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Precipitation of Heparin Products With Calcium Gluconate: The Activity of Inactive Ingredients

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ABBREVIATIONS FDA, Food and Drug Administration; PN, parenteral nutrition

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Heparin is an anticoagulant commonly used in neonatal and pediatric patients for varying indications, including systemic anticoagulation and maintenance of line patency for arterial or small-bore catheters.[1] Exposure to heparin often occurs during periods of critical illness. This population also has a high exposure to calcium-containing products. Calcium gluconate is a standard component of neonatal and pediatric parenteral nutrition (PN) and can be utilized to provide inotropic support in neonates and infants.[2] Limited intravenous access in neonatal and pediatric patients often results in co-infusion of medications, with providers relying heavily on accurate compatibility information. Standard drug compendia document the compatibility of heparin and calcium gluconate in varying concentrations. Heparin is also cited as being compatible with 2-in-1 PN.[3–5]

There are numerous Food and Drug Administration (FDA)—approved heparin products in the United States provided from several manufacturers. The inactive ingredients vary based on manufacturer and concentration. Sodium phosphate (dibasic, monobasic, and anhydrous) is an FDA-approved inactive ingredient that can be used for adjustment of pH. The concentration of this ingredient varies widely in products, and no specifications exist to define a maximum acceptable concentration when adjusting for pH.[6] Therefore, clinically significant amounts of phosphate may be present in heparin products, potentially altering compatibility with calcium-containing solutions, including PN.

In this letter, we describe our experience with and the plausibility of commercially available heparin containing phosphate as a buffer precipitating with calcium gluconate. Our institution uses three commercially available heparin products at varying concentrations for arterial and transduced line patency, systemic anticoagulation, and for addition to intravenous fluids to maintain line patency for patients in the neonatal intensive care unit. Despite reported compatibility, we have experienced several precipitations that resulted in loss of intravenous access during concurrent administration of commercially available heparin 2 units/mL (Baxter Healthcare Corporation, Deerfield, IL) and calcium gluconate 100 mg/mL continuous infusion (Fresenius Kabi, Lake Zurich, IL). Upon further investigation, two of our commercially available heparin solutions contained significant concentrations of phosphate as a buffer (Table). Based on the evaluation of the products, we performed a rudimentary experiment to test the compatibility of our heparin products with calcium gluconate and PN, with the purpose of replicating what we experienced in clinical practice.

Calcium gluconate (100 mg/mL) and 8 PN formulations were mixed in glass vials with each of the available heparin products at concentrations and ratios simulating co-infusion during therapeutic y-site administration. Macroscopic inspection of the solutions was done at 1, 10, 30, and 60 minutes. Visual precipitation occurred by 1 minute with calcium gluconate and heparin 2 units/mL containing phosphate as a buffer. No macroscopic precipitation was seen with the 2 other heparin products in any of the solutions.

The issue of calcium and phosphate compatibility is challenging. It has been revisited numerous times by several leading authorities, including the FDA and the American Society of Health-System Pharmacists.[7,8] The compatibility of calcium and phosphate is dependent on a multitude of factors, including the concentration, temperature, and pH of the solution. Even with a good understanding of the calcium and phosphate relationship and under close scrutiny, small variability can result in precipitation in clinical practice.[7] In this context, accurate compatibility information is vital in pediatric practice as medications are often co-infused with calcium-containing solutions in patients with limited intravenous access. Notably, neither manufactured heparin product that contains phosphate as a buffer provides recommendations, warnings, or precautions in the package insert regarding the significant amount of phosphate.[9,10] This is concerning, given our clinical observations and *in vitro* replication.

Our clinical experience and replication were not surprising after analysis of the heparin solutions used. Both commercially available products contain high amounts of phosphate (15 and 16 mMol/L), and the feasibility of

Table. Heparin Solutions

Manufacturer	Concentration Units/mL	Diluent	Phosphate Concentration, mMol/L	pH (range)	Institutional Use
500-mL bag; Baxter Healthcare Corporation, Deerfield, IL	2	NS	16	7 (6–8)	Intravenous line patency
250-mL bag; BD, Franklin Lakes, NJ	100	D5W	15	5.6 (4.5–7)	Therapeutic heparin
5 mL syringe; B. Braun, Bethlehem, PA	100	NA	0	*	Added to compounded intravenous fluids

D5W, dextrose 5% water; NA, not applicable; NS, normal saline
*Not reported.

precipitation was predicted based on available calcium-phosphate solubility curves.[7] Of the 2 commercially available products with phosphate buffer, we likely only saw precipitation from the 2 unit/mL heparin product because this product has a higher pH, leading to an increased likelihood of precipitation (Table). Similarly, no precipitations were observed with PN solutions in our experiments, likely because solutions with high baseline calcium/phosphate ratios contain TrophAmine and cysteine, which decrease pH and increase calcium and phosphate solubility. These assumptions are supported by our clinical experience to date.

Overall, our compatibility experiment lacks the precision needed to truly confirm the incompatibility of these products, and a more robust analysis is required and highly encouraged. However, our experiment does corroborate our experience in clinical practice and highlights the importance and role of excipients when evaluating the compatibility of products.

In the context of the mechanism of action of heparin, phosphate is inactive; however, our experience has proved that this description is a misnomer. Manufacturers should consider compatibility when adding excipients to products, and further analysis should be done when excipients could alter previously reported compatibility results. The variability in compatibility based on manufacturer-specific additives increases the complexity of safely co-infusing medications in clinical practice. Caution should be used when administering heparin that contains phosphate as a buffer with any calcium-containing fluid.

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REFERENCES

1. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(suppl 2):e737S–e801S.
2. Jain A, Agarwal R, Sankar MJ, et al. Hypocalcemia in the newborn. *Indian J Pediatr.* 2010;77(10):1123–1128.
3. Trissel LA. *Handbook on Injectable Drugs.* 19th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2016:623–648.
4. King Guide [online database]. In: Lexicomp Online [online database]. Hudson, OH: Lexi Comp. http://www.cronline.com. Accessed June 19, 2017.
5. Micromedex IV Compatibility [online database]. Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com. Accessed June 19, 2017.
6. US Food and Drug Administration (FDA). Drug databases inactive ingredient search for approved drug products. https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Accessed June 19, 2017.
7. Newton DW, Driscoll DF. Calcium and phosphate compatibility: revisited again. *Am J Health Syst Pharm.* 2008;65(1):73–80.
8. Lumpkin MM, Burlington DB. *FDA Safety Alert: Hazards of Precipitation Associated With Parenteral Nutrition.* Rockville, MD: Food and Drug Administration; 1994.
9. Baxter Healthcare Corporation. *Heparin Sodium and Sodium Chloride Prescribing Information.* Deerfield, IL: Baxter Healthcare Corporation; 2014. Revised 2016.
10. B. Braun. *Heparin Sodium in Dextrose.* Bethlehem, PA: B. Braun; 2016.