

Digoxin Immune Fab (ovine) (DigiFab®)

Digoxin is a cardiac glycoside indicated for the treatment of heart failure and for rate control in atrial fibrillation. It has a narrow therapeutic index, is mainly renally eliminated, has a large volume of distribution, and is highly protein bound. The main causes of digoxin toxicity include acute overdose, therapeutic errors, and accumulation due to changes in renal function or digoxin/drug interactions. Non-cardiac manifestations of digoxin toxicity include nausea, anorexia, fatigue, visual disturbances (flashing lights, halo vision, green-yellow perception impairment), confusion, hallucinations and hyperkalemia. Cardiac manifestations include tachyarrhythmias, bradyarrhythmias, ventricular arrhythmias, and conduction disturbances.

Mechanism/Indications:

Digoxin Immune Fab consists of antigen binding fragments (Fab) derived from specific anti-digoxin antibodies produced in sheep. The antibody is papain digested, and digoxin-specific Fab fragments are isolated and purified. Digoxin has higher binding affinity for the Fab fragments than for its physiologic receptor. The Fab fragments bind to digoxin and the digoxin-antibody complex accumulates in the plasma where it can be eliminated in the urine. This changes the equilibrium and promotes redistribution of digoxin from the tissues to the plasma reversing toxicity. Improvement in symptoms is usually seen in less than 30 minutes. Digoxin immune Fab is indicated for:

- Manifestations of severe digoxin toxicity due to overdose (life-threatening ventricular arrhythmias, progressive bradycardia, second- or third-degree heart block not responsive to atropine, refractory hypotension)
- Rapid progression of clinical signs and symptoms of toxicity such as cardiac and gastrointestinal toxicity plus one or more of the following:
 - Acute digoxin ingestion of greater than 10mg in adults or greater than 4mg in children Acute digoxin ingestions with post distribution digoxin >10ng/mL (by 6 hours post ingestion)
 - Acute/chronic digoxin toxicity presenting with hyperkalemia ($K > 5.0 \text{ mEq/L}$)

Dosing:

Each 40 mg vial of digoxin immune Fab will bind 0.5 mg of digoxin. The dose of digoxin immune Fab (number of vials) can be estimated based on the amount of digoxin ingested in acute exposures. Doses should be rounded up to the next full vial. In chronic exposures, a partial reversal dose may reduce risk of abrupt loss of all therapeutic digoxin effect leading to a loss of benefit – i.e., A fib with RVR or acute exacerbation of CHF.

- Acute ingestion of unknown amount: Administer 10 vials IV; observe response; administer another 10 vials IV if necessary.
- Acute ingestion of known amount: dose (vials) = digoxin ingested (mg) X bioavailability / 0.5 mg of digoxin bound per vial. Bioavailability factor is 0.8 for digoxin tablets or 1 for Lanoxicaps.
- Chronic digoxin toxicity: Administer 1-2 vials IV; observe response; administer another 1-2 vials IV if necessary. If no improvement seen, consider other contributing factors (other medications like calcium channel blockers or beta blockers) or medical causes like sick sinus syndrome.

Digoxin Immune Fab (continued)

Adverse Effects/Contraindications:

There are no known contraindications to digoxin immune Fab use. Use caution in patients with allergies to sheep products, papain or other papaya extracts, bromelain (pineapple enzyme), or latex allergies due to possible cross reactivity. Although rare, monitor for signs and symptoms of anaphylaxis. Digoxin toxicity causes potassium to shift from inside to the outside of the cell resulting in hyperkalemia. When toxicity is reversed, the potassium reenters the cell resulting in rapid hypokalemia. Monitor potassium repeatedly, especially early in therapy and treat cautiously with potassium as needed. In patients with renal insufficiency, elimination can be slowed to the point where digoxin immune Fab may be metabolized by the liver. Some authors suggest that this may result in rebound toxicity due to release of the previously bound digoxin. Similarly, recurrent toxicity may occur in patients who receive less than the estimated required dose of digoxin immune Fab. Other adverse reactions include exacerbation of low cardiac output and congestive heart failure and rapid ventricular response in patients with atrial fibrillation caused by digoxin withdrawal. It is also important to note that most labs report total serum digoxin (free and bound); therefore, treatment with digoxin immune Fab causes elevation of serum digoxin levels. Treatment decisions should not be based on serum digoxin levels after starting digoxin immune Fab therapy.

For more on digoxin immune Fab:

- *Vivo RP, Krim RK, Perez J, Inklab M, Tenner, Jr. T, Hodgson J. Digoxin: Current use and approach to toxicity. Am J Med Sci 2008;336(5):423-428.*
- *Bauman JL, DiDomenico RJ, and Galanter WL. Mechanisms, manifestations, and management of digoxin toxicity in the modern era. Am J Cardiovasc drugs 2006;6(2):77-86.*
- *Howland MA. Antidotes in Depth: Digoxin-specific antibody fragments (Fab). In: Hoffman RS, Howland MA, Lewin NA Nelson LS, Goldfrank LR, editors: Goldfrank's Toxicologic Emergencies. 10th ed. New York NY, 2015;904-908.*
- *Chan BS, Buckley NA. Digoxin-specific antibody fragments in treatment of digoxin toxicity. Clin Toxicol 2014;52:824-36.*
- *Chan BS, Isbister GK, O'Leary M, Chiew A, Buckley NA. Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1). Clin Toxicol (Phila). 2016;54(6):488-494.*

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