Acute opiod analgesics poisoning.
Acute paracetamol and salicylate poisoning.
antihypertensives and cardiac glycosides poisoning

Pain

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain serves the purpose to prevent tissue damage and protect the body while it is healing. Under certain conditions, pain can become maladaptive and persist as chronic pain. This pain serves no protective function and is described as pathological pain as opposed to physiological pain; it is then no longer a symptom of another disease, but a disease in its own right.

Painful stimuli are detected by nociceptors, which are free nerve endings located in tissues and organs. They have high thresholds and, under normal circumstances, only respond to noxious stimuli.

There are two distinct types of nociceptors

- High threshold mechanoreceptors which stimulate small myelinated Aδ-fibres and transmit a well-localised sharp or pricking sensation that lasts as long as the stimulus. Aδ-fibres are fast conducting and transmit the first sharp pain on initial stimulation.
- Polymodal nociceptors that stimulate small unmyelinated slowly conducting C fibres. C fibres are unmyelinated slow conducting fibres which transmit a less well localised persistent aching pain that lasts after the initial stimulus has gone. As well as responding to mechanical stimuli they are activated by thermal and chemical stimuli

Pain is transmitted by primary afferents, which have their cell bodies in the dorsal root ganglion (DRG). They terminate in the dorsal horn of the spinal cord. The dorsal horn cells are divided into specific regions or laminae called Rexed's laminae with lamina I being the most superficial.

Ascending systems

Noxious information is conveyed from the dorsal horn to the brain via several ascending tracts in the spinal cord.

Descending control

The dorsal horn receives inputs from higher centres that modulate the response to nociceptor input.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs comprise a class of xenobiotics with analgesic, antipyretic and anti-inflammatory properties. These desirable clinical effects account for the extensive list of approved clinical uses, including the treatment of pain, inflammation and fever.

NSAIDs are typically divided into groups based on their chemical structure and selectivity: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen, acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam) anthranilic acids (meclofenamate, mefenamic acid), naphthylalanine (nabumetone), and selective COX-2 inhibitors (celecoxib, etoricoxib).

The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). Cyclooxygenase is required to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins. The therapeutic effects of NSAIDs are attributed to the lack of these eicosanoids. Specifically, thromboxanes play a role in platelet adhesion, prostaglandins cause vasodilation, increase the temperature set-point in the hypothalamus, and play a role in anti-nociception.

There are two cyclooxygenase isoenzymes, COX-1 and COX-2. COX-1 gets constitutively expressed in the body, and it plays a role in maintaining gastrointestinal mucosa lining, kidney function, and platelet aggregation. COX-2 is not constitutively expressed in the body, and instead it inducibly expresses during an inflammatory response. Most of the NSAIDs are nonselective and inhibit both COX-1 and COX-2. However, COX-2 selective NSAIDs (ex. celecoxib) only target COX-2 and therefore have a different side effect profile. Importantly, because COX-1 is the prime mediator for ensuring gastric mucosal integrity and COX-2 is mainly involved in inflammation, COX-2 selective NSAIDs should provide anti-inflammatory relief without compromising the gastric mucosa.

Most NSAID's are organic acids with extensive protein binding(>90%). Oral absorption occurs rapidly, resulting in bioavailabilities above 80%. Serum half-lives with therapeutic dosing vary from as short as 1 to 2 hours for diclofenac and ibuprofen to 50 to 60 hours for oxaprozin and piroxicam. Most NSAID undergo hepatic metabolism with renal excretion of metabolites.

NSAIDs have well-known adverse effects affecting the gastric mucosa, renal system, cardiovascular system, hepatic system, and hematologic system.

Gastric adverse effects are likely due to the inhibition of COX-1, preventing the creation of prostaglandins that protect the gastric mucosa. The damage is more likely in a patient that has a prior history of peptic ulcers. Since it is COX-1 specific, the use of COX-2 selective NSAIDs is a lower risk alternative.

Renal adverse effects are because COX-1 and COX-2 facilitate the production of prostaglandins that play a role in renal hemodynamics. In a patient with normal renal function, inhibition of prostaglandin synthesis does not pose a large problem; however, in a patient with renal dysfunction, these prostaglandins play a greater role and can be the source of problems when reduced via NSAIDs. Complications that can occur due to this are acute renal dysfunction, fluid and electrolyte disorders, renal papillary necrosis, and nephrotic syndrome/ interstitial nephritis.

Cardiovascular adverse effects can also be increased with NSAID use; these include MI, thromboembolic events, and atrial fibrillation. Diclofenac seems to be the NSAID with the highest reported increase in adverse cardiovascular events.

Hepatic adverse effects are less common; NSAID-associated risk of hepatotoxicity (raised aminotransferase levels) is not very common, and liver-related hospitalization is very rare. Among the various NSAIDs, Diclofenac has a higher rate of hepatotoxic effects.

Hematologic adverse effects are possible, particularly with nonselective NSAIDs due to their antiplatelet activity. This antiplatelet effect typically only poses a problem if the patient has a history of GI ulcers, diseases that impair platelet activity (hemophilia, thrombocytopenia, von Willebrand, etc.), and in some perioperative cases.

Other minor adverse effects include anaphylactoid reactions that involve the skin and pulmonary systems, like urticaria and aspirin-exacerbated respiratory disease.

NSAID toxicity can manifest as GI bleeding, hypertension, hepatotoxicity, and renal damage. Typically, acute NSAID overdose is asymptomatic or has negligible gastrointestinal symptoms. However, other symptoms of toxicity complications may include anion gap metabolic acidosis, coma, convulsions, and acute renal failure. Also, NSAIDs can confer gastrointestinal damage by inhibiting COX-1, which causes decrease gastric mucosa production. Nephrotoxicity can also occur with NSAID use because these medications reduce prostaglandin levels, which are essential for the vasodilation of the renal arterioles. Lastly, neurologic toxicity can present with drowsiness, confusion, nystagmus, blurred vision, diplopia, headache, and tinnitus.

Treatment: gastric lavage with activated charcoal, symptomatic

Opiod analgesics

Opioid analgesic overdose is a preventable and potentially lethal condition that results from prescribing practices, inadequate understanding on the patient's part of the risks of medication misuse, errors in drug administration, and pharmaceutical abuse.

Opioids receptors are mu, delta, and kappa opioid receptors. Opioid receptors are activated by endogenous peptides and exogenous ligands; morphine is the prototypical compound of the latter. The receptors are widely distributed throughout the human body. The mu 1 receptors are responsible for supraspinal analgesia and for the euphoria sometimes engendered by these xenobiotics. The stimulation of mu 2 receptors produces spinal-level analgesia and respiratory depression. The kappa receptors are responsible for spinal analgesia, miosis and diuresis(via inhibition of antidiuretic hormone release). Delta receptors are responsible for spinal and supraspinal analgesia and for cough suppression. The receptorsfound in the anterior and ventrolateral thalamus, the amygdala, and the dorsal-root ganglia mediate nociception. Brain-stem opioid receptors modulate respiratory responses to hypercarbia and hypoxemia, and receptors in the Edinger–Westphal nucleus of the oculomotor nerve control pupillary constriction. Opioid agonists bind to receptors in the gastrointestinal tract to decrease gut motility.

The pharmacokinetics of particular opioid analgesic agents — their absorption, onset of action, clearance, and biologic half-life — are often irrelevant in overdose. For example, bezoars formed after large ingestions of pills may produce erratic rates of drug absorption, and the delayed gastric emptying and diminished gastrointestinal motility caused by opioids may prolong drug absorption. After absorption, most medications, including opioid analgesics, undergo first-order elimination pharmacokinetics, in which a constant fraction of the drug is converted by enzymatic processes per unit of time. In the case of an overdose, however, high concentrations of the drug may overwhelm the ability of an enzyme to handle a substrate, a process known as saturation. Saturated biologic processes are characterized by a transition from first-order to zero-order elimination kinetics. Two phenomena occur in zero-order elimination. First, small increases in the drug dose can lead to disproportionate increases in plasma concentrations and hence to intoxication. Second, a constant amount (as opposed to a constant proportion) of drug is eliminated per unit of time.[23] Collectively, these toxicokinetic effects converge to produce opioid toxicity that may be severe, delayed in onset, and protracted as compared with the expected therapeutic actions.

Symptoms: 1. Respiratory depression: reduction of ventilation by diminishing the sensitivity of the medullary chemoreceptors to hypercapnia. In addition to loss of hypercarbic stimulation, opioids depress the ventilatory response to hypoxia. The combined loss of hypercarbic and hypoxic drive leaves virtually no stimulus to breathe, and apnea ensues.\

2. Acute lung injury

3. Reduction in hearth rate and blood pressure

4.Miosis

5.Seizures – most likely due to the hypoxia.

6. Constipation

7.Hypothermia

treatment: ABCDE
3.2. GIT decontamination –precautions
3.3.Specific antidote- naloxone
Indication – RR<8/min , inadequate oxygenation
ampules 0,4mg (400mcg) in 1 ml

give 100-200mcg boluses iv up to 2mg preferably for reversal of acute/accidental overdose until clinical effects present – RR increasing sat02 increasing , patients regains consciousness and maintains sat02>94%

in drug addicts / poisonings with newer,synthetic opiods much larger doses might be needed(10mg)

SPECIAL NOTE: as opiods have greater affinity to the receptors , the effects of naloxone could start wearing off in 30-40mins if a large dose has been taken to maintain antidotal effects Naloxone could be run in an iv drip with the rate titrated to maintain the patient conscious and adequately breathing

patients might be very agitated and aggressive following rapid opiod reversal – potential risk of harm

Acute paracetamol and salicylate poisoning.

Salicylate toxicity is a medical emergency. Intentional ingestion or accidental overdose can cause severe metabolic derangements making treatment difficult. They are commonly used for their analgesic, antipyretic, and anti-thrombotic properties. Toxicity can occur due to acute ingestion or from chronic ingestions that result in an increased serum concentration.

Salicylate poisoning causes a variety of metabolic disorders. Direct stimulation of the cerebral medulla causes hyperventilation and respiratory alkalosis. As it is metabolized, it causes an uncoupling of oxidative phosphorylation in the mitochondria. Lactate levels then increase due to the increase in anaerobic metabolism. The lactic acid along with a slight contribution from the salicylate metabolites result in metabolic acidosis. Hyperventilation worsens in an attempt to compensate for the metabolic acidosis. Eventually, the patient fatigues and is no longer able to compensate via hyperventilation, and metabolic acidosis prevails. This results in hemodynamic instability and end-organ damage.

The ionization constant of aspirin is 3, which makes it is more readily absorbed in acidic environments such as the stomach. A variety of factors can affect absorption. The formulation of the salicylate (extended vs. immediate release)

being one. Food in the stomach at the time of ingestion can delay absorption. Aspirin has the propensity to form bezoars which will delay absorption. Aspirin can cause pyloric sphincter spasms, which increases the amount of time in the stomach allowing for more absorption. Absorption continues in the small intestine.

The liver metabolizes salicylates by first-order elimination, and the inactive metabolites are then excreted in the urine. With increased salicylate levels, these pathways become saturated resulting in zero order elimination. Elimination is further delayed in patients with underlying renal and liver disease.

In an acute salicylate overdose, the onset of symptoms will occur within 3 to 8 hours. The severity of symptoms is dependent on the amount ingested. For mild ingestions (salicylate levels 40 to 80 mg/dL) nausea, vomiting, and generalized abdominal pain are common. Tachypnea is usually present. Headaches and dizziness may also occur. The classic finding of tinnitus may also be present. However, this can occur at lower, non-toxic levels.

Patients with moderate salicylate toxicity (80 to 100 mg/dL) will experience more severe neurological symptoms. These can include confusion, slurred speech, and hallucinations. Tachypnea is more pronounced and is accompanied by tachycardia and orthostatic hypotension. Expect these symptoms 6 to 18 hours after ingestion.

Salicylate levels greater than 100 mg/dL are considered severe toxicity and occur 12 to 24 hours after ingestion. Damage to the basement membranes will cause cerebral and pulmonary edema. Patients may become obtunded and develop seizures. Hypoventilation may replace hyperventilation, which is concerning for impending respiratory failure. Endotracheal intubation, while not ideal for the metabolic disorders, may be necessary for airway protection. Hypotension due to acidosis and hypovolemia is possible. Cardiac dysrhythmias may occur. Sinus tachycardia is the most common. Cardiac arrest may also occur with asystole being the most common rhythm.

Patients suffering from chronic salicylate toxicity will experience similar symptoms as acute toxicity but at lower levels. Pediatric patients will progress from mild symptoms to severe symptoms more quickly than adults.

Patients with salicylate toxicity are volume depleted due to hyperventilation, fever, and increased metabolic activity. Fluid resuscitation.
-crystaloid solutions – saline, ringers, hartmans
- dextrose will treat the central nervous system (CNS) hypoglycemia.
-sodium bicarb will help correct the metabolic acidosis.
also alkalizing the patient with NaHC03 1mmol/kg will enhabce the eliminations of aspirin (as weak acid)
-Potassium may be supplemented if hypokalemia is present.
Goal urine output is 2 to 3 mL/kg per hour. Following initial stabilization, attempts should be made to decrease the serum salicylate levels. Activated charcoal has been shown to decrease salicylate levels. However, no morbidity or mortality benefit has been shown. Gastric lavage may be considered if the patient presents after acute ingestion of enteric-coated aspirin. If there is any concern for aspiration, these options should be avoided. Whole bowel irrigation has shown no benefit and may increase absorption. Fluid resuscitation and serum alkalization will increase salicylate elimination. Hemodialysis can also accomplish this. Indications for hemodialysis include severe acidosis or hypotension despite fluid resuscitation; salicylate levels are greater than 100 mg/dL, mechanical ventilation, or end-organ damage. Common signs of end-organ damage in salicylate toxicity include seizures, rhabdomyolysis, pulmonary edema, cerebral edema, and renal failure. Hemodialysis removes salicylates and lactate, which should improve the patient's metabolic acidosis.

Seizures should be treated with benzodiazepines. Glucose should also be administered as CNS hypoglycemia may be present. Expect the patient's metabolic acidosis to be worse following a seizure and consider administering a bicarbonate bolus.

Acetaminophen (N-acetyl-para-aminophenol, paracetamol, APAP) toxicity is common primarily because the medication is so readily available, and there is a perception that it is very safe. Acetaminophen is a non-steroidal anti-inflammatory drug (NSAID), with a mechanism of action different from other NSAIDs. Its mode of action is not clearly understood, but it appears to inhibit cyclooxygenase (COX) in the brain selectively. This results in its ability to treat fever and pain. It may also inhibit prostaglandin synthesis in the central

nervous system (CNS). Acetaminophen directly acts on the hypothalamus producing an antipyretic effect.

Acetaminophen is rapidly absorbed from the gastrointestinal (GI) tract and reaches therapeutic levels in 30 minutes to 2 hours. Overdose levels peak at 4 hours unless other factors could delay gastric emptying, such as a co-ingestion of an agent that slows gastric motility, or if the acetaminophen is in an extended-release form.[5]

Acetaminophen has an elimination half-life of 2 hours, but can be as long as 17 hours in patients with hepatic dysfunction. It is metabolized by the liver, where it is conjugated to nontoxic, water-soluble metabolites that are excreted in the urine.[10]

Metabolism primarily occurs through glucuronidation and sulfuration, both of which occur in the liver. In an overdose, these pathways are saturated, and more acetaminophen is subsequently metabolized to NAPQI by cytochrome P450. NAPQI is a toxic substance that is safely reduced by glutathione to nontoxic mercaptate and cysteine compounds, which are then renally excreted. An overdose depletes the stores of glutathione, and once they reach less than 30% of normal, NAPQI levels increase and subsequently binds to hepatic macromolecules causing hepatic necrosis. This is irreversible.[12][13]

The clinical course of acetaminophen toxicity is divided into four stages.[15]

- During the first stage (30 min to 24 hours), the patient may be asymptomatic or may have emesis.
- In the second stage (18 hours to 72 hours), there may be emesis plus right upper quadrant pain and hypotension.
- In the third stage (72 hours to 96 hours), liver dysfunction is significant with renal failure, coagulopathies, metabolic acidosis, and encephalopathy. Gastrointestinal (GI) symptoms reappear, and death is most common at this stage.
- The fourth stage (4 days to 3 weeks) is marked by recovery.

The treatment of acetaminophen poisoning depends on when the drug was ingested. If the patient presents within 1 hour of ingestion, GI decontamination may be attempted. In alert patients, activated charcoal can be used. Orogastric lavage or whole bowel irrigation is not effective.

All patients with high levels of acetaminophen need admission and treatment with N-acetyl-cysteine (NAC). This agent is fully protective against liver toxicity if given within 8 hours after ingestion. NAC works through multiple routes. It prevents binding of NAPQI to hepatic macromolecules, acts as a substitute for glutathione, is a precursor for sulfate, and reduces NAPQI back to acetaminophen.

dose regimen for NAC
- use Rumack-Matthew chart to ascertain if treatment is deemed needed blood concentration/time of ingestion
- oral protocol
140mg/kg loading dose + 17 further doses 70mg/kg q4h
-iv protocol in
150mg/kg iv in 200ml 5% dextrose loading dose in 30min
50mg/kg in 500ml 5%dextrose for 4h
100mg/kg in 1000ml 5% dextrose for 16h

Cardiac glycosides are an important cause of poisoning, reflecting their widespread clinical usage. Poisoning can manifest as varying degrees of toxicity. Predominant clinical features include gastrointestinal signs, bradycardia and heart block. Death occurs from ventricular fibrillation or tachycardia.

The pharmacokinetics of digoxin vary, including absorption, duration of distribution (2–6 h) and elimination half-life (mean 40 h, range 20–50 h), and elimination is predominantly renal . The onset of digoxin's effect is delayed by approximately 6 h, which reflects the time for distribution to a peripheral compartment and/or time-dependent binding to the Na^+-K^+-ATPase. Digitalis cardiac glycosides are thought to undergo enterohepatic recycling, given that multiple doses of activated charcoal (MDAC) increase clearance (discussed later).

Cardiac glycosides inhibit the Na^+-K^+-ATPase on cardiac and other tissues, causing intracellular retention of Na^+, followed by increased intracellular Ca^{2+} concentrations through the effect of the Na^+-Ca^{2+} exchanger. The elevated intracellular Ca^{2+} concentration promotes inotropy and bradycardia, and the

intracellular accumulation of Na^+ and Ca^{2+} causes partial membrane depolarization which increases automaticity and ventricular ectopy. Digoxin also increases vagal tone, contributing to bradycardia and impaired conduction through the atrio-ventricular node, and may block voltage-gated Na^+ channels.

The predominant features of acute poisoning include gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhoea), hyperkalaemia, generalized weakness, drowsiness and, importantly, cardiotoxicity (bradycardia and heart block, dysrhythmias). These may appear within a few hours of acute poisoning. Vision changes .

The most common cardiac abnormality in poisoning is sinus bradycardia. ECG changes in therapeutic dosing (or mild poisoning) include flattening or inversion of the T wave and depression of the ST segment. Moderate poisoning manifests as prolonged PR interval (first degree heart block) or sinus bradycardia. Severe poisoning manifests as second or third degree heart block due to inhibition of the atrioventricular node. Sinus arrest or exit block are also reported. Deaths occur due to ventricular fibrillation resistant to electrical cardioversion or asystolic arrest .

A single dose of activated charcoal 50–100 g should be administered to all patients with acute ingestion of a potentially toxic exposure, regardless of the time of ingestion.

Atropine antagonizes cardiac glycoside vagal activation, increasing heart rate

specific antidote- Fab (Digifab) monoclonal antibody fragments

Beta-blockers

Beta-blockers antagonize beta-adrenergic receptors and are used mainly in the treatment of hypertension, heart failure, tachydysrhythmias, and angina pectoris. In addition to cardiovascular disorders, beta-blockers are also used in the management of anxiety, migraine headache, glaucoma, tremor, hyperthyroidism, and various other disorders.

Traditionally, beta-blockers are classified as selective and non-selective, beta-blockers are classified as lipophilic or lipophobic. Highly lipophilic beta-blockers can easily cross the blood-brain barrier and may cause various central nervous system (CNS) manifestations.

While hypotension, bradycardia, decreased myocardial contractility and oxygen consumption account for the hemodynamic instability, hypoglycemia secondary to inhibition of glycogenolysis and gluconeogenesis may also occur.

Beta-blockers are readily absorbed when ingested with peak absorption within one to four hours. Absorption may also be delayed in cases involving the co-ingestion of drugs which can decrease gastrointestinal motility. While most of the beta-blockers are moderately lipophilic, certain beta-blockers have extensive lipophilicity and have a large volume of distribution. Propranolol, the most lipophilic beta-blocker, can easily cross the lipid cell and blood-brain barrier and may cause seizures in overdose cases.

The liver excretes beta-blockers most frequently. Atenolol, carteolol, and nadolol are the only exceptions that undergo renal excretion. Various beta-blockers may cause sodium or potassium channel blockade and therefore cause prolongation in QRS and QTc interval, respectively.

Bradycardia associated with hypotension may be the first clue to diagnose beta-blocker overdose. patients with BB toxicity have hypoglycemia and altered mental status.

Administer activated charcoal to limit drug absorption to patients with minor symptoms who present later than an hour after ingestion. Benzodiazepines are the first line of treatment for seizures that may occur due to the high lipophilicity of certain beta-blockers. Prompt recognition of QRS widening and prolongation of QTc interval is crucial.

Administer sodium bicarbonate for QRS widening and magnesium sulfate for QTc prolongation. Although there have been no controlled trials to prove the efficacy of glucagon in poisoning beta-blocker overdose, glucagon is considered as a useful treatment of choice. Premedication with antiemetic may be considered since treatment with glucagon may induce vomiting.

Due to intrinsic lipophilicity, certain beta-blockers may cause CNS depression. Prompt management of the airway is, therefore crucial. The airway should be protected with a cuffed endotracheal tube in all deeply obtunded patients. Premedication with atropine may be necessary especially in children since laryngeal manipulation during intubation may cause additive vagal stimulation and bradycardia. Bronchospasm due to beta-blockade may be treated with supplemental oxygen and inhaled bronchodilators like albuterol. Gastrointestinal decontamination with gastric lavage may be necessary for patients who present shortly after massive ingestions and/or with serious symptoms.

Prompt initiation of ECMO and continuation of mechanical life support may be needed until the xenobiotic effect wears off. Toxicity secondary to water-soluble and renally excreted beta-blockers (e.g., acebutolol, atenolol, nadolol, and sotalol) may respond to enhanced elimination techniques such as multiple doses activated charcoal, hemoperfusion or hemodialysis.

-glucagon
-pacing of atropine not efficient for haemodynamicly unstable bradycardia
-intralipid therapy
-High Insulin Euglycemic therapy

Calcium-channel blockers

Calcium channel blockers (CCBs) are among the most commonly used cardiovascular drugs in the adult population. They are used to treat a broad array of clinical conditions, including hypertension, supraventricular tachycardia, vasospasm, and migraine headaches.

Calcium channel blockers in all their subtypes target the L-type voltage-gated calcium channels. L type voltage-gated calcium channels are predominant in the following sites and roles:

Depolarization of the sinoatrial node (SA) and impulse propagation through the atrioventricular node (AV). Calcium entry during the plateau phase of the action potential in myocardial cells releases calcium from the sarcoplasmic reticulum to the cytosol, triggering myocardial contraction. Contraction strength is directly proportional to intracellular calcium concentration, allowing actin and myosin to interact. Cytosolic calcium concentration mediated by

membrane gated influx of calcium is responsible for maintaining vascular smooth muscle tone. The influx of calcium is also responsible for insulin secretion. All CCBs are very well absorbed orally across the subtypes, undergo extensive hepatic first-pass metabolism, are lipophilic, bind readily to plasma proteins, and have a large volume of distribution (> 2 liters/kg). Elimination by hemodialysis or hemofiltration is ineffective.

At higher doses clearance slows, because hepatic clearance changes from first-order to zero-order kinetics.

Conventionally used CCBs belong to three main chemical classes, with each subclass having differing affinities for cardiac tissue and vascular smooth muscle:

- Phenylalkylamines (verapamil)
- Benzothiazepines (diltiazem)
- Dihydropyridines (nifedipine, amlodipine, felodipine, isradipine, nicardipine, nimodipine)

Verapamil has a strong affinity for both myocardium and vascular smooth muscle. It suppresses cardiac contractility, SA nodal automaticity, AV nodal conduction and causes potent vasodilation. Diltiazem has a similar range of effects as verapamil with less vasodilation; its effect is more potent on chronotropic action. Dihydropyridines are very effective vasodilators but exert less influence on cardiac pacemakers and myocardial contractility.

With significant overdoses, the serum and tissue concentration of these drugs are so excessive that the pharmacological difference in affinity and action between subclasses is overwhelmed. Thus, both verapamil and diltiazem causes significant bradycardia, hypotension, conduction disturbances, and escape rhythms. Nifedipine triggers hypotension and reflex sinus tachycardia. Calcium channel blockers of all subclasses reduce pancreatic insulin secretion and induce end-organ insulin resistance, causing hyperglycemia. Additionally, CCBs interfere with calcium-stimulated mitochondrial action and glucose catabolism; this results in lactate production and ATP hydrolysis, contributing to acidosis.

Initial symptoms may be as nonspecific as dizziness, fatigue, and lightheadedness, and in severe toxicities, it may rapidly decline to alter mental status, coma, and fatal shock.

The most common ECG abnormalities involving calcium channel blockers other than dihydropyridines are sinus bradycardia, variable degrees of atrioventricular blocks, bundle branch block, QT prolongation, and junctional rhythms. Dihydropyridines maintain normal sinus rhythm and can cause reflex sinus tachycardia.

Hypotension and bradycardia, when progressive, can eventually lead to cardiogenic shock. Also, hyperglycemia is common with all subclasses of CCBs and can be a useful clinical marker for poisoning severity. Both of these effects lead directly to metabolic acidosis. It is also common to develop mild hypokalemia and mild to severe hypocalcemia.

Profound hypoperfusion and end-organ ischemia with a severe overdose can cause clinical evidence of end-organ failures like seizures, myocardial infarction, acute respiratory distress syndrome (ARDS), renal failure, bowel infarction and ischemia, and stroke.

The basic tenets of critically ill patient management remain focused on initial attention to airway, breathing, and circulations. Atropine is mostly ineffective in severe CCB toxicity.

Conventional decontamination measures like urinary alkalinization, hemodialysis, or hemofiltration are ineffective in CCB toxicity because of their large volume of distribution and lipophilic nature. Whole bowel irrigation is the mainstay of elimination in extended-release preparations.

Calcium administration: The rationale behind calcium administration is that increased extracellular concentration will promote calcium influx via unblocked L type calcium channels. Calcium may improve hypotension and conduction disturbances but is less effective in the management of bradycardia.

CCBs also reduce insulin secretion, creates tissue insulin resistance, and interfere with glucose catabolism leading to lactic academia and metabolic acidosis. Insulin administered in such a setting helps to reverse all of those derangements of metabolism. Insulin has a direct positive inotropic effect that contributes to its clinical role here.

Intravenous lipid emulsion is an oil-in-water emulsion that creates a lipid phase within the plasma and pulls a lipid-soluble drug into the lipid phase in blood. Lipid emulsion infusion can sequester intensely lipophilic drugs like verapamil and diltiazem and thus reduce their volume of distribution.