Toxicity of Cardiovascular Drugs

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Cardiovascular system (CVS) consist of:-

1. Myocardium.
2. Vascular vessels (arteries, veins and capillaries).

Both has important functions in:-

1. Supplying the tissues and cells of the body with nutrients, respiratory gases, hormones and metabolites.
2. Removing the waste products of tissue and cellular metabolism as well as foreign materials such as microorganisms.

3. Maintain the optimal internal homeostasis of the body temperature and cellular pH.

4. Play a critical role in well-being and survival of other major organs of the body especially high vascularized organs that are depend on nutrients and O2.
General Mechanisms of toxicity

1. Interference with Ion Homeostasis
   A. Inhibition of Na⁺,K⁺-ATPase
   B. Na⁺ Channel Blockade
   C. K⁺ Channel Blockade
   D. Ca²⁺ Channel Blockade

2. Altered Coronary Blood Flow
   A. Coronary Vasoconstriction
   B. Ischemia-Reperfusion Injury
Characteristic cardiac action potential and electrocardiogram (ECG).
Deleterious effects of reactive oxygen species in myocardial ischemia and reperfusion

Myocardial Ischemia/Reperfusion

Generation of Reactive Oxygen Species

Lipid Peroxidation

- Impaired Membrane Integrity
- Mitochondrial and Sarcoplasmic Reticulum Dysfunction
- Altered Ca\(^{2+}\) Homeostasis

- Arrhythmias
- Myocardial Stunning
- Cardiac Myocyte Death
General Mechanisms of toxicity

3. Oxidative Stress
4. Organellar dysfunction:
   A. Sarcolemmal Injury, SR Dysfunction, and Ca\(^{2+}\) Overload.
   B. Mitochondrial Injury
5. Apoptosis and Oncosis
Drugs produce CVS toxicity

Drug classes that affect this system:-

1. Digitalis glycosides.
2. Beta-adrenergic blockers.
3. Calcium channel blockers.
4. Diuretics, vasodilators and angiotensin blockers.
Digitalis glycosides

- Used in the treatment of congestive heart failure.
- Management of certain supraventricular rhythm disturbances.
- Used by 15% of hospitalized persons.
- 20-30% of patient taking digitalis will experience toxicity.
- This drug posses narrow therapeutic index.
Digitalis toxicity

- Therapeutic dose of digoxin is 1.2-1.7 ng/ml
- Toxic dose is only 2-3 times greater.
- Mortality rate with toxic doses is reported to be as great as 25%.
Factors enhance digoxin toxicity

- Concurrent administration of a diuretic that induces potassium loss is the most cause of toxicity.
- Narrow therapeutic index: 0.5–2.0 ng/mL.
- Drug-drug interaction: quinidine and verapamil.
- The anaerobic microorganism Eubacterium lentum affect digitalis level?
- Renal disease
- Electrolyte imbalance (hypokalemia)
- Enhanced sympathomimetic amine release, example: during period of stress such as dental office visits.
## Pharmacokinetics

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Digoxin</th>
<th>Digitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time (oral ingestion)</td>
<td>1.5-6hr</td>
<td>3-6hr</td>
</tr>
<tr>
<td>Peak</td>
<td>4-6hr</td>
<td>6-12hr</td>
</tr>
<tr>
<td>Half life</td>
<td>31-40hr</td>
<td>4-6days</td>
</tr>
<tr>
<td>Protein binding</td>
<td>20-25%</td>
<td>90-97%</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>7-8L/kg</td>
<td>0.6L/kg</td>
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<tr>
<td>Route of elimination</td>
<td>Renal, 75%</td>
<td>Hepatic, 80%</td>
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<tr>
<td>Toxic blood levels</td>
<td>2.4ng/ml</td>
<td>Over 30ng/ml</td>
</tr>
<tr>
<td>Enterohepatic cycling</td>
<td>Small</td>
<td>Large (6.6%/day)</td>
</tr>
</tbody>
</table>
Mechanism of toxicity

- A toxic dose of digitalis interferes with transport of Na\(^+\) and Ca\(^{+2}\).
- It binds with high affinity to an inhibitory site on the portion of the NaK-ATPase structure that faces the outside of the cell, thus Na\(^+\) and K\(^+\) transport are blocked.
- Since K\(^+\) transport back into the cells is blocked, its concentration in the extracellular fluid increases.
- Positive inotropic effect from elevated intracellular (cytosolic) Ca during systole.
- Digitals overdose causes a reduction in resting membrane potentials and cardiac pacemaker cells cannot function properly.
- Peripheral vasodilation and reduced afterload.
The diagram illustrates the interaction of 

- $\text{Ca}^{++}$ (calcium)
- $\text{Na}^+$ (sodium)
- $\text{K}^+$ (potassium)

with the 

- $\text{Na}^+/\text{Ca}^{++}$ exchanger
- $\text{Na}^+/\text{K}^+$ ATPase

The effects include:

- Increased $\text{Ca}^{++}$ binding to $\text{Ca}^{++}$
- Increased $\text{Na}^+$
- Increased $\text{K}^+$

The diagram also shows the impact of Digitalis on these processes, indicated by an 'X' and an increased inotropy (force of contraction).
Digoxin

Na+/K+ ATPase inhibition

Intracellular concentration of Na+ of K+

Decrease of cellular polarization

Activation of the Na+/Ca²⁺ exchanger
Calcium entry

Myocardium
Vascular smooth muscles

Inotropic+
Tonotopic+
Cardiac output
Vasoconstriction
Vasodilation

Sympathetic tone
Characteristics of Poisoning

- The symptoms involve not only the heart, but also the GIT and CNS.
- Early manifestations occur in 50% of all cases involve:
  1. CVS: Dysrhythmias, atrioventricular block and severe bradycardia
  2. GIT disturbance: anorexia, abdominal pain; nausea and vomiting?
  3. Blurred vision: loss of visual acuity, green-yellow halos
  4. CNS effects: a variety of neuropsychiatric disturbances
General Management

- Discontinue digoxin, gastrointestinal decontamination, especially with AC.
- Orogastric lavage preferred to emesis in a digoxin-toxic patient already vomiting.
- AC and sorbitol, then MDAC up to 1 g/kg every 2–4 hours. Slow absorption and an enterohepatic circulation make digoxin very amenable to decontamination, with both AC and MDAC.
- Steroid-binding resins: Cholestyramine and colestipol to bind digoxin and interrupt enterohepatic circulation along with MDAC.
- Hemoperfusion and hemodialysis ineffective due to high molecular weight and increased volume of distribution.
Specific Management

- Digoxin-specific antibody fragments — Fabs (DigiBind®): Will decrease free digoxin but elevate total serum digoxin levels; Fabs will also decrease levels of K and increase excretion of Fab-bound digoxin.
- K > 5 mEq/L: Fab > insulin and glucose > NaHCO₃ > sodium polystyrene sulfonate.
- Supraventricular tachycardia (SVT): Fab preferred over β-blockers.
- Tachy or bradyarrhythmia associated with hypokalemia can be treated with K supplement only.
Specific Management

• Atrial and ventricular arrhythmia that do not respond to K therapy should be treated with phynetoin and lidocaine. We can not use quinidine and procainamide??

• Ventricular tachycardia (VT)/ventricular fibrillation (VF): Cardioversion/defibrillation preferred over Fab, phenytoin, and lidocaine.
Contraindicated medications

1) Catecholamines may precipitate more serious ectopic arrhythmias
2) calcium, due to increased intracellular calcium stores.
3) Potassium in digitalis induced hyperkalemia?? Heart block terminating in sinus arrest.
Digoxin-Specific Fabs

Indication

- Rising K or K > 5 mEq/L at any time.
- Severe ventricular dysrhythmias: VT and VF
- Progressive bradydysrhythmias refractory to atropine.
- Serum [dig] > 10–15 ng/mL anytime.
- Ingestion of > 4 mg of digoxin by a child; and > 10 mg by adult.
**Beta-Blockers**

**Indications**

- Hypertension: $\beta_1$-selective > nonselectives.
- Angina: Reduce anginal attacks and decrease post-myocardial infarction mortality.
- Tachydysrhythmias: Used in theophylline overdose.
- Tremor: Propranolol.
- Hyperthyroidism: $\beta$-blockers moderate the sympathetic, hyperdynamic effects of thyroid storm.
- Open-angle glaucoma.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>β₁</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3–4 hours</td>
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<tr>
<td>Atenolol</td>
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<td>No</td>
<td>Low</td>
<td>6–9 hours</td>
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<td>Bisoprolol</td>
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<td>Carteolol</td>
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<td>No</td>
<td>Low</td>
<td>6 hours</td>
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<tr>
<td>Carvedilol¹</td>
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<td>No</td>
<td>No data</td>
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<tr>
<td>Celiprolol</td>
<td>β₁</td>
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<td>No data</td>
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<tr>
<td>Esmolol</td>
<td>β₁</td>
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<td>No</td>
<td>Low</td>
<td>10 minutes</td>
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<td>Labetalol¹</td>
<td>None</td>
<td>Yes¹</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
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<tr>
<td>Metoprolol</td>
<td>β₁</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>14–24 hours</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>5 hours</td>
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<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
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<tr>
<td>Propranolol</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td>3.5–6 hours</td>
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<td>Sotalol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
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<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4–5 hours</td>
</tr>
</tbody>
</table>
Mechanism of toxicity

- It bind to beta receptors and block the actions of beta agonists.
- In overdoses the membrane stabilizing activity or quinidine like action predominant. This is responsible for severe myocardial depression which lead to heart block and CNS effect.
- ISA cause HT and tachycardia.
- High lipid solubility increase CNS effects.
- Toxicity occur after 20 min. post ingestion but usually appear after 1-2 hrs.
Mechanism of action

Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum
Characteristics of poisoning

- The major features of beta-adrenergic blocker toxicity are related to their antagonistic action on cardiac beta receptors.
- Produce bradycardia in 92% and severe hypotension in 77% leads to cardiogenic shock.
- ECG changes include AV block (prolonged PR interval), QRS widening, absence of P waves, and prolongation of QT interval.
Characteristics of poisoning

- CNS effects involves seizures results from hypoglycemia, cerebral hypoxia, or from membrane-stabilizing effect. It occurs in 58% of patients following the ingestion of more than 1600 mg propranolol.
<table>
<thead>
<tr>
<th>Cardiac</th>
<th>CNS</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias</td>
<td>Sleepiness</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Dizziness</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>AV block</td>
<td>Unconsciousness</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Coma</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>Respiratory depression</td>
<td></td>
</tr>
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</table>
General management

- Asymptomatic: No ipecac, AC preferred over lavage.
- Mild toxicity: AC and atropine for bradycardia and fluid bolus for hypotension.
- Moderate toxicity: All of the above and glucagon (hormone secreted by pancreatic α cells in response to decreased levels of glucose and elevated catechols); administer 2–5 mg bolus of glucagon IV push to bypass β-receptors and to increase intracellular cAMP; CaCl₂ IV up to 1 g; consider more atropine, up to 3 mg IV.
Specific Management of Severe Toxicity

- General management and invasive monitoring.
- Catecholamine infusion: Dobutamine ($\beta_1$) preferred over norepinephrine (NE) ($\alpha$ and $\beta$) and isoproterenol.
- Isoproterenol is the least preferred catecholamine due to peripheral vasodilation with hypotension (from $\beta_2$ stimulation).
Specific Management of Severe Toxicity

• Add a phosphodiesterase inhibitor: Amrinone or milrinone and theophylline to bypass β-receptors and increase intracellular cAMP restoring cardiac contractility.

• Consider IV insulin (positive inotropic activity) and glucose therapy.

• Hemodialysis or Hemoperfusion may be indicated when the toxicity due to Nadolol or Atenolol specially when there are sign of renal failure.

• Other β-blockers are poor candidate for HD & HP. Why? Protein binding & volume of distribution.
The major action of these drugs is to diminish the inward movement of Ca\(^{2+}\) through the L-type voltage-dependent Ca\(^{2+}\) channels located in sarcolemma. These drugs are also termed Ca\(^{2+}\) channel blockers.
Ca\textsuperscript{2+} channel antagonists affect the contractility of both smooth and cardiac muscle cells. At least three distinct mechanisms have been suggested to lead to increased levels of cytosolic Ca\textsuperscript{2+} and the subsequent contraction of smooth muscle:

1. extracellular Ca\textsuperscript{2+} influx through voltage-sensitive Ca\textsuperscript{2+} channels in response to the depolarization of the membrane;
2. second messenger- (i.e., inositol triphosphate) mediated release of a Ca\textsuperscript{2+} from the SR; and
3. influx of extracellular Ca\textsuperscript{2+} via receptor-operated Ca\textsuperscript{2+} channels in response to receptor occupancy.
Clinical uses

- Ca\textsuperscript{2+} channel antagonists are efficacious in the treatment of various types of CV disorders, including
  1. Hypertension
  2. angina pectoris
  3. myocardial infarction
  4. cardiac arrhythmias.
Mechanism of toxicity

- Ca\textsuperscript{2+} channel antagonists inhibit the voltage-dependent Ca\textsuperscript{2+} channels in vascular smooth muscle cells inducing relaxation of vascular smooth muscle, leading to vasodilation.

- The contraction of cardiac muscle is dependent on the influx of extracellular Ca\textsuperscript{2+} through the L-type channels, and the subsequent Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release from the SR. Thus, Ca\textsuperscript{2+} channel antagonists exert a negative inotropic effect on myocardium.
In the SA and AV nodes, depolarization is largely dependent on the influx of extracellular Ca$^{2+}$ through the L-type channels. Therefore, Ca$^{2+}$ channel antagonists have the potential to depress the rate of sinus node pacemaker and slow AV conduction.

In addition, all approved Ca$^{2+}$ channel antagonists are able to decrease coronary vascular resistance and thereby increase coronary blood flow.
CLINICAL MANIFESTATIONS OF TOXICITY

- **Excessive vasodilation.** These effects may be manifest as dizziness, hypotension, headache, flushing, and nausea.

- Patients may also experience **constipation,** peripheral edema, coughing, wheezing, and pulmonary edema.

- With severe overdoses that result in dramatic Ca\(_{2+}\) channel blockage, all Ca\(_{2+}\) channel antagonists exert a **negative inotropic effect** with depressed cardiac contraction, conduction blockage, hypotension, and shock.
Metabolic acidosis with hyperglycemia (The mechanism is related to the suppressive effect by Ca$^{2+}$ channel antagonists on pancreatic B cell insulin release coupled with whole-body insulin resistance).
Clinical management of intoxication

• (1) providing supportive care.
• (2) decreasing drug absorption, and decontamination of the GI tract via the use of activated charcoal is crucial
• (3) augmenting myocardial function with cardiotonic agents.

Intravenous injection of calcium salts is the first-line treatment of Ca\textsuperscript{2+} channel antagonist overdoses (Multiple IV boluses of 10 cc of 10% calcium chloride every 15-30 minutes to keep the serum calcium between 10 – 15 mEq/L is reasonable).
Because there is no specific antidote, other cardiotonic drugs may include glucagon (the inotropic action of glucagon seems to be related to an increase of cAMP levels in the myocardium), atropine, and catecholamines.

The other line agent is amrinone, which is a noncatecholamine inotropic agent that increases cAMP intracellularly.
Vasodilators

- This class includes a broad spectrum of medications that dilate peripheral arteries and veins, producing ↓BP e.g. alpha-adrenergic blockers and direct acting agents (Hydralazine, Minoxidil sulfate, Diazoxide) and nitroprusside represent another class of antihypertensive drugs in addition to nitrite. These drugs produce vascular smooth muscle relaxation independent of innervation or known pharmacological receptors.
Nitrate and Nitrite

● Nitrate

● Sources:

2. Food production.
3. Food processing.
4. As a main or by product during manufacture of different chemicals and drugs.
5. Animal waste products.

All these result in high level of nitrate.
Nitrite

• Sources:-
  • Recreational drugs: amyl, butyl, and isobutyl nitrite.

Nitrite undergo nitrosation with amines producing nitrosamines (carcinogenic chemicals).

Nitrate convert to nitrite, and this may be subjected to nitrosation in vivo (animal study).

• Antioxidants like vitamins E & C, butylated hydroxytoluene and butylated hydroxyanisole are added to nitrite-treated foods and some drug products.
The drug affect the myocardium and the vascular system.

It produce aging of the vessels.

This drug is NO donor and this will increase cGMP (by activating guanylyl cyclase) which is responsible for smooth muscle relaxation including vasculature, as a result fall in blood pressure will occur.
Mechanism of Nitrate toxicity

- During toxicity excessive amount of nitrate produce intense vasodilation, which can precipitate several bad outcomes staring with throbbing headache passing through flushing and rapid fall in blood pressure ending with cardiogenic shock.

- The heart will compensate by:
  1. Baroreceptor stimulation.
  2. Reflex sympathetic activation.

Through these reflex mechanisms result in increase heart rate and force of contraction.
The second important mechanism of toxicity is the production of methemoglobin.

The drug will cause oxidation of ferrous (HbFe$^{+2}$) iron in hemoglobin to the ferric (HbFe$^{+3}$) state.

Methemoglobin is unable to transport oxygen so cyanosis will occur.
The spontaneous (NADH) and dormant (NADPH) methemoglobin reductase systems.
The characteristic mainly due to the formation of methemoglobinemia:-

1. Arterial blood is chocolate-brown in color.
2. Gray cyanosis not respond to oxygen therapy.
3. Easy fatigability.
4. Dyspnea; respiratory distress.
5. Tachycardia.
6. Dizziness with exertion.
7. Decreased oxygen carrying capacity.
Many chemical agents contribute to the production of methemoglobinemia like dapsone, aniline, sulfonamide, local anesthetic.....etc. table 5.3 page 101.

Nitrites are more potent than nitrates in producing methemoglobin.

Hem oxidation also occur spontaneously from environment or from certain foods.

1% - 2% of total hemoglobin are present in methemoglobin form without inducing any pathogenesis.
• Erythrocytes contain several enzyme systems that reduce methemoglobin back to hemoglobin. These are diaphorase I and diaphorase II which are methemoglobin reductase enzyme.

• These two enzymes dependent on concentration of NADH & NADPH.

• When MetHb increase diaphorase II activity can increase 60 fold.

• Normal erythrocytic MetHb. Reductase can reduce methemoglobin to hemoglobin at a rate 250 times its rate of formation.
Toxicity occur when these enzymatic system become saturated, when the person ingest large amounts of oxidizing agent.

Toxic MetHb. can result from a congenital disorder, hereditary MetHb. This condition characterized by absence of NADH-dependent MetHb. reductase. The condition characterized by cyanosis at birth.
Nitrate induced MetHb. In infants is of special concern for several reason:-

1. Gastric pH is less acidic.
2. Fetal Hb. Is more susceptible to oxidation to MetHb. than is adult Hb. Why ?
3. Incomplete hepatic microsomal enzyme system.
Methylene blue (tetramethylthionine chloride) is the specific antidote for MetHb. It is a dye that serves as an intermediate in electron transfer between methemoglobin reductase (diaphorase II) and methemoglobin.

If MetHb is less than 30%:-
1. Remove the toxic agent.
2. Give oxygen 100%.
If MetHb exceed 30%:
- Methylene blue 1% solution is administered at 1-2mg/kg intravenously.
- Other reducing agent may be used such as ascorbic acid as a substitute for methylene blue.

Methylene blue should be used with caution since larger doses may actually produce MetHb.
A dose of 5mg/kg has been reported to increase methemoglobin level.
Doses greater than 15mg/kg are associated with hemolysis.
Mechanism of action of Methylene blue

- Explain the mechanism of action of methylene blue in methemoglobinemia, support your answer by figure.
- Determine the dose of methylene blue that produce hemolysis.
- At which concentration of MetHb. Methylene blue is indicated?
1. Gastric pH in infant affect Nitrate poisoning.
2. Person with genetically absence NADH-dependent methemoglobin reductase experience more toxicity after i.v. dose of sodium nitrite than normal subject.