Accupro; **Denm.:** Accupro; **Fin.:** Accupro; **Fr.:** Acuitel; Korec; **Ger.:** Accupro; QuinaLich; **Gr.:** Accupron; **Hong Kong:** Accupril; **Hung.:** Accupro; Acumerck; **Indon.:** Accupril; **Irl.:** Accupro; Quinapro; **Ital.:** Accuprin; Acequin; Quinazil; **Jpn:** Conan; **Malaysia:** Accupril†; **Mex.:** Acupril; **Neth.:** Acupril; **NZ:** Accupril; **Philipp.:** Accupril; **Pol.:** Accupro; Acurenal; AprilGen; **Port.:** Acupril; Vasocor†; **Rus.:** Accupro (Аккупро); **S.Afr.:** Accupril; Quinaspen; **Singapore:** Accupril†; **Spain:** Acuprel; Acuretic; Ectren; Lidaltrin; **Swed.:** Accupro; **Switz.:** Accupro; **Thai.:** Accupril; **Turk.:** Acuitel; **UK:** Accupro; Quinil; **USA:** Accupril; **Venez.:** Accupril; Quinalar; Solpres.

Multi-ingredient: **Arg.:** Accuretic; **Austral.:** Accuretic; **Austria:** Accuzide; **Belg.:** Accuretic; Co-Quinapril; **Canad.:** Accuretic; **Chile:** Accuretic; **Cz.:** Accuzide; Stadapress; **Fin.:** Accupro Comp; **Fr.:** Acuilix; Koretic; **Ger.:** Accuzide; QuinaLich comp; Quinaplus; Quinapril comp; **Gr.:** Accuretic; Quimea; **Hung.:** Accuzide; **Irl.:** Accuretic; **Ital.:** Accuretic; Acequide; Quinazide; **Neth.:** Acuzide; **NZ:** Accuretic; **Philipp.:** Accuzide; **Pol.:** Accuzide; **Port.:** Acuretic; **S.Afr.:** Accuretic; **Spain:** Bicetil; Lidaltrin Diu; **Swed.:** Accupro Comp; **Switz.:** Accuretic; **Turk.:** Accuzide; **UK:** Accuretic; **USA:** Accuretic; Quinaretic; **Venez.:** Accuretic; Quinaretic.

Quinethazone *(BAN, rINN)* ⊗

Chinethazonum; Kinetatsoni; Kinetazon; Quinetazona; Quinéthazone; Quinethazonum. 7-Chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxoquinazoline-6-sulphonamide.

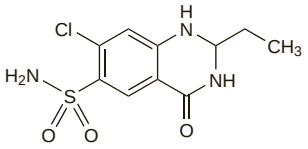
Хинетазон

$C_{10}H_{12}ClN_3O_3S$ = 289.7.

CAS — 73-49-4.

ATC — C03BA02.

ATC Vet — QC03BA02.



Profile

Quinethazone is a diuretic that is related chemically to metolazone and has properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1307). It has been used for oedema, including that associated with heart failure, and for hypertension.

Quinidine *(BAN)*

Chinidinum; Chinidyna; Kinidiini; Kinidin; Kinin; Quinidina. (8*R*,9*S*)-6′-Methoxycinchonan-9-ol; (+)-(α*S*)-α-(6-Methoxy-4-quinolyl)-α-[(2*R*,4*S*,5*R*)-(5-vinylquinuclidin-2-yl)]methanol.

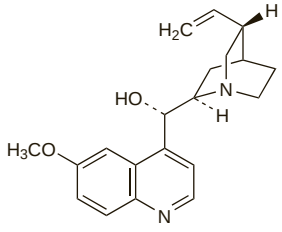
Хинидин

$C_{20}H_{24}N_2O_2$ = 324.4.

CAS — 56-54-2 (anhydrous quinidine); 6317-04-4 (quinidine dihydrate); 72402-50-7 (± quinidine).

ATC — C01BA01.

ATC Vet — QC01BA01.



Description. Quinidine is an isomer of quinine, obtained from the bark of species of *Cinchona* and their hybrids; it may also be obtained from *Remijia pedunculata*, or prepared from quinine.

Quinidine Bisulfate

Quinidina, bisulfato de; Quinidine Bisulphate *(BANM)*.

Хинидина Бисульфат

$C_{20}H_{24}N_2O_2,H_2SO_4$ = 422.5.

CAS — 747-45-5 (anhydrous quinidine bisulfate); 6151-39-9 (quinidine bisulfate tetrahydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

Pharmacopoeias. In *Br.*

BP 2008 (Quinidine Bisulphate). Colourless, odourless or almost odourless, crystals. It contains not more than 15% of hydroquinidine bisulfate. Freely soluble in water and in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 2.6 to 3.6. Protect from light.

Quinidine Gluconate *(BANM)*

Quinidina, gluconato de; Quinidinium Gluconate.

Хинидина Глюконат

$C_{20}H_{24}N_2O_2,C_6H_{12}O_7$ = 520.6.

CAS — 7054-25-3.

ATC — C01BA01.

ATC Vet — QC01BA01.

Pharmacopoeias. In *US.*

USP 31 (Quinidine Gluconate). A white, odourless powder. It contains not more than 20% of hydroquinidine gluconate. Freely soluble in water; slightly soluble in alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adsorption. More than 40% of a dose of quinidine gluconate was lost when the drug was given by intravenous infusion using a PVC infusion bag and tubing.[1]

1. Darbar D, *et al.* Loss of quinidine gluconate injection in a polyvinyl chloride infusion system. *Am J Health-Syst Pharm* 1996; **53:** 655–8.

Quinidine Polygalacturonate

Quinidina, poligalacturonato de. Quinidine poly(D-galacturonate) hydrate.

Хинидина Полигалактуронат

$C_{20}H_{24}N_2O_2,(C_6H_{10}O_7)_x,xH_2O$.

CAS — 27555-34-6 (anhydrous quinidine polygalacturonate); 65484-56-2 (quinidine polygalacturonate hydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

Quinidine Sulfate

Chinidin sulfát dihydrát; Chinidini sulfas; Chinidino sulfatas; Chinidinsulfate; Chinidinum Sulfuricum; Chinidyny siarczan; Kinidiinisulfaatti; Kinidin Sülfat; Kinidinsulfat; Kinidin-szulfát; Quinidina, sulfato de; Quinidine, sulfate de; Quinidine Sulphate *(BANM)*; Quinidini Sulfas; Quinidini Sulfas Dihydricus.

Хинидина Сульфат

$(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$ = 782.9.

CAS — 50-54-4 (anhydrous quinidine sulfate); 6591-63-5 (quinidine sulfate dihydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Quinidine Sulphate). White or almost white, crystalline powder, or silky, colourless needles. It contains not more than 15% of hydroquinidine sulfate. Slightly soluble in water; soluble in boiling water and in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.0 to 6.8. Protect from light.

USP 31 (Quinidine Sulfate). Fine, needle-like, white crystals, frequently cohering in masses, or a fine, white powder. It is odourless and darkens on exposure to light. It contains not more than 20% of hydroquinidine sulfate. Its solutions are neutral or alkaline to litmus. Soluble 1 in 100 of water, 1 in 10 of alcohol, and 1 in 15 of chloroform; insoluble in ether. Protect from light.

Stability. Quinidine sulfate was reported[1] to be stable for up to 60 days in several extemporaneously prepared oral liquid formulations.

1. Allen LV, Erickson MA. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampin, and tetracycline hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1804–9.

Adverse Effects and Treatment

Quinidine and its salts have both cardiac and non-cardiac adverse effects. Gastrointestinal irritation is common, with nausea, vomiting, and diarrhoea.

Hypersensitivity similar to that occurring with quinine may also occur and a test dose has been recommended (see Uses and Administration, below). Reactions include respiratory difficulties, urticaria, pruritus, skin rashes, purpura, thrombocytopenia and other blood dyscrasias, and, rarely, fever and anaphylaxis. Granulomatous hepatitis and a lupus-like syndrome have been reported.

Quinidine may give rise to cinchonism (see Quinine, p.612) with tinnitus, impaired hearing, visual disturbances, headache, confusion, vertigo, vomiting, and abdominal pain; it is usually associated with large doses, but may occur in idiosyncratic subjects given small doses.

Quinidine may induce hypotension, particularly in overdosage or if intravenous infusions are given too rapidly. It prolongs the QT interval and may precipitate ventricular arrhythmias, including torsade de pointes.

In quinidine overdosage, the cardiac symptoms of intoxication predominate. Quinidine is cumulative in action and inappropriately high plasma concentrations may induce ECG changes, heart block, asystole, ventricular tachycardia, ventricular fibrillation, syncope, seizures, coma, and sometimes death. Treatment of adverse effects and overdosage is symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion.

◊ Reviews.

1. Kim SY, Benowitz NL. Poisoning due to class IA antiarrhythmic drugs quinidine, procainamide and disopyramide. *Drug Safety* 1990; **5:** 393–420.

Effects on the blood. Quinidine-induced thrombocytopenia is not uncommon and it is one of the best documented causes of drug-dependent thrombocytopenia.[1] It appears to be a hypersensitivity reaction, with quinidine inducing the production of autoantibodies that cause platelet destruction. Highly specific quinidine-dependent antibodies have been detected in patients with thrombocytopenia, and may have a role in diagnosis.[2] The exact mechanism of the reaction is unclear but it is generally thought that binding of quinidine to the platelet surface induces antibody production;[1] alternatively, an antibody-quinidine complex may be formed, which is then deposited on the platelets.[1,3] The antigenic constituent of the platelet membrane may be glycoprotein Ib although other surface glycoproteins have also been implicated.[3,4]

1. van den Bemt PMLA, *et al.* Drug-induced immune thrombocytopenia. *Drug Safety* 2004; **27:** 1243–52.
2. Reid DM, Shulman NR. Drug purpura due to surreptitious quinidine intake. *Ann Intern Med* 1988; **108:** 206–8.
3. Stricker RB, Shuman MA. Quinidine purpura: evidence that glycoprotein V is a target platelet antigen. *Blood* 1986; **67:** 1377–81.
4. Visentin GP, *et al.* Characteristics of quinine- and quinidine-induced antibodies specific for platelet glycoproteins IIb and IIIa. *Blood* 1991; **77:** 2668–76.

Effects on the eyes. Corneal deposits resembling those found in keratopathy developed in a patient who had been taking quinidine for 2 years.[1] Symptoms had improved and both corneas had cleared completely within 2 months of stopping the drug.

A small number of patients have also been identified[2] who developed uveitis during quinidine treatment.

1. Zaidman GW. Quinidine keratopathy. *Am J Ophthalmol* 1984; **97:** 247–9.
2. Fraunfelder FW, Rosenbaum JT. Drug-induced uveitis: incidence, prevention and treatment. *Drug Safety* 1997; **17:** 197–207.

Effects on the joints. Quinidine has been associated with a number of rheumatic disorders.[1] It is a recognised, though uncommon, cause of drug-induced lupus (see below), but there have also been reports[2-4] of reversible, symmetrical polyarthritis developing in patients with no evidence of antinuclear antibodies. Symptoms were generally milder than in drug-induced lupus, and onset was more rapid; recovery occurred within a week of stopping quinidine and in some patients symptoms recurred on rechallenge. Polymyalgia rheumatica-like symptoms have also been reported.[1]

1. Alloway JA, Salata MP. Quinidine-induced rheumatic syndromes. *Semin Arthritis Rheum* 1995; **24:** 315–22.
2. Kertes P, Hunt D. Polyarthritis complicating quinidine treatment. *BMJ* 1982; **284:** 1373–4.
3. Cohen MG, *et al.* Two distinct quinidine-induced rheumatic syndromes. *Ann Intern Med* 1988; **108:** 369–71.
4. Naschitz JE, Yeshurun D. Quinidine and rheumatic syndromes. *Ann Intern Med* 1988; **109:** 248–9.

Effects on the liver. Hypersensitivity reactions involving the liver have been reported in about 2% of patients receiving quinidine.[1,2] The main clinical symptom is fever[1-3] but skin rash,[1-3] purpura,[2] and hepatomegaly[1] may also occur. Liver enzyme values are raised[1-4] and the platelet count may be reduced.[3] The reaction is reversible on withdrawing quinidine with fever resolving in about 48 hours and liver enzymes values returning to normal within about 2 weeks. Liver biopsy often shows granulomatous hepatitis,[1-3] but other inflammatory changes[2] and cholestatic jaundice[4] have been found.

1. Geltner D, *et al.* Quinidine hypersensitivity and liver involvement: a survey of 32 patients. *Gastroenterology* 1976; **70:** 650–2.
2. Knobler H, *et al.* Quinidine-induced hepatitis. *Arch Intern Med* 1986; **146:** 526–8.
3. Bramlet DA, *et al.* Granulomatous hepatitis as a manifestation of quinidine hypersensitivity. *Arch Intern Med* 1980; **140:** 395–7.
4. Hogan DB, *et al.* Unusual hepatotoxic reaction to quinidine. *Can Med Assoc J* 1984; **130:** 973.

Effects on mental state. Gradually progressive cerebral dysfunction characterised by intermittent confusion, agitation, restlessness, personality change, and paranoid features occurred in a 62-year-old man who had taken quinidine for about 15 years.[1] Within 24 hours of stopping quinidine there was a marked improvement and after 5 days he had returned to normal with no

cognitive deficits. It was considered that quinidine had precipitated or exacerbated the functional psychosis.

1. Johnson AG, *et al.* A functional psychosis precipitated by quinidine. *Med J Aust* 1990; **153:** 47–9.

Effects on the skin. Skin reactions reported with quinidine include exacerbation of psoriasis,[1] blue-grey pigmentation,[2] photosensitivity,[3] and fatal toxic epidermal necrolysis.[4] Purpuric bruising, attributed to inhalation of quinidine dust in the workplace, has also been reported.[5]

1. Harwell WB. Quinidine-induced psoriasis. *J Am Acad Dermatol* 1983; **9:** 278.
2. Mahler R, *et al.* Pigmentation induced by quinidine therapy. *Arch Dermatol* 1986; **122:** 1062–4.
3. Marx JL, *et al.* Quinidine photosensitivity. *Arch Dermatol* 1983; **119:** 39–43.
4. Adornato MC. Toxic epidermal necrolysis associated with quinidine administration. *N Y State Dent J* 2000; **66:** 38–40.
5. Salom IL. Purpura due to inhaled quinidine. *JAMA* 1991; **266:** 1220.

Hypoglycaemia. Mean plasma-insulin concentrations increased and mean plasma-glucose concentrations decreased in 8 healthy subjects and 10 patients with malaria given quinidine intravenously.[1] Profound hypoglycaemia occurred in 1 patient with cerebral malaria and acute renal failure. These effects were considered to be associated with stimulation of β-cell secretion of insulin by quinidine and it was concluded that hypoglycaemia may occur in any severely ill fasting patient given parenteral quinidine.

1. Phillips RE, *et al.* Hypoglycaemia and antimalarial drugs: quinidine and release of insulin. *BMJ* 1986; **292:** 1319–21.

Lupus erythematosus. There are several well-documented reports of quinidine-induced lupus erythematosus.[1-4] The syndrome involves polyarthritis with a positive antinuclear antibody test. Symptoms do not usually occur until several months after starting quinidine and resolve slowly on stopping the drug. A recurrence of lupus-like symptoms has occurred in patients with a previous reaction to procainamide.[2]

1. West SG, *et al.* Quinidine-induced lupus erythematosus. *Ann Intern Med* 1984; **100:** 840–2.
2. Amadio P, *et al.* Procainamide, quinidine, and lupus erythematosus. *Ann Intern Med* 1985; **102:** 419.
3. Lavie CJ, *et al.* Systemic lupus erythematosus (SLE) induced by quinidine. *Arch Intern Med* 1985; **145:** 446–8.
4. Cohen MG, *et al.* Two distinct quinidine-induced rheumatic syndromes. *Ann Intern Med* 1988; **108:** 369–71.

Oesophageal stricture. Oral quinidine is a recognised cause of oesophageal injury[1,2] and has been associated with ulceration and stricture formation.

1. McCord GS, Clouse RE. Pill-induced esophageal strictures: clinical features and risk factors for development. *Am J Med* 1990; **88:** 512–18.
2. Jaspersen D. Drug-induced oesophageal disorders: pathogenesis, incidence, prevention and management. *Drug Safety* 2000; **22:** 237–49.

Precautions

Quinidine is contra-indicated in complete heart block (unless the patient has a pacemaker). It should be used with extreme caution in patients with a prolonged QT interval or a history of torsade de pointes, incomplete heart block, uncompensated heart failure, myocarditis, or severe myocardial damage. Patients should be monitored closely for hypersensitivity reactions after the first dose and quinidine should not be given to those who develop a reaction or those with a history of hypersensitivity to quinidine, including patients who have previously developed thrombocytopenia with quinidine or quinine. Antiarrhythmic therapy with quinidine should be begun with extreme caution, if at all, during acute infections or fever as hypersensitivity reactions may be masked. Care is also required in patients with myasthenia gravis as quinidine can exacerbate the symptoms and may reduce the effectiveness of parasympathomimetic drugs.

When quinidine is used to treat atrial flutter or fibrillation, the reduction in AV block may result in a very rapid ventricular rate. This can be avoided by prior digitalisation or by use of a rate-limiting calcium-channel blocker or beta blocker. However, quinidine should be avoided in digitalis overdosage as markedly increased plasma concentrations of digoxin may occur.

Reduced dosage should be considered for the elderly, for patients with hepatic or renal impairment, and on the occasions when it is used in heart failure.

Breast feeding. A woman[1] receiving 2.1 g quinidine daily throughout pregnancy had milk and serum concentrations 5 days after delivery of 6.4 and 9.0 micrograms/mL respectively, giving a milk to serum ratio of 0.71. It was estimated that the amount of quinidine that would be ingested by an infant would be far below the therapeutic range for its weight. No adverse effects have been reported in infants and the American Academy of Pediatrics considers[2] that quinidine is therefore usually compatible with breast feeding.

1. Hill LM, Malkasian GD. The use of quinidine sulfate throughout pregnancy. *Obstet Gynecol* 1979; **54:** 366–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Pregnancy. In a report[1] on the use of quinidine sulfate by a woman throughout pregnancy, concentrations in the infant's serum at delivery were similar to the mother's although amniotic fluid concentrations were raised. The infant's weight, ECG, haemoglobin concentration, and platelet count were all found to be within normal limits.

1. Hill LM, Malkasian GD. The use of quinidine sulfate throughout pregnancy. *Obstet Gynecol* 1979; **54:** 366–8.

Interactions

Quinidine has the potential for both pharmacodynamic and pharmacokinetic interactions with many other drugs.

Use of quinidine with drugs that increase the QT interval or have arrhythmogenic effects should generally be avoided, since there is an increased risk of toxicity. Although quinidine is sometimes given with other antiarrhythmics, caution is required since there may be both pharmacodynamic and pharmacokinetic interactions (see below). Interactions may also occur with other drugs because of the antimuscarinic and alpha-adrenoceptor blocking properties of quinidine; potentiation of the effects of neuromuscular blockers has also been reported.

Quinidine is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, and may interact with inhibitors or inducers of this isoenzyme. Rifampicin, phenobarbital, and phenytoin increase the metabolism of quinidine and increased doses may be required; HIV-protease inhibitors, which inhibit CYP3A4, may produce toxic concentrations of quinidine.

Urinary excretion of quinidine is dependent on urinary pH; drugs that increase urinary pH such as sodium bicarbonate, some antacids, and carbonic anhydrase inhibitors tend to increase the plasma concentration of quinidine since the proportion of nonionised drug in the urine is increased allowing greater renal tubular reabsorption.

Quinidine itself may also have effects on other drugs; it inhibits cytochrome P450 isoenzyme CYP2D6 and may affect drugs metabolised by this route. Examples of further drugs that may be affected by quinidine include oral anticoagulants, beta blockers, and digoxin; more details are given under the monographs for these drugs.

Antiarrhythmics. *Amiodarone* may increase the plasma concentration of quinidine, increasing the risk of toxicity; prolongation of the QT interval with torsade de pointes has been reported.[1] This is probably because amiodarone inhibits hepatic or renal clearance of quinidine or displaces quinidine from binding sites. If the two drugs are used together the dose of quinidine may need to be reduced and the patient should be closely monitored. *Verapamil* given intravenously has been reported[2] to cause severe hypotension in patients also taking quinidine by mouth. Studies *in vitro* suggest this is due to the additive blockade of α-adrenergic receptors by both drugs and the simultaneous blockade of calcium channels by verapamil; verapamil may also increase the plasma concentration of quinidine. Quinidine itself may increase the plasma concentration of some other antiarrhythmics (see Ajmaline, p.1206, Digoxin, p.1261, Disopyramide, p.1270, Flecainide Acetate, p.1289, Procainamide, p.1378, and Propafenone Hydrochloride, p.1380).

1. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; **17:** 130–40.
2. Maisel AS, *et al.* Hypotension after quinidine plus verapamil. *N Engl J Med* 1985; **312:** 167–70.

Antibacterials. Torsade de pointes has been reported[1] in a patient taking *erythromycin* with quinidine. Like quinidine, erythromycin prolongs the QT interval, and the effect may be greater if the drugs are given together;[2] there is also some evidence[3-5] that erythromycin reduces quinidine clearance.

1. Lin JC, Quasny HA. QT prolongation and development of torsades de pointes with the concomitant administration of oral erythromycin base and quinidine. *Pharmacotherapy* 1997; **17:** 626–30.
2. Stanford RH, *et al.* Effect of oral erythromycin on quinidine pharmacodynamics in healthy volunteers. *Pharmacotherapy* 1997; **17:** 1111.
3. Spinler SA, *et al.* Possible inhibition of hepatic metabolism of quinidine by erythromycin. *Clin Pharmacol Ther* 1995; **57:** 89–94.
4. Stanford RH, *et al.* Effect of oral erythromycin on quinidine pharmacokinetics in healthy volunteers. *Pharmacotherapy* 1998; **18:** 426–7.
5. Damkier P, *et al.* Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* 1999; **48:** 829–38.

Antifungals. *Ketoconazole* temporarily increased the plasma-quinidine concentration in a patient through reduced hepatic elimination.[1] Another antifungal that inhibits hepatic metabolism, *itraconazole*, has also been reported[2] to increase plasma-quinidine concentrations.

1. McNulty RM, *et al.* Transient increase in plasma quinidine concentrations during ketoconazole-quinidine therapy. *Clin Pharm* 1989; **8:** 222–5.
2. Kaukonen K-M, *et al.* Itraconazole increases plasma concentrations of quinidine. *Clin Pharmacol Ther* 1997; **62:** 510–17.

Beta blockers. Quinidine and beta blockers may have additive adverse effects, and pharmacokinetic interactions may also occur. Sinus bradycardia has been reported in a patient prescribed oral quinidine and *timolol* eye drops,[1] and orthostatic hypotension has occurred when quinidine was used with *atenolol*.[2] Use of quinidine or the beta blocker alone was well tolerated in each case with no adverse effects.

1. Dinai Y, *et al.* Bradycardia induced by interaction between quinidine and ophthalmic timolol. *Ann Intern Med* 1985; **103:** 890–1.
2. Manolis AS, Estes NAM. Orthostatic hypotension due to quinidine and atenolol. *Am J Med* 1987; **82:** 1083–4.

Calcium-channel blockers. *Nifedipine* has been reported[1] to reduce plasma-quinidine concentrations and increasing the dose of quinidine to up to 20 mg/kg failed to increase the plasma concentration. Withdrawal of nifedipine resulted in a doubling of the quinidine concentration. A pharmacokinetic and pharmacodynamic study in healthy subjects, however, failed to show that modified-release *felodipine* or nifedipine had any effect on quinidine disposition.[2] Another study in healthy subjects suggested that quinidine may inhibit nifedipine metabolism.[3] *Diltiazem* has also been reported[4] to decrease the clearance and increase the half-life of quinidine in healthy subjects, although it was noted that another study had failed to show any interaction.

For the effects of *verapamil* used with quinidine, see Antiarrhythmics, above.

1. Green JA, *et al.* Nifedipine-quinidine interaction. *Clin Pharm* 1983; **2:** 461–5.
2. Bailey DG, *et al.* Quinidine interaction with nifedipine and felodipine: pharmacokinetic and pharmacodynamic evaluation. *Clin Pharmacol Ther* 1993; **53:** 354–9.
3. Bowles SK, *et al.* Evaluation of the pharmacokinetic and pharmacodynamic interaction between quinidine and nifedipine. *J Clin Pharmacol* 1993; **33:** 727–31.
4. Laganière S, *et al.* Pharmacokinetic and pharmacodynamic interactions between diltiazem and quinidine. *Clin Pharmacol Ther* 1996; **60:** 255–64.

Diuretics. *Carbonic anhydrase inhibitors* increase urinary pH and may increase plasma-quinidine concentrations by increasing renal tubular reabsorption. *Thiazides* and *loop diuretics* may increase the risk of arrhythmias by causing hypokalaemia. Arrhythmias occurred in 4 of 10 patients receiving *amiloride* when given quinidine,[1] possibly due to additive sodium-channel blockade.

1. Wang L, *et al.* Amiloride-quinidine interaction: adverse outcomes. *Clin Pharmacol Ther* 1994; **56:** 659–67.

Histamine H_2-antagonists. *Cimetidine* inhibits the hepatic metabolism of quinidine and increases in plasma concentration and half-life with a reduction in clearance have been reported.[1-3]

1. Hardy BG, *et al.* Effect of cimetidine on the pharmacokinetics and pharmacodynamics of quinidine. *Am J Cardiol* 1983; **52:** 172–5.
2. Kolb KW, *et al.* Effect of cimetidine on quinidine clearance. *Ther Drug Monit* 1984; **6:** 306–12.
3. MacKichan JJ, *et al.* Effect of cimetidine on quinidine bioavailability. *Biopharm Drug Dispos* 1989; **10:** 121–5.

Pharmacokinetics

Quinidine is rapidly absorbed from the gastrointestinal tract; the time to peak plasma concentration depends on the salt and formulation but is about 2 hours for quinidine sulfate immediate-release tablets. Bioavailability is variable, owing to first-pass metabolism in the liver.

Quinidine is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, to a number of metabolites, at least some of which are pharmacologically active. It is excreted in the urine, mainly in the form of its metabolites. The proportion excreted unchanged is dependent on urinary pH; in acidic urine about 20% is excreted as unchanged quinidine but in

alkaline urine this is reduced to about 5% due to increased renal tubular reabsorption.

Quinidine is widely distributed throughout the body and is 80 to 90% bound to plasma proteins including α_1-acid glycoprotein. It has a plasma half-life of about 6 to 8 hours but this may show wide variation. Its therapeutic effect has been correlated with plasma concentrations of about 1 to 6 micrograms/mL, depending on the assay method used; older methods that do not differentiate quinidine from its metabolites may give misleading results.

Quinidine crosses the placenta and is distributed into breast milk. Only small amounts are removed by haemodialysis.

◊ Considerable intersubject and intrasubject variability in the pharmacokinetics of quinidine has been noted;[1] in one study the half-life ranged from about 1 to 16 hours regardless of whether the drug was given as a tablet, capsule, oral solution, or intramuscular injection. There may also be considerable variations in absorption depending upon the formulation and the salt used.[2,3] The effect of food on absorption is not clear.[4,5] The heart condition being treated or associated with the arrhythmia may alter quinidine's pharmacokinetics[6,7] as may the age of the patient.[8-10] Hepatic impairment may affect protein binding and prolong quinidine's half-life.[11] Protein binding increases in patients with renal impairment, although it returns to normal during dialysis procedures.[12] Accumulation of quinidine metabolites may occur in patients with renal dysfunction.[13-15]

1. Mason WD, *et al*. Comparative plasma concentrations of quinidine following administration of one intramuscular and three oral formulations to 13 human subjects. *J Pharm Sci* 1976; **65:** 1325–9.
2. Frigo GM, *et al*. Comparison of quinidine plasma concentration curves following oral administration of some short- and long-acting formulations. *Br J Clin Pharmacol* 1977; **4:** 449–54.
3. Mahon WA, *et al*. Comparative bioavailability study of three sustained release quinidine formulations. *Clin Pharmacokinet* 1987; **13:** 118–24.
4. Woo E, Greenblatt DJ. Effect of food on enteral absorption of quinidine. *Clin Pharmacol Ther* 1980; **27:** 188–93.
5. Martinez MN, *et al*. Effect of dietary fat content on the bioavailability of a sustained release quinidine gluconate tablet. *Biopharm Drug Dispos* 1990; **11:** 17–29.
6. Ueda CT, Dzindzio BS. Quinidine kinetics in congestive heart failure. *Clin Pharmacol Ther* 1978; **23:** 158–64.
7. Ueda CT, Dzindzio BS. Bioavailability of quinidine in congestive heart failure. *Br J Clin Pharmacol* 1981; **11:** 571–7.
8. Drayer DE, *et al*. Prevalence of high (3S)-3-hydroxyquinidine/quinidine ratios in serum, and clearance of quinidine in cardiac patients with age. *Clin Pharmacol Ther* 1980; **27:** 72–5.
9. Szefler SJ, *et al*. Rapid elimination of quinidine in pediatric patients. *Pediatrics* 1982; **70:** 370–5.
10. Pickoff AS, *et al*. Age-related differences in the protein binding of quinidine. *Dev Pharmacol Ther* 1981; **3:** 108–15.
11. Kessler KM, *et al*. Quinidine pharmacokinetics in patients with cirrhosis or receiving propranolol. *Am Heart J* 1978; **96:** 627–35.
12. Kessler KM, Perez GO. Decreased quinidine plasma protein binding during haemodialysis. *Clin Pharmacol Ther* 1981; **30:** 121–6.
13. Kessler KM, *et al*. Quinidine elimination in patients with congestive heart failure or poor renal function. *N Engl J Med* 1974; **290:** 706–9.
14. Drayer DE, *et al*. Steady-state serum levels of quinidine and active metabolites in cardiac patients with varying degrees of renal function. *Clin Pharmacol Ther* 1978; **24:** 31–9.
15. Hall K, *et al*. Clearance of quinidine during peritoneal dialysis. *Am Heart J* 1982; **104:** 646–7.

Uses and Administration

Quinidine is a class Ia antiarrhythmic (p.1153). It also has antimuscarinic and alpha-adrenoceptor blocking properties. Quinidine is used in the management of supraventricular and ventricular arrhythmias, including cardioversion and maintenance of sinus rhythm in atrial fibrillation, but other drugs or methods are usually preferred.

Quinidine is an isomer of quinine and may be used as an alternative to quinine in the treatment of malaria when quinine is not immediately available.

Quinidine is usually given orally and various salts have been used, including the bisulfate, the gluconate, the polygalacturonate, and the sulfate. Strengths of preparations and doses used may be expressed in terms of the salt actually contained in the preparation, but are commonly expressed as the equivalent amount of anhydrous quinidine base or quinidine sulfate dihydrate. Quinidine bisulfate (anhydrous) 260 mg, quinidine gluconate (anhydrous) 321 mg, quinidine sulfate (dihydrate) 241 mg, and quinidine sulfate (anhydrous) 230 mg are each equivalent to about 200 mg of quinidine (anhydrous).

For the management of **cardiac arrhythmias**, a typical dose of *quinidine sulfate dihydrate* is 200 to 400 mg three or four times daily, adjusted according to response; an initial test dose of 200 mg has been recommended for detecting hypersensitivity. Modified-release preparations may be preferred for maintenance.

Quinidine has also been given parenterally but absorption after intramuscular injection is erratic and incomplete, and intravenous use is associated with a risk of severe hypotension. If parenteral use is necessary for acute conversion of supraventricular or ventricular arrhythmias, *quinidine gluconate* may be given by intravenous infusion at a rate no faster than 250 micrograms/kg per minute; most patients respond to a total dose of less than 5 mg/kg, but up to 10 mg/kg may be given if required. ECG and blood pressure should be monitored throughout the infusion.

For the use of quinidine in the management of **malaria**, see below.

◊ General references.

1. Grace AA, Camm AJ. Quinidine. *N Engl J Med* 1998; **338:** 35–45.

Cardiac arrhythmias. Quinidine is a class Ia antiarrhythmic and has been used in the management of supraventricular and ventricular arrhythmias, but other drugs or non-pharmacological therapies are usually preferred (see Cardiac Arrhythmias, p.1160). Although use of quinidine may have increased after the CAST studies, which found an increased mortality with the use of encainide, flecainide, and moracizine in asymptomatic ventricular arrhythmias, a meta-analysis[1] of studies using quinidine for benign or potentially lethal ventricular arrhythmias found that it was associated with at least as high an incidence of adverse events, including death and early proarrhythmia, as the class Ic drugs flecainide and propafenone. Another meta-analysis[2] found that quinidine was more effective than placebo in maintaining sinus rhythm after cardioversion of atrial fibrillation, but again total mortality was increased.

Quinidine has been used[3] in patients with Brugada syndrome, a congenital channelopathy that predisposes to ventricular arrhythmias, and may have a role as an alternative to an implantable cardioverter defibrillator.

1. Morganroth J, Goin JE. Quinidine-related mortality in the short-to-medium-term treatment of ventricular arrhythmias: a meta-analysis. *Circulation* 1991; **84:** 1977–83.
2. Coplen SE, *et al*. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990; **82:** 1106–16. Correction. *ibid*. 1991; **83:** 714.
3. Belhassen B, *et al*. Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation* 2004; **110:** 1731–7.

Congenital myasthenia. Although quinidine may exacerbate the symptoms of myasthenia gravis and should be used with great caution in such patients, beneficial responses have been reported in patients with the slow-channel congenital myasthenic syndrome (see p.630).

Hiccup. Quinidine is one of several drugs that have been tried in intractable hiccups. For details of a protocol for the control of hiccups see Chlorpromazine, p.976.

Malaria. Quinidine may be more potent than quinine as an antimalarial but it is more likely to cause cardiac toxicity and hypersensitivity and WHO[1,2] has recommended that parenteral formulations of quinidine should only be used when parenteral quinine or artemisinin derivatives are not immediately available. In these situations intravenous infusions of quinidine could be used to begin treatment for severe chloroquine-resistant malaria. Patients should be transferred to oral therapy with quinine as soon as possible to complete a 7-day course; alternatively a single oral treatment of pyrimethamine-sulfadoxine may be given.

In the USA, the CDC[3,4] have recommended parenteral quinidine gluconate as the drug of choice for the treatment of complicated falciparum malaria, but only because of the lack of availability of parenteral quinine.

Quinidine is given intravenously as the gluconate and doses have been expressed in terms of the base or salt; it should be given under close control, preferably with continuous ECG monitoring and frequent measurements of blood pressure. Regimens used include one[1,5] where the equivalent of 15 mg of the base per kg is infused over 4 hours as a loading dose followed by the equivalent of 7.5 mg of the base per kg every 8 hours as infusions over 4 hours; the patient should be transferred to an oral form of antimalarial as soon as possible. An alternative regimen[6] consists of a loading dose of 10 mg of quinidine gluconate per kg given by intravenous infusion over a period of 1 to 2 hours followed by a constant intravenous infusion of 20 micrograms/kg per minute for a maximum of 72 hours or until oral therapy with quinine can be instituted to complete a total 3-day course of treatment. It is generally recommended that loading doses should not be used if the patient has received quinine or quinidine within the previous 24 hours or mefloquine within the preceding 7 days.

The overall management of malaria is discussed in the chapter on Antimalarials, p.594.

1. WHO. *Management of severe malaria: a practical handbook*. Geneva: WHO, 2000. Available at: http://www.who.int/malaria/docs/hbsm_toc.htm (accessed 16/07/07)
2. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 10/07/07)
3. CDC. Treatment with quinidine gluconate of persons with severe Plasmodium falciparum infection: discontinuation of parenteral quinine from CDC drug service. *MMWR* 1991; **40** (RR-4): 21–3. Also available at http://www.cdc.gov/mmwr/preview/mmwrhtml/00043932.htm (accessed 10/07/07)
4. CDC. Availability and use of parenteral quinidine gluconate for severe or complicated malaria. *MMWR* 2000; **49:** 1138–40.
5. Phillips RE, *et al*. Intravenous quinidine for the treatment of severe falciparum malaria: clinical pharmacokinetic studies. *N Engl J Med* 1985; **312:** 1273–8.
6. Miller KD, *et al*. Treatment of severe malaria in the United States with a continuous infusion of quinidine gluconate and exchange transfusion. *N Engl J Med* 1989; **321:** 65–70.

Neurological disorders. For reference to the use of quinidine with dextromethorphan for the management of amyotrophic lateral sclerosis, see p.1556.

Preparations

BP 2008: Quinidine Sulphate Tablets;
USP 31: Quinidine Gluconate Extended-release Tablets; Quinidine Gluconate Injection; Quinidine Sulfate Capsules; Quinidine Sulfate Extended-release Tablets; Quinidine Sulfate Oral Suspension; Quinidine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Kinidin; ***Belg.:*** Kinidine†; ***Braz.:*** Quinicardine; ***Canad.:*** Biquin; ***Cz.:*** Kinidin†; ***Denm.:*** Kinidin; ***Fin.:*** Kiniduron; ***Gr.:*** Kinidine; Ydroquinidine; ***Hong Kong:*** Kinidin†; ***Irl.:*** Kinidin; ***Israel:*** Quiniduran; ***Ital.:*** Chinteina; Longachin; Naticardina†; Natisedina; Ritmocor; ***Mex.:*** Quini†; ***Neth.:*** Kinidine†; ***Philipp.:*** Kinidin; ***S.Afr.:*** Quinaglute; ***Spain:*** Longacor†; ***Swed.:*** Kinidin; ***Switz.:*** Kinidin; Longacor†; ***Turk.:*** Longacor; Natisedine; Quinicardine; ***UK:*** Kinidin†; ***USA:*** Quinidex†.

Multi-ingredient: ***Fr.:*** Quinimax; ***Ger.:*** Cordichin.

Ramipril *(BAN, USAN, rINN)*

Hoe-498; Ramipriili; Ramiprilis; Ramiprilum. (2*S*,3a*S*,6a*S*)-1-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]L-alanyl}perhydrocyclopenta[*b*]pyrrole-2-carboxylic acid.

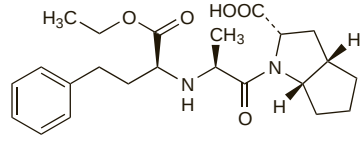
Рамиприл

$C_{23}H_{32}N_2O_5$ = 416.5.

CAS — 87333-19-5.

ATC — C09AA05.

ATC Vet — QC09AA05.



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

Ph. Eur. 6.2 (Ramipril). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Protect from light.

USP 31 (Ramipril). A white to almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Ramipril acts as a prodrug of the diacid ramiprilat, its active metabolite. After oral doses at least 50 to 60% is absorbed. Ramipril is metabolised in the liver to ramiprilat; other metabolites are inactive. Peak plasma concentrations of ramiprilat are achieved 2 to 4 hours after an oral dose of ramipril. Ramiprilat is about 56% bound to plasma proteins. After oral doses ramipril is excreted primarily in the urine, as ramiprilat, other metabolites, and some unchanged drug. About 40% of an oral dose appears in the faeces; this may represent both biliary excretion and unabsorbed drug. The effective half-life for accumulation of ramiprilat is 13 to 17 hours after multiple doses of ramipril 5 to 10 mg, but is much longer for doses of 1.25 to 2.5 mg daily; the difference relates to the long terminal half-life associated