectoris (p.1157), and glaucoma (p.1873).

In **hypertension** betaxolol hydrochloride is given in an initial oral dose of 10 mg once daily, which may be doubled if necessary after 1 to 2 weeks. Doses above 20 mg daily do not usually give additional benefit, but up to 40 mg daily has been tolerated. Similar doses are used in **angina pectoris**.

An initial dose of 5 mg daily is suggested for elderly patients. Reduced dosages should also be used in patients with severe renal impairment (see below).

Eye drops containing the equivalent of 0.25 or 0.5% betaxolol as the hydrochloride are instilled twice daily to reduce raised intra-ocular pressure in ocular hypertension and open-angle **glaucoma**.

◊ General references.

1. Buckley MM-T, *et al.* Ocular betaxolol: a review of its pharmacological properties, and therapeutic efficacy in glaucoma and ocular hypertension. *Drugs* 1990; **40:** 75–90.

Administration in renal impairment. The clearance of betaxolol is reduced in patients with renal impairment and the dose may therefore need to be reduced. Licensed US product information recommends an initial dose of betaxolol hydrochloride 5 mg daily in patients with severe renal impairment or on dialysis; the dose may be increased by 5 mg every 2 weeks, to a maximum of 20 mg daily.

Speech disorders. A 50-year-old man who had stuttered since childhood obtained striking improvement in his stuttering when he was given betaxolol 20 mg daily for essential hypertension.[1]

1. Burris JF, *et al.* Betaxolol and stuttering. *Lancet* 1990; **335:** 223.

Preparations

BP 2008: Betaxolol Eye Drops, Solution; Betaxolol Eye Drops, Suspension; ***USP 31:*** Betaxolol Ophthalmic Solution; Betaxolol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Betasel; Tonobexol; ***Austral.:*** Betoptic; Betoquin; ***Austria:*** Betoptic; Kerlone; ***Belg.:*** Betoptic; Kerlone; ***Braz.:*** Betoptic; Presmin; ***Canad.:*** Betoptic; ***Chile:*** Bemaz; Beof; Betoptic; ***Cz.:*** Betalmic; Betaxa; Betoptic; Lokren; ***Denm.:*** Betoptic; Kerlon†; ***Fin.:*** Betoptic; Kerlon; ***Fr.:*** Betoptic; Kerlone; ***Ger.:*** Betoptima; Kerlone; ***Gr.:*** Armament; Betoptic; Eifel; Kerlone; Pertaxol†; ***Hong Kong:*** Betoptic; ***Hung.:*** Betoptic; Lokren; ***India:*** Optipres; ***Indon.:*** Betoptima; Optibet; ***Irl.:*** Betoptic; ***Israel:*** Betoptic; Kerlone; ***Ital.:*** Betoptic; Kerlon; ***Jpn:*** Kerlong; ***Malaysia:*** Betac; Betoptic; Kerlone; ***Mex.:*** Beofta†; Betoptic; BTX-HA Ofteno; ***Neth.:*** Betoptic; Kerlon; ***Norw.:*** Betoptic; ***NZ:*** Betoptic; ***Philipp.:*** Betoptic; Kerlone; ***Pol.:*** Betabion; Betoptic; Lokren; Optibetol; ***Port.:*** Bertocil; Betaglau; Betoptic; Davixolol; ***Rus.:*** Betac (Бетак); Betoptic (Бетоптик); Lokren (Локрен); ***S.Afr.:*** Betoptic; ***Singapore:*** Betac; Betoptic; Kerlone; ***Spain:*** Betoptic; ***Swed.:*** Betoptic; Kerlon†; ***Switz.:*** Betoptic; Kerlon†; ***Thai.:*** Betoptic; ***Turk.:*** Betoptic; ***UK:*** Betoptic; ***USA:*** Betoptic; Kerlone; ***Venez.:*** Betaxol; Betoptic.

Bevantolol Hydrochloride *(BANM, USAN, rINNM)* ⊗

Bévantolol, Chlorhydrate de; Bevantololhydroklorid; Bevantololi Hydrochloridum; Bevantololihydrokloridi; CI-775; Hidrocloruro de bevantolol; NC-1400. 1-(3,4-Dimethoxyphenethylamino)-3-*m*-tolyloxypropan-2-ol hydrochloride.

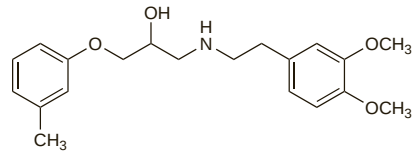
Бевантолола Гидрохлорид

$C_{20}H_{27}NO_4$,HCl = 381.9.

CAS — 59170-23-9 (bevantolol); 42864-78-8 (bevantolol hydrochloride).

ATC — C07AB06.

ATC Vet — QC07AB06.



(bevantolol)

Profile

Bevantolol is a cardioselective beta blocker (p.1225). It is reported to lack significant intrinsic sympathomimetic activity but has weak membrane-stabilising properties and also has vasodilator activity. It has been given orally as the hydrochloride in the management of hypertension and angina pectoris.

◊ References.

1. Frishman WH, *et al.* Bevantolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. *Drugs* 1988; **35:** 1–21.