Digitalis lanata leaf is used as a source for the manufacture of digoxin and other glycosides.

◊ There have been reports[1] of toxicity after ingestion of dietary supplements contaminated with digitalis lanata.

1. Slifman NR, *et al.* Contamination of botanical dietary supplements by digitalis lanata. *N Engl J Med* 1998; **339:** 806–11.

Digitoxin *(BAN, rINN)*

Digitaline Cristallisée; Digitoksiini; Digitoksinas; Digitoksyna; Digitoxina; Digitoxine; Digitoxinum; Digitoxoside; Dijitoksin. 3β-[(*O*-2,6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14β-hydroxy-5β-card-20(22)-enolide.

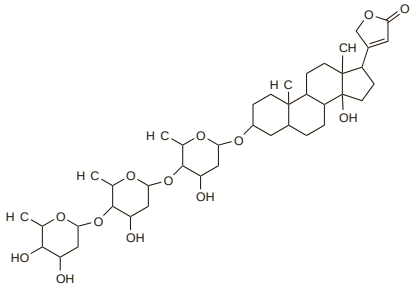
Дигитоксин

$C_{41}H_{64}O_{13}$ = 764.9.

CAS — 71-63-6.

ATC — C01AA04.

ATC Vet — QC01AA04.



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

Ph. Eur. 6.2 (Digitoxin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in a mixture of equal volumes of chloroform and methyl alcohol. Protect from light.

USP 31 (Digitoxin). A cardiotonic glycoside obtained from *Digitalis purpurea*, *Digitalis lanata* (Scrophulariaceae), or other suitable species of *Digitalis*. A white or pale buff-coloured, odourless, microcrystalline powder. Practically insoluble in water; soluble 1 in 150 of alcohol and 1 in 40 of chloroform; very slightly soluble in ether. Store in airtight containers.

Adsorption. Binding to an in-line intravenous filter containing a cellulose ester membrane accounted for a reduction[1] in digitoxin concentration of up to 25% from solutions of digitoxin 200 micrograms in 50 mL of glucose 5% or sodium chloride 0.9%. Pretreatment of the filter with a polymer coating reduced adsorption by about half.[2]

Digitoxin was found to be adsorbed onto glass and plastic in substantial amounts from simple aqueous solutions but not from solutions in 30% alcohol, or in plasma, or urine.[3]

1. Butler LD, *et al*. Effect of inline filtration on the potency of low-dose drugs. *Am J Hosp Pharm* 1980; **37:** 935–41.
2. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.
3. Molin L, *et al.* Solubility, partition, and adsorption of digitalis glycosides. *Acta Pharm Suec* 1983: **20:** 129–44.

Adverse Effects, Treatment, and Precautions

As for Digoxin, below. Toxicity may be more prolonged after withdrawal of digitoxin because of the longer half-life.

◊ References.

1. Lely AH, van Enter CHJ. Large-scale digitoxin intoxication. *BMJ* 1970; **3:** 737–40.
2. Gilfrich H-J, *et al.* Treatment of massive digitoxin overdose by charcoal haemoperfusion and cholestyramine. *Lancet* 1978; **i:** 505.
3. Pond S, *et al*. Treatment of digitoxin overdose with oral activated charcoal. *Lancet* 1981; **ii:** 1177–8.
4. Kurowski V, *et al.* Treatment of a patient with severe digitoxin intoxication by Fab fragments of anti-digitalis antibodies. *Intensive Care Med* 1992; **18:** 439–42.
5. Schmitt K, *et al*. Massive digitoxin intoxication treated with digoxin-specific antibodies in a child. *Pediatr Cardiol* 1994; **15:** 48–9.
6. Lehmann G, *et al.* Digitoxin intoxication in a 79-year-old patient: a description of a case and review of the literature. *Int J Cardiol* 2000; **75:** 109–13.
7. Hippius M, *et al.* Adverse drug reaction monitoring—digitoxin overdosage in the elderly. *Int J Clin Pharmacol Ther* 2001; **39:** 336–43.

Interactions

As for Digoxin, below. Since digitoxin is significantly metabolised in the liver it may be affected by drugs that induce microsomal enzymes, including rifampicin (see below) and antiepileptics such as phenobarbital.

Antibacterials. Acute heart failure has been reported in a patient taking digitoxin when treatment with *rifampicin* and isoniazid was started; plasma-digitoxin concentrations fell from a pretreatment steady-state value of 27 nanograms/mL to 10 nanograms/mL. The reduction in the digitoxin concentration was attributed to induction of digitoxin metabolism by rifampicin.[1]

Digitoxin toxicity has been described in 2 patients after addition of *azithromycin* to their therapy.[2]

1. Boman G, *et al*. Acute cardiac failure during treatment with digitoxin—an interaction with rifampicin. *Br J Clin Pharmacol* 1980; **10:** 89–90.
2. Thalhammer F, *et al.* Azithromycin-related toxic effects of digitoxin. *Br J Clin Pharmacol* 1998; **45:** 91–2.

Antineoplastics. A mean overall increase of 109% was seen in digitoxin clearance in 5 patients also given *aminoglutethimide*. The interaction was attributed to the induction of hepatic enzymes by aminoglutethimide.[1]

1. Lønning PE, *et al*. Effect of aminoglutethimide on antipyrine, theophylline, and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* 1984; **36:** 796–802.

Calcium-channel blockers. Steady-state plasma concentrations of digitoxin increased by an average of 35% over 2 to 3 weeks in 8 of 10 patients when *verapamil* 240 mg daily was added to their therapy. Total body clearance and extra-renal clearance of digitoxin were reduced by 27% and 29% respectively although renal excretion was unchanged. Plasma-digitoxin concentrations increased by a mean of 21% in 5 of 10 patients treated with *diltiazem* but were not increased by *nifedipine*.[1]

1. Kuhlman J. Effects of verapamil, diltiazem, and nifedipine on plasma levels and renal excretion of digitoxin. *Clin Pharmacol Ther* 1985; **38:** 667–73.

Diuretics. *Spironolactone* has been reported to decrease the half-life and the urinary elimination of unchanged digitoxin when given for at least 10 days to 8 patients on oral maintenance digitoxin therapy.[1] However, increased digitoxin half-life has been reported[2] in 3 healthy subjects when spironolactone was added to digitoxin therapy. The interaction was judged to be of minor clinical importance.

1. Wirth KE, *et al*. Metabolism of digitoxin in man and its modification by spironolactone. *Eur J Clin Pharmacol* 1976; **9:** 345–54.
2. Carruthers SG, Dujovne CA. Cholestyramine and spironolactone and their combination in digitoxin elimination. *Clin Pharmacol Ther* 1980; **27:** 184–7.

Pharmacokinetics

Digitoxin is readily and completely absorbed from the gastrointestinal tract. Therapeutic plasma concentrations may range from 10 to 35 nanograms/mL but there is considerable interindividual variation. Digitoxin is more than 90% bound to plasma proteins. It is very slowly eliminated from the body and is metabolised in the liver. Most metabolites are inactive; the major active metabolite is digoxin. Enterohepatic recycling occurs and digitoxin is excreted in the urine, mainly as metabolites. It is also excreted in the faeces and this route becomes significant in renal impairment. Digitoxin has an elimination half-life of up to 7 days or more. The half-life is generally unchanged in renal impairment.

The pharmacokinetics of digitoxin may be affected by age and by concurrent diseases (see under Uses and Administration, below).

Uses and Administration

Digitoxin is a cardiac glycoside with positive inotropic activity. It has actions similar to those of digoxin (below) and is used in the management of some cardiac arrhythmias (p.1160) and in heart failure (p.1165).

Digitoxin is the most potent of the digitalis glycosides and is the most cumulative in action. The onset of its action is slower than that of the other cardiac glycosides and it may therefore be less suitable than digoxin for rapid digitalisation; after oral doses its effects may be evident in about 2 hours and its full effects in about 12 hours. Its effects persist for about 3 weeks.

As described under digoxin, dosage should be carefully adjusted to the needs of the individual patient. Steady-state therapeutic plasma concentrations of digitoxin may range from 10 to 35 nanograms/mL; higher values may be associated with toxicity. In adults 1 to 1.5 mg has been given orally in divided doses over 24 hours for rapid digitalisation, while for slow digitalisation an oral dose of 200 micrograms twice daily for 4 days has been given. The usual maintenance dose is 100 to 200 micrograms daily, but 100 micrograms on alternate days may be adequate. Digitoxin may also be given by slow intravenous injection when vomiting or other conditions prevent oral use; maintenance doses of 70 to 100 micrograms daily have been used. It has also been given intramuscularly but injections may be irritant.

Administration in children. Children were found to have a greater volume of distribution of digitoxin than adults and a shorter mean half-life, although individual variation was considerable. The increase in total clearance in children compared with adults was attributed to greater metabolic clearance. Digitalisation doses of 20 micrograms/kg were well tolerated.[1]

1. Larsen A, Storstein L. Digitoxin kinetics and renal excretion in children. *Clin Pharmacol Ther* 1983; **33:** 717–26.

Administration in the elderly. Digitoxin half-life, apparent volume of distribution, and clearance were not found to differ in elderly subjects compared with young adults after intravenous injection in a single-dose study. The long half-life may make once weekly dosing possible in poorly compliant patients.[1]

1. Donovan MA, *et al*. The effect of age on digitoxin pharmacokinetics. *Br J Clin Pharmacol* 1981; **11:** 401–2.

Administration in renal disease. The pharmacokinetics of digitoxin were changed significantly in 5 patients with nephrotic syndrome. The apparent volume of distribution of digitoxin was increased and protein binding decreased. Such patients should be maintained at lower serum-digitoxin concentrations than other patients but will need larger doses because of the shortened serum half-life and the increased renal excretion of digitoxin and its cardioactive metabolites.[1]

1. Storstein L. Studies on digitalis VII: influence of nephrotic syndrome on protein binding, pharmacokinetics, and renal excretion of digitoxin and cardioactive metabolites. *Clin Pharmacol Ther* 1976; **20:** 158–66.

Malignant neoplasms. There has been some interest in the potential anticancer activity of digitoxin and related compounds.

References.

1. Haux J. Digitoxin is a potential anticancer agent for several types of cancer. *Med Hypotheses* 1999; **53:** 543–8.
2. Haux J, *et al*. Digitoxin medication and cancer: case control and internal dose-response studies. *BMC Cancer* 2001; **1:** 11.
3. Johansson S, *et al*. Cytotoxicity of digitoxin and related cardiac glycosides in human tumor cells. *Anticancer Drugs* 2001; **12:** 475–83.
4. López-Lázaro M, *et al*. Digitoxin inhibits the growth of cancer cell lines at concentrations commonly found in cardiac patients. *J Nat Prod* 2005; **68:** 1642–5.
5. López-Lázaro M. Digitoxin as an anticancer agent with selectivity for cancer cells: possible mechanisms involved. *Expert Opin Ther Targets* 2007; **11:** 1043–53.

Preparations

BP 2008: Digitoxin Tablets;
USP 31: Digitoxin Injection; Digitoxin Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Digimerck; Ditaven†; ***Belg.:*** Digitaline†; ***Braz.:*** Digitaline; ***Ger.:*** Coramedan†; Digimed; Digimerck; Tardigal†; ***Hung.:*** Digimerck; ***Swed.:*** Digitrin†; ***USA:*** Crystodigin.

Digoxin *(BAN, rINN)*

Digoksiini; Digoksin; Digoksinas; Digoksyna; Digoxina; Digoxine; Digoxinum; Digoxosidum. 3β-[(*O*-2,6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14β-dihydroxy-5β-card-20(22)-enolide.

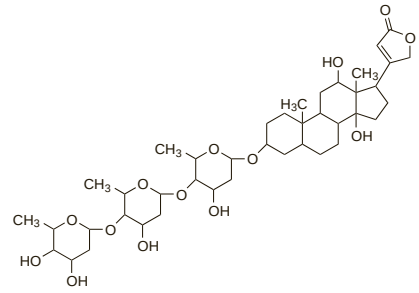
Дигоксин

$C_{41}H_{64}O_{14}$ = 780.9.

CAS — 20830-75-5.

ATC — C01AA05.

ATC Vet — QC01AA05.



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

Ph. Eur. 6.2 (Digoxin). A white or almost white powder or colourless crystals. Practically insoluble in water; slightly soluble in alcohol; freely soluble in a mixture of equal volumes of dichloromethane and methyl alcohol. Protect from light.

USP 31 (Digoxin). A cardiotonic glycoside obtained from the leaves of *Digitalis lanata* (Scrophulariaceae). Clear to white, odourless, crystals, or a white, odourless, crystalline powder. Practically insoluble in water and in ether; slightly soluble in diluted alcohol and in chloroform; freely soluble in pyridine. Store in airtight containers.

Adverse Effects

Digoxin and the other cardiac glycosides commonly produce adverse effects because the margin between the therapeutic and toxic doses is small; plasma concentrations of digoxin in excess of 2 nanograms/mL are considered to be an indication that the patient is at special risk although there is considerable interindividual variation. There have been many fatalities, particularly due to cardiac toxicity.

Nausea, vomiting, and anorexia may be among the earliest symptoms of digoxin toxicity or overdosage; diarrhoea and abdominal pain may occur. Certain neurological effects are also common symptoms of digoxin overdosage and include headache, facial pain, fatigue,

weakness, dizziness, drowsiness, disorientation, mental confusion, bad dreams and more rarely delirium, acute psychoses, and hallucinations. Convulsions have been reported. Visual disturbances including blurred vision may occur; colour vision may be affected with objects appearing yellow or, less frequently, green, red, brown, blue, or white. Hypersensitivity reactions are rare; thrombocytopenia has been reported. The cardiac glycosides may have some oestrogenic activity and occasionally cause gynaecomastia at therapeutic doses.

Rapid intravenous injection of digoxin may cause vasoconstriction and transient hypertension. Intramuscular or subcutaneous injection can cause local irritation.

The most serious adverse effects are those on the heart. Toxic doses may cause or aggravate heart failure. Supraventricular or ventricular arrhythmias and defects of conduction are common and may be an early indication of excessive dosage, particularly in children. In general the incidence and severity of arrhythmias is related to the severity of the underlying heart disease. Almost any arrhythmia may ensue, but particular note should be made of supraventricular tachycardia, especially AV junctional tachycardia and atrial tachycardia with block. Ventricular arrhythmias including extrasystoles, sinoatrial block, sinus bradycardia, and AV block may also occur.

Hypokalaemia predisposes to digoxin toxicity; adverse reactions to digoxin may be precipitated if hypokalaemia occurs, for example after prolonged use of diuretics. Hyperkalaemia occurs in acute digoxin overdosage.

As digoxin has a shorter half-life than digitalis or digitoxin any toxic effects will tend to resolve more rapidly.

◊ General references to digitalis toxicity.

1. Pentel PR, Salerno DM. Cardiac drug toxicity: digitalis glycosides and calcium-channel and β-blocking agents. *Med J Aust* 1990; **152:** 88–94.
2. Wells TG, *et al.* Age-related differences in digoxin toxicity and its treatment. *Drug Safety* 1992; **7:** 135–51.
3. Johnston GD. Adverse reaction profile: digoxin. *Prescribers' J* 1993; **33:** 29–35.
4. Kernan WN, *et al.* Incidence of hospitalization for digitalis toxicity among elderly Americans. *Am J Med* 1994; **96:** 426–31.
5. Li-Saw-Hee FL, Lip GYH. How safe is digoxin? *Adverse Drug React Bull* 1998; (Feb): 715–18.
6. Gittelman MA, *et al.* Acute pediatric digoxin ingestion. *Pediatr Emerg Care* 1999; **15:** 359–62.
7. López-Gómez D, *et al.* Intoxicación grave por digoxina: utilización exitosa del tratamiento clásico. *Rev Esp Cardiol* 2000; **53:** 471–2.
8. Ma G, *et al.* Electrocardiographic manifestations: digitalis toxicity. *J Emerg Med* 2001; **20:** 145–52.
9. Demiryürek AT, Demiryürek S. Cardiotoxicity of digitalis glycosides: roles of autonomic pathways, autacoids and ion channels. *Auton Autacoid Pharmacol* 2005; **25:** 35–52.
10. Bauman JL, *et al.* Mechanisms, manifestations, and management of digoxin toxicity in the modern era. *Am J Cardiovasc Drugs* 2006; **6:** 77–86.

Effects on the blood. Thrombocytopenia has been reported[1] in a small number of patients taking digoxin. An association between several cardiovascular drugs, including digitalis glycosides (digoxin and acetyldigoxin), and agranulocytosis was also found in an international study[2] although again the incidence was low.

1. George JN, *et al.* Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998; **129:** 886–90.
2. Kelly JP, *et al.* Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: the international agranulocytosis and aplastic anemia study. *Clin Pharmacol Ther* 1991; **49:** 330–41.

Effects in the elderly. Elderly patients may be particularly susceptible to digoxin toxicity, even at therapeutic plasma concentrations.[1] Adverse effects reported in elderly patients with toxic plasma-digoxin concentrations have included chorea,[2] profuse watery diarrhoea,[3] and dysphagia with dysphonia.[4]

1. Miura T, *et al.* Effect of aging on the incidence of digoxin toxicity. *Ann Pharmacother* 2000; **34:** 427–32.
2. Mulder LJMM, *et al.* Generalised chorea due to digoxin toxicity. *BMJ* 1988; **296:** 1262.
3. Andrews PA, Wilkinson PR. Diarrhoea as a side effect of digoxin. *BMJ* 1990; **301:** 1398.
4. Cordeiro MF, Arnold KG. Digoxin toxicity presenting as dysphagia and dysphonia. *BMJ* 1991; **302:** 1025.

Hypersensitivity. Hypersensitivity reactions to cardiac glycosides are rare but skin reactions have been reported. An 86-year-old man developed a generalised, pruritic, erythematous rash after digoxin was given intravenously.[1] The rash recurred on rechallenge with digoxin tablets.

1. Martin SJ, Shah D. Cutaneous hypersensitivity reaction to digoxin. *JAMA* 1994; **271:** 1905.

Treatment of Adverse Effects

In *acute poisoning*, gastric lavage may be considered if the patient presents within one hour of ingestion. Repeated doses of activated charcoal may be given to reduce the absorption and enterohepatic recycling of cardiac glycosides; colestyramine and colestipol have also been tried. Attempts to remove cardiac glycosides by haemodialysis or peritoneal dialysis have generally been ineffective and the value of haemoperfusion is controversial. Forced diuresis with furosemide is generally ineffective and may be dangerous; serious electrolyte imbalance may result from the use of such potent diuretics.

Cardiac toxicity in acute or chronic poisoning should be treated under ECG control and serum electrolytes should be monitored. Antiarrhythmic treatment may be necessary and should be determined by the specific arrhythmia present (see p.1160). Atropine is given intravenously to correct bradycardia and in patients with heart block. Pacing may be necessary if atropine is not effective. Potassium chloride may be given in hypokalaemic patients provided that renal function is normal and heart block is not present. Potassium has also been given to normokalaemic patients but caution is needed since hyperkalaemia can occur rapidly. Other electrolyte imbalances should be corrected.

In *massive overdosage* progressive hyperkalaemia occurs and is fatal unless reversed. Soluble insulin with glucose has been given and, if the hyperkalaemia is refractory, dialysis may be tried. Massive life-threatening overdosage has been treated successfully with digoxin-specific antibody fragments (p.1443).

For the treatment of *chronic poisoning* temporary withdrawal of digoxin or other cardiac glycosides may be all that is necessary, with subsequent doses adjusted according to the needs of the patient. Serum electrolytes should be measured and the ECG monitored. Potassium supplements should be given to correct hypokalaemia.

◊ References.

1. Allen NM, Dunham GD. Treatment of digitalis intoxication with emphasis on the clinical use of digoxin immune Fab. *DICP Ann Pharmacother* 1990; **24:** 991–8.
2. Dick M, *et al.* Digitalis intoxication recognition and management. *J Clin Pharmacol* 1991; **31:** 444–7.
3. Critchley JAJH, Critchley LAH. Digoxin toxicity in chronic renal failure: treatment by multiple dose activated charcoal intestinal dialysis. *Hum Exp Toxicol* 1997; **16:** 733–5.

Precautions

Digoxin is generally contra-indicated in patients with hypertrophic obstructive cardiomyopathy unless there is severe cardiac failure, since the outflow obstruction may be worsened. It is also contra-indicated in patients with the Wolff-Parkinson-White syndrome or other evidence of an accessory pathway, especially if it is accompanied by atrial fibrillation, since ventricular tachycardia or fibrillation may be precipitated. Digoxin is not an appropriate form of therapy for any ventricular arrhythmia.

Digoxin toxicity is common and may result from raised plasma concentrations or an increase in sensitivity to digoxin. Almost any deterioration in the condition of the heart or circulation may increase the sensitivity to digoxin and it should be used with caution in all patients with cardiovascular disease. Early signs of digoxin toxicity should be watched for and the heart rate should generally be maintained above 60 beats per minute. Toxicity may result from giving loading doses too rapidly and from accumulation of maintenance doses as well as from acute poisoning. Even with intravenous doses a response may take a number of hours, and persistence of tachycardia is therefore not a reason to exceed the recommended intravenous dose.

Digoxin should be used with caution in partial heart block since complete heart block may be induced; it should also be used with care in sinus node disorders. Caution is also required in acute myocarditis (such as rheumatic carditis), in acute myocardial infarction, in advanced heart failure, and in severe pulmonary disease, due to the increased myocardial sensitivity. Digoxin may also enhance the occurrence of arrhythmias in patients undergoing cardioversion and should be withdrawn 1 to 2 days before such procedures if possible. If cardioversion is essential and digoxin has already been given, low energy shocks must be used.

Electrolyte imbalances may affect the sensitivity to digoxin, as may thyroid dysfunction. The effects of digoxin are enhanced by hypokalaemia, hypomagnesaemia, hypercalcaemia, hypoxia, and hypothyroidism and doses may need to be reduced until these conditions are corrected. Resistance to the effects of digoxin may occur in hyperthyroidism. Digoxin should be given with care, and possibly in reduced dosage, to patients who have received it or other cardiac glycosides within the previous 2 to 3 weeks.

Digoxin doses should generally be reduced and plasma-digoxin concentrations monitored in patients with renal impairment, in the elderly, and in premature infants (see Uses and Administration, below).

Breast feeding. Studies[1,2] have shown that digoxin is distributed into breast milk, although the amount was considered too small to have an effect on the child. No adverse effects have been seen in breast-feeding infants whose mothers were receiving digoxin, and the American Academy of Pediatrics considers[3] that it is therefore usually compatible with breast feeding.

1. Levy M, *et al.* Excretion of drugs in human milk. *N Engl J Med* 1997; **297:** 789.
2. Chan V, *et al.* Transfer of digoxin across the placenta and into breast milk. *Br J Obstet Gynaecol* 1978; **85:** 605–9.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Gastrointestinal disorders. Absorption from tablets of digoxin may be decreased due to inadequate dissolution in patients with malabsorption syndromes or small bowel resections and it has been recommended that liquid dosage forms of digoxin should be used in the latter case.[1] However, only 40 to 60% of a digoxin dose given as elixir was absorbed in a patient with a small bowel resection[2] compared with about 80% in patients with normal gastrointestinal function, suggesting a need for slightly increased oral maintenance doses of digoxin in patients with resections. In a further patient with a similar resection[3] a therapeutic plasma-digoxin concentration was not achieved with any oral formulation.

1. Kumer KP, *et al.* Perspectives on digoxin absorption from small bowel resections. *Drug Intell Clin Pharm* 1983; **17:** 121–3.
2. Vetticaden SJ, *et al.* Digoxin absorption in a patient with short-bowel syndrome. *Clin Pharm* 1986; **5:** 62–4.
3. Ehrenpreis ED, *et al.* Malabsorption of digoxin tablets, gel caps, and elixir in a patient with an end jejunostomy. *Ann Pharmacother* 1994; **28:** 1239–40.

Heart surgery. Patients undergoing cardiac surgery appear to have increased sensitivity to digoxin toxicity and thus an increased risk of arrhythmias.[1] Digoxin has been found[2] to be no better than placebo in preventing postoperative arrhythmias after coronary artery bypass surgery, and actually induced supraventricular arrhythmias in 2 patients. Arrhythmias compatible with digoxin intoxication have occurred postoperatively[1] although serum-digoxin concentrations ranged from 0 to 2.8 nanograms/mL; therefore, the arrhythmias may have been due to either the surgical procedures or to increased sensitivity to digoxin.

1. Rose MR, *et al.* Arrhythmias following cardiac surgery: relation to serum digoxin levels. *Am Heart J* 1975; **89:** 288–94.
2. Weiner B, *et al.* Digoxin prophylaxis following coronary artery bypass surgery. *Clin Pharm* 1986; **5:** 55–8.

Interference with digoxin assays. The presence of endogenous digoxin-like substances in neonates, and in patients with liver or kidney dysfunction, may be responsible for elevated values or false-positive results in some plasma-digoxin assays.[1] Some patients may have antibodies that react with the assay system and produce falsely elevated values.[2]

Some drugs may also interfere with plasma-digoxin assays; these include prednisolone[1] and ginseng.[3] Raised serum-digoxin concentrations (but without signs of digoxin toxicity) were noted in an elderly man after the use of Siberian ginseng (*Eleutherococcus senticosus*). However, concentrations remained high even when digoxin was discontinued and returned to the therapeutic range only after the ginseng was stopped. Siberian ginseng contains eleutherosides, which are chemically related to cardiac glycosides such as digoxin, and the assay may have measured these compounds, or their derivatives, as well as digoxin. Although it has been suggested that this reaction may have been due to the substitution of the unrelated cardiotoxic herb *Periploca sepium*,[4] both ginseng and Siberian ginseng have been shown to interfere with some digoxin assays *in vitro* and *in vivo*.[5] Spironolactone may interfere with digoxin assays but may also

produce changes in digoxin concentrations (see Diuretics under Interactions, below).

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9:** 67–89.
2. Liendo C, *et al.* A new interference in some digoxin assays: antimurine heterophilic antibodies. *Clin Pharmacol Ther* 1996; **60:** 593–8.
3. McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *Can Med Assoc J* 1996; **155:** 293–5.
4. Awang DVC. Siberian ginseng toxicity may be case of mistaken identity. *Can Med Assoc J* 1996; **155:** 1237.
5. Dasgupta A, *et al.* Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays: significant variation in digoxin-like immunoreactivity among commercial ginsengs. *Am J Clin Pathol* 2003; **119:** 298–303.

Pregnancy. There is considerable evidence that digoxin crosses the placenta freely with serum-digoxin concentrations at term similar in the newborn and mother. No significant adverse effects attributed to digoxin have been noted in the fetus or neonate although adverse fetal effects, including fetal death, have been reported in mothers with digitalis toxicity. Some concern has been expressed that maternal digitalis therapy may occasionally cause low birth-weights in infants of mothers with heart disease, but the underlying disease might also be important.[1] The presence of endogenous digoxin-like immunoreactive substances in the serum of pregnant women and neonates could make the interpretation of digoxin assays difficult. In one study,[2] high concentrations of endogenous digoxin-like immunoreactivity in cord blood suggested that it might be synthesised during delivery, in which case the placental transfer of digoxin might be overestimated.

1. Rotmensch HH, *et al.* Management of cardiac arrhythmias during pregnancy: current concepts. *Drugs* 1987; **33:** 623–33.
2. Lupoglazoff JM, *et al.* Endogenous digoxin-like immunoreactivity during pregnancy and at birth. *Br J Clin Pharmacol* 1993; **35:** 251–4.

Interactions

There may be interactions between digoxin and drugs that alter its absorption, interfere with its excretion, or have additive effects on the myocardium. Drugs that cause electrolyte disturbances increase the risk of toxicity from cardiac glycosides. Thiazides and loop *diuretics* cause hypokalaemia and also hypomagnesaemia which may lead to cardiac arrhythmias. Other causes of hypokalaemia include treatment with *corticosteroids*, *beta$_2$ agonists* (such as salbutamol), *amphotericin B, sodium polystyrene sulfonate, carbenoxolone*, and dialysis. Hypercalcaemia may also increase toxicity and intravenous use of *calcium salts* is best avoided in patients taking cardiac glycosides. Serum-digoxin concentrations may be significantly increased by *quinidine, amiodarone*, and *propafenone* and reduction of digoxin dosage may be required. Other antiarrhythmics may have additive effects on the myocardium increasing the likelihood of adverse effects; *beta blockers* may potentiate bradycardia due to digoxin. *Calcium-channel blockers* may increase digoxin concentrations.

Digoxin is a substrate for P-glycoprotein and interactions may occur with drugs that affect P-glycoprotein function (see Metabolism and Excretion under Pharmacokinetics, below).

◊ Reviews of drug interactions occurring with digoxin.

1. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988; **15:** 227–44.
2. Magnani B, Malini PL. Cardiac glycosides: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 97–109.

ACE inhibitors. Although increased serum-digoxin concentrations have been reported in patients with severe chronic heart failure given *captopril*,[1] other studies have failed to confirm this effect.[2,3] Studies with various other ACE inhibitors have also failed to show any significant effect on serum-digoxin concentrations. However, ACE inhibitors may cause a deterioration in renal function and this could lead to an increase in serum-digoxin concentration due to impaired digoxin excretion.[4]

1. Cleland JGF, *et al.* Interaction of digoxin and captopril. *Br J Clin Pharmacol* 1984; **17:** 214P.
2. Magelli C, *et al.* Lack of effect of captopril on serum digoxin in congestive heart failure. *Eur J Clin Pharmacol* 1989; **36:** 99–100.
3. Rossi GP, *et al.* Effect of acute captopril administration on digoxin pharmacokinetics in normal subjects. *Curr Ther Res* 1989; **46:** 439–44.
4. Mignat C, Unger T. ACE inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 334–47.

Alpha blockers. *Prazosin*[1] has been reported to increase the mean plasma-digoxin concentration in patients receiving a maintenance dose of digoxin.

1. Çopur S, *et al.* Effects of oral prazosin on total plasma digoxin levels. *Fundam Clin Pharmacol* 1988; **2:** 13–17.

Angiotensin II receptor antagonists. In a study[1] in healthy subjects, *telmisartan* increased peak serum-digoxin concentrations but trough concentrations were unaffected and it was suggested that the effect was unlikely to be clinically significant. No interaction was found when digoxin was given with *losartan*[2] or with *eprosartan*[3] in healthy subjects.

1. Stangier J, *et al.* The effect of telmisartan on the steady-state pharmacokinetics of digoxin in healthy male volunteers. *J Clin Pharmacol* 2000; **40:** 1373–9.
2. de Smet M, *et al.* Effect of multiple doses of losartan on the pharmacokinetics of single doses of digoxin in healthy volunteers. *Br J Clin Pharmacol* 1995; **40:** 571–5.
3. Martin DE, *et al.* Lack of effect of eprosartan on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers. *Br J Clin Pharmacol* 1997; **43:** 661–4.

Antiarrhythmics. ***AMIODARONE.*** An interaction between digoxin and amiodarone resulting in increased plasma-digoxin concentrations has been reported[1-5] on several occasions; the concentration may be doubled.[5] An increase in serum-digoxin concentrations of 68 to 800% has been reported[2] during amiodarone therapy in children. The interaction does not appear to be due to a reduction in urinary excretion alone[3,4] and seems to be dose-related. It has been recommended[1,6] that the initial dose of digoxin should be halved when amiodarone is given.

1. Moysey JO, *et al.* Amiodarone increases plasma digoxin concentrations. *BMJ* 1981; **282:** 272.
2. Koren G, *et al.* Digoxin toxicity associated with amiodarone therapy in children. *J Pediatr* 1984; **104:** 467–70.
3. Douste-Blazy P, *et al.* Influence of amiodarone on plasma and urine digoxin concentrations. *Lancet* 1984; **i:** 905.
4. Mingardi G. Amiodarone and plasma digoxin levels. *Lancet* 1984; **i:** 1238.
5. Johnston A, *et al.* The digoxin-amiodarone interaction. *Br J Clin Pharmacol* 1987; **24:** 253P.
6. Naccarelli GV, *et al.* Adverse effects of amiodarone: pathogenesis, incidence and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 246–53.

DISOPYRAMIDE. Disopyramide appears to have no clinically significant effect on the pharmacokinetics of digoxin in healthy subjects[1,2] but has been reported to modify the cardiovascular effects of digoxin.[1]

1. Elliott HL, *et al.* Pharmacodynamic and pharmacokinetic evaluation of the interaction between digoxin and disopyramide. *Br J Clin Pharmacol* 1982; **14:** 141P.
2. Risler T, *et al.* On the interaction between digoxin and disopyramide. *Clin Pharmacol Ther* 1983; **34:** 176–80.

FLECAINIDE. Giving flecainide 200 mg twice daily to 15 healthy subjects taking digoxin caused a mean increase of 24% in predose digoxin concentrations and of 13% in digoxin concentrations 6 hours after the digoxin dose.[1] It was considered that in most cases these increases in plasma-digoxin concentrations would not present a clinical problem, but that patients with higher plasma-digoxin concentrations or atrioventricular nodal dysfunction should be monitored.

1. Weeks CE, *et al.* The effect of flecainide acetate, a new antiarrhythmic, on plasma digoxin levels. *J Clin Pharmacol* 1986; **26:** 27–31.

PROPAFENONE. Increased serum-digoxin concentrations have been reported when propafenone is also given.[1-4] There is considerable interindividual variation in the extent of the interaction; increases in serum-digoxin concentrations of up to 254% have been reported. If digoxin and propafenone are given together, the dose of digoxin should be reduced and serum-digoxin concentration should be monitored.

1. Nolan PE, *et al.* Effects of coadministration of propafenone on the pharmacokinetics of digoxin in healthy volunteer subjects. *J Clin Pharmacol* 1989; **29:** 46–52.
2. Calvo MV, *et al.* Interaction between digoxin and propafenone. *Ther Drug Monit* 1989; **11:** 10–15.
3. Zalzstein E, *et al.* Interaction between digoxin and propafenone in children. *J Pediatr* 1990; **116:** 310–12.
4. Bigot M-C, *et al.* Serum digoxin levels related to plasma propafenone levels during concomitant treatment. *J Clin Pharmacol* 1991; **31:** 521–6.

QUINIDINE. Quinidine causes an increase in serum-digoxin concentration in almost all patients given the two drugs together.[1-3] The serum-digoxin concentration may be increased by up to 500% but is usually approximately doubled.[1] Signs and symptoms of digoxin toxicity may occur although some workers[4] have suggested that these may be accounted for by an additive effect of the 2 drugs rather than by the effect on serum-digoxin concentration. The exact mechanism of interaction is not clear but a substantial decrease in the renal and nonrenal clearance of digoxin has been found.[5] The distribution volume of digoxin may also be reduced[2] reflecting impaired tissue binding, and there is increased systemic availability.[1] It is generally recommended that the dose of digoxin is halved in digitalised patients who are to be given quinidine.[2] Subsequently, serum-digoxin concentrations should be monitored, especially during the first 1 to 2 weeks after which the new steady-state digoxin concentration should be achieved.[2]

1. Bigger JT, Leahey EB. Quinidine and digoxin: an important interaction. *Drugs* 1982; **24:** 229–39.
2. Pedersen KE. Digoxin interactions: the influence of quinidine and verapamil on the pharmacokinetics and receptor binding of digitalis glycosides. *Acta Med Scand* 1985; **697** (suppl): 1–40.
3. Mordel A, *et al.* Quinidine enhances digitalis toxicity at therapeutic serum digoxin levels. *Clin Pharmacol Ther* 1993; **53:** 457–62.
4. Walker AM, *et al.* Drug toxicity in patients receiving digoxin and quinidine. *Am Heart J* 1983; **105:** 1025–8.
5. Hedman A, *et al.* Interactions in the renal and biliary elimination of digoxin: stereoselective difference between quinine and quinidine. *Clin Pharmacol Ther* 1990; **47:** 20–6.

VERAPAMIL. For a discussion on the interaction between digoxin and verapamil, see under Calcium-channel Blockers, below.

Antibacterials. About 10% of patients receiving digoxin may metabolise 40% or more of the drug to cardio-inactive metabolites.[1] Gut flora contribute greatly to this process, and the use of antibacterials such as *erythromycin* or *tetracycline* in these patients appears to reduce this metabolic process resulting in higher serum concentrations.[2] Digoxin toxicity has been reported in digitalised patients given erythromycin,[3,4] *azithromycin*,[5] *clarithromycin*,[6-8] and *roxithromycin*.[9] It has been postulated[5,10] that the macrolide antibacterials may also inhibit P-glycoprotein-mediated renal tubular secretion of digoxin. Oral *neomycin* may reduce serum-digoxin concentrations by reducing digoxin absorption.

Rifampicin may reduce serum-digitoxin concentrations by inducing its metabolism (see p.1259) although a study[11] in healthy subjects suggested that this reduction might rather be due to induction of intestinal P-glycoprotein. Digoxin is mainly excreted unchanged in the urine but rifampicin increased digoxin dose requirements substantially in 2 patients dependent on dialysis.[12] When rifampicin was stopped digoxin requirements fell by about 50%.

1. Doherty JE. A digoxin-antibiotic drug interaction. *N Engl J Med* 1981; **305:** 827–8.
2. Lindenbaum J, *et al.* Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *N Engl J Med* 1981; **305:** 789–94.
3. Maxwell DL, *et al.* Digoxin toxicity due to interaction of digoxin with erythromycin. *BMJ* 1989; **298:** 572.
4. Morton MR, Cooper JW. Erythromycin-induced digoxin toxicity. *DICP Ann Pharmacother* 1989; **23:** 668–70.
5. Ten Eick AP, *et al.* Possible drug interaction between digoxin and azithromycin in a young child. *Clin Drug Invest* 2000; **20:** 61–64.
6. Midoneck SR, Etingin OR. Clarithromycin-related toxic effects of digoxin. *N Engl J Med* 1995; **333:** 1505.
7. Nawarskas JJ, *et al.* Digoxin toxicity secondary to clarithromycin therapy. *Ann Pharmacother* 1997; **31:** 864–6.
8. Laberge P, Martineau P. Clarithromycin-induced digoxin intoxication. *Ann Pharmacother* 1997; **31:** 999–1002.
9. Corallo CE, Rogers IR. Roxithromycin-induced digoxin toxicity. *Med J Aust* 1996; **165:** 433–4.
10. Wakasugi H, *et al.* Effect of clarithromycin on renal excretion of digoxin: interaction with P-glycoprotein. *Clin Pharmacol Ther* 1998; **64:** 123–8.
11. Greiner B, *et al.* The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. *J Clin Invest* 1999; **104:** 147–53.
12. Gault H, *et al.* Digoxin-rifampin interaction. *Clin Pharmacol Ther* 1984; **35:** 750–4.

Antidepressants. In a study[1] in healthy subjects, use of digoxin together with an extract of *St John's wort* for 10 days resulted in a significant decrease in the plasma-digoxin concentration. It was suggested that the interaction might be due to induction of the P-glycoprotein transporter. In a study[2] in healthy male subjects, *nefazodone* increased steady-state plasma-digoxin concentrations by about 30% but no adverse or clinical effects were associated with the increase. However, due to the narrow therapeutic range of digoxin, it was suggested that plasma-digoxin concentrations should be monitored in patients also given nefazodone. Similar recommendations have been made for *trazodone*.

Digoxin toxicity developed in a patient shortly after starting *paroxetine* and was associated with increased serum-digoxin concentrations.[3] However, the role of paroxetine in the reaction has been queried.[4,5]

1. Johne A, *et al.* Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum). *Clin Pharmacol Ther* 1999; **66:** 338–45.
2. Dockens RC, *et al.* Assessment of pharmacokinetic and pharmacodynamic drug interactions between nefazodone and digoxin in healthy male volunteers. *J Clin Pharmacol* 1996; **36:** 160–7.
3. Yasui-Furukori N, Kaneko S. Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; **367:** 788.
4. Bateman DN, *et al.* Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; **368:** 1962–3.
5. Hallberg P, Melhus H. Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; **368:** 1963.

Antidiabetics. Subtherapeutic plasma-digoxin concentrations were noted in a diabetic woman receiving *acarbose* and digoxin.[1] The plasma concentration of digoxin increased to a therapeutic level when acarbose was stopped. A study[2] in healthy subjects suggested that the interaction was due to inhibition of the absorption of digoxin by acarbose.

1. Serrano JS, *et al.* A possible interaction of potential clinical interest between digoxin and acarbose. *Clin Pharmacol Ther* 1996; **60:** 589–92.
2. Miura T, *et al.* Impairment of absorption of digoxin by acarbose. *J Clin Pharmacol* 1998; **38:** 654–7.

Antiepileptics. *Phenytoin* caused a marked decrease in steady-state serum-digoxin concentrations when given with digoxin and acetyldigoxin to 6 healthy subjects for 7 days.[1] Total digoxin clearance was increased by an average of 27% and elimination

half-life was reduced by an average of 30%. This interaction may be more likely with digitoxin, since digitoxin is more dependent on the liver for elimination.

A brief report of an open study[2] in 12 subjects indicated a slight but significant decrease in digoxin bioavailability when *topiramate* was also given, although half-life and renal clearance of digoxin did not appear to be affected.

1. Rameis H. On the interaction between phenytoin and digoxin. *Eur J Clin Pharmacol* 1985; **29:** 49–53.
2. Liao S, Palmer M. Digoxin and topiramate drug interaction study in male volunteers. *Pharm Res* 1993; **10** (suppl): S405.

Antifungals. Two men given *itraconazole* while receiving digoxin developed signs and symptoms of digoxin toxicity and elevated serum-digoxin concentrations.[1,2] A further case report[3] suggested that the interaction was due to a reduction in the renal clearance of digoxin when itraconazole was given.

Additive adverse effects due to hypokalaemia may occur when digoxin is given with *amphotericin B*.

1. Rex J. Itraconazole–digoxin interaction. *Ann Intern Med* 1992; **116:** 525.
2. Alderman CP, Jersmann HPA. Digoxin–itraconazole interaction. *Med J Aust* 1993; **159:** 838–9.
3. Alderman CP, Allcroft PD. Digoxin-itraconazole interaction: possible mechanisms. *Ann Pharmacother* 1997; **31:** 438–40.

Antimalarials. In 6 subjects given *quinine sulfate*, total body clearance of digoxin after an intravenous dose was decreased by 26%, primarily through a reduction in nonrenal clearance.[1] Increased urinary excretion of digoxin was consistent with alterations in the nonrenal clearance of digoxin and might be due to changes in the metabolism or biliary secretion of digoxin. Quinine increased the mean elimination half-life of digoxin from 34.2 to 51.8 hours but did not consistently change the volume of distribution.

An increase in the plasma-digoxin concentration, but without symptoms of toxicity, was noted in 2 women given *hydroxychloroquine* (for rheumatoid arthritis) in addition to long-term digoxin therapy.[2]

1. Wandell M, *et al.* Effect of quinine on digoxin kinetics. *Clin Pharmacol Ther* 1980; **28:** 425–30.
2. Leden I. Digoxin–hydroxychloroquine interaction? *Acta Med Scand* 1982; **211:** 411–12.

Antineoplastics. A study[1] in patients undergoing antineoplastic therapy found that the absorption of digoxin from tablets was reduced by an average of 46.5%, whereas that of digoxin from liquid-filled capsules was not significantly changed. Another study[2] in similar patients found that the steady-state concentration of digoxin after giving acetyldigoxin was reduced, but that digitoxin concentrations were maintained. It was suggested that the interaction was due to reduced absorption of digitalis glycosides through the damaged gastrointestinal mucosa and that liquid-filled capsules or digitoxin might be preferred in these patients.

Licensed product information for *lenalidomide* states that it may increase plasma exposure of digoxin and recommends that digoxin concentrations should be monitored.

1. Bjornsson TD, *et al.* Effects of high-dose cancer chemotherapy on the absorption of digoxin in two different formulations. *Clin Pharmacol Ther* 1986; **39:** 25–8.
2. Kuhlmann J. Inhibition of digoxin absorption but not of digitoxin during cytostatic drug therapy. *Arzneimittelforschung* 1982; **32:** 698–704.

Antithyroid drugs. Reduced peak serum-digoxin concentrations were noted in 9 of 10 healthy subjects after a single oral dose of *carbimazole* although conversely in the tenth subject digoxin concentrations rose.[1] Caution is also needed since changes in thyroid function may independently affect sensitivity to digoxin (see Precautions, above).

1. Rao BR, *et al.* Influence of carbimazole on serum levels and haemodynamic effects of digoxin. *Clin Drug Invest* 1997; **13:** 350–4.

Antivirals. A woman stabilised on digoxin and tolerating lamivudine, indinavir and stavudine for HIV infection, developed symptoms of digoxin toxicity 3 days after *ritonavir* was added to her treatment.[1] It was suggested that the interaction might be due to inhibition of the P-glycoprotein transporter system by ritonavir. A pharmacokinetic study[2] showing significant inhibition of renal digoxin clearance by ritonavir seemed to support this hypothesis.

1. Phillips EJ, *et al.* Digoxin toxicity and ritonavir: a drug interaction mediated through p-glycoprotein? *AIDS* 2003; **17:** 1577–8.
2. Ding R, *et al.* Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers. *Clin Pharmacol Ther* 2004; **76:** 73–84.

Benzodiazepines. Raised serum-digoxin concentrations have been reported in patients also taking *diazepam*[1] or *alprazolam*.[2,3] The clearance of digoxin was reduced by these benzodiazepines.

1. Castillo-Ferrando JR, *et al.* Digoxin levels and diazepam. *Lancet* 1980; **ii:** 368.
2. Tollefson G, *et al.* Alprazolam-related digoxin toxicity. *Am J Psychiatry* 1984; **141:** 1612–14.
3. Guven H, *et al.* Age-related digoxin-alprazolam interaction. *Clin Pharmacol Ther* 1993; **54:** 42–4.

Beta$_2$ agonists. A single intravenous[1,2] or oral[3] dose of *salbutamol* has been reported to decrease steady-state serum-digoxin concentrations by up to 16% and 22% respectively in healthy subjects. Although salbutamol had no significant effect on the concentration of digoxin in skeletal muscle, it was considered that increased binding to skeletal muscle could explain the interaction. Beta$_2$ agonists such as salbutamol can also cause hypokalaemia which may increase susceptibility to digoxin-induced arrhythmias.

1. Edner M, Jogestrand T. Effect of salbutamol on digoxin concentration in serum and skeletal muscle. *Eur J Clin Pharmacol* 1989; **36:** 235–8.
2. Edner M, *et al.* Effect of salbutamol on digoxin pharmacokinetics. *Eur J Clin Pharmacol* 1992; **42:** 197–201.
3. Edner M, Jogestrand T. Oral salbutamol decreases serum digoxin concentration. *Eur J Clin Pharmacol* 1990; **38:** 195–7.

Beta blockers. Beta blockers may increase the risk of heart block and bradycardia with digoxin. In addition, *carvedilol* has been reported[1-3] to increase plasma concentrations of digoxin, although the effect is generally small and probably not clinically significant. However, a study[4] in 8 children (aged 2 weeks to 7.8 years) found that the clearance of digoxin was about halved by carvedilol and 2 of the children developed digoxin toxicity. An increase in digoxin bioavailability has also been reported with *talinolol*.[5]

1. Grunden JW, *et al.* Augmented digoxin concentrations with carvedilol dosing in mild-moderate heart failure. *Am J Ther* 1994; **1:** 157–161.
2. Wermeling DP, *et al.* Effects of long-term oral carvedilol on the steady-state pharmacokinetics of oral digoxin in patients with mild to moderate hypertension. *Pharmacotherapy* 1994; **14:** 600–6.
3. De Mey C, *et al.* Carvedilol increases the systemic bioavailability of oral digoxin. *Br J Clin Pharmacol* 1990; **29:** 486–90.
4. Ratnapalan S, *et al.* Digoxin-carvedilol interactions in children. *J Pediatr* 2003; **142:** 572–4.
5. Westphal K, *et al.* Oral bioavailability of digoxin is enhanced by talinolol: evidence for involvement of intestinal P-glycoprotein. *Clin Pharmacol Ther* 2000; **68:** 6–12.

Calcium-channel blockers. Studies on interactions between digoxin and calcium-channel blockers appear to show that *verapamil* increases plasma-digoxin concentrations[1-3] by up to 70%. The effect of *nifedipine* is not as clear. Although it has been reported[1] to produce a 45% increase in plasma-digoxin concentrations, other studies[4,5] have reported little or no increase and the interaction is unlikely to be of clinical significance for most patients. Studies on the interaction between digoxin and *diltiazem* have also produced conflicting results. Increases in plasma-digoxin concentrations of 20% and up to 59% have been reported[6,7] and an increase in metildigoxin concentrations[7] of up to 51%. However, other studies[8,9] have shown no diltiazem-induced change in digoxin pharmacokinetics or plasma concentration. *Bepridil*,[10] *gallopamil*,[1] *mibefradil*,[11] *nisoldipine*,[12] and *nitrendipine*[13] have all been reported to increase plasma-digoxin concentrations. Bepridil increased the concentration by 34% and it was recommended that patients given this combination be monitored carefully. *Felodipine*[14,15] and *isradipine*[3] have both been reported to increase peak serum-digoxin concentrations, but steady-state digoxin concentrations were not affected and the interactions were unlikely to be of clinical relevance.

The mechanism of interaction between calcium-channel blockers and digoxin is not completely understood but appears to be related to decreased renal and nonrenal clearance of digoxin. The pharmacodynamic effects of digoxin and calcium-channel blockers may also be additive.

1. Belz GG, *et al.* Interaction between digoxin and calcium antagonists and antiarrhythmic drugs. *Clin Pharmacol Ther* 1983; **33:** 410–17.
2. Pedersen KE, *et al.* Influence of verapamil on the inotropism and pharmacokinetics of digoxin. *Eur J Clin Pharmacol* 1983; **25:** 199–206.
3. Rodin SM, *et al.* Comparative effects of verapamil and isradipine on steady-state digoxin kinetics. *Clin Pharmacol Ther* 1988; **43:** 668–72.
4. Schwartz JB, Migliore PJ. Effect of nifedipine on serum digoxin concentration and renal digoxin clearance. *Clin Pharmacol Ther* 1984; **36:** 19–24.
5. Kleinbloesem CH, *et al.* Interactions between digoxin and nifedipine at steady state in patients with atrial fibrillation. *Ther Drug Monit* 1985; **7:** 372–6.
6. Rameis H, *et al.* The diltiazem-digoxin interaction. *Clin Pharmacol Ther* 1984; **36:** 183–9.
7. Oyama Y, *et al.* Digoxin-diltiazem interaction. *Am J Cardiol* 1984; **53:** 1480–1.
8. Beltrami TR, *et al.* Lack of effects of diltiazem on digoxin pharmacokinetics. *J Clin Pharmacol* 1985; **25:** 390–2.
9. Elkayam U, *et al.* Effect of diltiazem on renal clearance and serum concentration of digoxin in patients with cardiac disease. *Am J Cardiol* 1985; **55:** 1393–5.
10. Belz GG, *et al.* Digoxin and bepridil: pharmacokinetic and pharmacodynamic interactions. *Clin Pharmacol Ther* 1986; **39:** 65–71.
11. Siepmann M, *et al.* The interaction of the calcium antagonist RO 40-5967 with digoxin. *Br J Clin Pharmacol* 1995; **39:** 491–6.
12. Kirch W, *et al.* Influence of nisoldipine on haemodynamic effects and plasma levels of digoxin. *Br J Clin Pharmacol* 1986; **22:** 155–9.
13. Kirch W, *et al.* Nitrendipine increases digoxin plasma levels dose dependently. *J Clin Pharmacol* 1986; **26:** 553.
14. Rehnqvist N, *et al.* Pharmacokinetics of felodipine and effect on digoxin plasma levels in patients with heart failure. *Drugs* 1987; **34** (suppl 3): 33–42.
15. Dunselman PHJM, *et al.* Digoxin-felodipine interaction in patients with congestive heart failure. *Eur J Clin Pharmacol* 1988; **35:** 461–5.

Diuretics. *Amiloride* increased renal clearance of digoxin and reduced the extrarenal digoxin clearance in 6 healthy subjects after a single intravenous dose of digoxin.[1] Amiloride also inhibited the digoxin-induced positive inotropic effect, but the clinical implications in cardiac patients are unknown. A further study[2] failed to confirm this effect.

Spironolactone and its metabolites have been reported to interfere with serum-digoxin determinations by radio-immunoassay or fluorescence-polarisation immunoassay resulting in falsely elevated measurements.[3,4] The interference with digoxin assays is neither consistent nor predictable and falsely low readings have also been reported.[5] Serum-digoxin concentrations should be interpreted with caution when digoxin is given together with spironolactone or *canrenoate*, especially since spironolactone has also been reported to decrease digoxin clearance by a median of 26% resulting in a true increase in the serum-digoxin concentration.[6]

Diuretic therapy with *triamterene* in association with a thiazide or loop diuretic increased the mean serum-digoxin concentration; this interaction was considered unlikely to be of clinical importance, except perhaps in patients with renal impairment.[7]

1. Waldorff S, *et al.* Amiloride-induced changes in digoxin dynamics and kinetics: abolition of digoxin-induced inotropism with amiloride. *Clin Pharmacol Ther* 1981; **30:** 172–6.
2. Richter JP, *et al.* The acute effects of amiloride and potassium canrenoate on digoxin-induced positive inotropism in healthy volunteers. *Eur J Clin Pharmacol* 1993; **45:** 195–6.
3. Paladino JA, *et al.* Influence of spironolactone on serum digoxin concentration. *JAMA* 1984; **251:** 470–1.
4. Foukaridis GN. Influence of spironolactone and its metabolite canrenone on serum digoxin assays. *Ther Drug Monit* 1990; **12:** 82–4.
5. Steimer W, *et al.* Intoxication due to negative canrenone interference in digoxin drug monitoring. *Lancet* 1999; **354:** 1176–7.
6. Waldorff S, *et al.* Spironolactone-induced changes in digoxin kinetics. *Clin Pharmacol Ther* 1978; **24:** 162–7.
7. Impivaara O, Iisalo E. Serum digoxin concentrations in a representative digoxin-consuming adult population. *Eur J Clin Pharmacol* 1985; **27:** 627–32.

Gastrointestinal drugs. Some gastrointestinal drugs can affect the absorption of digoxin by binding to it or by changing gastrointestinal motility. The problem has often been related to the bioavailability of the digoxin formulation and appears to be less important with currently used preparations. Some *antacids*,[1,2] particularly liquid formulations, and *adsorbents*[1] such as kaolin-pectin, can reduce the absorption of digoxin from the gastrointestinal tract and doses should probably be separated by at least 2 hours. *Activated charcoal*, and *ion-exchange resins* such as colestyramine and colestipol, also reduce digoxin absorption. *Sucralfate*[3] may also reduce the absorption of digoxin.

Omeprazole and possibly other gastric acid inhibitors may reduce the gastrointestinal metabolism and enhance the absorption of unchanged digoxin,[4] although the clinical relevance of this is uncertain.[5]

Drugs that increase gastrointestinal motility can reduce the absorption of digoxin, especially if digoxin is given as a slowly dissolving formulation. Reduced absorption of digoxin has occurred when digoxin and *metoclopramide* have been given together,[6] and a similar effect has been reported with *cisapride*[7] and *tegaserod*.[8] Conversely, *anticholinergics* reduce motility, and propantheline has increased digoxin absorption.

Sulfasalazine has been found to impair the absorption of digoxin and to reduce the serum-digoxin concentration,[9] but the mechanism is unclear.

1. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988; **15:** 227–44.
2. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18:** 210–19.
3. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP Ann Pharmacother* 1991; **25:** 745–6.
4. Cohen AF, *et al.* Influence of gastric acidity on the bioavailability of digoxin. *Ann Intern Med* 1991; **115:** 540–5.
5. Oosterhuis B, *et al.* Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. *Br J Clin Pharmacol* 1991; **32:** 569–72.
6. Johnson BF, *et al.* Effect of metoclopramide on digoxin absorption from tablets and capsules. *Clin Pharmacol Ther* 1984; **36:** 724–30.
7. Kubler PA, *et al.* Possible interaction between cisapride and digoxin. *Ann Pharmacother* 2001; **35:** 127–8.
8. Zhou H, *et al.* The effects of tegaserod (HTF 919) on the pharmacokinetics and pharmacodynamics of digoxin in healthy subjects. *J Clin Pharmacol* 2001; **41:** 1131–9.
9. Juhl RP, *et al.* Effect of sulfasalazine on digoxin bioavailability. *Clin Pharmacol Ther* 1976; **20:** 387–94.

Ginseng. Varieties of ginseng may interfere with plasma-digoxin assays (see under Precautions, above).

Immunosuppressants. Increased serum-digoxin concentrations with symptoms of toxicity have been reported in patients when *ciclosporin* was added to their digoxin therapy.[1,2]

1. Dorian P, *et al.* Digoxin-cyclosporine interaction: severe digitalis toxicity after cyclosporine treatment. *Clin Invest Med* 1988; **ii:** 108–12.
2. Robieux I, *et al.* The effects of cardiac transplantation and cyclosporine therapy on digoxin pharmacokinetics. *J Clin Pharmacol* 1992; **32:** 338–43.

Lipid regulating drugs. Small increases in plasma-digoxin concentrations have been reported with some *statins*, although the clinical significance is not clear. *Atorvastatin* at doses of 80 mg, but not of 10 mg, has been shown[1] to increase plasma-

digoxin concentrations by about 20%. This may be due to the inhibition of P-glycoprotein-mediated secretion of digoxin in the intestine by atorvastatin.

1. Boyd RA, *et al.* Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion. *J Clin Pharmacol* 2000; **40:** 91–98.

Neuromuscular blockers. *Pancuronium* or *suxamethonium* may interact with digitalis glycosides resulting in an increased incidence of arrhythmias; the interaction is more likely with pancuronium.[1]

1. Bartolone RS, Rao TLK. Dysrhythmias following muscle relaxant administration in patients receiving digitalis. *Anesthesiology* 1983; **58:** 567–9.

NSAIDs. An increase in serum-digoxin concentration has been reported with *aspirin*, *ibuprofen*, *indometacin*, *fenbufen*, and *diclofenac*.[1] Potentially toxic serum-digoxin concentrations occurred in preterm infants[2] with patent ductus arteriosus receiving digoxin when given indometacin orally in a mean total dose of 320 micrograms/kg; it was recommended that the dose of digoxin should be halved initially if indometacin is also given. (For the possible effect of digoxin on indometacin see Half-life, under Pharmacokinetics of Indometacin, p.68.) Lack of increase in serum-digoxin concentrations has also been reported with aspirin or indometacin, as well as with *ketoprofen*, and *tiaprofenic acid*,[1] and also with *rofecoxib*,[3] but some of these studies were in healthy subjects and it is advised that digoxin therapy be monitored carefully whenever any NSAID is started or stopped in digitalised patients.

1. Verbeeck RK. Pharmacokinetic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1990; **19:** 44–66.
2. Koren G, *et al.* Effects of indomethacin on digoxin pharmacokinetics in preterm infants. *Pediatr Pharmacol* 1984; **4:** 25–30.
3. Schwartz JI, *et al.* Effect of rofecoxib on the pharmacokinetics of digoxin in healthy volunteers. *J Clin Pharmacol* 2001; **41:** 107–112.

Pharmacokinetics

The absorption of digoxin from the gastrointestinal tract is variable depending upon the formulation used. About 70% of a dose is absorbed from tablets which comply with BP or USP specifications, 80% is absorbed from an elixir, and over 90% is absorbed from liquid-filled soft gelatin capsules. The generally accepted therapeutic plasma concentration range is 0.5 to 2.0 nanograms/mL but there is considerable interindividual variation. Digoxin has a large volume of distribution and is widely distributed in tissues, including the heart, brain, erythrocytes, and skeletal muscle. The concentration of digoxin in the myocardium is considerably higher than in plasma. From 20 to 30% is bound to plasma proteins. Digoxin has been detected in CSF and breast milk; it also crosses the placenta. It has an elimination half-life of 1.5 to 2 days.

Digoxin is mainly excreted unchanged in the urine by glomerular filtration and tubular secretion; reabsorption also occurs. Extensive metabolism has been reported in a minority of patients (see under Metabolism and Excretion, below). Excretion of digoxin is proportional to the glomerular filtration rate. After intravenous injection 50 to 70% of the dose is excreted unchanged. Digoxin is not removed from the body by dialysis, and only small amounts are removed by exchange transfusion and during cardiopulmonary bypass.

◊ Reviews of the clinical pharmacokinetics of digoxin.

1. Iisalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet* 1977; **2:** 1–16.
2. Aronson JK. Clinical pharmacokinetics of digoxin 1980. *Clin Pharmacokinet* 1980; **5:** 137–49.
3. Mooradian AD. Digitalis: an update of clinical pharmacokinetics, therapeutic monitoring techniques and treatment recommendations. *Clin Pharmacokinet* 1988; **15:** 165–79.

Absorption. Studies in 6 healthy subjects found that food decreased the rate but not the extent of absorption of digoxin.[1]

1. Johnson BF, *et al.* Effect of a standard breakfast on digoxin absorption in normal subjects. *Clin Pharmacol Ther* 1978; **23:** 315–19.

Bioavailability. Large variations in the content, disintegration, and dissolution of solid dosage forms of digoxin preparations have led to large variations in plasma concentrations from different proprietary preparations. Other factors involved in varying bioavailability include the pharmaceutical formulation and presentation (capsules, solution, or tablets), particle size, and biological factors. Serious problems occurred in the UK[1] in 1972 and in Israel[2] in 1975 after changes in the manufacturing procedure for *Lanoxin* led to a twofold increase in bioavailability.

1. Anonymous. Therapeutic non-equivalence. *BMJ* 1972; **3:** 599–600.
2. Danon A, *et al.* An outbreak of digoxin intoxication. *Clin Pharmacol Ther* 1977; **21:** 643–6.

Distribution and protein binding. Digoxin has been reported to be 5 to 60% bound to plasma proteins,[1] depending partly on the method of measurement, but the figure is usually around 20%. Protein binding is reduced in patients undergoing haemodialysis; mean reductions of about 8 and 10% have been reported.[1,2] Injection of heparin has produced a similar reduction.[2]

Digoxin is widely distributed to tissues and serum-digoxin concentrations have been reported to be increased during immobilisation[3] and decreased during exercise[4,5] due to changes in binding to tissues such as skeletal muscle.

1. Storstein L. Studies on digitalis V: the influence of impaired renal function, hemodialysis, and drug interaction on serum protein binding of digitoxin and digoxin. *Clin Pharmacol Ther* 1976; **20:** 6–14.
2. Storstein L, Janssen H. Studies on digitalis VI: the effect of heparin on serum protein binding of digitoxin and digoxin. *Clin Pharmacol Ther* 1976; **20:** 15–23.
3. Pedersen KE, *et al.* Effects of physical activity and immobilization on plasma digoxin concentration and renal digoxin clearance. *Clin Pharmacol Ther* 1983; **34:** 303–8.
4. Joreteg T, Jogestrand T. Physical exercise and digoxin binding to skeletal muscle: relation to exercise intensity. *Eur J Clin Pharmacol* 1983; **25:** 585–8.
5. Joreteg T, Jogestrand T. Physical exercise and binding of digoxin to skeletal muscle—effect of muscle activation frequency. *Eur J Clin Pharmacol* 1984; **27:** 567–70.

The elderly. For references to alterations in the pharmacokinetics of digoxin in the elderly, see under Uses and Administration, below.

Infants and neonates. Digoxin has been widely used in the treatment of cardiac disorders in neonates and infants and its pharmacokinetics in this age group have been reviewed.[1,2] In full-term neonates or infants, 80 to 90% of a dose of digoxin given orally in liquid form is absorbed, with peak plasma concentrations occurring within 30 to 120 minutes. The rate of absorption may be slower in preterm and low birth-weight infants, with peak concentrations achieved at 90 to 180 minutes, and may be significantly reduced in severe heart failure and in malabsorption syndromes. After digoxin is given intravenously there is a rapid distribution phase with an apparent half-life of 20 to 40 minutes followed by a slower exponential decay of plasma concentrations. In full-term neonates, digoxin has an apparent volume of distribution of 6 to 10 litres/kg. Low birth-weight infants have a volume of distribution of 4.3 to 5.7 litres/kg while in older infants the volume may range from 10 to 22 litres/kg which is 1.5 to 2 times reported adult values. This large volume of distribution in full-term neonates and infants is thought to be due to increased tissue binding, a larger extracellular fluid volume, and slightly lower plasma protein binding.

The apparent plasma half-life in healthy and sick neonates is generally very long and may range from 20 to 70 hours in full-term neonates or from 40 to 180 hours in preterm neonates. Digoxin is eliminated at a considerably faster rate in infants than in neonates and, in parallel with maturation of kidney function, a marked increase in clearance rate is usually observed between the second and third month of life. The large apparent volume of distribution, higher clearance values, and greater concentrations of digoxin in the myocardial tissue and red cells of infants might justify the traditional assumption that infants tolerate digoxin better than adults and that higher doses are consequently needed in infants. However, studies have shown that in infants, as in adults, toxic signs become evident at plasma-digoxin concentrations above 3 nanograms/mL and that the therapeutic range may be 1.5 to 2 nanograms/mL.

1. Morselli PL, *et al.* Clinical pharmacokinetics in newborns and infants: age-related differences and therapeutic implications. *Clin Pharmacokinet* 1980; **5:** 485–527.
2. Besunder JB, *et al.* Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface. *Clin Pharmacokinet* 1988; **14:** 189–216 (part I) and 261–86 (part II).

Metabolism and excretion. Although digoxin is reported to be excreted mainly unchanged in the urine there is evidence to suggest that metabolism may sometimes be extensive. Metabolites that have been detected in the urine include digoxigenin, dihydrodigoxigenin, the mono- and bisdigitoxosides of digoxigenin, and dihydrodigoxin. Digoxigenin mono- and bisdigitoxosides are known to be cardioactive whereas dihydrodigoxin is probably much less active than digoxin.[1]

In about 10% of patients there is considerable reduction to cardio-inactive metabolites, chiefly dihydrodigoxin, and 40% or more of a dose may be excreted in the urine as dihydrodigoxin.[2-4] Bacterial flora in the gastrointestinal tract appear to be responsible for this metabolism and antibacterials can reduce the process. Oral digoxin formulations with a high bioavailability are mostly absorbed in the stomach and upper small intestine and little digoxin is available in the lower intestine for bacterial degradation to dihydrodigoxin.[4]

The excretion of digoxin is thought to be mediated by the efflux pump, P-glycoprotein,[5] which transports its substrates out of the cell. This may be the basis for some interactions hitherto poorly understood,[6] although the hypothesis has been questioned.[7]

1. Iisalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet* 1977; **2:** 1–16.
2. Doherty JE. A digoxin-antibiotic drug interaction. *N Engl J Med* 1981; **305:** 827–8.
3. Rund DG, *et al.* Decreased digoxin cardioinactive-reduced metabolites after administration of an encapsulated liquid concentrate. *Clin Pharmacol Ther* 1983; **34:** 738–43.
4. Lofts F, *et al.* Digoxin metabolism to reduced products: clinical significance. *Br J Clin Pharmacol* 1986; **21:** 600P.
5. Tanigawara Y. Role of P-glycoprotein in drug disposition. *Ther Drug Monit* 2000; **22:** 137–40.
6. Fromm MF. P-glycoprotein: a defense mechanism limiting oral bioavailability and CNS accumulation of drugs. *Int J Clin Pharmacol Ther* 2000; **38:** 69–74.
7. Chiou WL, *et al.* A comprehensive account on the role of efflux transporters in the gastrointestinal absorption of 13 commonly used substrate drugs in humans. *Int J Clin Pharmacol Ther* 2001; **39:** 93–101.

Renal impairment. For references to alterations in the pharmacokinetics of digoxin in patients with renal impairment, see under Uses and Administration, below.

Uses and Administration

Digoxin is a cardiac glycoside used in the management of supraventricular arrhythmias, particularly atrial fibrillation (p.1160), and in heart failure (p.1165).

The principal actions of digoxin are an increase in the force of myocardial contraction (positive inotropic activity) and a reduction in the conductivity of the heart, particularly in conduction through the atrioventricular (AV) node. Digoxin also has a direct action on vascular smooth muscle and indirect effects mediated primarily by the autonomic nervous system, and particularly by an increase in vagal activity. There are also reflex alterations in autonomic activity due to the effects on the circulation. Overall, these actions result in positive inotropic effects, negative chronotropic effects, and decreased AV nodal activity.

Cardiac arrhythmias. In atrial arrhythmias digoxin's actions cause a decrease in the conduction velocity through the AV node and an increase in the effective refractory period, thus reducing ventricular rate. In addition there is a decrease in the refractory period of the cardiac muscle and depression of the sinus node partly in response to the increase in vagal activity.

Digoxin is thus given to slow the increased ventricular rate that occurs in response to *atrial fibrillation*, although other drugs may be preferred; treatment is usually long term. In patients with the Wolff-Parkinson-White syndrome and atrial fibrillation, digoxin can cause rapid ventricular rates, and possibly ventricular fibrillation, and should be avoided. In *atrial flutter*, the ventricular rate is normally more difficult to control with digoxin. Drug therapy is not the preferred method of treatment, but treatment with digoxin may restore sinus rhythm, or it may convert the flutter to fibrillation and sinus rhythm may then be induced by subsequent withdrawal of digoxin. Digoxin may be given to relieve an attack of *paroxysmal supraventricular tachycardia* and has also been given to prevent further attacks.

Heart failure. Digoxin and other cardiac glycosides directly inhibit the activity of the enzyme sodium-potassium adenosine triphosphatase (Na/K-ATPase), which is required for the active transport of sodium from myocardial cells. The result is a gradual increase in the intracellular sodium concentration and a decrease in the intracellular potassium concentration. The increased concentration of sodium inside the cells leads, by stimulation of sodium-calcium exchange, to an increase in the intracellular calcium concentration with enhancement of mechanical contractile activity and an increased inotropic effect.

When used in heart failure the increased force of myocardial contraction results in increased cardiac output, decreased end-systolic volume, decreased heart size, and decreased end-diastolic pressure and volume. Increased blood flow through the kidneys results in diuresis with a reduction in oedema and blood volume. The decrease in pulmonary venous pressure relieves dyspnoea and orthopnoea. Digoxin may thus provide symptomatic improvement in patients with heart failure and is mainly used for adjunctive therapy.

Dosage. When given orally, digoxin may take effect within about 2 hours and the maximum effect may be reached in about 6 hours. Initially a loading dose may be given to digitalise the patient, although this may not be necessary in, for example, mild heart failure.

Dosage should be carefully adjusted to the needs of the individual patient. Factors which may be considered include the patient's age, lean body-mass, renal status, thyroid status, electrolyte balance, degree of tissue oxygenation, and the nature of the underlying cardiac or pulmonary disease. Bearing in mind the above factors, steady-state plasma-digoxin concentrations (in a sample taken at least 6 hours after a dose) of 0.5 to 2 nanograms/mL are generally considered acceptable, although in patients with heart failure concentrations at the lower end of the range may be more appropriate. For reference to therapeutic drug monitoring, see below.

If rapid digitalisation is required then a loading dose is given to allow for the large volume of distribution. A total loading dose of 750 to 1500 micrograms of digoxin may be given by mouth during the initial 24-hour period, either as a single dose, or where there is less urgency or greater risk of toxicity, in divided doses at 6-hourly intervals. In some patients, for example those with mild heart failure, a loading dose may not be necessary, and digitalisation may be achieved more slowly with doses of 250 micrograms once or twice daily; steady-state plasma concentrations are achieved in about 7 days in patients with normal renal function. The usual maintenance dose of digoxin is 125 to 250 micrograms by mouth daily, but may range from 62.5 to 500 micrograms daily. In elderly patients therapy should generally start gradually and with smaller doses (but see under Administration in the Elderly, below).

In urgent cases, provided that the patient has not received cardiac glycosides during the previous 2 weeks, digoxin may be given intravenously initially. The intravenous dose ranges from 500 to 1000 micrograms and generally produces a definite effect on the heart rate in about 10 minutes, reaching a maximum within about 2 hours. It is given by intravenous infusion, either as a single dose given over 2 or more hours, or in divided doses each over 10 to 20 minutes. Maintenance treatment is then usually given by mouth. Digoxin has also been given intramuscularly but this route is not generally recommended since such injections may be painful and tissue damage has been reported. Digoxin should not be given subcutaneously as intense local irritation may occur.

Children's doses are complex. They are based on bodyweight and the developmental stage of the child as well as on response. Premature infants are especially sensitive to digoxin but, along with all other neonates, infants, and children up to about 10 years of age, still require doses that are higher per kg body-weight than those used for adults. Preterm infants receive lower doses than full-term infants, while children aged 2 to 10 years require lower doses than children up to 2 years of age. As an indication of the doses used, oral loading doses recommended by licensed product information in the UK range from 25 to 45 micrograms/kg over 24 hours and in the USA the range is 20 to 60 micrograms/kg; the range for intravenous loading doses given over 24 hours is 20 to 35 micrograms/kg in the UK and 15 to 50 micrograms/kg in the USA.

Doses should be reduced in patients with renal impairment (see below).

◊ General reviews on the actions and uses of digoxin and the other cardiac glycosides.

1. Opie LH. Digitalis and sympathomimetic stimulants. *Lancet* 1980; **i:** 912–18.
2. Taggart AJ, McDevitt DG. Digitalis: its place in modern therapy. *Drugs* 1980; **20:** 398–404.
3. Chamberlain DA. Digitalis: where are we now? *Br Heart J* 1985; **54:** 227–33.
4. Doherty JE. Clinical use of digitalis glycosides: an update. *Cardiology* 1985; **72:** 225–54.
5. Smith TW. Digitalis: mechanisms of action and clinical use. *N Engl J Med* 1988; **318:** 358–65.
6. Hampton JR. Digoxin. *Br J Hosp Med* 1997; **58:** 321–3.
7. Riaz K, Forker AD. Digoxin use in congestive heart failure: current status. *Drugs* 1998; **55:** 747–58.
8. Campbell TJ, MacDonald PS. Digoxin in heart failure and cardiac arrhythmias. *Med J Aust* 2003; **179:** 98–102.

Administration in the elderly. The volume of distribution of digoxin and the elimination half-life increase with age.[1] Therefore there are problems in giving digoxin to elderly patients since steady-state plasma concentrations may not be reached for up to 2 weeks. Fears of toxicity have led some practitioners to use a fixed 'geriatric' dose of 62.5 micrograms daily. However, such a dose can produce subtherapeutic concentrations.[2] The routine use of very low doses of digoxin in the elderly is inappropriate and dosage should be individualised.

1. McMurray J, McDevitt DG. Treatment of heart failure in the elderly. *Br Med Bull* 1990; **46:** 202–29.
2. Nolan L, *et al*. The need for reassessment of digoxin prescribing for the elderly. *Br J Clin Pharmacol* 1989; **27:** 367–70.

Administration in renal impairment. The pharmacokinetics of cardiac glycosides in patients with renal impairment have been reviewed.[1] The rate but not the extent of digoxin absorption is reduced in renal impairment but this is unlikely to be clinically important. Plasma-protein binding may also be reduced but since digoxin is poorly bound to these proteins and has a large apparent volume of distribution this also is unlikely to be important. The apparent volume of distribution is reduced by one-third to one-half and the loading dose of digoxin should therefore be reduced; an oral loading dose of 10 micrograms/kg is suggested (but see also under Therapeutic Drug Monitoring, below). Non-renal clearance of digoxin is unaffected or only slightly reduced but renal clearance is reduced, the extent being closely related to creatinine clearance. The elimination half-life of digoxin is prolonged and it therefore takes longer to reach steady state and longer for toxicity to resolve. Because of the reduction in renal clearance of digoxin, maintenance doses must be reduced in line with renal function. Serum-digoxin concentration should be monitored although the presence of digoxin-like immunoreactive substances may make interpretation difficult. In addition, the presence of hyperkalaemia in patients with renal impairment may reduce sensitivity to the effects of digoxin.[2]

Since digoxin has such a large distribution volume, procedures such as peritoneal dialysis and haemodialysis remove only very small amounts of drug from the body and no dosage supplement is needed.

1. Aronson JK. Clinical pharmacokinetics of cardiac glycosides in patients with renal dysfunction. *Clin Pharmacokinet* 1983; **8:** 155–78.
2. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency: minimising renal and extrarenal toxicity. *Drug Safety* 1997; **16:** 205–31.

Therapeutic drug monitoring. Digoxin has a narrow therapeutic index. It is generally considered that plasma-digoxin concentrations required for a therapeutic effect are usually between 0.5 and 2.0 nanograms/mL,[1-3] although some studies[4-6] have suggested that concentrations of 0.5 to 0.9 nanograms/mL are adequate for heart failure; concentrations at the upper end of the range may be associated with worse outcomes.[5,6] The factor for converting nanograms/mL to nanomoles/litre is 1.28.

Digoxin dosage can be calculated in uncomplicated cases by considering the patient's weight, renal function, and clinical status. Therapeutic drug monitoring is *not* considered to be necessary in patients with a satisfactory clinical response to conventional doses in the absence of signs or symptoms of toxicity.[1,2] Measurement of plasma-digoxin concentrations is useful if poor compliance is suspected, if response is poor or there is a deterioration in response without apparent reason, if renal function is fluctuating, when it is unknown if a cardiac glycoside has been previously taken, during drug interactions, and to confirm clinical toxicity.[1,3,7] A plasma concentration should never be considered in isolation and should be used with other patient data as an important component in clinical decision making. This is particularly important in the diagnosis of digoxin toxicity since signs and symptoms of toxicity may be difficult to distinguish from the underlying disease and can occur within the usual therapeutic range.

A number of factors may influence the response to digoxin and thus the interpretation of digoxin assays. These include renal impairment, extremes of age, thyroid disease, patient compliance, drug interactions, and electrolyte disturbances.[1-3,7] Variations in the bioavailability of different digoxin preparations have also caused problems. Renal impairment and hypokalaemia are two of the most important factors affecting dosage of digoxin and whenever plasma-digoxin concentrations are assayed renal function and plasma potassium should also be measured. A dosing nomogram has been proposed[8] relating dose in patients with heart failure to renal function and either height or ideal body weight: for most patients with moderate or severe renal impairment (creatinine clearance below 60 mL/minute) an oral dose of 125 micrograms every other day was considered sufficient. The interpretation of digoxin assays is further confounded by the presence of digoxin-like immunoreactive substances in patients with renal or hepatic impairment, in pregnant women, and in neonates. Blood samples for digoxin assay should be taken at least 6 hours after a dose to allow for distribution.[1,3,7]

The usefulness of plasma-digoxin concentrations in the diagnosis of toxicity in children is unclear. For children older than 12 months the adult guidelines can probably be followed, and for younger children the trend for increased risk of toxicity at increased plasma-digoxin concentrations appears to hold but the threshold for toxicity may be higher, especially in children less than 3 months old.[1]

1. Aronson JK. Indications for the measurement of plasma digoxin concentrations. *Drugs* 1983; **26:** 230–42.
2. Lee TH, Smith TW. Serum digoxin concentration and diagnosis of digitalis toxicity: current concepts. *Clin Pharmacokinet* 1983; **8:** 279–85.
3. Aronson JK, Hardman M. Digoxin. *BMJ* 1992; **305:** 1149–52.
4. Adams KF, *et al*. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002; **39:** 946–53.
5. Rathore SS, *et al*. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; **289**: 871–8.
6. Adams KF, *et al*. Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group trial: a retrospective analysis. *J Am Coll Cardiol* 2005; **46:** 497–504.
7. Brodie MJ, Feely J. Practical clinical pharmacology: therapeutic drug monitoring and clinical trials. *BMJ* 1988; **296:** 1110–14.
8. Bauman JL, *et al*. A method of determining the dose of digoxin for heart failure in the modern era. *Arch Intern Med* 2006; **166:** 2539–45.

Preparations

BP 2008: Digoxin Injection; Digoxin Tablets; Paediatric Digoxin Injection; Paediatric Digoxin Oral Solution;
USP 31: Digoxin Elixir; Digoxin Injection; Digoxin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cardiogoxin; Digocard-G; Lanicor; Lanoxin; ***Austral.:*** Lanoxin; Sigmaxin; ***Austria:*** Lanicor; ***Belg.:*** Lanoxin; ***Braz.:*** Cardcor; Cardionil; Cimecard; Digitax; Digixina†; Digobal; Digox†; Digoxan†; Digoxen; Digoxil; Lanoxin†; Valoxin; ***Canad.:*** Lanoxin; ***Fr.:*** Hemigoxine Nativelle; ***Ger.:*** Digacin; Digoregen†; Dilanacin†; Lanicor; Lenoxin; ***Hong Kong:*** Lanoxin; ***India:*** Cardioxin†; Lanoxin; ***Indon.:*** Fargoxin; Lanoxin; ***Irl.:*** Lanoxin; ***Israel:*** Lanoxin; ***Ital.:*** Eudigox; Lanoxin; ***Jpn:*** Digosin; ***Malaysia:*** Lanoxin; ***Mex.:*** Lanoxin; Mapluxin; ***Neth.:*** Lanoxin; ***Norw.:*** Lanoxin; ***NZ:*** Lanoxin; ***Philipp.:*** Lanoxin; ***Port.:*** Lanoxin; ***S.Afr.:*** Lanoxin; Purgoxin; ***Singapore:*** Lanoxin; ***Spain:*** Lanacordin; ***Swed.:*** Lanacrist; Lanoxin; ***Thai.:*** Grexin; Lanoxin; Toloxin; ***UK:*** Lanoxin; ***USA:*** Digitek; Lanoxicaps†; Lanoxin; ***Venez.:*** Lanicor.

Dihydralazine Sulfate *(rINNM)*

Dihidralazino sulfatas, hidratuotas; Dihidralazin-szulfát-hidrát; Dihydralatsiinisulfaatti, hydratoitu; Dihydralazine, Sulfate de; Dihydralazine (sulfate de) hydraté; Dihydralazine Sulphate *(BANM)*; Dihydralazini Sulfas; Dihydralazini sulfas hydricus; Dihydralazinsulfát; Dihydralazinsulfat, hydratiserat; Dihydralazinum Sulfuricum; Dihydralazyny siarczan; Dihydrallazine Sulphate; Sulfato de dihidralazina. Phthalazine-1,4-diyldihydrazine sulfate hemipentahydrate.

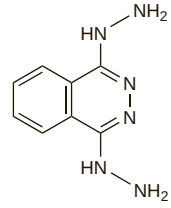
Дигидралазина Сульфат

$C_8H_{10}N_6.H_2SO_4.2/H_2O$ = 333.3.

CAS — 484-23-1 (dihydralazine); 7327-87-9 (dihydralazine sulfate).

ATC — C02DB01.

ATC Vet — QC02DB01.



(dihydralazine)

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

Ph. Eur. 6.2 (Dihydralazine Sulphate, Hydrated). A white or slightly yellow crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol. It dissolves in dilute mineral acids.

Profile

Dihydralazine is a vasodilator with actions and uses similar to those of hydralazine (p.1305). It is given orally as the sulfate. Dihydralazine sulfate hemipentahydrate 14.45 mg is equivalent to about 12.5 mg of anhydrous dihydralazine sulfate. In hypertension (p.1171) the usual initial dose is the equivalent of 12.5 mg of anhydrous dihydralazine sulfate twice daily and the maximum recommended dose is 50 mg twice daily. Higher doses have been used in the management of heart failure.

Other salts of dihydralazine that have been used in oral preparations include the hydrochloride and the tartrate. The mesilate is given by injection.

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

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Nepresol; ***Belg.:*** Nepresol; ***Cz.:*** Nepresol†; ***Fr.:*** Nepressol; ***Ger.:*** Depressan; Nepresol; ***Gr.:*** Nepresol; ***Hong Kong:*** Nepresol†; ***Hung.:*** De-