Digoxin and Inotropes

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Digoxin

Case hisotory

A 65-year-old man with Heart failure (EF-20)is receiving

- captopril 50 mg tds
- carvedilol 25 mg bd
- furosemide 40 mg bd
- spironolactone 25 mg daily

Despite these therapies, he continues to complains of dyspnea with minimal exertion

Oral digoxin, 0.125 mg daily, is added.

After 3 weeks of maintenance therapy with digoxin, the patient feels better.

History

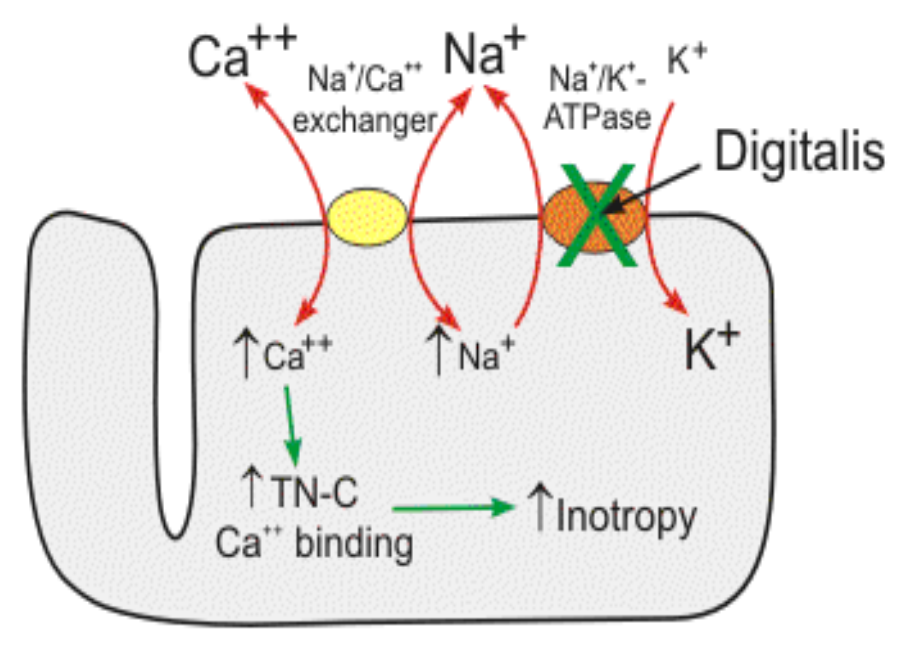
- Plant glycosides with specific action on heart
- Historical use: arrow poisons
- Historical sources:South American toad skins, African plant extracts

Digoxin

- A cardiac glycoside

Mechanism of action

Inhibit the sodium-potassium ATPase in the myocardium → Promotes sodium calcium exchange → calcium exchange increases → Increased intracellular calcium → increase in the force of myocardial contraction



also has important parasympathetic effects, particularly on the atrioventricular node.(slows conduction)

Mechanism of action

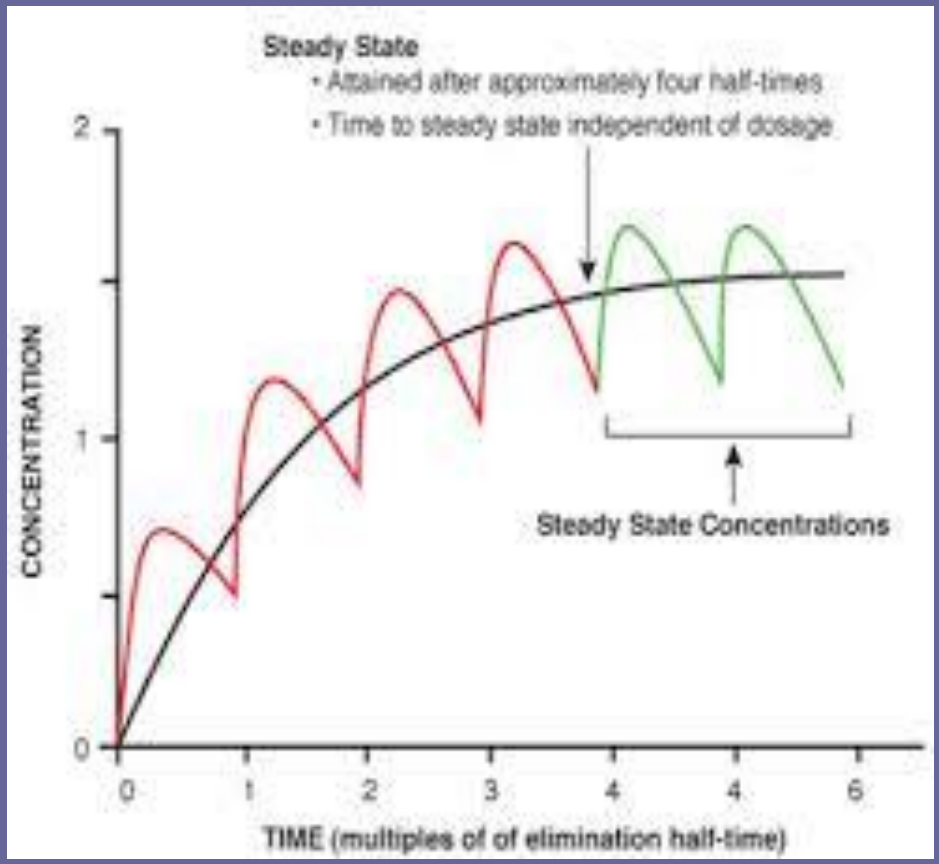
- binds to and partially inhibits Na^+/K^+-ATPase pumps in the cardiac myocyte membrane.
- This causes a rise in intracellular sodium, which in turn leads to a rise in intracellular calcium by slowing sodium/calcium exchange.
- The intracellular calcium is stored in the sarcoplasmic reticulum during diastole and is released during systole, increasing myocardial contractility.

- Digoxin also has an indirect action stimulating the central vagal nucleus, which decreases the rate of sino-atrial (SA) node activity, with resultant slowing of heart rate, and increases the refractory period at the atrioventricular (AV) node.

- The latter action is useful in ventricular rate control in atrial flutter or fibrillation

Pharmacokinetics

- well absorbed in the gut
- half-life - 1.5 days
- loading doses are necessary for the first 24—36 hours to achieve a rapid onset of action



Pharmacokinetics

- metabolized and not renally excreted. However, it has a very long half-life that makes it much less suitable for use even in renal failure.
- half life in aneuric renal failure can be upto 5 days

Indications

- Patients with heart failure who are symptomatic despite other therapies
- Atrial fibrillation –rate control
- No mortality benefit

Adverse effects

has a low therapeutic index

most adverse effects are dose-related.

Reverse tick sign –ST depression with Digoxin –seen in therapeutic doses as well

Adverse effects

- visual disturbance -yellow vision
- Gynaecomastia(bind oestrogen receptors)
- Arrythmias

Digoxin toxicity

- Precipitated by

-drugs may slow the AV node (e.g. verapamil, β-blockers)

- hypokalaemia and hypomagnesaemia

-renal impairment

Digoxin overdose –clinical features

- Nausea/diarrhoea
- Arrythmias

-ventricular ectopics

-SVT/VT/VF

-heart block

- Confusion /agitation
- Xanthopsia
- Hyperkalaemia

Case scenario

- 67 year old lady with congestive cardiac failure develops fever and urinary symptoms. She was managed for a urinary tract infection by a GP and started on oral antibiotics.She became increasingly ill with confusion and vomitting
- She was admitted to the ward dehydrated and pulse rate was 80/min

- She was on digoxin, frusamide, beta blockers and ACE inhibitors for heart failure.She had taken the drugs regularly

- Her potassium level was low with high serum creatinine, and ECGs showed a second degree heart block.

- What is the diagnosis?

Inotropes

- Agents that affect the myocardial contractility
- Positively inotropic drugs are used to enhance myocardial contractility\
- Negatively inotropic drugs reduce the myocardial contractility

Positively inotropic	Negatively inotropic
Digoxin	Calcium channel blockers
Dopamine, Dobutamine , Adrenaline , Noradrenaline	Beta blockers
Phosphodiesterase inhibitors (Milrinone)	

Indications for inotropes

- Conditions where cardiac output is low

Ex-severe heart failure following myocardial infarction/sepsis

- Reduced CO--- tissue hypoperfusion ----- anerobic metabolism-----lactic acid formation----multi organ failure
- Inotropes are used to maintain vital organ perfusion until cardiac functions recover

Receptors that inotropes act on

Receptor	Location	Action
a_1	Peripheral, renal and coronary circulation	Vasoconstriction
$ß_1$	Heart	Increase in contractility and heart rate
$ß_2$	Lungs; peripheral and coronary circulation	Vasodilation, bronchodilation
Dopaminergic	Mesenteric, renal, coronary arteries	Vasodilation

Noradrenaline

- acts primarily via a_1 receptors
- increase systemic vascular resistance to maintain MAP
- Mostly used in conditions associated with peripheral vasodilatation (septic shock)
- Recent research evidence suggests that this has more survival benefit than other agents in cardiogenic shock as well

Dobutamine

- predominantly a $ß_1$ agonist
- increases cardiac contractility and heart rate.
- Also acts at $ß_2$ receptors causing vasodilation and decreasing afterload.

- Because of this vasodilation, and to ensure adequate MAP ,it may be necessary to administer in combination with a vasopressor (eg, noradrenaline).

Dobutamine-side effects

- Tachycardia
- Arrhythmias
- Raised myocardial oxygen demand (Causes myocardial ischaemia.)

Adrenaline

- active at all adrenergic receptors
- predominantly ß agonist in low doses
- Alpha agonist at higher doses
- used mainly during resuscitation after cardiac arrest - given as a bolus
- not recommended for cardiogenic shock

Dopamine

- has dose-dependent pharmacological effects
- low-dose dopamine (2–5µg/kg/min) - mainly dopaminergic effects- increase renal and coronary blood flow
- medium doses (5–10µg/kg/min) - $ß_1$ inotropic effects
- high doses (10–20µg/kg/min) - a_1 vasoconstriction