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AN OVERVIEW CALCIUM GLUCONATE INDICATION AND PHARMACEUTICAL PROPERTIES

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Abstract:

Calcium, a biologically occurring ion, induces the narrowing of blood vessels and exerts a beneficial effect on the force of heart contractions. The use of this method to avoid post-spinal hypotension has been proposed, but it has not been fully assessed for patients following cesarean section. Administering intravenous calcium gluconate in conjunction with morphine helps alleviate abdominal pain caused by lead poisoning resulting from the consumption of opium tainted with lead. Intravenous administration of calcium gluconate has been employed as a preventive measure against postoperative hypocalcemia (POH) subsequent to parathyroidectomy for secondary hyperparathyroidism in individuals with chronic kidney disease (CKD).

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INTRODUCTION:

Calcium gluconate, is an inorganic salt that is resonance-stabilized. It is commonly used therapeutically as a food additive, a nutritional supplement, an antacid, and a phosphate binder. Calcium gluconate is a highly prevalent chemical in the earth's crust and is frequently present in biological materials, including egg and oyster shells, the exoskeletons of crustaceans, and dark leafy greens like broccoli and kale [1]. The applications of calcium carbonate extend beyond the field of medicine. Calcium gluconate is utilized industrially as a filler in paint, paper, fire extinguishers, and adhesives. It is also employed as a constituent of agricultural and mining dust, as well as an ingredient in household cleaners, food coloring compounds, and cosmetics [1]. Calcium gluconate is a versatile compound used in the pharmaceutical industry. It serves as a food additive to provide nutritional benefits, a calcium supplement to address low serum calcium levels, an antacid for gastrointestinal issues, a phosphate binder for chronic kidney disease, and a tableting excipient for the production of other pharmaceutical agents and food products [1,2].

Calcium gluconate is prescribed for individuals with low levels of calcium in their blood, which can occur in conditions such as osteoporosis, osteomalacia, hypothyroidism, hypoparathyroidism, pseudohypoparathyroidism, DiGeorge syndrome, kidney dysfunction, pancreatitis, rheumatoid arthritis, Fanconi syndrome, during pregnancy, while breastfeeding, in post-menopausal women, and when taking specific medications [3,4].

Calcium gluconate is used as an antacid to treat various conditions such as heartburn caused by gastroesophageal reflux disease (GERD), damage to the upper gastrointestinal mucosa caused by NSAIDs, duodenal and gastric ulcers, biliary reflux, stress gastritis, exocrine pancreatic insufficiency, bile acid-mediated diarrhea, non-ulcer dyspepsia, and urinary alkalization [5,6]. Similar to aluminum and magnesium salts, calcium carbonate enhances gastrointestinal movement and is used to treat constipation [7].

Calcium gluconate is prescribed for the treatment of hyperphosphatemia in individuals with chronic renal disease. It acts as a phosphate binder and can also be used to induce urinary alkalization in cases of overdose. Additionally, it is used as a preventive measure in pregnant women prior to childbirth to prevent aspiration pneumonitis [8].

Recent studies indicate that calcium carbonate may have other applications in cancer treatment. These include employing calcium supplements to treat colorectal adenomas and utilizing rare-earth-doped calcium gluconate with cerium to eliminate tumor cells by X-ray-induced photodynamic therapy [9].

DISCUSSION:

The body naturally contains calcium. The majority of the body's calcium reserves are located in the bones and teeth in the form of hydroxyapatite. The remaining calcium in the body is distributed in the blood, extracellular fluid, muscle, and other tissues [10]. Within the bloodstream, approximately 40% of calcium is attached to albumin, 13% is connected to an anion such as phosphate and lactate, and the remaining 47% exists as unattached, ionized calcium (Ca^{2+}). The concentration of ionized calcium in the bloodstream is crucial and carefully regulated by homeostatic mechanisms due to its physiological activity and critical involvement in the cellular functions of excitable tissues, including blood vessels, muscles, glands, and neurons [1].

Calcium carbonate exerts its pharmacologic effects through three distinct modes of action. Calcium has an impact on the stomach, small intestine, and blood [11].

Calcium carbonate functions as an antacid by acting as a buffer in the acidic environment of the stomach, effectively neutralizing gastric acid. Upon entering the stomach, $CaCO_3$ undergoes dissociation, resulting in the formation of ionized calcium (Ca^{2+}) and a carbonate anion (CO_3^{2-}). The carbonate anion will then attach to the unbound protons (H^+) present in the stomach, so elevating the pH level by reducing the concentration of hydrogen ions. Elevating the pH level in the stomach leads to the inhibition of pepsin, bile acids, and the toxins produced by Helicobacter pylori [12].

By inhibiting pepsin, an enzyme that breaks down tissue protein, and bile acid, the damage to and healing of ulcers in the stomach and duodenum's mucosal lining, as well as the injury to the esophagus caused by GERD, can be reduced and promoted, respectively [12]. Some criticism remains regarding the ulcer-healing effects of calcium carbonate being solely attributed to its acid-neutralizing mechanism. This is because calcium carbonate can cause acid rebound by elevating plasma gastrin levels. Additionally, long-term use of calcium carbonate has been found to increase prostaglandins PGE2 and PGF2, which may

provide an alternative explanation for its ulcer-healing properties [13].

Calcium carbonate, in addition to its antacid properties, also enhances gastrointestinal motility and triggers peristalsis [14]. Chewing and partially digesting calcium carbonate triggers peristalsis in the esophagus, which helps to transfer the acid into the stomach and reduce sensations of heartburn.

Calcium carbonate functions in the small intestines as a phosphate binder and medication chelator. Hyperphosphatemia or overdose leads to the formation of an insoluble substance when calcium binds, which prevents the absorption of excessive dietary phosphate or drugs. This product is then excreted in the stool. In addition, calcium carbonate, which is used as a calcium supplement, also functions in the small intestine by forming a complex with oxalate to hinder its absorption and the production of kidney stones [1].

Furthermore, calcium carbonate is effective in addressing or preventing the adverse calcium imbalance observed in cases of low serum calcium levels. Following active absorption in the small intestines facilitated by vitamin D and passive diffusion, ionized calcium circulates in the bloodstream [15].

The main cause of hypocalcemic toxicity during therapeutic plasma exchange (TPE) is the infusion of pharmaceutical albumin, which strongly binds to ionized calcium in the plasma, acting as the replacement fluid [16]. Additional research has demonstrated that adding calcium gluconate to the albumin replacement solution is an excellent method for preventing this commonly occurring, albeit typically mild, problem [17,18].

The decrease in plasma calcium levels observed after donor apheresis procedures, such as peripheral blood hematopoietic progenitor cell collection, is caused by the reintroduction of plasma containing a citrate-based anticoagulant back to the donor or patient. Administering calcium infusion, typically in the form of gluconate salt, during the collection operation has been found to be successful in preventing a noticeable decrease in plasma calcium levels and mitigating any associated symptoms [19,20].

Not all methods of administering preventive calcium supplements are equally successful in cytapheresis procedures and therapeutic plasma exchange (TPE). When peripheral blood hematopoietic progenitor collection is done together with hemodialysis without giving additional calcium gluconate, the purpose of the hemodialysis is to keep the calcium level in the patients' plasma stable. However, when plasma exchange is done together with hemodialysis in similar conditions, the plasma calcium level decreases significantly [20].

Placing a ligature around the cervix of the second upper molar of rats caused significant reductions in body weight throughout the duration of the trial. This is likely due to difficulty with chewing caused by EPD, as indicated by previous research [21]. This shows that our model effectively caused periodontitis and loss of alveolar bone. Administration of calcium gluconate at all dosage levels effectively suppressed the body-weight reductions generated by EPD. In contrast, treatment with indomethacin led to even more dramatic declines in body-weight in EPD rats. Indomethacin, employed as a benchmark medication in this investigation, is a nonsteroidal anti-inflammatory medicine (NSAID) that exerts its anti-inflammatory properties by obstructing cyclooxygenase and impeding the formation of prostaglandins. Indomethacin medication can lead to ulceration and mucosal damage in the gastrointestinal system, which is believed to be responsible for the increased weight loss observed during EPD.

Treatment with calcium gluconate resulted in dose-dependent and significant reductions in alveolar bone loss scores, providing direct evidence of its ability to alleviate experimental periodontal disease (EPD). The alveolar bone loss scoring system relies on macroscopic evaluation to assess the extent of alveolar bone loss by measuring the exposure of dental roots from alveolar sockets. Higher scores indicate a more significant degree of alveolar bone loss [21,23].

The significance of the infiltration of acute inflammatory cells, particularly neutrophils, into the gingival tissue in the progression of periodontal disease has been previously demonstrated [24]. Inflammatory cells are crucial in removing factors that induce inflammation. However, activated polymorphonuclear leukocytes (PMNs) are a source of oxygen metabolites. Oxygen metabolites play a role in attracting neutrophils, namely polymorphonuclear leukocytes (PMNs), to damaged tissues [24]. Myeloperoxidase (MPO) is a harmful enzyme that is secreted from polymorphonuclear leukocytes (PMNs) and is significantly elevated in cases of periodontal disease. Decreased myeloperoxidase (MPO) activity

can provide as evidence for the decrease in neutrophil migration into gingival tissue [24].

Pharmacokinetics

Calcium carbonate tablets undergo gastric breakdown, resulting in the formation of soluble calcium salts. Consequently, calcium becomes accessible for absorption in the body. The process of calcium absorption takes place in the small intestine through active transport, which relies on the presence of Vitamin D, as well as diffusion. Calcium absorption, expressed as a fraction of the amount ingested, varies at different stages of life and reaches its peak during infancy, early puberty, and the final two trimesters of pregnancy in women. The deterioration in physical and cognitive abilities gradually occurs as an individual advances into old age, with a significant fall beginning after menopause for women and in their late 50s for men [16]. Calcium absorption can be influenced by various factors, including age, the kind of calcium carbonate, dosage, stomach acidity, estrogen levels, vitamin D levels, and genetic variations [12].

The largest level of fractional absorption occurs when 500 mg is consumed with food, and the stomach has an acidic environment. The fractional absorption is also enhanced in those who possess adequate levels of vitamin D, do not suffer from any absorption disorders, are young, have higher levels of estrogen, and have a larger physique [25]. The absorption of calcium carbonate is reduced in individuals with a mucosal lining disease or achlorhydria [25].

Calcium carbonate is available in tablet, chewable, oral solution, or powder formulations. Tablets should be ingested with a complete glass of water. Prior to calculating the dose, it is important to vigorously shake the oral suspension to guarantee the administration of the correct amount. Calcium carbonate exhibits greater bioavailability when consumed in powdered form [26]. Calcium citrate has a greater potential to be absorbed by the body compared to calcium carbonate. However, when it comes to foods that have been supplemented with calcium, calcium carbonate is more effective at being absorbed than other compounds used for calcium fortification [27].

Given the temporary and intermittent nature of calcium carbonate/antacid usage, as well as the low dosage of calcium carbonate used for supplementing, the majority of negative effects are insignificant. Nevertheless, an overdose may transpire when substantial quantities are consumed over a prolonged period or misused. The overdose can result in the patient experiencing negative effects ranging from moderate to severe [28].

Calcium carbonate is acknowledged by the FDA as a generally safe pharmaceutical and food supplement. For short-term usage, the recommended maximum dosage of calcium carbonate is 8 to 10 grams per day. Nevertheless, the prolonged consumption of more than 2 grams can result in detrimental consequences such as excessive levels of calcium in the blood (hypercalcemia), the formation of kidney stones (renal calculi), abnormally low levels of phosphate in the blood (hypophosphatemia), and kidney damage (nephrotoxicity), particularly in those with chronic kidney disease [1,12]. Additionally, fetotoxicity has been noted in pregnant women who consume more than 1500 mg/kg of body weight per day of calcium carbonate [1].

Calcium gluconate is contraindicated in people with hypercalcemia, hypersensitivity to calcium gluconate, and sarcoidosis. Furthermore, its utilization necessitates carefulness in those with profound hypophosphatemia. It is not recommended to give neonates intravenous calcium gluconate together with ceftriaxone because ceftriaxone can create tiny particles that cannot dissolve by binding to calcium. It is recommended to flush IV lines in elderly individuals before administering calcium and ceftriaxone [25]. IV calcium is not recommended for the treatment of hyperkalemia in cases of digoxin toxicity. Nevertheless, a research conducted in 2011 by Levin et al. demonstrated that none of the 23 individuals identified with digoxin toxicity and treated with calcium experienced any abnormal heart rhythm during a 4-hour period after calcium treatment. Therefore, the data supporting this contraindication is ambiguous. Calcium gluconate should not be withheld in cases of hyperkalemia that pose a significant risk to the patient's life [26].

INDICATIONS:
Hypocalcemia

Calcium gluconate is a calcium compound that is administered intravenously to restore low levels of calcium in the blood, a condition known as hypocalcemia. The prevalence of hypocalcemia in hospitalized adult patients ranges from 15 to 88%,

with variations according on the method of assessment (serum or ionized calcium). Most of the calcium in the body is found in bones, while just 1% of the total calcium is exchanged with the fluid outside the cells. Around 40% of calcium in the bloodstream is attached to protein, such as albumin, whereas around 50% of calcium in the bloodstream is in a biologically active state. 10% of the calcium is bound to anions to create calcium salts. The clinical symptoms of hypocalcemia vary based on the severity of blood calcium levels and the speed at which they decrease. Symptoms of a hypocalcemic crisis occur when the ionized calcium concentration reaches 2.8 mg/dL (0.7 mmol/L) [6]. The symptoms encompass circumoral paresthesias, muscle cramps, myalgias, dysphagia, sadness, disorientation, irritability, seizures, tetany, laryngospasm, and hypotension. The physical examination reveals hyperreflexia, carpopedal spasm, Trousseau sign, and Chvostek sign. Hypocalcemia is characterized by a longer QT interval on an EKG. However, it is uncommon for calcium imbalances to directly cause cardiac arrest, therefore the relevance of this finding is uncertain. Electrocardiogram (EKG) abnormalities associated with low levels of calcium in the blood, known as hypocalcemia, can be effectively treated with intravenous administration of calcium gluconate. This treatment restores the QT interval, a measure of electrical activity in the heart, to its normal duration [1,2].

The primary approach to treating hypocalcemia is to initially prioritize symptomatic management rather than solely focusing on restoring normal levels of calcium in the blood. For patients experiencing severe hypocalcemia accompanied by seizures, laryngospasm, hypotension, or tetany, it is crucial to administer immediate intravenous calcium gluconate to restore calcium levels and alleviate the severe and life-threatening symptoms. It is necessary to monitor magnesium levels when replenishing calcium since low magnesium levels are a significant cause of low calcium levels. Hypomagnesemia results in hypocalcemia through the inhibition of parathyroid hormone secretion and the reduction of renal resistance to parathyroid hormone, ultimately causing a decrease in the reabsorption of calcium by the kidneys [1].

Insufficient evidence exists to support the empirical use of calcium gluconate in cases of hypocalcemia or hypercalcemia during cardiac arrest, as it is uncommon for calcium imbalances to directly induce cardiac arrest. Calcium gluconate is administered in cases of cardiac arrest caused by hyperkalemia or hypermagnesemia, based on empirical evidence [2,27].

Hyperkalemia

Increased levels of potassium in the extracellular environment can lead to abnormal heart rhythms, known as cardiac arrhythmias, which can ultimately result in cardiac arrest and mortality. Calcium gluconate is utilized in the treatment of hyperkalemia to maintain the membranes of heart cells. Immediate administration of calcium is necessary for any patient who presents with hyperkalemia and EKG abnormalities, which indicate a hyperkalemic emergency. High amounts of potassium disrupt the stability of cardiac membranes by raising the threshold potential of cardiac myocytes. Supplementing with calcium reduces the level at which the transmembrane voltage gradient can be restored. Although calcium provides protection to myocytes against potassium, it does not effectively address the problem of hyperkalemia. In such cases, other medications are usually prescribed, including insulin and dextrose or sodium bicarbonate, which facilitate the movement of potassium into cells. Another option is sodium polystyrene sulfate, which enhances potassium excretion through stool. Nevertheless, dialysis is the most effective method of removing potassium from the body, especially in people with kidney disease [2,28].

Excessive levels of magnesium in the blood

Acute magnesium poisoning is an uncommon occurrence that usually occurs in individuals who are administered magnesium sulfate as a preventive measure against eclampsia in the field of obstetrics. Manifestations of magnesium poisoning may include reduced deep tendon reflexes, cardiac arrest, and respiratory depression. The toxicity arises from magnesium's ability to inhibit calcium and potassium channels, both on the outside and inside of cells. Calcium gluconate effectively treats hypermagnesemia by directly counteracting the effects of magnesium at specific locations such as the neuromuscular junction [5,29]. Furthermore, it is also used in the treatment of hydrofluoric acid burns.

Calcium is a crucial component in the treatment of hydrofluoric acid burns. It works by attaching to fluoride ions, so neutralizing them and preventing more harm. In addition, fluoride has the potential to induce hypocalcemia by forming fluorapatite (Ca(PO)F) salt, which subsequently reduces the concentration of free calcium in the bloodstream. Calcium gluconate immediately restores the levels of

ionized calcium in the blood in situations when there is a deficiency of calcium caused by fluoride.

Toxicity of beta-blockers and calcium channel blockers

Calcium can be beneficial in cases of beta-blocker overdose in patients who are unresponsive to other treatments and experiencing shock. The presence of calcium in beta-blocker toxicity is believed to be responsible for its impact on cardiac inotropy, as calcium influx into cardiac cells directly contributes to the contraction of myofibrils [30].The user's text is incomplete and does not provide any information.

Calcium gluconate is also utilized in the management of calcium channel blocker (CCB) toxicity. CCB poisoning induces hypotension, bradycardia, and a reduction in cardiac contractility. The rationale for calcium's action against CCB toxicity is to overpower the calcium receptors and counteract the CCB in a competitive manner. Therefore, by enhancing the strength of the heart's contractions, coupled with intravenous fluids, it is possible to improve the symptoms of low blood pressure caused by calcium channel blocker toxicity [3,30].

The administration of calcium as a treatment for abdominal discomfort is considered outdated and is no longer recommended in current textbooks and contemporary articles. Shelling stated that lead colic could be relieved nearly immediately by administering calcium chloride intravenously. This was believed to provide more proof that calcium facilitates the movement of lead into the bones [31]. Nevertheless, further research conducted by Aub and colleagues invalidated this idea, as the rapid relief of pain cannot be attributed to the deposition of lead in the bone tissue. Aub and his colleagues were thus inclined to argue that calcium's effect in this case is to induce relaxation of the intestinal tract [31]. Furthermore, it is hypothesized that this phenomenon may be attributed to the impact of calcium on the intestinal cells, resulting in enhanced relaxation of these cells. Our study also validates the swift commencement of calcium's effects in lead toxicity, since numerous patients experienced relief from stomach pain within one hour of commencing treatment.

Administering calcium gluconate intravenously in conjunction with morphine can enhance relief from abdominal discomfort caused by lead poisoning resulting from the consumption of opium tainted with lead. Additional research using bigger sample sizes is necessary to have a more comprehensive understanding of this phenomenon. Additionally, it is advisable to conduct interventional studies to determine whether the use of calcium salts in cases of suspected lead-induced stomach pain can confirm the presence of lead toxicity [32].

CONCLUSION:

Therefore, calcium gluconate has great potential as a viable option for the treatment of various disorders. Administration of intravenous calcium gluconate did not result in any statistically significant improvement in the nonrhythmic electrocardiogram (ECG) abnormalities observed in patients with hyperkalemia. IV Ca-gluconate was determined to have a restricted impact on treatment when rhythm abnormalities were seen on the ECG. It is necessary to evaluate the effectiveness of calcium salts on a bigger sample size. Administering intravenous (IV) calcium salts is commonly advised as a cardioprotective medication during the emergency management of severe hyperkalemia. Nevertheless, this recommendation is substantiated by a limited amount of research and is based on personal accounts.

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