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Managing the Intravenous Calcium Shortage: Evaluation of Calcium Chloride Stability in 0.9% Sodium Chloride and Dextrose 5% Water Polyvinyl Chloride Bags

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Abstract

Background: Intravenous calcium chloride (CaCl) is commonly used by inpatient practitioners for a myriad of indications from electrolyte abnormalities to advanced cardiac life support. Currently, a paucity of data is available regarding the stability of CaCl after preparation of intravenous admixtures.

Purpose: This study evaluated the physical and chemical stability of CaCl 10% diluted in 0.9% sodium chloride or dextrose 5% water polyvinyl chloride bags.

Method: CaCl 10% solution (1000 mg) was diluted with 0.9% sodium chloride or dextrose 5% water 100 mL for injection to a final concentration of 10 mg/mL. CaCl 10% solution (2000 mg) was diluted with 0.9% sodium chloride or dextrose 5% water 150 mL for injection to a final concentration of 13.3 mg/mL. Each of the preparations were stored at room temperature (23–25°C) and exposed to fluorescent light. Samples of each preparation were analyzed on days 0, 2, 3, 5, and 7. Sterility and physical stability were assessed. Chemical stability of CaCl was evaluated by indirect potentiometry.

Results: CaCl 10 mg/mL and 13.3 mg/mL solutions in polyvinyl chloride bags were physically stable during the entire 7-day study period. CaCl retained >90% of the original concentration at 7 days after preparation in 0.9% sodium chloride and dextrose 5% water.

Conclusion: CaCl diluted to 10 mg/mL or 13.3 mg/mL with 0.9% sodium chloride or dextrose 5% water for injection is both physically and chemically stable for a period of 7 days with 10% degradation under conditions of room temperature with fluorescent lighting.

Keywords

calcium chloride; stability; electrolyte; drug shortage

The increasing number of drug shortages in the United States is placing considerable burden upon patients, clinicians, and health system institutions. Efforts dedicated to providing optimal patient care by utilizing first-line agents are frequently obstructed for several medication classes. Added to this is the resultant strain on health system financial and personnel resources. In many instances, clinicians dedicate significant time toward locating and procuring shorted agents through atypical channels such as secondary drug distributors or borrowing medications from other institutions. When these channels have been exhausted, the procurement of costlier or less rigorously studied alternative agents becomes compulsory. This is often associated with changes to typical medication practice guidelines, requiring additional education and training to a broad spectrum of health care professionals, including physicians, nurses, pharmacists, and technicians.

A recent shortage of parenteral calcium formulations necessitated reserving and rationing intravenous calcium gluconate in critical areas of hospital practice, for example, the neonatal intensive care unit and patients in hypocalcemic crisis who lack central venous access but still require urgent intravenous calcium repletion. The calcium gluconate shortage also led to consideration of intravenous calcium chloride (CaCl) in nonemergent circumstances where administration of parenteral calcium was desired. However, CaCl is most typically administered as an intravenous push formulation for cardiac resuscitation, and peripheral intravenous administration can lead to severe skin necrosis if extravasated.¹ Therefore, it is recommended that CaCl be administered via a central line or diluted prior to administration into a peripheral vein.

Diluting CaCl in intravenous solutions provides a safer and more consistent administration option for the patient and nursing staff. Previous stability studies have shown that CaCl is stable in a variety of solutions for at least 24 hours when diluted to 1 mg/mL and mixed with amikacin sulfate 5 mg/mL in polyvinyl chloride (PVC) bags.² However, most stability studies to date do not measure actual calcium concentrations or durations longer than 24 hours, significantly limiting their applicability to clinical practice.

The purpose of this study was to determine the physical and chemical stability of intravenous CaCl diluted with either 0.9% sodium chloride or dextrose 5% water and placed in standard PVC bags. Stability of the CaCl admixtures while stored at room temperature and exposed to normal fluorescent lighting was evaluated over a 7-day period.

METHODS

Sample Preparation

All study samples were prepared by the University of Colorado Hospital (UCH) Pharmacy in a class 100 hood under standard aseptic technique. Samples A and B were prepared by diluting CaCl^a 1000 mg into PVC bags containing 100 mL of 0.9% sodium chloride^b and 100 mL of dextrose 5% water^c, respectively, to a final concentration of approximately 10 mg/mL. Samples C and D were prepared by diluting CaCl 2000 mg into PVC bags

^aCalcium Chloride Injection, USP. 100 mg/mL, 10 mL vial, Manufactured by American Regent, Inc. Shirley, NY 11967. Lot 0356.

^bSodium Chloride 0.9% 100 mL Polyvinyl Chloride Bag. Baxter Healthcare Corporation. Deerfield, IL 80015. Lot P265611.

^cDextrose 5% Water 100 mL Polyvinyl Chloride Bag. Baxter Healthcare Corporation. Deerfield, IL 80015. Lot P265538.

containing 150 mL of 0.9% sodium chloride^d and 150 mL of dextrose 5% water^e, respectively, to a final concentration of approximately 13.3 mg/mL. Due to the ongoing calcium shortage at the time of this study, only one admixture was prepared for each of the 4 study conditions. The preparations were then stored at room temperature (23-25°C) under normal fluorescent lighting. Samples for each storage condition were assessed for physical and chemical stability over a total period of 7 days. Chemical stabilities were assessed on days 0, 1, 2, 3, 5, and 7.

Physical Evaluation

Physical stability of CaCl was assessed by visual examination. Solutions were evaluated against a black and white background for visible particulate matter, cloudiness, or color change. Sterility of the samples was assessed by taking aliquots of each solution and placing it into a micro broth solution. Sterility was assessed under incubation (38°C) and at room temperature (23-25°C). The sample was deemed sterile if absence of microbial growth was demonstrated at 7 days.

Chemical Stability Analysis

Total calcium concentrations were determined by using indirect potentiometry utilizing a calcium ion selective electrode in conjunction with a sodium reference electrode. Sample analysis was performed utilizing a Beckman Coulter DXC-800 analytical platform (Beckman Coulter, Inc, Indianapolis, IN) and assay validated by the University of Colorado Hospital Clinical Laboratory. Day 0 sample aliquots were taken directly to the laboratory for analysis after admixture preparation. Sample aliquots on days 1, 2, 3, 5, and 7 were analyzed at 24, 48, 72, 120, and 168 hours, respectively. One sample aliquot was analyzed for each study admixture and time point. The percentage of calcium remaining at each time point was determined. The product was deemed stable if there was less than or equal to 10% degradation of the initial product.

RESULTS

CaCl diluted to 10 mg/mL and 13.3 mg/mL with 0.9% sodium chloride or dextrose 5% water for injection was physically stable throughout the study. Solutions remained clear throughout the study. No precipitation or antimicrobial growth was observed over the study period.

The results of the chemical stability analysis are shown in Table 1. The actual initial measured concentrations were lower than predicted due to the overfill volume in the 100 mL and 150 mL PVC bags, and because the 10 mL CaCl was added to the total volume. At least 90% of the original day 0 calcium concentration remained in all sample preparations over the 7-day study period. On average, 92.5% of the original total calcium concentration was remaining in each of the 4 admixtures. The largest decrease in calcium concentrations appeared to occur in the first 24 hours. No degradation or decreases in measured calcium concentrations were seen from days 1 to 7 after admixture.

^dSodium Chloride 0.9% 150 mL Polyvinyl Chloride Bag, Baxter Healthcare Corporation, Deerfield, IL 80015. Lot C826834.

^eDextrose 5% Water 150 mL Polyvinyl Chloride Bag, Baxter Healthcare Corporation, Deerfield, IL 80015. Lot C823930.

DISCUSSION

The manufacturer of CaCl recommends that unopened vials of CaCl be stored at controlled room temperature.³ Opened vials are to be discarded after use. Our study demonstrates that calcium chloride is stable for at least 7 days when diluted with 0.9% sodium chloride or dextrose 5% water for injection and stored in PVC bags. Measured calcium concentrations were similar from study days 1 to 7 and were within the standard error limits of the analytical assay, demonstrating that no degradation of calcium occurred during this period. The only measured decreases in calcium concentrations occurred from day 0 to day 1. Given the polarity of calcium, it is unlikely due to adsorption to the PVC material; however, our methodology is unable to verify that assumption or validate if calcium degradation actually occurred. Physical stability and sterility of the samples were maintained throughout the study period.

Our performance of these stability tests was necessitated by the shortage of parenteral calcium products. Initially, a shortage of calcium gluconate was recognized, but soon after followed a shortage of CaCl and an ensuing unavailability or, at best, erratic supply of both intravenous CaCl and calcium gluconate. Compounding this, inability to verify CaCl stability in the currently available literature resulted in unacceptable drug waste from unused CaCl admixtures. Prior to generating this stability data, UCH wasted 41 CaCl admixtures in 1 week. Waste was due mostly to the drug being ordered but not administered to the patient. After implementation of the new 7-day expiration and application of the USP 797 guidelines for low-risk compounded sterile preparations, the CaCl admixture waste due to expiration was reduced to zero.

In addition to reducing drug waste with increased stability data, UCH distributed the following guidelines to its medical staff for utilization until an adequate supply of parenteral calcium products was obtained:

- Please give critical attention when prescribing intravenous calcium.
 - Are patients exhibiting symptoms of hypocalcemia?
 - Is there an emergent indication?
 - Has an ionized calcium, albumin, potassium, or magnesium serum level been ordered or reviewed?
- Intravenous calcium gluconate, if available, will be restricted to patients postthyroidectomy, or other patients in hypocalcemic crisis or other crisis, eg, marked hyperkalemia but lacking central venous access.
- Patients requiring large amounts of calcium repletion, but having central venous access, eg, patients on dialysis, should receive CaCl diluted to a suitable volume for intermittent infusion.
- Oral calcium supplementation will be considered for nonurgent instances of calcium repletion.

The above recommendations to the medical staff were accompanied by hospitalwide education aimed especially at nursing staff who are responsible for administering parenteral calcium. Key points for consideration were the following:

- Ensure patency of venous access. CaCl, even when diluted, is very irritating and has been associated with tissue necrosis, sloughing, and abscess formation in instances of extravasation.¹
- Calcium gluconate is the preferentially reserved form of calcium for emergent circumstances in patients lacking central venous access.
- Heighten awareness of differences between calcium gluconate and CaCl, including the differences of elemental calcium, as the chloride form when compared to calcium gluconate would represent an approximately 3-fold increase in elemental calcium.
 - 10% solution of calcium gluconate = 9.3 mg (0.465 mEq) of elemental calcium per 1 mL
 - 10% solution of calcium chloride = 27 mg (1.4 mEq) of elemental calcium per 1 mL
- Because of the differences in elemental calcium, especially for indications that may be emergent but deemed not to be life-threatening, CaCl is to be administered at a slower rate of infusion (eg, 1 hour infusion suggested).

CONCLUSION

CaCl 10% solution diluted to a final concentration of 10 mg/mL or 13.3 mg/mL with either 0.9% sodium chloride or dextrose 5% water for injection was stable for at least 7 days when stored at room temperature (23°C –25°C) exposed to normal fluorescent lighting. Utilization of this new extended stability data may help pharmacies reduce drug waste during this critical time of intravenous calcium shortage.

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Table 1.

Stability of calcium chloride intravenous admixtures over a 1-week period

CaCl admixture	Percentage of initial calcium concentration remaining					
	Day 0: actual initial calcium concentration (mg/mL)	Day 1	Day 2	Day 3	Day 5	Day 7
CaCl 1000 mg in 100 mL 0.9% sodium chloride	9.3	90%	93%	92%	90%	92%
CaCl 1000 mg in 100 mL dextrose 5% water	8.9	91%	97%	94%	94%	94%
CaCl 2000 mg in 150 mL 0.9% sodium chloride	11.5	92%	94%	93%	93%	92%
CaCl 2000 mg in 150 mL dextrose 5% water	11.5	92%	94%	91%	90%	92%

Note: CaCl = calcium chloride.