Clinical Toxicology
Toxicity of Digitalis Glycosides
5th Year
(Lab 3)

Lecturer: Rua Abbas Al-Hamdy
Department of Pharmacology & Toxicology
University of Al-Mustansiriyah
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Introduction:

- Digitalis glycosides are life-saving drugs when used in therapeutic doses in the treatment of congestive heart failure (CHF), & for management of certain supraventricular arrhythmia.

- Digitalis protects ventricles during certain atrial arrhythmias.

- Digoxin is the one of the most widely prescribed drugs.
- It is estimated that 20-30% of patients taking a digitalis preparation will experience toxicity because the drugs have an extremely narrow therapeutic index.
- The serum concentration of digoxin for therapeutic activity is in the normal range of 1.2-1.7 ng/mL & clinically significant toxicity usually occurs with concentrations 2-3 times higher.
- The mortality rate with toxic dose is reported to be as great as 25%.

Factors that increase the risk of toxicity to digitalis glycosides:

- Concurrent administration of a diuretic that induces potassium loss is reported to be the most frequent cause of toxicity.

- Individuals with *Eubacterium lentum* in their colon may require larger doses of digitalis to achieve the desired therapeutic serum concentrations. This microorganism reduces the lactone ring of digitalis. Digitalis blood concentrations may become toxic when these patients receive antibiotics, such as tetracycline or erythromycin, which eradicate the organism.

❖ Many factors can increase the risk of toxicity to digitalis glycosides such as:

- renal diseases,
- stress,
- interactions with other drugs such as verapamil & quinidine (they cause increase in plasma concentration of digoxin probably by digoxin displacement from tissue-binding sites),
- hypokalemia,
- & hypothyroidism.

Characteristics of poisoning:

- Early manifestations of intoxication that occur in approximately 50% of all cases generally involve the gastrointestinal tract.

- Anorexia, nausea, vomiting, & abdominal pain are common.

- Nausea & vomiting occur from direct drug action on the chemoreceptor trigger zone (CTZ).

- Blurred vision, loss of visual acuity, & green yellow halos have been described as early-appearing symptoms.

- CNS effects include a variety of neuropsychiatric disturbances.

- Digitalis intoxication can provoke a large number of arrhythmias. These include bradyarrhythmias or tachyarrhythmias, or a combination of both.

Management of poisoning:

- Management of acute digitalis toxicity involves removal of ingested drug, maintenance of a normal potassium concentration, reversal of arrhythmias, & the use of a specific antidote (digoxin immune Fab).

- Gastric lavage should be performed to remove the unabsorbed drug, although vomiting may already have accomplished this.

- Repeated administration of one the adsorbents (activated charcoal, cholestyramine, or colestipol) is recommended to enhance elimination of the glycoside by interrupting to entero-hepatic cycling exhibited by digitoxin, & possibly digoxin.

- Hyperkalemia (5.5-13.5 mEq/L) is caused by acute digitalis toxicity, while hypokalemia is more common after chronic digitalis toxicity.

- Hyperkalemia may require treatment with insulin, dextrose, bicarbonate, & sodium polystyrene sulfonate, with frequent monitoring of ECG & electrolyte determination.

- If hypokalemia is encountered with tachy- or bradyarrhyhthmias, continuous potassium replacement alone may be sufficient.

- For atrial & ventricular arrhythmias that do not respond to potassium therapy, the treatment of choice includes phenytoin & lidocaine.

- Potassium administration in a person with digitalis-induced hyperkalemia can result in heart block.

- If digitalis has produced atrioventricular (AV) block, atropine is given to produce vagolytic effect to increase the heart rate & AV conduction.

- β-blockers, such as propranolol, are useful to suppress supraventricular & ventricular arrhythmias but may depress the sinoatrial (SA) node & AV conduction especially in a patient with an already failing heart, that limiting their usefulness.

- Because digoxin has a large volume of distribution, hemodialysis is not a successful method to enhance elimination of digoxin. However, hemodialysis is still sometimes required to control hyperkalemia.

Digoxin Immune Fab (Digibind):

❖ Digoxin immune Fab is used as an antidote reserved for life-threatening overdoses.

❖ Indications of such toxicity include:

- ingestion of more than 10 mg of digoxin by healthy adults or 4 mg by children,
- Steady-state serum concentrations greater than 10 ng/mL;
- or if blood potassium concentration exceeds 5 mEq/L.

- Dosage of digibind can be calculated according to the amount of digoxin or digitoxin in the patient's body.

- When steady-state serum concentrations of digoxin or digitoxin is known, the total body load can be estimated as shown below:

$$\text{Body load(mg)} = \frac{(\text{SDC})(\text{mean Vd})(\text{wt in Kg})}{1000}$$

SDC is the serum digitalis concentration in ng/mL.

Vd of digoxin = 5.6 L/kg

Vd of digitoxin = 0.56 L/kg

- Each vial of antidote contains 40 mg of digibind. This will bind 0.6 mg digoxin or digitoxin.

- The total number of vials needed can be obtained by dividing the total body load of drug in mg, by 0.6 mg/vial.

- Adverse effects to digibind have been minimal including sensitivity, erythema at the site of injection, & rash & urticaria have been reported.

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