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.

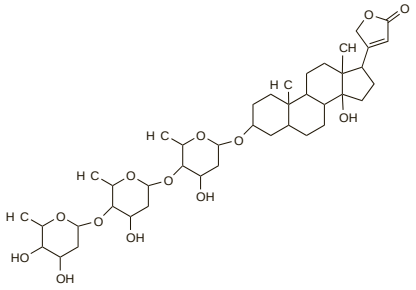
Дигитоксин

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

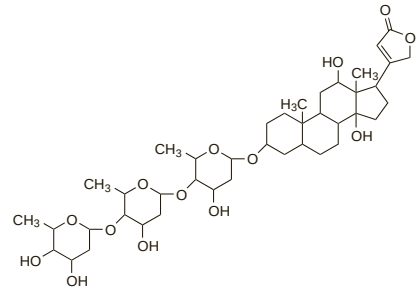
Дигоксин

$C_{41}H_{64}O_{14}$ = 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,