



## **Digoxin Poisoning Management**

### **Introduction**

- Digoxin is a cardioactive glycoside indicated for atrial flutter, atrial fibrillation, and heart failure
- Acts as a sodium/potassium pump inhibitor for cardiac myocytes → toxicity arises with too much intracellular Na<sup>+</sup> inhibiting the sodium/calcium pump from working properly (increasing intracellular calcium)
  - Increased inotropy within the cardiac myocytes → dysrhythmias
- EKG abnormalities: premature ventricular contractions, biphasic T wave, shortened QT interval, AV block
- Digoxin therapeutic levels range from 0.8-2.0 ng/ml (toxicity can begin >2 ng/ml)

| <b>Pharmacology</b>        |                                                                                                                                                                                                                                                                                                                                                                                                                     |
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|                            | <b>Digoxin Immune Fab<br/>(DigiFab or DigiBind)</b>                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Dose</b>                | <ul style="list-style-type: none"> <li>• 1 vial = 40mg (binds to 0.5mg of digoxin)</li> <li>• <b><u>Unknown toxicity level: Initial → 10vials</u></b></li> <li>• Vials = Total body load (mg) x 2</li> <li>• For chronic ingestion of unknown amount               <ul style="list-style-type: none"> <li>◦ 3-6 vials can be given for adults</li> <li>◦ 1-2 vials can be given for children</li> </ul> </li> </ul> |
| <b>Administration</b>      | <ul style="list-style-type: none"> <li>• IV infusion over 30 minutes</li> <li>• If cardiac arrest is imminent a bolus injection can be given</li> </ul>                                                                                                                                                                                                                                                             |
| <b>PK/PD</b>               | <ul style="list-style-type: none"> <li>• <b>Onset: 20-90 minutes</b></li> <li>• Duration of action: 15 – 20 hrs</li> </ul>                                                                                                                                                                                                                                                                                          |
| <b>Adverse Effects</b>     | <ul style="list-style-type: none"> <li>• Orthostatic hypotension, ventricular tachycardia, hypokalemia</li> </ul>                                                                                                                                                                                                                                                                                                   |
| <b>Mechanism of Action</b> | <ul style="list-style-type: none"> <li>• Immune antigen-binding fragments that rapidly bind with digoxin to decrease free digoxin levels within the body</li> </ul>                                                                                                                                                                                                                                                 |
| <b>Compatibility</b>       | <ul style="list-style-type: none"> <li>• 0.9% NS Only</li> </ul>                                                                                                                                                                                                                                                                                                                                                    |

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| <b>Comments</b> | <ul style="list-style-type: none"> <li>• Monitor <b>K+</b> closely as it shifts intracellularly potentially causing hypokalemia.</li> <li>• <b>Total concentration of digoxin may be <u>falsely elevated</u> after administration due to ↑ in free drug &amp; bounded drug.</b></li> <li>• Free digoxin concentrations are more clinically useful</li> </ul> |
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## Overview of Evidence

| Author, year        | Design/ sample size      | Intervention & Comparison                                                                                                                                                                                                                    | Outcome                                                                                                                                                                                                                                                                                     |
|---------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wei et al., 2021    | Case reports (n=121)     | <b>DigiBind</b> vs <b>DigiFab</b> adverse events reported to FAERS from 1986-2019                                                                                                                                                            | <ul style="list-style-type: none"> <li>• <b>87.2% of DigiBind</b> reports were serious AEs vs. <b>62.8% of DigiFab</b></li> <li>• Hypotension, cardiac arrest, and death were among the most serious AEs</li> </ul>                                                                         |
| Ward et al, 2000    | Observational (n=16)     | <b>DigiBind</b> vs <b>DigiFab</b> in healthy volunteers                                                                                                                                                                                      | <ul style="list-style-type: none"> <li>• Both Fab products reduced free digoxin serum concentrations to <b>below assay detection</b></li> <li>• Total digoxin serum concentrations increased approximately 10-fold (indicated fab product binding digoxin)</li> </ul>                       |
| Renard et al., 1997 | Observational (n=16)     | Influence of <b>age &amp; renal dysfunction</b> on digoxin-specific Fab pharmacokinetics <ul style="list-style-type: none"> <li>• Doses 80-800mg infused over 0.25-2hr</li> <li>• Patients aged 35-90 with CrCl 10.6-122.1 ml/min</li> </ul> | <ul style="list-style-type: none"> <li>• <b>Linear decrease</b> of total body clearance is linked to renal function and age, but not Vd</li> <li>• Plasma half-lives ranged from <b>11-34.5hrs</b></li> <li>• <u>All patients recovered</u> and no adverse effects were reported</li> </ul> |
| Antman et al., 1990 | Open-label trial (n=150) | Digoxin-specific Fab fragment dosed based on <u>total ingested amount (mg)</u> or <u>digoxin serum concentration (ng/ml)</u>                                                                                                                 | <ul style="list-style-type: none"> <li>• <b>90%</b> of patient toxicity <u>resolved or improved</u> with <b>10%</b> <u>showing no response</u></li> <li>• Median dose ~ 200mg (5 vials)</li> <li>• Highest dose ~ 1600mg (40 vials)</li> </ul>                                              |

## Conclusions

- Digoxin toxicity is a serious & life-threatening condition if not appropriately reversed by an available antidote
- For unknown amount of ingestion, administer 10 vials of digoxin Immune Fab to treat digoxin toxicity
- Age and renal function are proven not to be factors prohibiting digoxin toxicity treatment

## References

1. Bismuth C, Gaultier M, Conso F, Efthymiou ML. Hyperkalemia in acute digitalis poisoning: prognostic significance and therapeutic implications. *Clin Toxicol*. 1973;6(2):153-162. doi:10.3109/15563657308990513
2. David MNV, Shetty M. Digoxin. [Updated 2022 Sep 5]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK556025/>
3. Lexicomp Online, Lexi-Drugs Online. Waltham, MA: UpToDate, Inc.; January 2023. Accessed January 16, 2023. <https://online.lexi.com>.
4. Antman et al. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. *Circulation*. 1990;81(6):1744-1752. doi:10.1161/01.cir.81.6.1744
5. Renard C, Grene-Lerouge N, Beau N, Baud F, Scherrmann JM. Pharmacokinetics of digoxin-specific Fab: effects of decreased renal function and age. *Br J Clin Pharmacol*. 1997;44(2):135-138. doi:10.1046/j.1365-2125.1997.00654.x
6. Roberts DM, Gallapathy G, Dunuwille A, Chan BS. Pharmacological treatment of cardiac glycoside poisoning. *Br J Clin Pharmacol*. 2016;81(3):488-495. doi:10.1111/bcp.12814
7. Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet*. 1995;28(6):483-493. doi:10.2165/00003088-199528060-00006
8. Wei, S., Niu, M.T. & Dores, G.M. Adverse Events Associated with Use of Digoxin Immune Fab Reported to the US Food and Drug Administration Adverse Event Reporting System, 1986–2019. *Drugs - Real World Outcomes* 8, 253–262 (2021). <https://doi.org/10.1007/s40801-021-00242-x>
9. Ward SB, Sjostrom L, Ujhelyi MR. Comparison of the pharmacokinetics and in vivo bioaffinity of DigiTab versus DigiBind. *Ther Drug Monit*. 2000 Oct;22(5):599-607. doi: 10.1097/00007691-200010000-00016. PMID: 11034267.