Digoxin

2019

Newborn use only

Alert	Digoxin has a narrow therapeutic index, check the dose carefully. Lanoxin adult injection is 10 times more concentrated than Lanoxin infant injection. Check product selection carefully. Rapid IV injection may cause hypertension and reduced coronary flow. Lanoxin Paediatric Elixir contains ethanol of approximately 84 mg/mL, equivalent to 10.6% absolute volume. The long-term effects of prolonged exposure to ethanol content from medicines have not been studied.
Indication	Supraventricular tachycardia [atrioventricular reciprocating tachycardia or atrioventricular nodal re-entrant tachycardia, excluding Wolff-Parkinson-White] Atrial fibrillation and atrial flutter Heart failure [add-on treatment in infants with reduced ejection fraction if not otherwise contraindicated].
Action	Slows heart rate and reduces AV nodal conduction by an increase in vagal tone and a reduction in sympathetic activity. A Na^+/K^+-ATPase inhibitor which increases the force of myocardial contraction by increasing the release and availability of stored intracellular calcium.
Drug Type	Cardiac glycoside
Trade Name	Lanoxin PG, Sigmaxin-PG, Lanoxin, Sigmaxin, Lanoxin Paediatric Elixir, Lanoxin Infant injection, Lanoxin injection
Presentation	**ORAL:** Lanoxin PG, Sigmaxin-PG tablet 62.5microgram Lanoxin, Sigmaxin, tablet 250 microgram (scored) Lanoxin Paediatric Elixir oral liquid 50 microgram/mL (contains propylene glycol: approximately 52 mg/mL and ethanol: Approximately: 84 mg/mL, equivalent to 10.6% absolute volume) **INTRAVENOUS:** Lanoxin Infant injection 50 microgram/2mL Lanoxin inj (500 microgrm/2mL) CAUTION: CONCENTRATED product Both contain ethanol, propylene glycol, citric acid and sodium phosphate.
Dosage/Interval	**Term neonate (37^{+0} weeks and over)** PO: Loading dose of 10 microgram/kg/dose 8-hourly for 3 doses, followed by Maintenance dose of 8 microgram/kg/dose daily (may increase up to 12 microgram/kg/day according to therapeutic drug monitoring and in consultation with cardiologist) IV: Loading and maintenance doses are 75% of oral dose. **Preterm neonate:** PO: Loading dose of 10 microgram/kg/dose 8-hourly for 3 doses, followed by Maintenance dose of **5–7.5** microgram/kg/dose daily (up to 12 microgram/kg/day according to therapeutic monitoring and in consultation with cardiologist) IV: Loading and maintenance doses are 75% of oral dose. **Infants aged 2–24 months:** PO: Loading dose 10 microgram/kg/dose 8-hourly for 2–3 doses, followed by Maintenance dose: 8–10 microgram/kg/dose daily or in 2 divided doses. IV: Loading and maintenance doses are 75% of oral dose. Doses should be titrated to the lowest dose needed to achieve effect. **Renal impairment:** Predominantly renally cleared (about 70%); reduce dose by at least half in renal impairment. When switching from oral to IV therapy, reduce the digoxin dosage by 20–25%.
Maximum daily dose	250 microgram daily.

Route	Oral Intravenous
Preparation/Dilution	IV **CHECK PRODUCT SELECTION CAREFULLY. Dilution only applies to Lanoxin Infant Injection.** Lanoxin Infant Injection: Add 2 mL (50 microgram) of digoxin to 8 mL of sodium chloride 0.9% or glucose 5% to make a 5 microgram/mL solution.
Administration	ORAL: May be taken with or without food.[32] However, administer consistently at the same time with respect to meals to avoid day to day variation.[33] IV: Give over at least 10 minutes. IM: Do not give IM (unpredictable absorption, local irritation).
Monitoring	Check renal function and electrolyte concentrations before starting digoxin. For intravenous infusion, continuous cardiac monitoring is recommended. It may not be necessary when IV injection is used to temporarily replace oral dosing in a patient stabilised on digoxin. Check local guidelines. The onset of effect is approximately 5 to 10 minutes, with a maximum effect being achieved after 2 hours. Take drug levels at least 6 hours after the dose is given. For oral treatment without loading dose, steady state is reached after about 7 days if renal function is normal (half-life is 36 hours); this may be prolonged in renal impairment. The therapeutic range for those with atrial tachyarrhythmias is 0.5 to 2 microgram/L (0.6 to 2.6 nmol/L) as toxicity is more common at digoxin concentrations >2 microgram/L. However, toxic effects can occur at lower concentrations, particularly in the elderly or in those with electrolyte disturbance, hypoxia or hypothyroidism. GI symptoms (e.g. nausea, anorexia) may precede cardiac symptoms (e.g. arrhythmias). Heart failure: Consider maintaining lower concentrations of 0.5 to 0.8 microgram/L (0.6 to 1 nmol/L) in patients with heart failure who are in sinus rhythm. Therapeutic drug monitoring for digoxin should be performed using an assay free from interference with digoxin-like immunoreactive factors, spironolactone, canrenoate, digoxin metabolites and steroids.
Contraindication	Contraindicated in second‑ or third-degree heart block (without pacemaker), SVT involving accessory pathway (Wolff-Parkinson-White syndrome), ventricular tachycardia and ventricular fibrillation, hypertrophic obstructive cardiomyopathy, cor pulmonale (acute and chronic) or constrictive pericarditis.
Precautions	In acute myocardial infarction, ischaemic heart disease or myocarditis, digoxin increases risk of arrhythmias. Use digoxin cautiously in sick sinus syndrome (risk of severe bradycardia or sinoatrial block). Digoxin may worsen cardiac function in severe aortic stenosis because it increases the force of myocardial contraction. Digoxin increases risk of arrhythmias after DC cardioversion; withhold digoxin for 1–2 days before cardioversion or use lowest effective energy. Hyperthyroidism—may decrease digoxin concentration and increase sympathetic tone; monitor digoxin concentration and alter dose when required or combine with another agent; dosage adjustment may be required when condition is corrected. Hypothyroidism—may increase digoxin concentration; monitor digoxin concentration and alter dose as required; dosage adjustment may be required when condition is corrected. Hypokalaemia, hypomagnesaemia, hypercalcaemia, acidosis, hypoxia—may increase sensitivity to digoxin (especially hypokalaemia); symptoms of toxicity may occur at lower digoxin concentrations.
Drug Interactions	Treatment with drugs that slow cardiac conduction, cause bradycardia or arrhythmias may potentiate the cardiac adverse effects of digoxin; use combinations carefully and monitor cardiac function.

	Treatment with drugs that inhibit or induce P-glycoprotein (ABCB1) may increase the risk of adverse effects or decrease digoxin's efficacy. Use of beta blockers and digoxin increases risk of bradycardia and AV block - additive effect. Use of digoxin and amiodarone increases risk of dysrhythmias and torsade de pointes as amiodarone blocks P-glycoprotein (ABCB1). Torsade de pointes might by facilitated by bradycardia caused by digoxin. Use of digoxin and azoles, clarithromycin and some HIV-protease inhibitors increases risk of dysrhythmias by inhibition of P-glycoprotein (ABCB1). Use of digoxin and non-dihydropyridine calcium channel blockers increases risk of bradycardia, asystole and sinus arrest by inhibition of P-glycoprotein (ABCB1) and their synergistic effect on the heart. Use of digoxin and loop or thiazide diuretics, amphotericin B, corticosteroids increase risk of dysrhythmias as hypokalaemia potentiates digoxin toxicity. Use of digoxin and IV calcium increases risk of dysrhythmias as hypercalcemia increases effect of cardiac glycosides. Use of digoxin and propafenone increases risk of dysrhythmia probably by inhibition of P-glycoprotein (ABCB1) by propafenone. P-glycoprotein (ABCB1)-inducers: Carbamazepine; phenytoin; rifampicin; St John's wort; tipranavir. P-glycoprotein (ABCB1)-inhibitors: Amiodarone, azithromycin, carvedilol, ciclosporin, clarithromycin, cobicistat, daclatasvir, erythromycin, everolimus, glecaprevir with pibrentasvir, isavuconazole, itraconazole, ketoconazole, lapatinib, ledipasvir, ritonavir, ticagrelor, tolvaptan, vandetanib, velpatasvir, vemurafenib, venetoclax, verapamil.
Adverse Reactions	Digoxin may worsen arrhythmias (proarrhythmic effect). Digoxin has a narrow therapeutic range; adverse effects are related to its plasma concentration and very few occur at <0.8 microgram/L (1 nmol/L). Digoxin usually has an effect on the ECG and may result in prolonged PR interval, ST depression or T wave inversion (these changes do not necessarily indicate digoxin toxicity or myocardial ischaemia). In children, arrhythmias (including sinus bradycardia) are the earliest and most frequent indicators that digoxin dosage is too high. Common (>1%): Anorexia, nausea, vomiting, diarrhoea, visual disturbances (e.g. blurred vision), drowsiness, dizziness, headache, rash, bradycardia, arrhythmia Infrequent (0.1–1%): Depression, shortened QRS complex, atrial or ventricular extrasystoles, paroxysmal atrial tachycardia with AV block, ventricular tachycardia or fibrillation, heart block. Rare (<0.1%): Thrombocytopenia, seizures, confusion, psychosis, gynaecomastia (long-term use).
Compatibility	Fluids: Glucose 5%, Hartmann's, sodium chloride 0.9%. Y-site: Anidulafungin, bivalirudin, ceftaroline fosamil, ceftobiprole medocaril, ciprofloxacin, cisatracurium, dexmedetomidine, heparin sodium, hydrocortisone sodium succinate, levosimendan, linezolid, midazolam, milrinone, morphine sulfate, pethidine, potassium chloride, remifentanil
Incompatibility	Fluids: No information Drugs: Adrenaline (epinephrine), amiodarone, caspofungin, fluconazole, foscarnet, pentamidine, propofol
Stability	Infusion solution: Stable for up to 6 hours at 25° C.
Storage	Ampoule and oral elixir: Store below 25° C. Protect from light.
Special Comments	Bioavailability of oral dose 60 to 85%. Half-life in infants 18 to 25 hours. 50 to 70% excreted in urine unchanged. Minimally metabolised by hepatic and intestinal enzymes to active and inactive metabolites. Onset of effect occurs 0.5–2 hours after initial oral dose of 500–750 micrograms and 5–30 minutes after initial IV dose of 400–600 micrograms; maximal effect occurs after 1–4 hours (IV) or 2–6 hours (oral).

	Regularly assess patients for digoxin toxicity (including resting heart rate); routine measurement of pulse rate before giving next dose of digoxin is not necessary Assume that any arrhythmia that occurs in a child taking digoxin is due to the drug until proven otherwise. DigiFab (digoxin immune Fab) is available for the treatment of life-threatening overdoses of digoxin: • Dose initially with one vial (40 mg diluted in 4 mL of water for injections) and repeat if symptoms persist or recur. • Full neutralisation dose of DigiFab is: Number of vials = serum digoxin concentration (nanogram/mL) x weight (kg) / 100 (rounded up to nearest vial). However, this is rarely indicated.
Evidence summary	**Efficacy** **Heart failure:** Digoxin has traditionally been used in the setting of atrial fibrillation and advanced heart failure. In a systematic review of the effects on total mortality in patients with systolic heart failure, digoxin did not reduce all-cause and heart failure mortality but did reduce heart failure symptoms and readmissions for heart failure by 32% (OR 0.68, 95% CI 0.61–0.75, P <0.00001). Benefits appeared greater in patients with severely reduced ejection fraction (≤25%) or NYHA III–IV functional class. Post-hoc subgroup analyses by serum digoxin concentrations (SDC) found patients within the range 0.5–0.8 ng/mL had their risk of all-cause mortality reduced by 20% (HR 0.80, 95% CI 0.68–0.94, P = 0.005). Increased arrhythmic complications have been identified in patients with SDC concentrations ≥1.2 ng/mL. If used in the context of any renal impairment, digoxin requires very careful dose and level monitoring to prevent toxicity.[1, 2] In a systematic review of RCTs of digoxin therapy for cor pulmonale in adult patients, 4 studies with only 76 patients were included and found overall there was no statistically significant improvement in RVEF, exercise capacity, NYHA class, heart failure score or body weight.[3] However, there are no RCTs comparing digoxin versus placebo or other drug therapy in infants with heart failure. Digoxin has been a component of standard treatment in several trials of other drug therapy in paediatric populations with heart failure in the context of congenital heart disease [4-7] and dilated cardiomyopathy [8, 9]. One of these trials, Buchhorn et al 2001 in an RCT of propranolol and standard therapy versus standard therapy alone (digoxin and diuretics) in 20 infants with congenital heart disease and left-to-right shunts reported propranolol treatment but not digoxin and diuretics alone reduced clinical symptoms of heart failure. ***Recommendation:*** The Pediatric Cardiac Intensive Care Society 2014 Consensus Statement reported that digoxin is not currently used as a first-line therapy in the management of heart failure. Digoxin has a class IIa recommendation to potentially decrease heart failure-related admissions in adult patients with reduced left ventricular ejection fraction unless otherwise contraindicated. The current recommendations are based on results from the Digitalis Investigation Group study that showed no mortality benefit over placebo, but did document a reduction in overall hospitalizations and heart failure–related hospitalizations). Careful attention to dosing and concomitant renal dysfunction must be considered when using digoxin. Serum levels of 0.5–0.9 ng/mL are typically targeted for optimal benefit. Digoxin should be used with caution in patients receiving drugs that can affect sinoatrial or atrioventricular nodal function or therapies that may alter digoxin levels including amiodarone and/or beta blockers.[10] [LOE III-2 GOR D] **Treatment of symptomatic patent ductus arteriosus (PDA):** A single RCT reported 15 preterm infants weighing ≤1,500 gm at birth who had a symptomatic PDA were treated according to a medical management protocol (fluid restriction, digoxin and frusemide) versus 10 treated with early surgical closure protocol. Two of the medically treated infants had PDA ligated as a back-up treatment. The role of digoxin for management of symptomatic PDA is unclear. [LOE II GOR D]

Management of supraventricular tachycardia in children: [11]
Haemodynamically unstable: Cardioversion is the definitive intervention to terminate SVT in children who are haemodynamically unstable. Adenosine may be given while preparing to cardiovert if the drug is readily available and the child has intravenous (IV) access. Similarly, vagal manoeuvres can be attempted while preparing for cardioversion or drug therapy, but cardioversion should not be delayed to administer vagal manoeuvres. Cardioversion — direct current cardioversion at 0.5 to 2.0 J/kg should be performed.
Haemodynamically stable: Antiarrhythmic therapy — if the vagal manoeuvre does not convert SVT that is haemodynamically stable to normal rhythm, an intravenous (IV) catheter should be placed for the administration of antiarrhythmic drugs. Adenosine is the drug of choice for acute management of SVT; procainamide and amiodarone are sometimes given for tachycardia that is refractory to adenosine. For SVT that is refractory to adenosine, choices for IV antiarrhythmic therapy include procainamide and amiodarone. Digoxin is not usually used because of the delay in achieving therapeutic levels and the narrow therapeutic margin with the risk of serious toxicity. In addition, digoxin should not be given if WPW syndrome is suspected, since it may potentiate accessory pathway conduction.

Sanatini et al 2012 [12] in a RCT of 61 infants <4 months with SVT (atrioventricular reciprocating tachycardia or atrioventricular nodal re-entrant tachycardia excluding Wolff-Parkinson-White) compared digoxin (loading dose 30 microgram/kg/day, maintenance 10.5 microgram/kg/day) versus propranolol (0.5 mg/kg as a single dose then 1.0 mg/kg/dose 8-hourly). SVT recurred in 19% of patients on digoxin and 31% of patients on propranolol (P = 0.25). No first recurrence occurred after 110 days of treatment. The 6-month recurrence-free status was 79% for patients on digoxin and 67% for patients on propranolol (P = 0.34), and there were no first recurrences in either group between 6 and 12 months. There were no deaths and no serious adverse events related to study medication.

Hornik et al 2014 [13] in a retrospective cohort of infants with SVT from the Pediatrix Medical Group neonatal ICU database compared 342 infants exposed to digoxin versus 142 infants exposed to propranolol. The incidence rate of treatment failure was 6.7/1,000 infant-days of exposure to digoxin and 15.4/1,000 infant-days of exposure to propranolol. Treatment failure was higher on propranolol when compared with that on digoxin (adjusted hazard ratio, 1.97; 95% CI 1.05–3.71). Hypotension was more frequent during exposure to digoxin versus propranolol (39.4 vs 11.1/1,000 infant-days; p <0.001). There was no difference in frequency of other clinical adverse events.

Bolin et al 2017 [14] reported a retrospective cohort of infants with SVT from the Pediatric Health Information System database admitted at ≤2 days of age with structurally normal hearts and treated with an antiarrhythmic medication. 2,657 neonates were identified with a median gestational age of 37 weeks (interquartile range 34 to 39). Digoxin and propranolol were most commonly prescribed; digoxin use steadily decreased to 23% of antiarrhythmic medication administrations over the study period, whereas propranolol increased to 77%. Multivariable comparisons revealed that the odds of mortality for neonates on propranolol were 0.32 times those on digoxin (95% CI 0.17 to 0.59; p <0.001). Propranolol for the neonate with SVT is associated with lower in-hospital mortality and hospital costs compared with digoxin.

Recommendation: ANZCOR recommendation for pharmacological management of specific dysrhythmias in the paediatric advanced life support guideline is that, for SVT, adenosine is the drug of choice. Amiodarone may be used to treat haemodynamically stable or unstable SVT. Alternative drugs are procainamide, digoxin, a beta blocker or a calcium channel blocker. Calcium channel blockers should not be used to treat SVT in infants and should be avoided or used cautiously in children because they may induce hypotension and cardiac depression.[15]

	Atrial fibrillation — Atrial fibrillation is uncommon in children and most paediatric cases are associated with CHD, cardiomyopathy or Wolff-Parkinson-White syndrome.[16] The management of neonatal atrial fibrillation is unclear with use of digoxin and cardioversion reported.[17, 18] In adult populations, systematic review found when digoxin was compared with all control interventions there was no evidence of a difference in all-cause mortality (RR 0.82; CI 0.02 to 31.2); serious adverse events (RR 1.65; CI 0.24 to 11.5); quality of life; heart failure (RR 1.05 CI 0.00 to 1141.8) or stroke (RR 2.27; CI 0.00 to 7887.3). Digoxin was superior compared with placebo in reducing the heart rate, but inferior compared with beta blockers. Meta-analyses on acute heart rate control showed that digoxin was inferior compared with both calcium antagonists (MD 21.0 bpm; CI -30.3 to 72.3) and with amiodarone (MD 14.7 bpm; CI -0.58 to 30.0). Meta-analysis on acute conversion to sinus rhythm showed that digoxin compared with amiodarone reduced the probability of converting atrial fibrillation to sinus rhythm (RR 0.54; CI 0.13 to 2.21).[19] **Atrial flutter:** Atrial flutter can occur in fetuses and neonates with structurally normal hearts. Comorbid conditions are not usually present; however, cases of atrial flutter associated with neonatal Coxsackie myocarditis and following maternal treatment with lithium have been reported. Neonatal atrial flutter rarely reoccurs following cardioversion with or without medical treatment. In the newborn with atrial flutter, initial therapy with digoxin has been the traditional approach. However, this has never been demonstrated to be any more efficacious than primary electrical cardioversion. [16] Casey et al reported a case series of 25 newborns with atrial flutter; 7 of 21 converted to sinus rhythm with digoxin therapy and electrical conversion resulted in sustained sinus rhythm in 9 of 16 patients (13 after failure of digoxin and 3 as the first treatment). Sinus rhythm was achieved in 23 patients and two died of complications of prematurity without resolution of atrial flutter.[20] Texter et al 2006 reported a case series of 50 infants with atrial flutter, 72% presented within the first 48 hours of life. Sinus rhythm was restored in 20 of 23 (87%) attempts at direct current cardioversion and 7 of 22 (32%) attempts at transoesophageal pacing; 7 required antiarrhythmic therapy. An additional arrhythmia, all supraventricular, appeared in 11 (22%) infants. The recurrence of atrial flutter developed in 6 infants all with an additional arrhythmia. Twelve received digoxin loading as first-line therapy. Sinus rhythm occurred in 4 infants within hours of beginning the digoxin load; the remaining eight required additional intervention.[21] ***Recommendation:*** In the newborn with atrial flutter, initial therapy with digoxin has been the traditional approach. However, this has never been demonstrated to be any more efficacious than primary electrical cardioversion.[16] **Safety** In all age groups, digoxin is associated with a neutral effect on mortality in randomised trials and a lower rate of admissions to hospital across all study types.[22] However, in a meta-analysis of hospital adverse drug reactions (ADRs), the mean fatal ADR prevalence varied from 0.01% in paediatric patients to 0.44% in the elderly. Warfarin, aspirin, renin-angiotensin system inhibitors and digoxin accounted for 60% of fatal ADRs.[23] Ventricular fibrillation following adenosine therapy for SVT in a neonate with concealed Wolff-Parkinson-White syndrome treated with digoxin has been reported.[24] Digoxin toxicity may originate from or be exacerbated by drug interactions. Inhibitors of P-glycoprotein (ABCB1) such as verapamil, amiodarone or macrolide antibiotics can enhance oral bioavailability of digoxin by decreasing its efflux from the enterocytes into the lumen of the intestine and decrease its active tubular secretion into the urine in the kidney. As a result, plasma concentrations of digoxin may significantly increase to toxic levels [see drug interactions]. Recommended window of therapeutic concentrations is quite narrow (0.8–2.0 ng/mL) and more recent recommendations suggest even lower and more narrow range (0.5–1.0 ng/mL).[25] Increased arrhythmic complications have been identified in patients with serum digoxin concentrations ≥1.2 ng/mL. If used in the context of any renal impairment, digoxin requires very careful dose and level monitoring to prevent toxicity.[1]

	Hypokalaemia increases the incidence of arrhythmias and sudden cardiac death. The risk is increased in patients with pre-existing heart disease and in those treated with digoxin. Although cases of digoxin poisoning are fewer than those involving calcium channel and beta blockers, the mortality rate from digoxin is far greater. Specific antidote therapy with digoxin-specific antibody fragments (digoxin-Fab) should be used if there are arrhythmias associated with haemodynamic instability. Digoxin-Fab interferes with digoxin immunoassay measurement and can lead to overestimation of plasma digoxin concentrations.[26] Lanoxin Paediatric Elixir contains approximately 52 mg/mL of propylene glycol and 84 mg/mL of ethanol, equivalent to 10.6% absolute volume (email correspondence with the manufacturer on 21st March 2019). Long-term effects of prolonged exposure to ethanol content are unknown. **Pharmacokinetics/pharmacodynamics** Digoxin is a cardiac glycoside. Digoxin's mechanism of action is related to both causing an increase in parasympathetic tone as well as inhibition of the Na^+/K^+ ATPase, which indirectly increases intracellular calcium. Its onset of action is 5 to 60 minutes when given intravenously, with peak effect seen in 1 to 6 hours. When given orally, onset of action is 1 to 2 hours, with peak effect seen at 2 to 8 hours. The half-life of digoxin varies by age, ranging from 61 to 170 hours in preterm neonates, from 35 to 45 hours in full-term neonates and from 18 to 25 hours in infants.[27] Digoxin toxicity in neonates and infants can present as significant bradycardia or cardiac arrhythmias. Digoxin is contraindicated in patients with WPW because of its effect on the accessory pathway and the AV node causing predisposition for fatal arrhythmias.[28] **Monitoring** Digoxin has 11 different methodologies reported Australia and New Zealand laboratories for therapeutic drug monitoring (TDM). Digoxin immunoassays may have a problem with interference from digoxin-like immunoreactive factors, spironolactone, canrenoate, digoxin metabolites and steroids.[29]
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