Practical Clinical Toxicology

Toxicity of Digitalis Glycosides

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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.
- Digoxin is the one of the most widely prescribed drugs.
- Digoxin acts through inhibition of the Na^+/K^+-adenosine triphosphatase (ATPase) enzyme as shown in Figure 1.

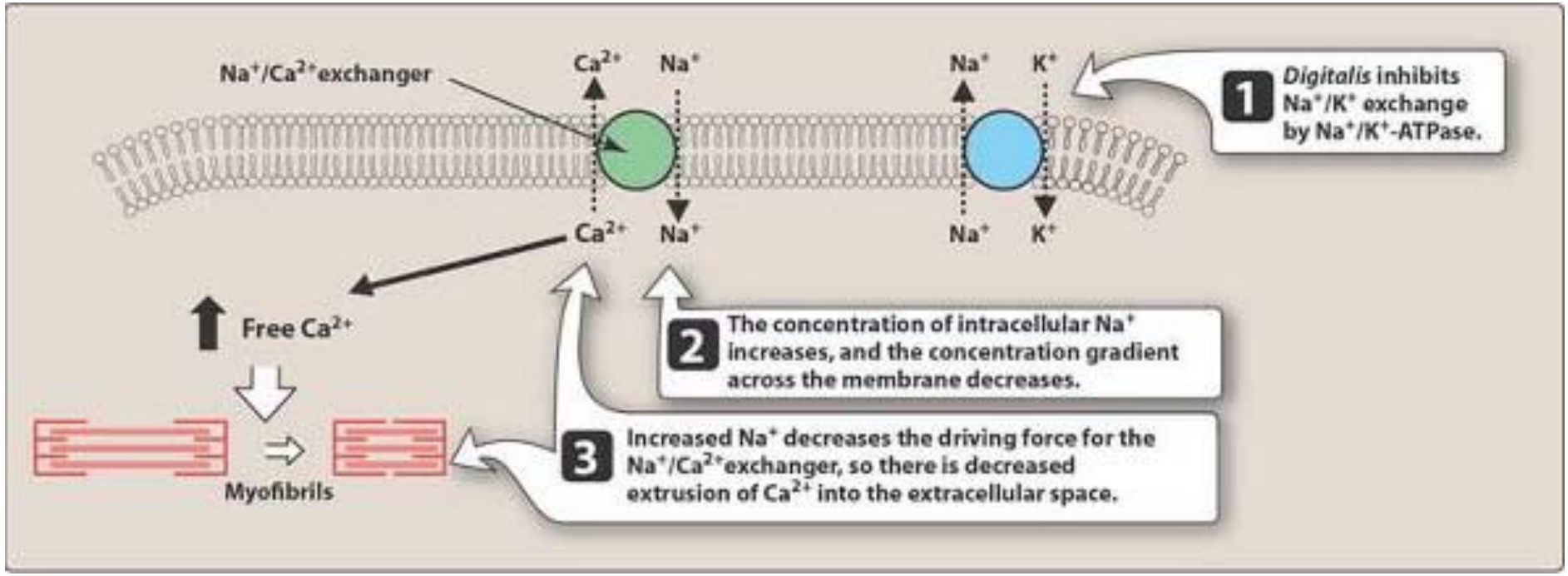

Figure 1. Mechanism of action of cardiac glycosides, or digitalis. ATPase = adenosine triphosphatase.

- 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.

- Since 60-80% of digoxin is excreted through the kidneys as shown in Table 1, decreased renal excretion would result in accumulation of digoxin & toxicity.

- 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.

Table 1 Pharmacology of Selected Cardioactive Steroids

Pharmacology	Digoxin	Digitoxin
Onset of Action		
PO	1.5–6 h	3–6 h
IV	5–30 min	30 min–2 h
Maximal effect		
PO	4–6 h	6–12 h
IV	1.5–3 h	4–8 h
Intestinal absorption	40%–90% (mean, 75%)	>95%
Plasma protein binding	25%	97%
Volume of distribution	5–7 L/kg (adults) 16 L/kg (infants) 10 L/kg (neonates) 4–5 L/kg (adults with renal failure)	0.6 L/kg (adults)
Elimination half-life	1.6 days	6–7 days
Route of elimination	Renal (60%–80%), with limited hepatic metabolism	Hepatic metabolism (80%)
Enterohepatic circulation	7%	26%.

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 activated charcoal or cholestyramine 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 with chronic digitalis use.

- Hyperkalemia may require treatment with insulin plus glucose, & sodium bicarbonate.

- If hypokalemia is encountered with tachy- or bradyarrhythmias, 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…..why?

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 mgof digoxin by healthy adults or 4 mg by children,
  - Steady-state serumconcentrations 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: volume of distribution

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.

How many milligrams & vials of digoxin-specific antibody fragment are required to treat a 40 years old male patient, weighing 70 kg in whom digoxin assay revealed a steady state serum concentration of 0.015 µg/mL?

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

Serum digitalis concentration in ng/mL= 15

Vd of digoxin = 5.6 L/kg

Body load= 15 x 5.6 x 70/1000= 5.88 mg of digoxin.

Each vial of digibind contains 40 mg

40 mg of digibind would bind 0.6 mg of digoxin

$$\frac{40 \text{ mg (digibind)}}{0.6 \text{ mg (digoxin)}} = \frac{x \text{ (digibind)}}{5.88 \text{ mg}}$$

X = 392 mg of digibind

$$\frac{}{} = 9.8$$ which means 10 vials

392 mg

40 mg/vial


Thank
you