



PD005-A01-00

5.4 Hypotension, Bradycardia, and Cardiac Arrhythmias with Rapid Administration

Rapid injection of Calcium Gluconate Injection may cause vasodilation, decreased blood pressure, bradycardia, cardiac arrhythmias, syncope and cardiac arrest. To avoid adverse reactions that may follow rapid intravenous administration, Calcium Gluconate Injection should be diluted with 5% dextrose or normal saline and infused slowly. If rapid intravenous bolus of Calcium Gluconate Injection is required, the rate of intravenous administration should not exceed 200 mg/minute in adults and 100 mg/minute in pediatric patients and ECG monitoring during administration is recommended [see Dosage and Administration (2.1)].

5.5 Aluminum Toxicity

Calcium Gluconate Injection contains aluminum, up to 400 mcg per liter, that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 mcg/kg/day to 5 mcg/kg/day accumulate aluminum levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

6 ADVERSE REACTIONS

The following serious adverse reactions associated with the use of calcium gluconate were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

- Arrhythmias with Concomitant Cardiac Glycoside Use [see Warnings and Precautions (5.1)]
- End-Organ Damage due to Intravascular Ceftriaxone-Calcium Precipitates [see Warnings and Precautions (5.2)]
- Tissue Necrosis and Calcinosis [see Warnings and Precautions (5.3)]
- Hypotension, Bradycardia, and Cardiac Arrhythmias [see Warnings and Precautions (5.4)]
- Aluminum toxicity [see Warnings and Precautions (5.5)]

The following adverse reactions associated with the use of calcium gluconate were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Cardiovascular : Vasodilation, decreased blood pressure, bradycardia, cardiac arrhythmia, syncope, cardiac arrest

Administration site reactions : Local soft tissue inflammation, local necrosis, calcinosis cutis and calcification due to extravasation

7 DRUG INTERACTIONS

7.1 Cardiac Glycosides

Hypercalcemia increases the risk of digoxin toxicity, while digoxin may be therapeutically ineffective in the presence of hypocalcemia. Synergistic arrhythmias may occur if calcium and cardiac glycosides are administered together. Avoid administration of Calcium Gluconate Injection in patients receiving cardiac glycosides; if considered necessary, administer Calcium Gluconate Injection slowly in small amounts and monitor ECG closely during administration.

7.2 Calcium Channel Blockers

Administration of calcium may reduce the response to calcium channel blockers.

7.3 Drugs that may cause Hypercalcemia

Vitamin D, vitamin A, thiazide diuretics, estrogen, calcipotriene and teriparatide administration may cause hypercalcemia. Monitor plasma calcium concentrations in patients taking these drugs concurrently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk summary

Limited available data with Calcium Gluconate Injection use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. There are risks to the mother and the fetus associated with hypocalcemia in pregnancy [see Clinical Considerations].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal risk

Maternal hypocalcemia can result in an increased rate of spontaneous abortion, premature and dysfunctional labor, and possibly preeclampsia.

Fetal/Neonatal adverse reactions

Infants born to mothers with hypocalcemia can have associated fetal and neonatal hyperparathyroidism, which in turn can cause fetal and neonatal skeletal demineralization, subperiosteal bone resorption, osteitis fibrosa cystica and neonatal seizures. Infants born to mothers with hypocalcemia should be carefully monitored for signs of hypocalcemia or hypercalcemia, including neuromuscular irritability, apnea, cyanosis and cardiac rhythm disorders.

8.2 Lactation

Risk summary

Calcium is present in human milk as a natural component of human milk. It is not known whether intravenous administration of Calcium Gluconate Injection can alter calcium concentration in human milk. There are no data on the effects of Calcium Gluconate Injection on the breastfed infant, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Calcium Gluconate Injection and any potential adverse effects on the breastfed child from Calcium Gluconate Injection or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of Calcium Gluconate Injection have been established in pediatric patients for the treatment of acute, symptomatic hypocalcemia.

Pediatric approval for Calcium Gluconate Injection, including doses, is not based on adequate and well-controlled clinical studies. Safety and dosing recommendations in pediatric patients are based on published literature and clinical experience [see Dosage and Administration (2.2)].

Concomitant use of ceftriaxone and Calcium Gluconate Injection is contraindicated in neonates (28 days of age or younger) due to reports of fatal outcomes associated with the presence of lung and kidney ceftriaxone-calcium precipitates. In patients older than 28 days of age, ceftriaxone and Calcium Gluconate Injection may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid [see Contraindications (4) and Warnings and Precautions (5.2)]. This product contains up to 400 mcg/L aluminum which may be toxic, particularly for premature neonates due to immature renal function. Parenteral administration of aluminum greater than 4 to 5 mcg/kg/day is associated with central nervous system and bone toxicity [see Warnings and Precautions (5.5)].

8.5 Geriatric Use

In general dose selection for an elderly patient should start at the lowest dose of the recommended dose range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

For patients with renal impairment, initiate Calcium Gluconate Injection at the lowest dose of the recommended dose ranges across all age groups. Monitor serum calcium levels every 4 hours [see Dosage and Administration (2.4)].

8.7 Hepatic Impairment

Hepatic function does not impact the availability of ionized calcium after calcium gluconate intravenous administration. Dose adjustment in hepatically impaired patients may not be necessary.

10. OVERDOSAGE

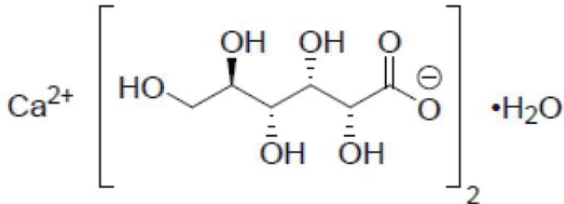
Overdosage of Calcium Gluconate Injection may result in hypercalcemia. Symptoms of hypercalcemia typically develop when the total serum calcium concentration is ≥12 mg/dL. Neurologic symptoms include depression, weakness, fatigue, and confusion at lower levels, with patients experiencing hallucinations, disorientation, hypotonicity, seizures, and coma. Effects on the kidney include diminished ability to concentrate urine and diuresis.

If overdose of Calcium Gluconate Injection occurs immediately discontinue administration and provide supportive treatments to restore intravascular volume as well as promote calcium excretion in the urine if necessary.

11. DESCRIPTION

Calcium Gluconate Injection, USP is a sterile, preservative-free, nonpyrogenic, supersaturated solution of calcium gluconate, a form of calcium, for intravenous use.

Calcium Gluconate is calcium D-gluconate (1:2) monohydrate. The structural formula is:



Molecular formula: C₁₂H₂₂CaO₁₄• H₂O

Molecular weight: 448.39

Solubility in water: 3.5 g/100 mL at 25°C

Calcium Gluconate Injection, USP is available as 1,000 mg per 10 mL (100 mg per mL) or 5,000 mg per 50 mL (100 mg per mL) in a single-dose vial, or 10,000 mg per 100 mL (100 mg per mL) in a pharmacy bulk package.

Each mL of Calcium Gluconate Injection, USP contains 100 mg of calcium gluconate (equivalent to 94 mg of calcium gluconate and 4.5 mg of calcium saccharate tetrahydrate), hydrochloric acid and/or sodium hydroxide for pH adjustment (6.0 to 8.2) and sterile water for injection, q.s. It contains no antimicrobial agent.

Each mL of Calcium Gluconate Injection, USP contains 9.3 mg (0.465 mEq) of elemental calcium.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Intravenous administration of calcium gluconate increases serum ionized calcium level. Calcium gluconate dissociates into ionized calcium in plasma. Ionized calcium and gluconate are normal constituents of body fluids.

12.3 Pharmacokinetics

Absorption

Calcium Gluconate Injection is 100% bioavailable following intravenous injection.

Metabolism

Calcium itself does not undergo direct metabolism. The release of ionized calcium from intravenous administration of calcium gluconate is direct and does not seem to be affected by the first pass through the liver.

Distribution

Calcium in the body is distributed mainly in skeleton (99%). Only 1% of the total body calcium is distributed within the extracellular fluids and soft tissues. About 50% of total serum calcium is in the ionized form and represents the biologically active part. 8% to 10% serum calcium is bound to organic and inorganic acid and approximately 40% is protein-bound (primarily to albumin).

Elimination

Studies have shown a relationship between urinary calcium excretion and the intravenous administration of calcium gluconate, with a significant increase in urinary calcium excretion observed after the intravenous administration of calcium gluconate.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of Calcium Gluconate Injection. Calcium gluconate was not mutagenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* (strains TA-1535, TA-1537, and TA-1538) or *Saccharomyces cerevisiae* (Strain D4). Fertility studies in animals have not been conducted with calcium gluconate administered by the intravenous route.

16. HOW SUPPLIED/STORAGE AND HANDLING

Calcium Gluconate Injection USP is a clear, colorless to slightly yellow solution supplied as follows:

Calcium Gluconate total Product Strength (Concentration)	Carton NDC and Package Configuration	Vial NDC
1,000 mg calcium gluconate per 10 mL (100 mg per mL)	65145-170-25 25 x 10 mL single dose vials	65145-170-01
5,000 mg calcium gluconate per 50 mL (100 mg per mL)	65145-171-25 25 x 50 mL single dose vials	65145-171-01
10,000 mg calcium gluconate per 100 mL (100 mg per mL)	65145-172-20 20 x 100 mL pharmacy bulk package	65145-172-01

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not freeze.

Preservative Free. Discard any unused portion in the single-dose vial immediately or the Pharmacy Bulk Package vial within 4 hours after initial closure puncture.

Each dose dispensed from the Pharmacy Bulk Package vial must be used immediately.

The diluted solution must be used immediately.

NOTE: Supersaturated solutions are prone to precipitation. The precipitate, if present, may be dissolved by warming the vial to 60° to 80°C, with occasional agitation, until the solution becomes clear. Shake vigorously. Allow to cool to room temperature before dispensing. Use injection only if clear immediately prior to use.

17. PATIENT COUNSELING INFORMATION

- Advise the patient that the risks associated with infusion including local tissue inflammation, local necrosis and calcinosis. [see Warnings and Precautions (5.3)].

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