- ## Acute Calcium Channel Antagonists[CCAs]toxicity:

  - ### Pharmacological background:

CCAs are characterized by their chemical structure, which confers selectivity regarding tissue binding and clinical effects of toxicity. At therapeutic concentrations, organic CCAs bind to the α-subunit of the L-type calcium channel, causing the channel to favor the closed state, thereby decreasing calcium entry during phase II depolarization. At very high concentrations, some CCAs (verapamil) may occupy the channel canal and prevent calcium from entering the L-channel altogether. **(Freher, et al.1999)**

Table [10] Relative Vascular Smooth Muscle Selectivity Compared with Negative Inotropic Effect of Calcium Channel Antagonists in Humans

Class	Trade Name	Vascular Selectivity
• Phenylalkylamines		
Verapamil	Calan, Verelan, Isoptin	1.0
Benzothiazepines		
Diltiazem	Cardiazem, Dilacor	1.0
• Dihydropyridines		
Nifedipine	Adalat	10
Amlodipine	Norvasc	10
Isradipine	Lomir	100
Felodipine	Plendil	100

(Grace, et al.2005)

Table [11] Pharmacokinetics of Calcium Channel Antagonists:

Name	Absorption	Time to Peak Concentration (After Oral Administration)	Time to Peak Toxicity	Biotransformation	Half-Life	Elimination
Amlodipine	Slowly and almost completely absorbed.	6–9 hr	6–12 hr	Minimal presystemic metabolism. Slow but extensive hepatic metabolism. Metabolites lack significant activity.	Elimination 35 hr in healthy volunteers; may be prolonged 65 hr in elderly, 60 hr in hepatic function impairment; not affected by renal function impairment	Renal: 60% (about 5% unchanged)
	Bioavailability 60–65%.					Biliary/fecal: 20–25%
						Not removed by hemodialysis
Felodipine	Very well absorbed.	2.5–5 hr	6–12 hr	Six metabolites identified with no significant vasodilating activity	Polyphasic	Renal: 70% (less than unchanged)

	Bioavailability 20%.				Terminal 11–16 hr	Biliary/fecal: 10% (less than 0.5% unchanged)
	Bioavailability increases with concentrated grapefruit juice.					
Diltiazem	Well absorbed.	Wide individual variation in concentration	Regular release 1–2 hr; extended release 3–5 hr	By cytochrome P-450.	IV—3.4 hr	Biliary and renal (2–4% unchanged)
	Bioavailability 40%	Cardizem CD 10–14 hr; regular release tablets 2–3 hr		Desacetyl diltiazem has one fourth to one half of the coronary dilatation activity of parent compound (this metabolite not detected after rapid intravenous administration)	Oral (biphasic)	Does not appear to be removed by hemodialysis or peritoneal dialysis
	Oral bioavailability nonlinear, increases				Cardizem cd 5–8 hr	

	with chronic use and increasing dose.					
Diphenylalkylamine Subgroup						
Verapamil	Absorption 90%.	Regular release tablet 1–2 hr	Regular release 1–2 hr	Principal metabolite is norverapamil, which has 20% of the hypotensive activity of verapamil. Eleven other metabolites in trace amounts.	Single oral dose: 3–7 hr	Renal: primarily as conjugated metabolites; 3% unchanged
	Bioavailability 20–35%.	Extended release tablets 5–7hr	Extended release 2–7hr (can be longer)		Repetitive oral dosage: 4.5–12 hr (half-life increases because of saturation of enzyme systems)	Biliary/fecal: 9–16%
					Early: 4 min	
					Terminal: 2–5 hr	

(Rockville, et al .1998)

- **Mechanism of toxicity:**

An increase in intracellular calcium causes smooth and cardiac muscle to contract and accelerates impulse formation in cardiac

pacemaker cells. Conversely, a deprivation of intracellular calcium causes smooth muscle relaxation, a decrease in cardiac contraction, and a slowing of automaticity. Clinically, these effects are recognized as hypotension, bradycardia, and shock. Verapamil is the most potent negative inotrope of all CCAs, causing equal depression of heart contraction and increase in smooth muscle dilation at any concentration. Because these effects are often undesirable in humans, dihydropyridines were developed to selectively relax smooth muscle at concentrations that produce less negative inotropy. **(Hockermon, et al.2006)**

Clinical Manifestations of toxicity:

1- Cardiovascular system:

Myocardial depression and peripheral vasodilation occur, producing bradycardia and hypotension. Myocardial conduction may be impaired, producing AV conduction abnormalities, idioventricular rhythms, and complete heart block. Junctional escape rhythms frequently occur in patients with significant poisonings. The negative inotropic effects may be so profound, particularly with verapamil, that ventricular contraction may be completely inhibited. Patients may present initially asymptomatic but deteriorate rapidly into severe cardiogenic shock. **(Durward, et al.2003)**

2-Other manifestations:

Early or mild symptoms include dizziness, fatigue, and lightheadness, whereas more severely poisoned patients may manifest lethargy, syncope, altered mental status, coma, and death.Cases of seizures, cerebral ischemic events, ischemic bowel, and renal failure, occurring in the setting of CCB-induced cardiogenic shock, also is reported.. **(Howarth, et al.2004)**

Numerous reports document hyperglycemia in patients with severe CCB poisoning. Insulin release from the Beta-islet cells in the pancreas is dependent on calcium influx via an L-type calcium channel. In CCB overdose, this channel is also antagonized, impairing normal calcium influx and reducing insulin release. The hyperglycemic effect may be exacerbated in a diabetic patient. **(Thomas, et al.2005)**

Management of acute toxicity:

A-Lab testing:

In the symptomatic patient, serum calcium and potassium levels should be serially monitored. Hypokalemia is frequently observed but carries little prognostic meaning. However, hyperkalemia suggests severe cellular poisoning and marked negative inotropy can be expected with hyperkalemia in CCA overdose. Hypercalcemia is not caused by CCA overdose, although hypocalcemia has been reported. If a patient presents with hypotension and bradycardia, a serum digoxin level

should be obtained if concomitant digoxin toxicity is suspected. **(Kuo, et al.1997)**

B-Treatment:

1- Supportive care:

Many patients are alert and cooperative, give a history of a nontoxic CCA overdose (<3 mg/kg for nifedipine, <5 mg/kg for diltiazem or verapamil), and demonstrate sinus rhythm with a low normal arterial blood pressure. These individuals can be closely observed in an intensive care setting without invasive monitoring or airway protection. Patients who are drowsy or manifest hypotension despite a 15-mL/kg normal saline bolus or show sinus arrest on an ECG should be managed aggressively by appropriate airway management and ECG monitoring, have supplemental oxygen administered, and have one to two large-bore intravenous catheters inserted with normal saline infusion begun. A 10- to 20-mL/kg 0.9 % bolus should be administered to otherwise healthy patients with a systolic blood pressure below 90 mm Hg or to patients with a history of hypertension who demonstrate a systolic blood pressure less than 100 mm Hg. In patients with shock, an intra-arterial catheter should be inserted for accurate monitoring of blood pressure. A central venous or pulmonary artery catheter should be inserted in any patient who remains hypotensive after a normal saline bolus or for any patient with documented congestive heart failure or anuric renal failure who manifests CCA toxicity. **(Aubier, et al.2004)**

2- Decreasing drug absorption:

Activated charcoal should be administered after the patient's airway is secured. In massive overdose, sustained-release preparations can form gastrointestinal concretions (with ileus), which can persist for days, rendering charcoal less useful. In this situation, whole-bowel irrigation with polyethylene glycol may accelerate removal of sustained-release CCA pill fragments.CCA elimination half-life is increased in overdose, and toxicity from massive overdose can last for days. **(Sporer, et al.1997)**

Drug elimination can be enhanced by extracorporeal removal. Charcoal hemoperfusion can lower verapamil and diltiazem concentrations but may be less useful in nifedipine poisoning. **(Rosansky, et al.2007)**

3-Atropine:

Given its availability, efficacy in mild poisonings, and safety profile, atropine should still be considered as initial therapy in patients with symptomatic bradycardia. Dosing should begin with 0.5-1.0 mg (0.02 mg/kg in children) IV every 2 or 3 minutes up to a maximum dose of 3 mg in all patients with symptomatic bradycardia. **(Proano, et al.2005)**

4-Calcium:

Although the exact mechanism is unclear, boluses of Ca^{2+} increase the extracellular Ca^{2+} concentration and increase the intracellular concentration gradient. This may drive Ca^{2+} intracellularly through unaffected calcium channels. Calcium salts are

beneficial in experimental models of CCB poisoning. **(Eccleston, et al.2006)**

Table (12) shows antidote Therapy with Intravenous Calcium:

Characteristics	10% Calcium Chloride	10% Calcium Gluconate
Unit volume	10 mL per ampule	10 mL per ampule
Calcium content	1.36 mEq/mL	0.46 mEq/mL
Dose to prevent calcium channel blockage	3 mL	10 mL
Dose to reverse calcium channel blockage	13.6 mEq (10 mL)	13.8 mEq (30 mL)

(Kenny, et al.2004)

The response to calcium may last only 10-15 minutes so the initial response to calcium should be followed by a continuous infusion at 0.3 to 0.7 mEq/ kg/hr. **(DeRoos, et al.2006)**

5-Inotropes and Vasopressors:

Either stimulation of Beta-adrenergic receptors on the myocardium or of alpha-adrenergic receptors on the peripheral vascular smooth muscle are the most logical targets, but which one depends upon the etiology of the hypotension. The choice of a

sympathomimetic drug is based on numerous factors, including the pharmacologic profile of each drug, the patient's underlying physiologic condition, and the physician's familiarity and comfort with the drug. If one sympathomimetic drug is unsuccessful, determining the cardiac output and systemic vascular resistance may be helpful in assessing whether the myocardial depressant or peripheral vasodilatory effects are responsible for the hypotension. This knowledge will help guide the subsequent choice of pharmacologic agents. **(Proano, et al.2005)**

Dopamine is predominantly an indirect acting pressor which acts by stimulating the release of norepinephrine from the distal nerve terminal, and not by direct alpha and beta adrenergic receptor stimulation. This may limit its effectiveness in severely stressed patients who may have catecholamine depletion. Published clinical experience of patients with severe CCB poisonings support these concerns. Improvement in blood pressure may be noted with dopamine at high dosing, when the drug has additional direct alpha and beta adrenergic effects. **(Hoffman, et al.2001)**

6-Rescue Treatments:

For patients with cardiogenic shock that is refractory to the above treatments, several options remain open. Electrical cardiac pacing may help restore heart rate and should be considered for patients with shock and a heart rate below 40 beats / minute. During CCA toxicity, the heart should not be paced above 60 beats / minute.

At the level of the heart cell, CCAs delay both systolic calcium transients and diastolic calcium reuptake. The heart cell cannot be forced into normal rhythmicity with electrical depolarization. In fact, ventricular stroke volume tends to be maximized at a heart rate of 45 to 50 beats per minute. Pacing faster than this rate may actually reduce stroke volume. As a result, electrical pacing may fail to improve cardiac output. Intra-aortic balloon counterpulsation has also been reported to improve shock from verapamil poisoning. Extracorporeal cardiopulmonary bypass may also provide a bridge to survival, especially if used in conjunction with hemodialysis or hemoperfusion. **(Melanson, et al.2003)**

- # Acute Digoxin Toxicity:

Pharmacological background:

Mechanism of action:

Digoxin is a weak positive inotrope that indirectly increases calcium availability to the contractile elements of the myofibril by inhibiting Na+-K+ ATPase. Inhibition of this ATPase results in an increase in intracellular Na+ which, in turn, causes the Na+- Ca2+ exchanger to increase intracellular Ca2+. **(Eichhorn, et al.2002)**

The effects of digoxin on the autonomic nervous system have also been well described. Digoxin has parasympathomimetic actions that clinically manifest by increasing vagal tone to the sinus and atrioventricular (AV) nodes, thus decreasing HR slowing conduction through the AV node. **(Smith, et al.1984)**

Pharmacokinetics:

Digoxin is a substrate for p-glycoprotein, a membrane transport pump that is present not only in the intestine but also in many other organs such the CNS and the kidney. P-glycoprotein modulates the oral absorption of digoxin, in addition it plays an important role in its renal excretion and movement across the blood-brain barrier. The bioavailability of oral intake of digoxin ranges from 70% to 90%. **(Ieiri, et al.2004)**

The mechanism of drug interactions with digoxin such as: verapamil, quinidine, and amiodarone can be attributed to the inhibition

of p-glycoprotein. By inhibiting p-glycoprotein, these agents increase serum digoxin concentrations by increasing its intestinal absorption and decreasing renal clearance. **(Yamreudeewong, et al.2003)**

The elimination half-life (t1/2) of digoxin in patients with normal renal function is about 1-6 days but can be 4–6 days in patients with end-stage renal dysfunction and, therefore, without appropriate intervention, toxic effects can persist for several days to weeks. Digoxin has a relatively large volume of distribution (5–7 L/kg) and is highly tissue bound, making dialysis ineffective in the treatment of toxicity. **(Iisalo, et al.1997)**

Mechanism of toxicity:

At high/toxic digoxin concentrations, the storage capacity of the sarcoplasmic reticulum for Ca^{2+} becomes saturated, causing spontaneous release and reuptake of Ca^{2+}. Ca^{2+} overload coupled with the Na^{+}- Ca^{2+} exchanger, causing the inward movement of Ca^{2+} and Na^{+} during diastole that results in small electrical depolarizations termed afterdepolarizations. **(Hauptman, et al.2006)**

Causes of toxicity:

Aside from purposeful overdoses or suicide gestures, one can assume that digoxin toxicity occurs because of some medical error made by either the clinician or the patient so, most of these cases are preventable. Clearly one of the most important risks is the presence of renal dysfunction: in one series, two-thirds of patients with digoxin

toxicity had moderate-to-severe renal disease (creatinine clearance <50 mL/min for women or <60 mL/min for men). **(Hickey, et al.2001)**

- ## Manifestations of toxicity:

They are traditionally divided into extra-cardiac and cardiac manifestations

A- Extra-cardiac manifestations:

1- Visual manifestations:

Although unusual, digoxin toxicity has been reported to result in curious visual disturbances such as flashing lights, halos, and color disturbances (green-yellow patterns). More commonly complain of hazy or blurred vision. **(Engl, et al.1997)**

2- CNS manifestations:

Hallucinations have been reported but more common is the non-specific complaint of acute fatigue. **(Williamson, et al.1998)**

3- GIT manifestations:

Anorexia and nausea are extremely common; vomiting is less likely but not uncommon. These gastrointestinal symptoms occur in 30–70% of patients with reported digoxin toxicity. **(Mahdyoon, et al.2000)**

4- Hyperkalemia: (i.e. serum potassium >5.0 mEq/L)

It results from digoxin blocking Na+-K+ ATPase throughout the body and the resultant leak of potassium from its intracellular home into extracellular spaces. Measurable hyperkalemia generally indicates extremely high concentrations

of digoxin, often in setting of renal dysfunction and traditionally needs emergency treatment measures. **(Abad-Santos, et al.2000)**

B- Cardiac manifestations:

Digoxin has also been reported to cause all types of arrythmias. Such as a new-onset of Mobitz type I AV block (Wenckebach periodicity), accelerated junctional rhythm with or without high-degree AV block, non-paroxysmal atrial tachycardia with AV block, and bidirectional ventricular new tachycardia. **(Ma, et al.2007)**

Management of digoxin toxicity:

LABORATORY STUDIES:

1-serum chemistry:

We should do Serum calcium and magnesium levels as well as routine electrolytes, BUN and serum creatinine levels, oxygen saturation. Arterial blood gas analysis should also be considered in those with an abnormal serum bicarbonate level. Patients who are asymptomatic after an acute exposure initially need only an ECG (or cardiac monitoring). (**Pervaiz, et al.2006)**

2-Serum Digoxin Level (SDL):

The SDL ideally should be obtained at least 6 hours after the most recent dose in patients with chronic drug exposure. It should be measured immediately in unstable patients, if chronic non-pharmaceutical digoxin (DG) poisoning is suspected, and 1 to 2 hours