Cardiac glycoside (digitalis): toxicity

By

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- Digitalis is a plant- derived (foxglove) plant. it also called cardiac glycoside or life- saving drug used in treatment of:

- Congestive heart failure.
- Supra ventricular tachycardia (SVT).
- Atrial fibrillation (AF).

- Digitalis have an extremely narrow therapeutic index
- The normal range of serum concentration of digoxin for therapeutic activity is 1.2- 1.7 ng/ml.
- Concentrations that cause clinically significant toxicity are usually 2-3 times greater.

- Excessive intake is a common cause of poisoning

1. Accidental over dosage usually occurs in children who ingest medication belonging to a relative.
2. Suicide with digitalis.
3. Concurrent administration of a diuretic that induce potassium loss is reported to be the most frequent cause of toxicity, due to depletion of K stores.

Mechanism of action

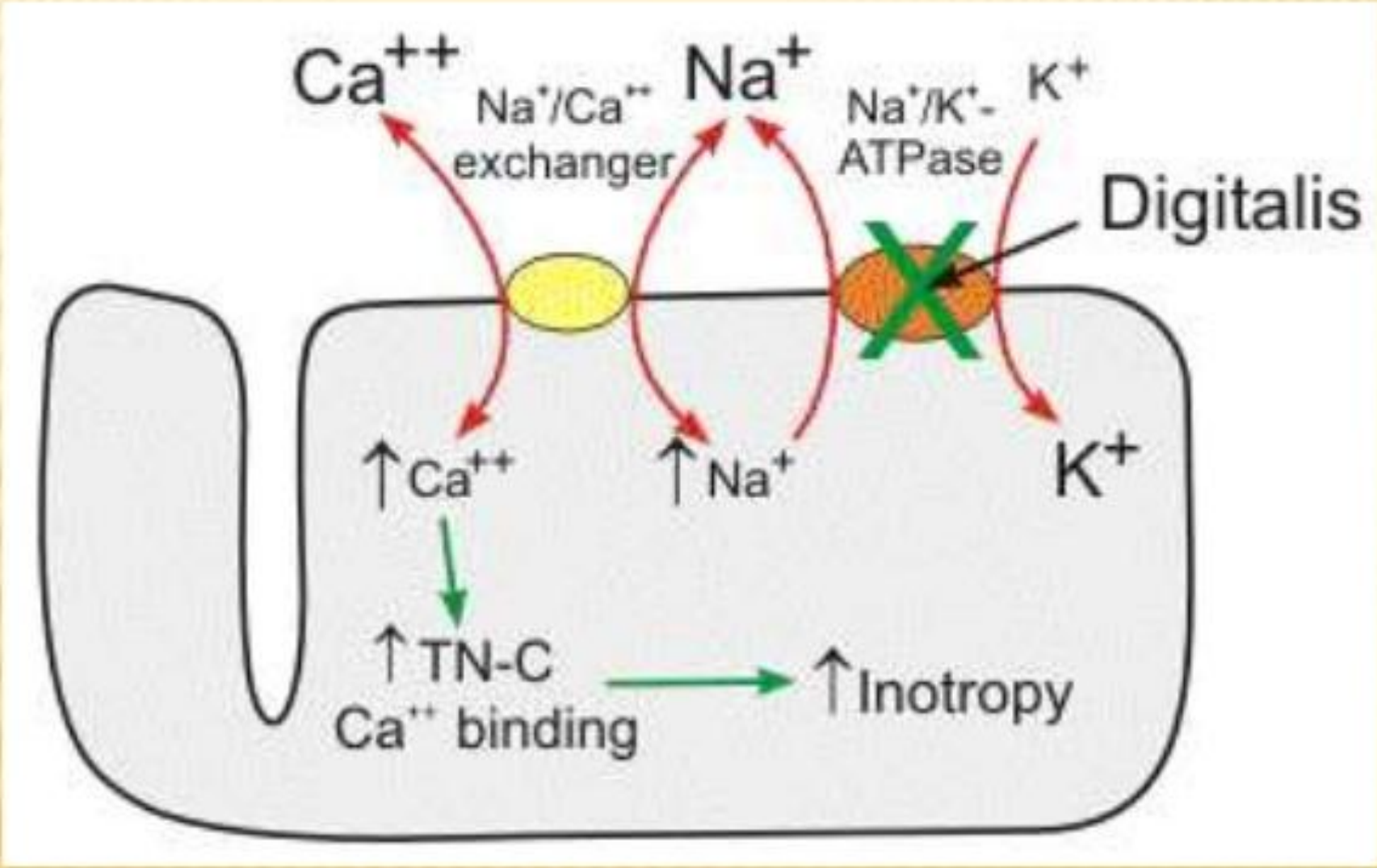
- The positive inotropic effect of digitalis has the following:
- Direct inhibition of membrane bound Na+/K+- ATP-ase, which pump 3 Na+ outside the cell in exchange with 2 K+ inside the cell which is responsible for maintenance of resting membrane potential (RMP) in most excitable cells.
- This lead to an increase intracellular sodium gradually and gradual small decrease in intracellular K+.

- This is why serum K+ conc. Is good indication of the extent of digitalis poisoning. The change in Na+fluxes across cardiac cell memberanes result in disturbed impulse conduction.

- Cardiac fiber (Ca+2) is exchanged for extracellular sodium (3:1) ratio by Na+/Ca+ exchange transport system that is driven by the conc. Gradient for these ions and the transmembrane potential.
- Accumulation of Ca+2 intracellularly produce a positive inotropic action.
- Over dose of digitalis causes:

  a reduction in resting membrane potentials. And cardiac pacemaker cells cannot function properly.

MECHANISM OF ACTION



pharmacokinetics

- Half life of digoxin is about 1.5 days (36hrs)
- Renal excretion is the major rout of elimination. digoxin has large volume of distribution(8L) which limits the usefelness of dialysis.
- Digitalis intoxication is influenced by the presence of other drugs:
- Combined use of quinidine, verapamile and amiodarone with digoxin increase digoxin plasma by 70-100 folds. The exact mechanism is displacement of digoxin from tissue binding sites and by competing with digoxin for renal excretion.

- In pregnancy digoxin is considered as category C . Increased digoxin dosage may be necessory during pregnancy because of increased renal clearance and expanded blood volume.

Clinical manifestations of digitalis toxicity

- Fatigue
- Arrhythmia (due to increased automaticity)
- headache
- Visual symptoms
- Weakness
- Vomiting
- Nausea

} due to increase vagal stimulation and activate chemoreceptor trigger zone.

- Anorexia
- Psychic complaints
- Dizziness

} arrhythmias can cause in adequate tissue perfusion causing CNS complications

- Abdominal pain
- diarrhea

Management of poisoning

Management of acute digitalis toxicity involves:

- Removal of ingested drug

1. (decontaminate the GI tract: the stomach should be lavaged to remove unabsorbed drug; vomiting may already have acomplished this).
2. Repeated administration of one of these adsorbants : activated charcoal, cholestyramine to enhance elimination of glycoside by interrupting enterohepatic circulation.

- Maintenance of normal K+ concentrations. (hyperkalemia is treated with (insulin, dextrose bicarbonate).

- Reversal of arrhythmias.
- Use of specific antidote (digoxin immune Fab).
- Hypokalemia occur with chronic digoxin toxicity.
- When hypokalemia is present with tachy- or bradyarrhythmias continuous k replacement alone may be sufficient. Even in the absence of hypokalemia. K administration may correct arrhythmias by restoring intracellular concentraions.
- For atrial and ventricular arrhythmias that do not respond to k- therapy the treatment of choice includes phenytoin and lidocaine.

- Advantage of these drugs: they depress ventricular automaticity with out slowing AV nodal conduction, as seen with quinidine and procainamide.

Digoxine immune Fab

- Is a specific antidot for treating digoxin toxicity and improve mortality rate.
- **Indications of use include**

1. ingestion of more than 10 mg digoxin by healthy adults or 4 mg by children.
2. Steady state serum concentrations greater than 10 ng/ml.
3. Or if the blood potassium concentration exceeds 5 mEq/L.

- Within minute of injecting the antidote free serum digoxin or digitoxin levels drop to almost un measurable concentrations.
- Dosage can be calculated from the amount of digoxin or digitoxin in the patients body.
- By actual amount of drug ingested, or
- by measuring its concentration in the serum.

- When steady state serum concentrations of digoxin are known, the total body load can be estimated:

- Digoxin (body load mg)= $\frac{(SDC)(5.6)(wt\ in\ kg)}{1000}$

Mechanism of action of digoxin immune fab

- (digoxin immune fab) binds molecules of digoxin, making them unavailable for binding at their site of action on cells in the body. The Fab fragment-digoxin complex accumulates in the blood, from which it is excreted by the kidney. The net effect is to shift the equilibrium away from binding of digoxin to its receptors in the body, thereby reversing its effects.

- Each vial of antidote contains 40 mg of digoxin- specific antibody fragments. Which is diluted with normal saline and infused over 30 minutes. This will bind 0.6 mg digoxin.

- The response begins about 20 minutes after administration.

- 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 effect of Fab

Minimum adverse effect include:

- Sensitivity
- Erythema at the site of injection
- Rash and urticaria

Case study: digoxin toxicity treated with digoxin immune Fab

- A 65 year old women was admitted to an emergency department after ingestion of seventy 0.0625- mg tablets of digoxin (4.375 mg total) in a suicide attempt, 5 hour previously her medical history revealed rheumatic fever and analgesic nephropathy. Usual therapy included digoxin 0.0625 mg/day.
- She underwent lavaged and received a slurry of activated charcoal via a nasogastric tube.
- Laboratory data included serum potassium 4.3 mmol/lserum creatinin 395µmol/l; serum digoxin 19.8 mmol/l; blood pressure was 135/85 mmhg; heart rate was 130 beats/minutes and irregular.

- The patient was nauseated and vomited several times. Her vision was blurred.
- An ECG revealed atrial and junctional tachycardia with intermittent 2:1 to 4:11 block, the occasional ventricular ectopic beat. After several hours her serum potassium conc. Was 5 mmol/l.
- Treatment included phenytoin 500mg. phenytoin. She did not respond to therapy. By now her serum k conc. Had risen

- To 5.4 mEq/L. vitals remained unchanged. She was then given 400mg of digoxin immune Fab over 30 min. her ECG remained unaltered, so an other 400 mg of antidote was administered 1hr later. 1hr after the second dose her ECG showed sinus rhythm of 110 beats/min. sr. K conc. Returned to 4.5 mEq/L. she maintained a sinus rhythm and her HR stabilized at 90 beat/min.
- an assay for free digoxin in the sr. revealed that non was present at 20 min after the first dose of the Fab fragments.

1. This patient ′s sr k conc. Rose during early part of her intoxication then fell after administration of the Fab fragments, explain the origin of this ion and its later fate.
2. For what specific purpose was the dose of phyntoin given?
3. Outline the mechanism by which digoxin immune Fab treats digoxin over dose?


Thank
you