



Digoxin Toxicity

DIGIFab[®]
digoxin immune fab (ovine)

Cardioactive Steroids

also known as cardiac glycosides

**Digitalis: Plant
derived cardioactive
steroid**

**Digoxin is the most
commonly prescribed
form of digitalis**

**Digitoxin is not
currently available in
the U.S.**

**Digitoxin is being
studied as an
anti-cancer agent for
various tumor types**

Cardioactive Steroids: Sources



Many plants contain cardioactive steroids

- *Digitalis purpurea* (foxglove), *Nerium oleander* (oleander), *Convallaria majalis* (lily of the valley), *Drimys maritima* (red squill)
- Toxicity may result from use of herbal products or teas derived from such plants or direct ingestion of the plant itself



Bufo marinus toad – dried secretions are a supposed aphrodisiac and contain a cardioactive steroid

Giardina EG, Sylvia L. Up to Date. Rose BD (ED). Waltham, MA, 2012.

Digoxin: Therapeutic Role

Formulations

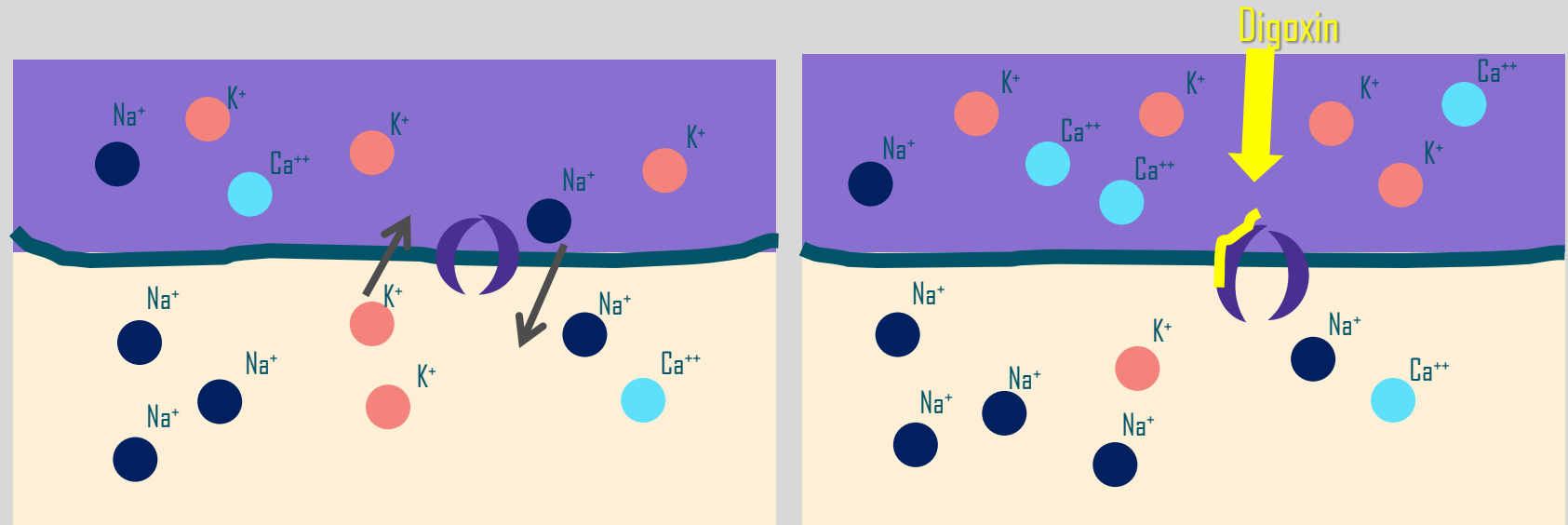
Injection
(IV; rarely used IM)

Oral Solution

Tablets

Mechanism of Action

Inhibits the ion transfer system known as sodium-potassium ATPase



Digoxin: Therapeutic Role

Disease states used in:

Atrial fibrillation

Heart failure

Supraventricular tachycardia

Used in adults and pediatrics



Giardina EG, Sylvia L. Up to Date. Rose BD (ED). Waltham, MA, 2012.

Digoxin: Kinetics

Volume of Distribution

6-7 L/kg

Protein Binding

25%

Half Life

Age, Renal, and cardiac function dependent

Approximately 38 Hours (parent drug)

Time to peak (serum)

Oral: 1-3 hours

Distribution phase: 6-8 hours

Steady state: 7-10 Days

Giardina EG, Sylvia L. Up to Date. Rose BD (ED). Waltham, MA, 2012.

Digoxin Toxicity

Overall use of digoxin has declined approximately 10%
(from 31.4% in 2001 to 23.5% in 2004)

Number of patients with admitted digoxin poisoning has remained stable
(approximately 1,500/year)

Use of digoxin-specific antibody fragments has increased
(approximately 20%)

In 2011, there were 2,513 cases involving cardiac glycosides reported to U.S. poison control centers. Of these, 90 experienced major effects (i.e., life threatening resulting in prolonged hospitalization) and 26 died.

Hussain Z, Swindle J, Hauptman PJ. J Card Fail 2006; 12: 343.
Bronstein AC, Spyker DA, Cantilena LR, et al. Clin Tox 2012; 50:911-1164

Risk Factors for Digoxin Toxicity

Kidney Injury: digoxin is primarily eliminated by the kidneys

Age: elderly are more likely to have decreased renal function and taking potentially interacting concomitant medications

Electrolyte Imbalance: increases sensitivity to digoxin effects

Fluid Status: fluid loss or poor fluid intake can lead to electrolyte imbalances

Digoxin: Causes of Toxicity

Hypokalemia

Results in increased digoxin binding increasing its therapeutic and toxic effects.

Hypercalcemia

Enhances digitalis-induced inotropy leading to possible Ca^{+2} overload and increased susceptibility to digitalis-induced arrhythmias.

Hypomagnesemia

Can sensitize the heart to digitalis-induced arrhythmias (includes any arrhythmia except supraventricular tachydysrhythmias).

Hack JM, Lewin NA. Cardioactive Steroids. Goldfrank's Toxicologic Emergencies, 8th edition. 971-982.

Digoxin: Causes of Toxicity

**Drug interactions:
many commonly used drugs interact
with digoxin**

Via decreased renal clearance of digoxin (class of drugs/examples)

- **calcium channel blockers:
(Nondihydropyridine): verapamil,
diltiazem**
- **NSAIDs: ibuprofen, naproxen sodium**



Giardina EG, Sylvia L. Up to Date. Rose BD (ED), Waltham, MA, 2012.
Gomes T, Mamdani MM, Juurlink DN. Clin Pharm & Therap 2009; 86: 383-386.

Digoxin: Causes of Toxicity

**Drug interactions:
many commonly used drugs interact
with digoxin**

**Via decreased serum potassium
levels (loop and thiazide diuretics):**

- **furosemide**
- **hydrochlorothiazide**



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Digoxin: Causes of Toxicity

**Drug interactions:
many commonly used drugs interact
with digoxin**

Via altering the mechanism of digoxin excretion (and hence elimination) via renal or intestinal p-glycoprotein activity

- **verapamil**
- **diltiazem**
- **quinidine**
- **amiodarone**



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Digoxin: Causes of Toxicity

Increased Serum Levels

- Amiodarone
- Benzodiazepines
- Bepridil
- Cyclosporine
- Diphenoxylate
- Indomethacin
- Itraconazole
- Macrolides
- Propafenone
- Propantheline
- Quinidine
- Quinine
- Spironolactone
- Tetracyclines
- Verapamil

Decreased Serum Levels

- Oral aminoglycosides
- Al⁺/Mg⁺ containing antacids
- Antineoplastics
- Activated charcoal
- Cholestyramine
- Colestipol
- Kaoline / pectin
- Metoclopramide
- Neomycin
- Penicillamine
- Rifampin
- St. John's wort
- Sulfasalazine

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Gomes T, Mamdani MM, Juurlink DN. Clin Pharm & Therap 2009; 86: 383-386.

Digoxin: Causes of Toxicity Con't

Enhanced Pharmacodynamic Effects

- **Beta-blockers**
- **Calcium**
- **Verapamil**
- **Diltiazem**
- **Succinylcholine**
- **Sympathomimetics**
- **Diuretics**

Antagonize Pharmacodynamic Effects

- **Thyroid hormones**

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Gomes T, Mamdani MM, Juurlink DN. Clin Pharm & Therap 2009; 86: 383-386.

Digoxin: Toxicity - Acute

Signs/symptoms of acute toxicity

Gastrointestinal

nausea, vomiting, abdominal pain

Neurological

weakness, confusion

Electrolyte

Hyperkalemia
(> 5.5 mEq/L is a poor prognostic sign)

Cardiac

bradycardia, heart block,
several types of arrhythmias

Schaeffer TH, Mlynarchek SL, Stanford CF. JADA 2010; 110: 587-592

Digoxin: Toxicity - Chronic

Signs/symptoms of chronic toxicity

Gastrointestinal

Patients may have more subtle signs of acute digoxin toxicity (nausea, anorexia)

Neurological

confusion, drowsiness, headache, hallucinations

Visual

sensitivity to light, yellow halos around lights, blurred vision

Schaeffer TH, Mlynarchek SL, Stanford CF. JADA 2010; 110: 587-592

Digoxin: Laboratory Analyses

Interpreting laboratory values in the digoxin poisoned patient

Hyperkalemia: > 5.5 mEq/L in the *acutely* poisoned digoxin patient

Poor prognostic sign in acute toxicity. Antidote warranted when > 5 mEq/L.

Hypokalemia: can predispose the patient to further dysrhythmias and should be corrected with close monitoring to avoid hyperkalemia



Hack JM, Lewin NA. Cardioactive Steroids. Goldfrank's Toxicologic Emergencies, 8th edition. 971-982.

Digoxin: Laboratory Analyses

Interpreting laboratory values in the digoxin poisoned patient

Hypomagnesemia may cause refractory hypokalemia

Administration of Magnesium is contraindicated in:

Bradycardia

Heart block

Pre-existing hypermagnesemia

Decreased renal function or failure



Hack JM, Lewin NA. Cardioactive Steroids. Goldfrank's Toxicologic Emergencies, 8th edition. 971-982.

Digoxin: Laboratory Analyses

Digoxin levels in the poisoned patient

Obtaining an immediate digoxin level in an acutely poisoned patient will not reflect the peak serum level as the distribution phase of digoxin is long. An initial 4-6 hour post-ingestion level is appropriate.

Free digoxin

Useful following administration of digoxin-specific Fab fragments

Total digoxin

- Serum concentrations predict cardiac concentrations
- Fab fragments of digoxin-specific antibodies will cause a rise in total digoxin levels (as Fab bound digoxin is also being measured)

Diagnosis of Digoxin Toxicity

What is needed?

History



Signs and symptoms



EKG



Digoxin levels



Electrolytes



Diagnosis of Digoxin Toxicity

What is needed?

History



Risk factors for digoxin toxicity including age of patient
(for patients chronically using digoxin therapeutically)

Initiation or
discontinuation of
drugs that
potentially
interact with
digoxin

Any disease
changes
(such as thyroid
disease)

Altered renal
function

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Diagnosis of Digoxin Toxicity

What is needed?

Signs and Symptoms



Acute overdose:

Gastrointestinal:
nausea, vomiting

Central Nervous System:
confusion, weakness,
lethargy

Electrolyte changes:
hyperkalemia

Cardiac Signs:
sinus bradycardia,
second or third degree
AV block. Any type of
dysrhythmia is
possible

Hack JM, Lewin NA. Cardioactive Steroids. Goldfrank's Toxicologic Emergencies, 8th edition. 971-982.

Diagnosis of Digoxin Toxicity

What is needed?

Signs and Symptoms



Chronic overdose (symptoms usually insidious in onset):

Gastrointestinal:
anorexia, nausea,
vomiting, weight loss

Central Nervous System: delirium,
hallucinations,
confusion,, lethargy
(seizures are possible but rare)

Visual:
photophobia,
changes in color
vision (such as yellow
halos around lights)

Electrolyte changes:
hyperkalemia
(sometimes hypokalemia
especially if diuretics
are used)

Cardiac Signs:
bradydysrhythmias
(often unresponsive
to atropine)
ventricular
tachydysrhythmias

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Diagnosis of Digoxin Toxicity

What is needed?

EKG



Almost any arrhythmia or conduction abnormality may be seen with digitalis toxicity.

Hack JM, Lewin NA. Cardioactive Steroids. Goldfrank's Toxicologic Emergencies, 8th edition. 971-982.

Diagnosis of Digoxin Toxicity

What is needed?

Digoxin levels



Therapeutic range of digoxin has historically been 0.5 - 2.0 ng/mL (although current medical practice is evolving and some experts now advocate target levels, < 1.0 ng/mL)

However, this can be misleading in the acutely poisoned patient

- Stat levels may not correlate with the severity of the poisoning especially in acute ingestions
- Digoxin's long distribution phase results in high serum levels for 6-12 hours prior to completed tissue distribution

Hack JM, Lewin NA. Cardioactive Steroids. Goldfrank's Toxicologic Emergencies, 8th edition. 971-982.

Diagnosis of Digoxin Toxicity

What is needed?

Electrolytes



Hypokalemia results in increased digoxin binding increasing its therapeutic and toxic effects.

Hypercalcemia enhances digitalis-induced inotropy leading to possible Ca^{+2} overload and increased susceptibility to digitalis-induced arrhythmias.

Hypomagnesemia can sensitize the heart to digitalis-induced arrhythmias.

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Digoxin Toxicity: Available Treatments

Decontamination/enhanced elimination

For acute overdose: Activated charcoal can adsorb digoxin in the gut

Enhanced elimination (dialysis, hemoperfusion) does not effectively remove digoxin due to large volume of distribution and relatively high protein binding

Hack JM, Lewin NA. Cardioactive Steroids. Goldfrank's Toxicologic Emergencies, 8th edition. 971-982.

Digoxin Toxicity: Available Treatments

Fab fragments of
digoxin-specific antibodies

Available U.S. products:

DigiFab®
digoxin immune fab (ovine)
BTG International Inc.

DigiFab[®]: Indications

Life-threatening or potentially life-threatening digoxin toxicity or overdose, which includes:

Known suicidal or accidental Ingestion of fatal digoxin doses:

- 10 mg or more in healthy adults
- 4 mg (0.1 mg/kg) or more in healthy children
- An amount that results in steady state digoxin concentrations of > 10 ng/mL

Chronic ingestions:

- Serum digoxin > 6 ng/mL in adults or 4 ng/mL in children

DigiFab[®]: Indications

Life-threatening or potentially life-threatening digoxin toxicity or overdose, which includes:

Severe ventricular arrhythmias

Progressive bradycardia

Second or third degree heart block unresponsive to atropine

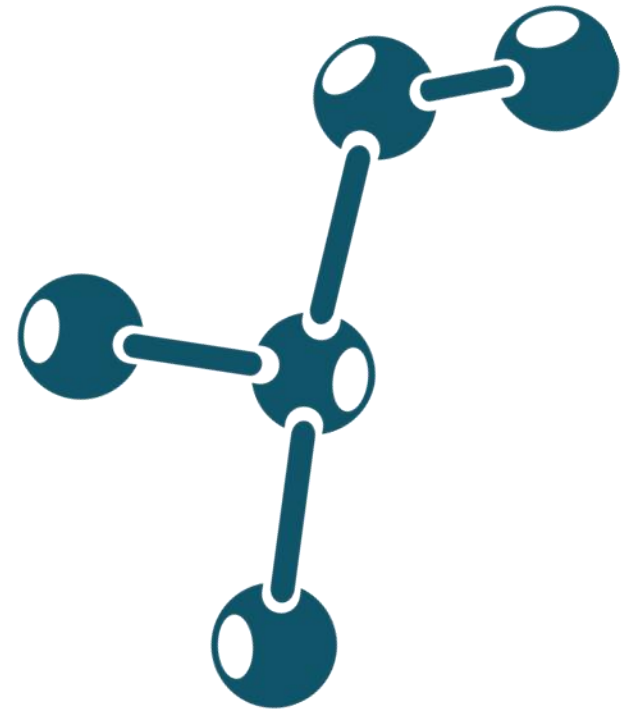
Serum potassium levels > 5.5 mEq/L (adults) or 6 mEq/L (children) with rapidly progressive signs and symptoms of digoxin toxicity

DigiFab[®]: Mechanism of Action

**Binds to digoxin molecules,
reducing free digoxin levels**

Results in a shift in the equilibrium away
from receptor binding

**Fab-digoxin complexes are
cleared by the kidney and
mononuclear phagocyte system**



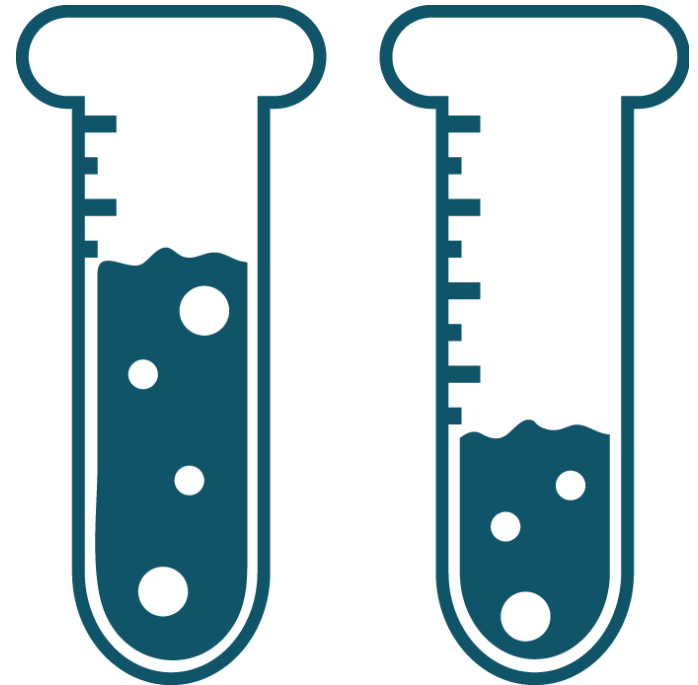
DigiFab[®]: Dosing – Acute Ingestion

Acute ingestion: unknown amounts of digoxin and unknown serum concentration

20 vials of DigiFab[®]

Monitor for volume overload in children < 20 kg

Can split dose into 10 vials followed by another 10 vials to avoid a febrile reaction



DigiFab[®] Prescribing Information, Jan 2012, BTG International, Inc.

DigiFab[®]: Dosing – Acute Ingestion

Acute ingestion: known amounts of digoxin

Dose In Vials =

Amount of digoxin ingested (mg)*

0.5 Mg/Vial

* multiply mg by bioavailability of the tablet formulation:

0.25 mg tabs (80% bioavailability)

0.2 mg tabs (100% bioavailability)

DigiFab[®]: Dosing – Chronic Ingestion

Chronic ingestion: unknown serum digoxin concentration

6 Vials of DigiFab[®] in Adults and Children \geq 20 Kg

1 Vial of DigiFab[®] in Infants and Children $<$ 20 Kg

DigiFab[®]: Dosing – Chronic Ingestion

Chronic ingestion: known digoxin serum concentration

Adult dose estimate of DigiFab[®] (in number of vials) from steady-state serum digoxin concentration²

Patient Weight (kg)	Serum Digoxin Concentration (ng/mL)						
	1	2	4	8	12	16	20
40	0.5 v	1 v	2 v	3 v	5 v	7 v	8 v
60	0.5 v	1 v	3 v	5 v	7 v	10 v	12 v
70	1 v	2 v	3 v	6 v	9 v	11 v	14 v
80	1 v	2 v	3 v	7 v	10 v	13 v	16 v
100	1 v	2 v	4 v	8 v	12 v	16 v	20 v

v=vials.

DigiFab[®]: Preparation

One vial contains 40 mg of digoxin immune Fab protein

- Contains no preservatives and is for one-time use only

Reconstitution: add 4 mL Sterile Water for Injection (10 mg/mL solution of digoxin immune Fab protein) and gently mix

Use immediately or store in refrigerator for up to 4 hours (do not freeze)



DigiFab[®]: Preparation

**Add reconstituted product to appropriate
0.9% sodium chloride for injection**

For infants and very small children

- use undiluted reconstituted solution using tuberculin syringe
- reconstituted vial can also be diluted with an additional 36 mL of isotonic saline for 1mg/mL concentration

Visual inspection

**Do not use if solution is cloudy, turbid or
contains particulates**



DigiFab[®]: Administration

30 minute slow IV infusion

Can be given by IV bolus
injection if cardiac arrest is
imminent

DigiFab[®] Prescribing Information, Jan 2012, BTG International, Inc.

BTG Confidential

Not For Distribution



DigiFab[®]: Dosing/administration

If toxicity is not adequately reversed or recurs,
measure free (not total) serum digoxin concentrations

Repeat doses may be guided by clinical judgment

If digoxin toxicity is not at all reversed,
consider another diagnosis

DigiFab[®]: Use in Special Populations

Pregnancy category C

Unknown if may cause fetal harm.
Should be given to pregnant patient
only if clinically indicated

Nursing mothers

Unknown if excreted in breast milk

Pediatric use

Pediatric safety data are limited.
Pediatric dosing estimations are
based on adult dosing

Geriatric patients

Renal function needs to be
monitored closely for
recurrent toxicity

DigiFab[®]: Warnings



Patients who require digoxin's inotropic action may deteriorate secondary to the withdrawal of digoxin's inotropic action by **DigiFab[®]**

Additional inotropic support may be required for these patients (e.g, dopamine, dobutamine or vasodilators)

Re-digitalization may need to be postponed until DigiFab[®] has cleared (several days to more than a week in impaired renal function)

DigiFab[®]: Warnings



Monitor potassium level frequently as a rapid drop in serum potassium may occur following DigiFab[®] administration

DigiFab[®]: Warnings



Do not administer DigiFab[®] to papaya- or papain-hypersensitive patients unless the benefits clearly outweigh the risks

Patients with allergies to sheep protein or prior treatment with ovine antibodies or Fab are at risk for an anaphylactic reaction

Standard emergency care and termination of DigiFab[®] are warranted for patients with anaphylaxis/hypersensitivity reactions

DigiFab[®]: Adverse effects (most common)

Worsening of congestive heart failure

13%

Hypokalemia

13%

A rapid shift of potassium back into the cell can occur when digoxin toxicity is reversed by DigiFab[®]

Serum potassium should be followed closely and supplementation should be given cautiously

Worsening atrial fibrillation

7%

DigiFab®

**Minimum stocking
recommendation:
15 vials (for approximately 8
hours of initial therapy)**

**Emergency department
stocking: for availability
within one hour**

Dart RC, Borron SW, Caravati EM, et al. Ann Emer Med 2009; 54: 386-394.

BTG Confidential

Not For Distribution

Resources

Website for product information

www.digifab.us

Poison control

800-222-1222

**BTG Medical Info/Adverse
Event Reporting**

877-377-3784

**Customer Service
including availability**

877-852-8542

Digoxin Toxicity: Case 1

76 year old woman with history of atrial fibrillation, hypertension, renal impairment, breast cancer, osteoarthritis. Stroke 1 month prior to admission.

Medications: digoxin 250 mcg once daily, amlodipine, lisinopril, indapamide SR, simvastatin, clopidogrel, bisoprolol, omeprazole, erythromycin

Presents with nausea, vomiting, change in vision, lethargy

VS: BP “normal”; HR 35-38 bpm

Labs

Digoxin levels: prior to admission:
3.4 ng/mL (0.8-2 ng/mL normal
range for this lab)

On admission:
2.9 ng/mL

Increased digoxin dose from 125
mcg/day to 250 mcg/day 28
days ago

Digoxin Toxicity: Case 1

Summary: elderly patient with renal impairment, signs/symptoms of (chronic) digoxin poisoning with elevated digoxin level

Potential drug interactions:

Amlodipine

(Ca channel blocker)
can increase digoxin
level and enhance
digoxin AV blocking
effect

Bisoprolol

(β blocker)
can enhance
digoxin's bradycardic
effect

Erythromycin

(macrolide antibiotic)
can increase digoxin
level

Kolev KK. Digoxin – a friend or foe. BMJ Case Reports 2012 Sept 24
Gomes T, Mamdani MM, Juurlink DN. Clin Pharmacol & Therap 2009; 86: 383-386.

Digoxin Toxicity: Case 1

Received digoxin-specific antibody fragments (Fab)

Weight 108 kg

Digoxin level: 2.9 ng/mL

Fab Dose In Vials =

(Serum Digoxin ng/mL) (Weight in kg)

100

3 vials administered

Kolev KK. Digoxin – a friend or foe.
BMJ Case Reports 2012 Sept 24

Digoxin Toxicity: Case 1

6 hours post digoxin Fab infusion: digoxin 1.9 ng/mL

At discharge (91 hours post digoxin Fab infusion): digoxin 1 ng/mL, HR 65 bpm, digoxin toxicity signs/symptoms resolved

Monitoring

HR: improved (35-38 bpm to 65 bpm at discharge)

BP: remained stable

EKG: unchanged from baseline (atrial fibrillation)

K⁺ not provided in this report (although this was a chronic toxicity not acute)

Digoxin Toxicity: Case 1



Approaches to digoxin poisoning in the chronically poisoned patient will depend on the status of the patient (signs/symptoms, age, renal function, cardiac status)

This was an elderly patient with impaired renal function who clearly had digoxin toxicity and an elevated level.

The clinical decision was made to treat promptly with digoxin Fab rather than prolong her clinical course.

Kolev KK. Digoxin – a friend or foe.
BMJ Case Reports 2012 Sept 24