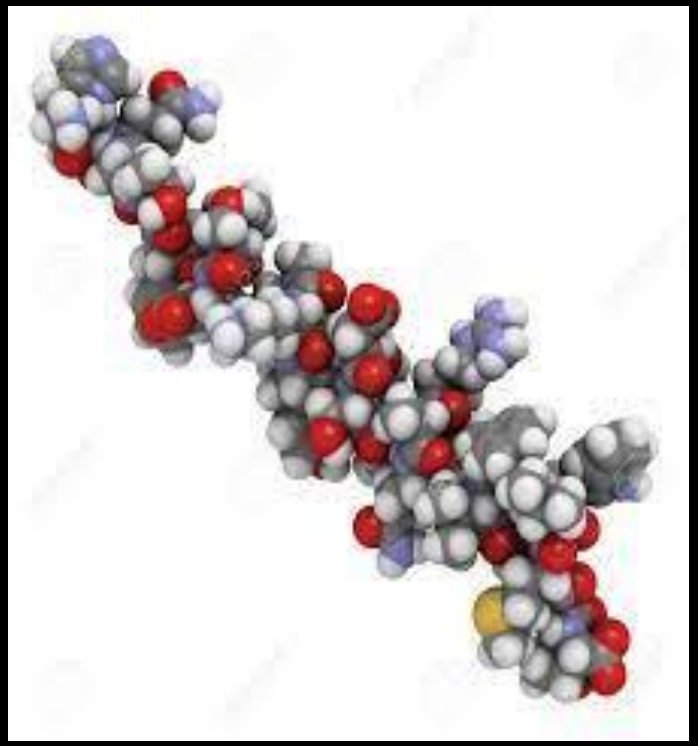
In the name of God

GLUCAGON



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Introduction

- The traditional role of glucagon was to reverse life-threatening **hypoglycemia** in patients with diabetes unable to receive dextrose in the outpatient setting.

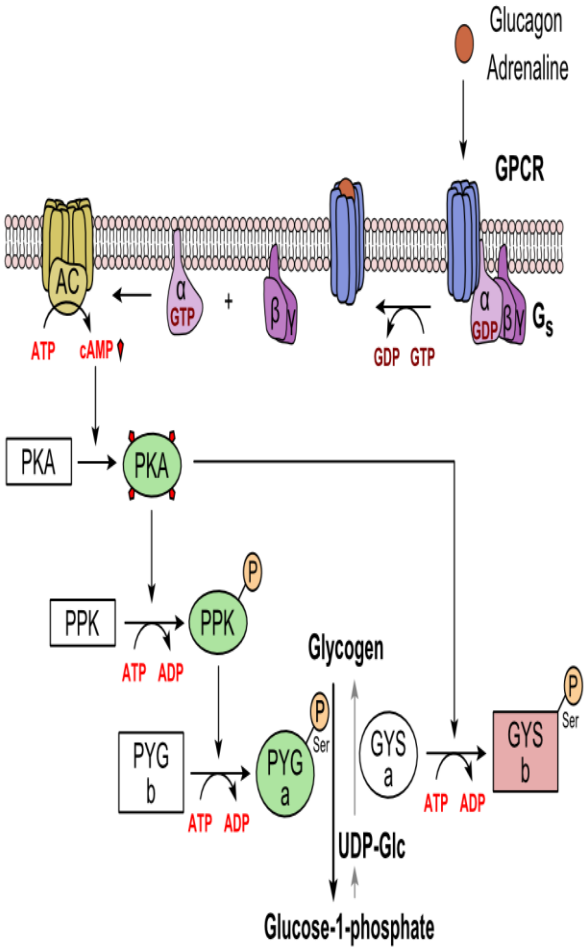
- However, in clinical toxicology, glucagon is used early in the management of *β- adrenergic antagonist and calcium channel blocker toxicity* to increase heart rate, contractility, and blood pressure by increasing myocardial cyclic adenosine monophosphate (cAMP) via a non–β-adrenergic receptor mechanism of action.

HISTORY

- Glucagon was discovered in **1922**, the year after insulin's discovery, when acetone precipitates of pancreatic extracts were found to produce "a distinctly hyperglycemic effect" in animals.
- The positive inotropic and chronotropic effects of glucagon were recognized in the **1960s**. Clinical use in human poisonings began in **1971**.

Mechanism of Action

- In both animals and humans, glucagon receptors are found in the **heart, brain, and pancreas.** Binding of glucagon to cardiac receptors is closely correlated with activation of cardiac adenylate cyclase.
- Binding of glucagon to its receptor results in coupling with two isoforms of the Gs protein and catalyzes the exchange of guanosine triphosphate (GTP) for guanosine diphosphate on the Gs protein. The GTP-Gs units stimulate adenylate cyclase to convert adenosine triphosphate (ATP) to cAMP.
- Glucagon inhibits the **phosphodiesterase PDE3**.



Additional Mechanism of Action

- Cardiac tissue metabolizes glucagon, liberating mini-glucagon, an active smaller terminal fragment. Mini-glucagon stimulates phospholipase A2, releasing ***arachidonic acid***. Arachidonic acid acts to increase *cardiac contractility* through an effect on calcium.

- Stimulation of glucagon receptors in the liver and adipose tissue increases cAMP synthesis, resulting in glycogenolysis, gluconeogenesis, and ketogenesis.

- Other properties of glucagon include relaxation of smooth muscle in the lower esophageal sphincter, stomach, small and large intestines, common bile duct, and ureters.

Cardiovascular Effects

- The *inotropic action* of glucagon is related to an increase in cardiac cAMP concentrations. Glucagon increases cAMP to augment the sarcoplasmic reticulum calcium pool. Glucagon improves ***chronotropy at both the sinus node and the atrioventricular (AV) junctional region***, even in the presence of escape rhythms. Both the positive inotropic and chronotropic actions of glucagon are very similar to those of the β-adrenergic agonists, except that they are not blocked by β-adrenergic antagonists.

- Glucagon also improves **coronary blood flow**.

- Although in some canine experiments, glucagon caused ventricular tachycardia, glucagon is not dysrhythmogenic in patients with severe chronic congestive heart failure or myocardial infarction–related acute congestive heart failure

- The effects of glucagon diminish markedly as the severity and chronicity of congestive heart failure increases.

Pharmacokinetics and Pharmacodynamics

- The plasma, liver, and kidney extensively metabolize glucagon with an elimination half-life of 8-18minutes.
- After a single IV bolus, the cardiac effects of glucagon begin within 1 to 3 minutes is maximal within 5 to 7 minutes, and persists for 10 to 15 minutes.
- The time to maximal glucose concentration is 5 to 20 minutes, with a duration of action of 60 to 90 minutes.

ROLE IN THE MANAGEMENT OF β- ADRENERGIC ANTAGONIST TOXICITY

- β-adrenergic antagonist toxicity is manifested by hypotension, bradycardia, prolonged AV conduction times, depressed cardiac output, and cardiac failure, seizures; and, rarely, hypoglycemia.
- Original management of β-adrenergic antagonist toxicity included provision of large doses of competitive β-agonists such as isoproterenol.
- Glucagon was found superior to this approach in animal evaluations and human cases.
- Glucagon may be effective initially for a brief period, but prolonged treatment may become ineffective due to *tachyphylaxis*.

Clinical improvement

- One recently review of the available controlled trials found that glucagon **increased heart rate (HR),** at least transiently, but had **minimal effect on mean arterial pressure (MAP).**

- No difference was detected **in HR, MAP, systolic BP, or cardiac output, except in the first hour.**

Combined Effects with Phosphodiesterase Inhibitors and Calcium

- Although the evidence for the effectiveness of combining glucagon with a PDE inhibitor(amrinone, milrinone) was demonstrated in animal models and human case reports, we recommend **against** the use of this approach.

- Maximal chronotropic effects of glucagon are dependent on a normal circulating ionized calcium. Both hypocalcemia and hypercalcemia blunt the maximal chronotropic response.

ROLE IN CALCIUM CHANNEL BLOCKER TOXICITY

- Calcium channel blocker toxicity produces a constellation of clinical findings including hypotension, bradycardia, conduction block, and myocardial depression.
- Animal studies demonstrate the ability of glucagon to improve *heart rate and AV conduction and reverse the myocardial depression produced by CCB.*
- However, there was *no survival* benefit attributed to glucagon.
- Its mechanism of action would seem to make its effectiveness in calcium channel antagonists less likely than in overdoses from β-adrenergic blocking agents.

ROLE IN OTHER CARDIOVASCULAR TOXINS

- A bolus of glucagon followed by infusion significantly increased the mean arterial pressure and decreased the QRS complex duration in amitriptyline poisoned rats.
- In human pediatric and adult cases of cyclic antidepressant overdoses refractory to multiple measures, glucagon produced immediate hemodynamic improvement. If appropriate therapeutic use of sodium bicarbonate fails to improve the hemodynamic status.

ROLE IN REVERSAL OF HYPOGLYCEMIA

- Glucagon was once proposed as part of the initial treatment for all comatose patients because it stimulates glycogenolysis in the liver. But glucagon requires time to act and will often be ineffective in a patient with depleted glycogen stores, such as in patients with prolonged fasting, severe liver disease, alcoholism, starvation, adrenal insufficiency, or chronic hypoglycemia.

- Patients with type 2 diabetes are more likely to respond than are patients with type 1 diabetes.

DOSAGE AND ADMINSTRATION

- An initial bolus of 5 mg intravenously is administered over one minute; if there is no increase in pulse or blood pressure after 10 to 15 minutes, a second bolus should be administered. The initial pediatric dose is 50–150 mg/kg.

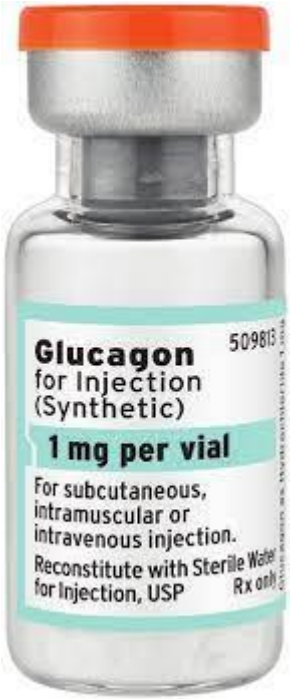
- *An effect should be observed within one to three minutes, with a peak response at five to seven minutes.*

- The effect of glucagon is often transient. We recommend either repeat doses of 3 to 5 mg as needed or a continuous infusion of 2 to 5 mg/h (10 mg/h or less) in 5% dextrose in water to be tapered as the patient improves and allows time for HDI to become effective.

- The goal is to maintain a mean arterial pressure of **60 mmHg.**

Glucagon

- one vial containing 1 mg (1 unit) of glucagon
- The glucagon powder should be reconstituted with 1 mL of sterile water for injection, after which the vial should be shaken gently until the powder completely dissolves.
- The final solution should be clear, without visible particles. The reconstituted glucagon should be used immediately after reconstitution and any unused part discarded. Concentrations greater than 1 mg/mL should not be used.



ADVERSE EFFECTS AND SAFETY ISSUES

- Dose-dependent nausea, vomiting, hyperglycemia, hypoglycemia, and hypokalemia; relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon; and, rarely, urticaria, respiratory distress, and hypotension.

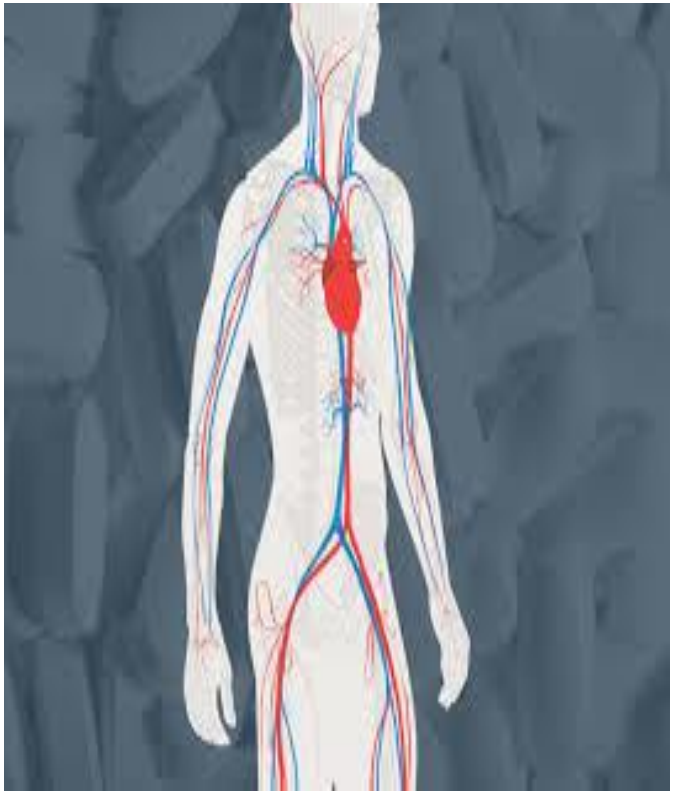
- Glucagon increases the anticoagulant effect of warfarin.

- Tachyphylaxia

Side effects

- Vomiting is common following administration of glucagon. We suggest prophylactic or concurrent administration of a serotonin antagonist antiemetic (eg, ondansetron).

- Diminishing the initial dose, rate of infusion, or both will limit the adverse effects.



Mechanisms of action of Tachyphylaxia

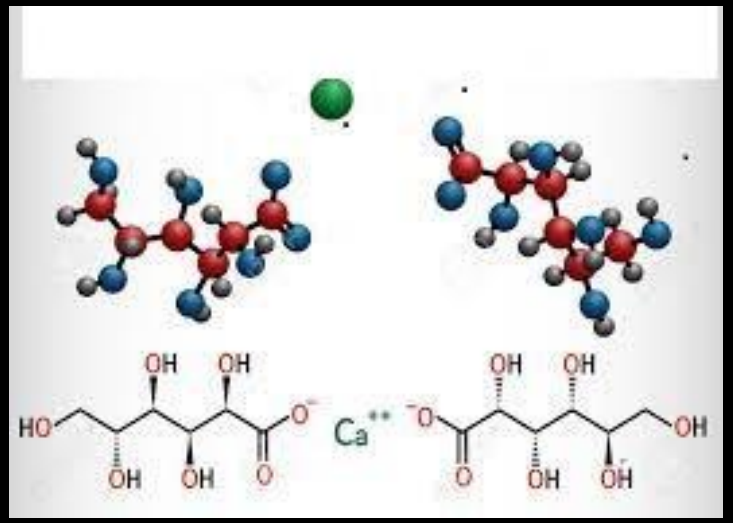
- Experimental heart preparations exposed to glucagon for varying lengths of time demonstrated *a decrease in the amount of generated cAMP.*

- Possible explanations for tachyphylaxis include uncoupling from the glucagon receptor, increased PDE hydrolysis of cAMP, or both.

PREGNANCY AND LACTATION

- Glucagon is FDA Pregnancy **Category B**. It is presumed that benefit exceeds risk.

- However, the size and peptide nature of glucagon suggest that the exposure to a lactating infant would be limited.



Calcium

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Introduction

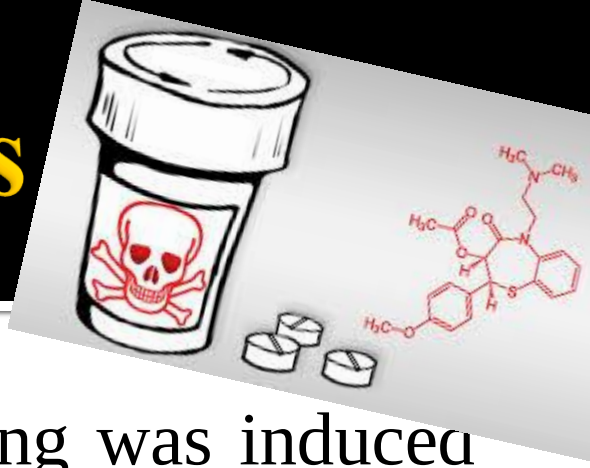
- Calcium is a divalent cation that is essential to maintain the normal function of the heart, vascular smooth muscle, the skeletal system, the nervous system, and intracellular signaling. It is vital in enzymatic reactions, neurohormonal transmission, blood coagulation, and the maintenance of cellular integrity.

- Calcium as *calcium chloride* or *gluconate* is a component of electrolyte, parenteral nutrition, dialysis, and cardioplegic solutions.

Calcium chloride or gluconate???

- Calcium chloride (200 mg/dose) increased serum ionized calcium by 6% to 8%.
- Calcium gluconate was thought to both have a lower bioavailability and to require gluconate metabolism for ionized calcium release.
- *Calcium gluconate and calcium chloride added to blood samples produced identical rises in plasma calcium ion concentrations.*
- These results support the concept that simple dissociation of calcium from gluconate is responsible for releasing calcium, rather than hepatic metabolism.

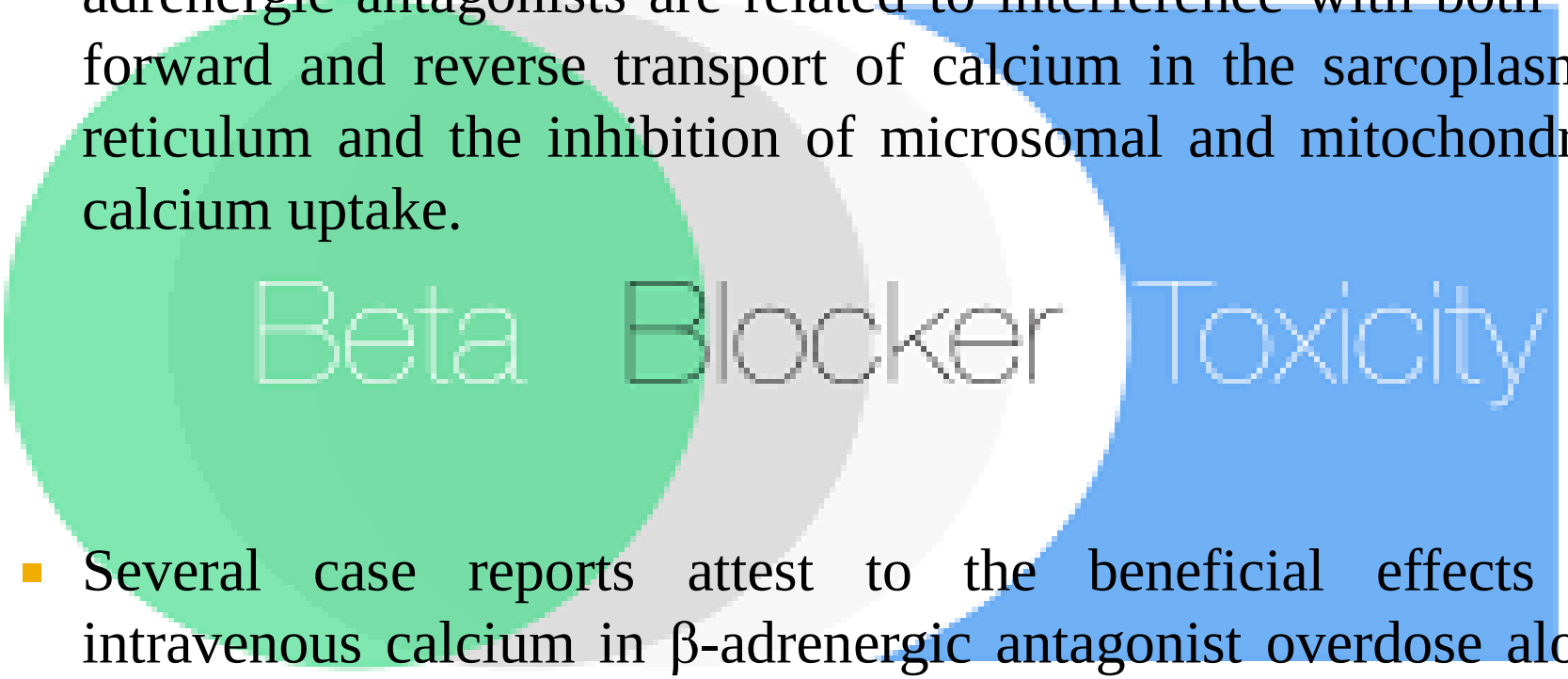
Toxicity with CC blockers



- Cardiac excitation-contraction coupling was induced calcium release, calcium binding to and activation of cardiac troponin C, and initiation of myofilament contraction.
- Calcium is recommended for symptomatic patients with CCB overdoses. Unfortunately, the most seriously ill patients respond inadequately, and other measures are often required.
- The dose of calcium needed to treat patients with CCB overdose is unknown.

Toxicity with beta-adrenergic blockers

- In vitro studies suggest that the negative inotropic action of β-adrenergic antagonists are related to interference with both the forward and reverse transport of calcium in the sarcoplasmic reticulum and the inhibition of microsomal and mitochondrial calcium uptake.



- Several case reports attest to the beneficial effects of intravenous calcium in β-adrenergic antagonist overdose alone or in combination with CCBs.

Treatment

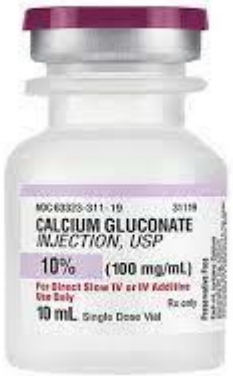
- The customary approach is to administer an initial IV dose of *3 g of calcium gluconate* (30 mL of 10% calcium gluconate) or *1 g of calcium chloride* (10 mL of 10% calcium chloride) to adults.
- Based on case reports, it is reasonable to repeat this dose every 10–20 minutes for up to 3–4 doses as necessary(60 to 120 mg/kg/hour).
- The pediatric dose is *20 mg/kg (maximum dose is 1 g); up to 60 mg/kg* may be given.
- The hypothesis is that sufficient calcium must be present to compete with the CCB for binding to the L-type calcium channel.

TABLE A32–1 Calcium Salts for Intravenous Use

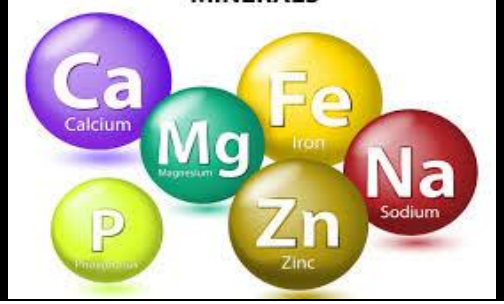
	Calcium Gluconate[a]	*Calcium Chloride ($CaCl_2$)*[a,b]
10% solution	10 mL = 1 g of Ca^{2+} gluconate 10 mL = 4.64 mEq = 93 mg = 2.32 mmol of elemental Ca^{2+} *or* 1 mL = 0.465 mEq = 9.3 mg = 0.23 mmol of elemental Ca^{2+}	10 mL = 1 g of $CaCl_2$ 10 mL = 13.6 mEq = 273 mg = 6.8 mmol of elemental Ca^{2+} *or* 1 mL = 1.36 mEq = 27.3 mg = 0.68 mmol of elemental Ca^{2+}
Adult dose	3 g (30 mL of 10% solution) over 10 minutes (unless in extremis—deliver over 60 seconds) Repeat every 10–20 minutes up to 3–4 doses as necessary	1 g (10 mL of 10% solution) over 10 minutes (unless in extremis—deliver over 60 seconds) Repeat every 10–20 minutes up to 3–4 doses as necessary
Pediatric dose (not to exceed the adult dose)	60 mg/kg (0.6 mL/kg) of 10% solution infused over 5–10 minutes (unless in extremis—deliver over 60 seconds) Repeat every 10–20 minutes up to 3–4 doses as necessary	20 mg/kg (0.2 mL/kg) infused over 5–10 minutes (unless in extremis—deliver over 60 seconds) Repeat every 10–20 minutes up to 3–4 doses as necessary

Effect in cardiovascular system

- Animal models suggest that calcium salts *increase blood pressure and cardiac output*, but *do not increase heart rate* following both in calcium channel blocker and beta blocker overdose.



Other



toxicity

- The administration of calcium to a patient with toxicity from cardioactive steroids such as *digoxin* is potentially harmful.
- Role in hypocalcemia secondary to *ethylene glycol*
- *Hydrofluric acid exposure*
- *Phosphate exposure*
- *Hpermagnesemia*
- *Hyperkalemia*
- *Citrate Toxicity*

Monitoring

- Electrocardiographic monitoring and frequent ionized calcium concentration measurements are required to prevent iatrogenic toxicity.

Adverse Effects

- Nausea, vomiting, constipation, ileus, polyuria, polydipsia, nephrolithiasis, cognitive alterations, hyporeflexia, coma, vascular alterations and dysrhythmias. Excessively aggressive calcium infusions in a patient with channel blocker overdose have led to death.
- Because calcium chloride (acidifying salt) is extremely irritating to small vessels, subcutaneous tissue, and muscle, and causes necrosis following extravasation, it is usually only administered through a central venous line.

Dose Adjustment

- Dosing: Renal Impairment: Adult Initiate with the lower limit of the dosage range (accumulation may occur with renal impairment and subsequent doses may require adjustment based on serum calcium concentrations).
- Dosing: Hepatic Impairment: Adult No initial dosage adjustment necessary

Disease-related concerns

- Hyperphosphatemia: may result in soft tissue and pulmonary arterial calcium-phosphate precipitation.
- Hypokalemia: may result in life-threatening cardiac arrhythmias.
- Kidney stones (calcium-containing)
- Renal impairment: Use with caution in patients with chronic renal failure to avoid hypercalcemia.

PREGNANCY AND LACTATION

- Calcium injection is U.S. Food and Drug Administration pregnancy *category C*.

- Calcium is excreted as a natural component in human breast milk, but no definitive evaluations have been performed on potential adverse effects in the breastfed child following maternal intravenous calcium administration.


Thank you for your Attention