

Cardiac Diseases and Therapies

HEART FAILURE

DIGOXIN IMMUNE FAB (DigiFab®) MANAGEMENT OF DIGOXIN TOXICITY

BACKGROUND

Increased susceptibility to digoxin toxicity:

- elderly
- co-existing diseases: heart disease, renal or hepatic dysfunction, hypothyroidism, COPD
- electrolyte disturbances: hypokalemia, hypomagnesemia, hypercalcemia, hypoxia
- drug interactions: beta blockers, calcium channel blockers, amiodarone, etc.

Signs and symptoms of digoxin toxicity:

Gastrointestinal:

- nausea, vomiting, diarrhea, anorexia

CNS:

- malaise, fatigue, drowsiness, confusion, visual disturbances (yellow-green halos around objects)

Cardiovascular:

- progressive bradyarrhythmias (sinus bradycardia, junctional escape rhythms, second or third degree AV block), supraventricular arrhythmias, frequent multifocal premature ventricular contractions, ventricular fibrillation or tachycardia

Electrolytes:

- progressive elevation in serum potassium especially in acute toxicity

Acute toxicity = acute ingestion of >10 mg of digoxin

MANAGEMENT OF DIGOXIN TOXICITY

- Discontinue digoxin
- STAT serum digoxin and potassium levels (both taken prior to digoxin immune Fab use)
- Continuous cardiac monitoring
- For acute poisoning: activated charcoal (1 g/kg)
- Correct fluid and electrolyte disturbances:
 - hypokalemia: replacement of potassium requires extreme caution since delayed hyperkalemia can develop in advanced digoxin toxicity
 - Note:** use IV sympathomimetics with extreme caution, as they can exacerbate or precipitate cardiac glycoside-induced ventricular arrhythmias
 - if hyperkalemia develops, administer glucose, insulin, sodium bicarbonate, potassium binding resin.
 - AVOID calcium gluconate or chloride injection
 - correct hypoxia, acid-base imbalances
- For bradyarrhythmias:
 - atropine 0.5-2 mg IV
 - pacemaker (external or transvenous)
 - consider digoxin immune Fab IV infusion (see below)
- For ventricular dysrhythmias:
 - digoxin immune Fab IV infusion (see below)
 - magnesium sulfate 2-4 g IV
 - lidocaine (1 mg/kg) or phenytoin infusion
 - direct electrical cardioversion (DCC) as last resort (use low setting since it can result in ventricular fibrillation)

Digoxin Immune Fab (DigiFab®)

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Digoxin-specific antibody fragments (DigiFab, digoxin immune Fab* (ovine)), **are sheep derived antibodies that bind to molecules of digoxin, which makes the latter unavailable for binding at their site of action.**

Note: Fab stands for "fragment antigen-binding" and is a region on an antibody that binds to antigens

DigiFab 40 mg vials replace Digibind– 38 mg vials discontinued by the manufacturer in 2011.

Digoxin immune Fab is indicated for the treatment of life threatening digoxin toxicity in patients with manifestations of severe toxicity. It is **NOT indicated** for mild cases of digoxin toxicity or in cases of elevated serum digoxin concentrations in the absence of signs and symptoms of digoxin toxicity.

Prescribing is restricted to Cardiology, Intensive Care, and Emergency Attending physicians. Physician must be available during administration.

NOTE: The following are criteria for use, but should not preclude use if, in the opinion of the clinician, it is medically indicated.

All cases should be reported to the Ontario Poison Centre, 416-813-5900.

DigiFab SHOULD BE CONSIDERED UNDER THE FOLLOWING CONDITIONS

- Patient is experiencing manifestations of life-threatening digoxin toxicity:
 - ventricular dysrhythmias (ventricular fibrillation or ventricular tachycardia) secondary to digoxin toxicity
 - hemodynamically significant bradyarrhythmias (symptomatic sinus bradycardia, second or third degree AV block unresponsive to atropine) refractory to conventional management
 - concurrent serum potassium greater than 5.0-5.5 mmol/L
- Ingestion of greater than 10 mg of digoxin in a previously *healthy* adult (threshold for elderly may be lower)
- Acute ingestion of an unknown amount resulting in a digoxin concentration greater than or equal to 12.8 nmol/L more than 6 hours* post ingestion (equivalent to 10 ng/mL as stated in product monograph)

Note: At least 6-8 hours are required for equilibration between serum and tissue after an oral dose.

- Symptoms of digoxin toxicity and steady state serum digoxin concentrations of digoxin >7.7 nmol/L, due to chronic ingestion (equivalent to 6 ng/mL, as stated in the product monograph)
- Serum concentration greater than 19 nmol/L at any time after ingestion
- Supraventricular arrhythmias

PRECAUTIONS

- Prior allergic reaction to ovine proteins
- Papain is used in the manufacturing process; trace amounts may still be present in the final product. Some dust mite and latex allergens share similar antigenic determinants with papain. Patients with an allergy to papain, chymopapain, other papaya extracts, or the pineapple enzyme, bromelain, may be at risk of developing a hypersensitivity reaction.

ADVERSE EFFECTS

- Sensitivity reactions (anaphylaxis, rash, flushing, facial swelling)
- Hypokalemia – monitor serum potassium levels for first few hours after digoxin immune Fab
- Tachycardia – if digoxin was used for rate control of atrial fibrillation, may see an increase in ventricular response rate
- Worsening of heart failure, possibly due to the loss of the positive inotropic effects of digoxin
- Phlebitis during infusion
- Fever, with doses above 10 vials

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MONITORING

- **Serum digoxin level *prior** to initiation of DigiFab infusion**

Note: Do not order serum digoxin level **AFTER** digoxin immune Fab administration, since it has no correlation to clinical toxicity (i.e., lab measures both bound and unbound digoxin, therefore false positive results). However, UNBOUND (free) digoxin levels are available at selected laboratories and might be considered for the patient who does not seem to respond to therapy. Contact the Ontario Poison Centre (416-813-5900). A toxicologist is available 24 hours/day.

- **Temperature**
- **Blood pressure**
- **Continuous ECG monitoring**
- **Potassium – hypokalemia may develop as DigiFab reverses the effects of digoxin on electrolyte balance**
- **Serum digoxin concentration measurement is NOT useful following administration of DigiFab**
- **Recurrence of toxicity – in the patient with renal failure, cardiac monitoring and careful observation may be required for up to 10 days post-administration**

Note: hemodialysis does not enhance elimination; consider plasma exchange.

Response to therapy:

- Serum potassium concentrations return to normal within 2 to 6 hours (hypokalemia may result as toxicity is reversed)
- Cardiac arrhythmias are controlled within 3 hours

Note: If dysrhythmias are controlled, cardiac monitoring is required for a further 4 hours. If the patient continues to be symptom free, they no longer require monitoring unless a renal failure patient.

DOSING

- Dose varies according to the amount to be neutralized—based on digoxin serum level or estimated dose ingested
- Each vial (40 mg) will bind approximately 0.5 mg of digoxin

- **Dosage for acute digoxin ingestion of an unknown amount with an unknown digoxin concentration**

- For the arrested digoxin poisoned patient, the usual recommendation is 10 vials over 5 minutes; Repeat if symptoms recur in an hour or if no resolution. The dosing interval should be shortened to 30 minutes if still doing CPR.

- **Dosage for acute digoxin ingestion of a known amount**

- Each vial of 40 mg binds approximately 0.5 mg of digoxin
- Oral tablets have a bioavailability of approximately 80%, therefore the digoxin load is multiplied by 0.8

$$\text{Dose (\# vials)} = \frac{(\text{total ORAL digoxin body load in mg}) (0.8)}{0.5}$$

- IV digoxin is 100% bioavailable; therefore, the formula is as follows:

$$\text{Dose (\# vials)} = \frac{\text{total IV digoxin body load in mg}}{0.5}$$

- **Dosage for toxicity during chronic therapy in a patient in acute distress with an unavailable digoxin concentration**

- One dose of six vials (= 240 mg of DigiFab)

- **Dosage for a known steady state serum digoxin concentration:***

$$\text{Dose (\# vials)} = \frac{(\text{serum digoxin concentration in nmol/L}) (0.781) (\text{weight in kg})}{0.5}$$

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Note: These formulas were derived, based on a steady state volume of distribution for digoxin equal to 5 L/kg (approximately) and molecular weight equal to 781 g, to convert serum digoxin to total body burden of digoxin and the assumption that 1 vial of DigiFab binds to 0.5 mg digoxin.

RECONSTITUTION

- Reconstitute each 40 mg vial with 4 mL Sterile Water for Injection to make a solution of 10 mg/mL. Gently mix. Do not shake.
- Use reconstituted solution immediately.

ADMINISTRATION

- Add dose to 50 or 100 mL of 0.9% sodium chloride. Infuse over at least 30 minutes.
- May infuse over a longer period if infusion rate-related reactions occur.

STABILITY/COMPATIBILITY

- Stable for 4 hours under refrigeration.
- Compatible with 0.9% sodium chloride only.

AVAILABILITY

Trade Name: DigiFab®
Manufacturer: BTG International Inc.
Supplied: 40 mg/vial (\$780/vial)
Locations at UHN: TGH; CICU, Night Cupboard
TWH; Emergency Department

REFERENCES

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Notice to Healthcare Providers:

The Pharmacotherapy Handbook is intended to be used as a tool to aid in the appropriate prescribing and administration of cardiovascular formulary agents.

This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

Due to the rapidly changing nature of cardiovascular treatments and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Your comments on the usefulness of the resources contained in the Handbook are welcomed and may be forwarded to Amita Woods, Department of Pharmacy Services (amita.woods@uhn.ca).