Published in final edited form as:

Am J Health Syst Pharm. 2010 April 1; 67(7): 562–565. doi:10.2146/ajhp090342.

Physical Compatibility of Magnesium Sulfate and Sodium Bicarbonate in a Pharmacy-compounded Bicarbonate-buffered Hemofiltration Solution

Brad Moriyama, PharmD[Clinical Pharmacist],
NIH Clinical Center Pharmacy Department, Bethesda, MD

Stacey A. Henning, PharmD[Clinical Pharmacist],
NIH Clinical Center Pharmacy Department, Bethesda, MD

Haksong Jin, PharmD, MS[Senior Pharmacist],
Pharmaceutical Development Section, NIH Clinical Center Pharmacy Department, Bethesda, MD

Mike Kolf, RPh[Senior Pharmacist],
Pharmaceutical Development Section, NIH Clinical Center Pharmacy Department, Bethesda, MD

Nadja N. Rehak, PhD[Senior Staff],
Department of Laboratory Medicine, NIH Clinical Center, Bethesda, MD

Robert L. Danner, MD[Senior Investigator],
Critical Care Medicine Department, NIH Clinical Center, Bethesda, MD

Thomas J. Walsh, MD[Senior Investigator], and
Chief, Immunocompromised Host Section, Pediatric Oncology Branch, National Cancer Institute,
Bethesda, MD

George J. Grimes, RPh[Chief]
Pharmaceutical Development Section, NIH Clinical Center Pharmacy Department, Bethesda, MD

Abstract

PURPOSE—To assess the physical compatibility of magnesium sulfate and sodium bicarbonate in a pharmacy-compounded bicarbonate-buffered hemofiltration solution used at the National Institutes of Health Clinical Center (<http://www.cc.nih.gov>).

METHODS—Two hemofiltration fluid formulations with a bicarbonate of 50 mEq/L and a magnesium of 1.5 mEq/L or 15 mEq/L were prepared in triplicate with an automated compounding device. The hemofiltration solution with a bicarbonate of 50 mEq/L and a magnesium of 1.5 mEq/L contains the maximum concentration of additives that we use in clinical practice. The hemofiltration solution of 15 mEq/L of magnesium and 50 mEq/L of bicarbonate was used to study the physicochemical properties of this interaction. The solutions were stored without light protection at 22 to 25 °C for 48 hours. Physical compatibility was assessed by visual inspection and microscopy. The pH of the solutions was assayed at 3 to 4 hours and 52 to 53 hours after compounding. In addition, electrolyte and glucose concentrations in the solutions were assayed at two time points after preparation: 3 to 4 hours and 50 to 51 hours.

Please address correspondence and requests for reprints to: George J. Grimes, RPh, NIH Clinical Center Pharmacy Dept., 10 Center Drive, Bethesda, MD 20892, TEL: 301-496-6143 (direct), FAX: 301-496-0210, ggrimes@cc.nih.gov.

Potential Conflict of Interest: None

RESULTS—No particulate matter was observed by visual and microscopic inspection in the compounded hemofiltration solutions at 48 hours. Electrolyte and glucose concentrations and pH were similar at both time points after solution preparation.

CONCLUSION—Magnesium sulfate (1.5 mEq/L) and sodium bicarbonate (50 mEq/L) were physically compatible in a pharmacy-compounded bicarbonate-buffered hemofiltration solution at room temperature without light protection at 48 hours.

INTRODUCTION

Continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF) are common modes of continuous renal replacement therapy (CRRT) performed in intensive care units.^{1,2} Hemofiltration has often required the use of replacement fluids that traditionally have been prepared by hand or by an automated compounding device. However, in recent years commercially available bicarbonate-buffered replacement solutions (PrismaSol®, Normocarb HF®) have been approved by the FDA for use during CRRT.^{3,4} While premixed solutions provide increased convenience and improved patient safety,⁵ there is still a role for hemofiltration fluids customized for individual patients. Unfortunately, there is limited published information on the compatibility of magnesium sulfate and sodium bicarbonate in these solutions. It is critical to understand the compatibility of additives in hemofiltration solutions, as they are given intravenously to patients during CRRT. For example, formation of precipitates created by the mixing of magnesium and bicarbonate salts might have serious clinical consequences if infused. The objective of this study therefore was to assess the physical compatibility of magnesium sulfate and sodium bicarbonate in a pharmacy-compounded bicarbonate-buffered hemofiltration solution.

METHODS

Analysis of compatibility, pH, and osmolality

Two bicarbonate-buffered hemofiltration solution formulations (low and high magnesium) were compounded in triplicate with an automated compounding device^a under a laminar flow hood using aseptic technique (Table 1). The specific concentrations of the high magnesium concentration formulation were chosen as a magnesium sulfate concentration of 16 mEq/L and sodium bicarbonate concentration of 80 mEq/L in dextrose 5% in water was cited as being incompatible in the *Handbook of Injectable Drugs*.⁶ The solutions were compounded following the normal procedures of our Pharmacy's IV additive service. The additive sequence of the stock solutions used to compound the hemofiltration fluids is listed in Table 1. The six hemofiltration bags were stored at 22 to 25 °C in our Pharmacy's IV room without light protection with the clear side of the bags facing upward for 48 hours.

The physical compatibility of the hemofiltration solutions was assessed by our Pharmaceutical Development Section (<http://www.cc.nih.gov/phar/index.html>). Visual analysis for precipitation was performed with a perpendicular high intensity lamp against a black and white background. In addition, the entire volume of each bag was filtered through a 37 mm 0.45 micrometer gridded filter^b. The filter was then removed from the casing and observed under a 125 to 1000 times power microscope for particulate matter. The pH of these hemofiltration solutions was measured 3 to 4 hours and 52 to 53 hours after preparation using a pH meter^c that was calibrated before use with buffer solutions of pH 7

^aMicroMacro 12 compounder, Baxa, Englewood, CO

^bMHWG03700, Millipore Corporation, Billerica, MA

^cPHI 300 series pH meter, Beckman Coulter Inc., Fullerton, CA

and pH 10. In addition, the osmolality of the solutions was measured with an osmometer^d 3 to 4 hours after solution preparation.

Determination of electrolyte and glucose concentrations

The hemofiltration solutions (Table 1) were compounded and their physical compatibility assessed using the same procedures as above. The six hemofiltration bags were stored at 22 to 23°C. One sample from each hemofiltration bag was assayed by our Department of Laboratory Medicine with a Synchron LX20 Clinical System^e for sodium, chloride, carbon dioxide, magnesium, potassium, and glucose at 3 to 4 hours and 50 to 51 hours after solution preparation.

Statistics

The pH, osmolality, and electrolyte and glucose concentrations were expressed as means $\pm$ SD.

RESULTS

No particulate matter was observed by visual or microscopic inspection in the compounded hemofiltration solutions. The pH values of the low magnesium hemofiltration solutions at 3 to 4 hours and 52 to 53 hours after compounding were 8.01 ± 0.02 and 8.04 ± 0.02 respectively. The pH values of the high magnesium hemofiltration solutions at 3 to 4 hours and 52 to 53 hours after compounding were 7.96 ± 0.02 and 7.98 ± 0.01 respectively. The electrolyte and glucose concentrations in the low and high magnesium hemofiltration solutions were similar at 3 to 4 hours and 50 to 51 hours after preparation (Table 2). The osmolality of the low and high magnesium hemofiltration solutions was 270 ± 2.08 mOsm/kg and 279 ± 2.65 mOsm/kg respectively.

DISCUSSION

Two bicarbonate-buffered hemofiltration fluid formulations were physically compatible, with no particulate matter seen by microscopy, when stored at room temperature without light protection for 48 hours. These observations are supported by the pH data that showed no change in values over the course of these tests. The low magnesium hemofiltration solution contains the maximum amount of additives that we may use in clinical practice at our intensive care unit. In clinical practice we give these solutions a 28 hour expiration date at room temperature after preparation for sterility reasons. While the high magnesium hemofiltration solution would never be used clinically as it would cause severe hypermagnesemia, we studied this formulation to investigate if a higher magnesium concentration would lead to formation of magnesium carbonate precipitates. The electrolyte and glucose concentrations in both formulations were similar at 3 to 4 hours and 50 to 51 hours after preparation. There was a small decrease in the carbon dioxide concentration in both formulations at 50 to 51 hours, possibly due to loss of carbon dioxide from the monolayer Exacta-Mix IV bags. The magnesium concentration of 0.64 ± 0.05 mmol/L in the low magnesium hemofiltration solution (Table 2) was lower than expected, which may have been due to precipitate formation, assay variability, and inaccuracy of the automated compounding device when measuring the small volume of magnesium. Precipitate formation was unlikely as particulate matter would have been seen by microscopy.

^dVAPRO Model 5520 osmometer, Wescor Inc., Logan, UT

^eBeckman Coulter Inc., Brea, CA

Bicarbonate has become the preferred buffer over lactate in hemofiltration solutions. In a study by Barenbrock et al., hypotensive episodes occurred more frequently in patients receiving lactate-buffered than bicarbonate-buffered replacement fluids during CVVH.⁷ However, the use of bicarbonate increases the risk of incompatibility with divalent cations such as calcium and magnesium. While precipitation is a well recognized problem with the addition of calcium to bicarbonate solutions, magnesium has not been extensively studied as an additive. In our intensive care unit, the incompatibility of calcium and bicarbonate has been handled by running a separate, adjustable calcium chloride infusion during CRRT. The ability to add physiological concentrations of magnesium sulfate to bicarbonate-buffered replacement fluids obviates the need for a second infusion or frequent intermittent doses of magnesium, as well as improving convenience and safety.

The potential incompatibility of sodium bicarbonate and magnesium sulfate is a potential concern for hospital pharmacies that compound hemofiltration solutions. Clinical studies of bicarbonate-buffered replacement solutions have used lower concentrations of bicarbonate, with some solutions also containing lactate for stability.^{2,7-10} More importantly, a magnesium sulfate concentration of 16 mEq/L and sodium bicarbonate concentration of 80 mEq/L in dextrose 5% in water is listed as incompatible in the *Handbook of Injectable Drugs*.⁶ However, no particulate matter was observed in our hemofiltration solution with a magnesium concentration of 15 mEq/L and bicarbonate concentration of 50 mEq/L. In further support of this solution's compatibility, the magnesium sulfate was added to the sodium bicarbonate before dilution with sterile water (Table 1).

The theoretical formation of precipitate in combining magnesium sulfate and sodium bicarbonate may be understood through the following formulas:

or

A review of the CRC Handbook (87th edition) found no solubility coefficient for magnesium bicarbonate. The solubility coefficients for magnesium sulfate and magnesium carbonate were 35.7 g / 100 g H₂O and 0.18 g / 100 g H₂O, respectively.¹¹ As no precipitate was observed microscopically in either low or high magnesium sulfate hemofiltration solutions, magnesium carbonate seems unlikely to form under hospital pharmacy conditions.

Chapter 788 of the USP recommends the use of light obscuration or microscopy to detect particulate matter in parenteral infusions or solutions for injection.¹² Recent studies of parenteral nutrition have used both tests to assess calcium and phosphate compatibility.¹³⁻¹⁵ While we did not have the equipment to perform light obscuration testing, our Pharmaceutical Development Section has used microscopy to determine physical compatibility for many investigational drugs.

CONCLUSION

A pharmacy-compounded hemofiltration solution with a magnesium of 1.5 mEq/L and bicarbonate of 50 mEq/L was physically compatible at 22 to 25 °C without light protection at 48 hours.

Acknowledgments

The authors thank Deborah Sperling and Dr. Gopal Potti for the measurement of osmolality and Dr. Barry Goldspiel, Dr. Scott Penzak, and Mr. Robert DeChristoforo for their thoughtful comments and review of the manuscript. This work was supported in part by the intramural research program of the National Institutes of Health.

References

1. Kellum JA, Mehta RL, Angus DC, et al. The first international consensus conference on continuous renal replacement therapy. *Kidney Int.* 2002; 62:1855–63. [PubMed: 12371989]
2. Manns M, Sigler MH, Teehan BP. Continuous renal replacement therapies: an update. *Am J Kidney Dis.* 1998; 32:185–207. [PubMed: 9708602]
3. PrismaSol Solution package insert. Gambro Renal Products; Daytona Beach, FL: November. 2006
4. Normocarb HF package insert. Apotex Inc.; Toronto, ON: August. 2006
5. Barletta JF, Barletta GM, Brophy PD, et al. Medication errors and patient complications with continuous renal replacement therapy. *Pediatr Nephrol.* 2006; 21:842–5. [PubMed: 16622714]
6. Trissel, LA. Handbook on injectable drugs. 14th ed.. American Society of Health-System Pharmacists; Maryland: 2007. p. 1032-1038.
7. Barenbrock M, Hausberg M, Matzkies F, et al. Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients. *Kidney Int.* 2000; 58:1751–7. [PubMed: 11012909]
8. Feriani M, Biasioli S, Borin D, et al. Bicarbonate buffer for CAPD solution. *Trans Am Soc Artif Intern Organs.* 1985; 31:668–72. [PubMed: 3939279]
9. Kierdorf H, Leue C, Heintz B, et al. Continuous venovenous hemofiltration in acute renal failure: is a bicarbonate- or lactate-buffered substitution better? *Contrib Nephrol.* 1995; 116:38–47. [PubMed: 8529380]
10. Bunchman TE, Maxvold NJ, Brophy PD. Pediatric convective hemofiltration: Normocarb replacement fluid and citrate anticoagulation. *Am J Kidney Dis.* 2003; 42:1248–52. [PubMed: 14655197]
11. Lide, DR. CRC Handbook of Chemistry and Physics. 87th edition. CRC Press; Florida: 2006. p. 4-73-4-74. 2006 – 2007
12. 2009 United States Pharmacopeia. 32nd revision. The United States Pharmacopeial Convention; Maryland: 2008. p. 310-312.
13. Driscoll DF. Stability and compatibility assessment techniques for total parenteral nutrition admixtures: setting the bar according to pharmacopeial standards. *Curr Opin Clin Nutr Metab Care.* 2005; 8:297–303. [PubMed: 15809533]
14. Parikh MJ, Dumas G, Silvestri A, et al. Physical compatibility of neonatal total parenteral nutrient admixtures containing organic calcium and inorganic phosphate salts. *Am J Health Syst Pharm.* 2005; 62:1177–83. [PubMed: 15914878]
15. Singh H, Dumas GJ, Silvestri AP, et al. Physical compatibility of neonatal total parenteral nutrition admixtures containing organic calcium and inorganic phosphate salts in a simulated infusion at 37 degrees C. *Pediatr Crit Care Med.* 2009; 10:213–6. [PubMed: 19188866]

Additive sequence of the stock solutions and contents of the compounded bicarbonate-buffered hemofiltration solutions

Table 1

Additive Sequence ^a	Product Description	Stock Solution Concentration	Manufacturer	Lot	Additive Amount per 3 L (low magnesium solution)	Additive Amount per 3 L (high magnesium solution)
1	sodium chloride	4 mEq/mL	Hospira	70871DW ^b 29212DM01 ^c	270 mEq	270 mEq
2	potassium chloride	2 mEq/mL	Hospira	73574DW ^b 27022DM01 ^c	15 mEq	15 mEq
3	sodium bicarbonate	0.6 mEq/mL	Baxter ^b Hospira ^c	G065649 ^b 26920DM01 ^c	150 mEq	150 mEq
4	dextrose	70%	Baxter	C757518 ^b C646844 ^c	4.5 g	4.5 g
5	magnesium sulfate	4 mEq/mL	Hospira	69362DK ^b 28222DK ^c	4.5 mEq	45 mEq
6	sterile water		Baxter	C765719 ^b 655829 ^c	2667 mL	2657 mL

^a IV bags used were 3 L Exacta-Mix (ethylene vinyl acetate) bags (Baxter, Englewood, CO). Lot 830537 was used in study for analysis of compatibility, pH, and osmolality and lot 520103 was used in study for determination of electrolyte and glucose concentrations.

^b Used in study for analysis of compatibility, pH, and osmolality

^c Used in study for determination of electrolyte and glucose concentrations

Table 2

Electrolyte and glucose concentrations in the hemofiltration solutions at 3 to 4 hours and 50 to 51 hours after preparation

Type of Hemofiltration Solution	Additive	Expected Result	Observed Results 3 to 4 h after Preparation ^a	Observed Results 50 to 51 h after Preparation ^a
low magnesium	sodium (mmol/L)	140	143 ± 3.21	144 ± 1.53
	chloride (mmol/L)	95	99 ± 2.31	98 ± 1.73
	carbon dioxide (mmol/L)	50	49 ± 1.15	48 ± 0.58
	magnesium (mmol/L)	0.75	0.64 ± 0.05	0.64 ± 0.03
	potassium (mmol/L)	5	5.1 ± 0.06	5.2 ± 0.0
	glucose (mg/dL)	150	138 ± 4.58	141 ± 4.51
high magnesium	sodium (mmol/L)	140	143 ± 5.2	144 ± 6.35
	chloride (mmol/L)	95	97 ± 5.2	97 ± 5.2
	carbon dioxide (mmol/L)	50	49 ± 1.15	48 ± 2.08
	magnesium (mmol/L)	7.5	7.71 ± 0.16	7.99 ± 0.17
	potassium (mmol/L)	5	4.6 ± 0.84	4.7 ± 0.87
	glucose (mg/dL)	150	141 ± 2.0	145 ± 1.53

^a values are mean ± SD, N = 3 to calculate SD