DIGOXIN

01. Assay Details

CH Labs Test Reference Guide

02. Therapeutic Range

Atrial fibrillation: 1.0-2.0 nmol/L
Congestive heart failure (normal sinus rhythm): 0.6-2.0 nmol/L

How well established:
Atrial fibrillation: there is good evidence that in atrial fibrillation, increasing the concentration of digoxin within the therapeutic range produces an increase in its effect of slowing the ventricular rate. However, in patients with sinus rhythm a relationship between the plasma concentration of digoxin and its therapeutic effect has not been clearly established.

Congestive heart failure: the original therapeutic range of 1.0-2.5nmol/L was developed based on toxicity not efficacy. The DIG investigators trial has shown a neutral effect of digoxin on congestive heart failure mortality, but a benefit with decreased hospitalisation and increased quality of life. Although it is difficult to detect any clinical effect of digoxin when the plasma concentration is less than 1.0 nmol/L, evidence from clinical trials and haemodynamic studies suggest clinical benefit (neurohormonal effects) from digoxin occur at concentrations of 0.5-0.9mg/mL (0.6-1.1nmol/L). Patient outcomes at these lower concentrations appear no different to those patients maintained within the normal therapeutic range. Indeed, there is some evidence suggestive that higher digoxin concentrations maybe associated with worse outcomes in congestive heart failure.

Toxicity: the risk of digoxin toxicity increases significantly at concentrations above 2.6 nmol/L and is almost invariable at concentrations greater than 3.8 nmol/L. Within the range 1.0-3.8 there is some evidence of dose responsiveness. Toxicity is more likely in the presence of:

- [Potassium] <3.5 or >5
- Serum creatinine >0.15 mmol/L
- Age >60 yr
- Daily maintenance dose >6microgms/L
- Hypercalcaemia, hypothyroidism or acidosis

03. Pharmacokinetics

F: 0.7	**Vd** (L/kg): 6 (4-7)	**Cl** (L/h/kg): 0.053 (0.033-0.073)	**t½:** 36 hr (adult)
Fe: 0.7 90.5-0.8)	**Elimination route:** Primarily renal, P-glycoprotein mediated efflux into bile and the GI tract, Metabolism (only 10-20%)		
CYP: minor		**Protein binding:** 0.25	

F = Bioavailability, Vd = volume of distribution, Cl = clearance, t½ = terminal half-life of elimination, Fe = fraction excreted unchanged in the urine, CYP = cytochrome P450 enzyme/s

Other PK data:

- Decreased elimination and Vd in renal disease.
- Renal elimination and Vd are increased in hyperthyroidism and decreased in hypothyroidism.
- t1/2 is shortened to ~20 hr in the time period immediately after acute overdose.

04. Indications

1. Atrial fibrillation, for ventricular rate control
2. Congestive heart failure (inotropic and neurohormonal effects)

05. Loading dose

See TABLE below (Maintenance Dose). Give one half of the total digitalizing dose (TDD) in the initial dose, then give one quarter of the TDD in each of two subsequent doses at 4 to 8 hour intervals. Based on lean body weight.

A usual total loading dose in adults is 1 mg. In renal failure, especially in for example a small elderly woman, the loading dose needs to be up to 50% lower, ie. 0.5 mg (digoxin Vd is reduced with renal impairment)

When changing from oral to IV therapy, dosage should be reduced by 20-25%. It is important to know that even if digoxin is given intravenously it will take about 6 hours to exert the full effect (drug is distributed from blood into less accessible tissues, including the site of action in cardiac muscle) giving NO advantage of IV over PO administration.

06. Maintenance dose

See table

Age	Oral Total Digitalizing (Loading) Dose (µg/kg)	Oral Daily Maintenance Dose (µg/kg)
Pre-term infant	20-30	5-7.5
Full-term infant	25-35	6-10
1 month -2 yr	35-60	10-15
2-5yr	30-40	7.5-10
5-10yr	20-35	5-10
>10yr	10-15	2.5-5
Adults	0.75-1.5mg	0.125-0.5mg/day

NB: Dosage recommendations for digoxin from Drug Information Handbook, 8th edn, 2000-2001 [4]

07. Notes on administration

IV: slow push over at least 5 mins
PO: take digoxin consistently with relation to meals and avoid taking with high fibre foods.

08. When to monitor

Take a trough concentration just prior to the next dose (at least 8 and preferably 12 hours post dose). The concentration does not normally need to be checked within 24 hours of a loading dose unless there is evidence of toxicity or poor control of ventricular rate. The concentration should be checked at least 5 days after starting therapy or changing the dose, if there is a clinically relevant question to be answered.

09. Dose Individualisation

Renal impairment: Dose adjustment is necessary according to calculated creatinine clearance using the Cockcroft and Gault formula and assuming a standard dose of 0.25 mg daily and normal CrCl of 1.5 mL/sec. ie. If CrCl is 0.8 mL/sec then the dose should be halved to 0.125 mg daily

Occasionally dosing may need to be every 48 hours (0.0625 mg) in the elderly with renal impairment

Reduce loading dose by 50% in end stage renal disease

Hepatic impairment: no specific dosage adjustment is necessary.

10. Adverse Effects

>10%

GI: nausea, vomiting, anorexia

1-10%

GI: diarrhoea and abdominal pain

<1%

CNS: confusion, dizziness, drowsiness, bad dreams, psychosis, delirium, restlessness, nervousness, agitation, amnesia
CVS: arrhythmias, ventricular ectopics, SVT, junctional tachycardia, heart block, prolonged PR interval, bradycardia, ST segment changes
ENDO: increased serum oestrogen, gynaecomastia
EYES: (up to 95% in those with digoxin toxicity): disturbance of colour vision, especially xanthopsia, blurred vision, photophobia, ocular muscle palsies, alteration of pupillary size, retrobulbar neuritis, central scotomas
GI: abdominal pain, diarrhoea
MISC: hyperkalaemia

11. Drug interactions

Drugs that decrease digoxin concentration:
(predominantly via reduced absorption)

- Antidiarrhoeal agents: kaolin, pectin
- Hypocholesterolaemic agents: cholestyramine, colestipol

- Antimicrobials: neomycin, para aminosalicylic acid, rifampicin (~50% reduction in digoxin concentration)
- Cytotoxics: cyclophosphamide, vincristine, cytarabine, prednisone, procarbazine, doxorubicin, bleomycin
- Other: antacids, activated charcoal, metoclopramide, cisapride, sulphasalazine, fibre-containing agents, ?cimetidine

Drugs that increase digoxin concentration

- Increased bioavailability: erythromycin, clarithromycin, tetracycline, propantheline
- Significantly increase levels (by inhibiting p-glycoprotein): amiodarone, quinidine, verapamil, diltiazem
- Minor increase: propafenone, spironolactone (decreases renal clearance), triamterine, disopyramide/flecainide. Other calcium channel blockers are probably not significant, although reports are conflicting. There are some case reports for captopril and indomethacin.

Other interactions:

(predispose towards digoxin toxicity)

- Potassium depleting drugs, eg. diuretics, corticosteroids, liquorice.
- Drugs causing hypercalcaemia, eg. calcium supplements, vitamin D derivatives.

12. Factors that may give a false assay result

Serum from some patients (eg. pregnant women, neonates, patients with chronic renal and/or hepatic failure) has been reported to contain an unidentified component that gives positive results for digoxin with a number of immunoassays. This component has been called digoxin-like immunoreactive factor (DLIF) or substance (DLIS). The presence of DLIF in a sample may result in falsely elevated digoxin assay results.

13. Overdose

TOXINZ

14. Dialysability

Digoxin is not dialysable (0-5%).

15. Comments

Nil

16. Key references

1. Aronson, JK. Digoxin. BMJ 1992; 305: 1149-1152.
2. Barrow SW et al. Advances in the management of digoxin toxicity in the older patient. Drugs and Aging 1997; 10(1): 18-33.

3. Rodin S and Johnson B. Pharmacokinetic interactions with digoxin. Clinical Pharmacokinetics 1988; 15: 227-244.
4. Drug Information Handbook, 8th edn 2000-2001. Lacey et al. Lexi-Comp Inc.
5. Terra, S. et al. Pharmacotherapy 1999: 19:1123-26

17. Last updated

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