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CLINICAL INVESTIGATION

Aminophylline Compatibility with Neonatal Total Parenteral Nutrition

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OBJECTIVES Aminophylline has proven useful for treating renal failure in preterm infants. Previous reports state that aminophylline is incompatible with some neonatal total parenteral nutrition (TPN) solutions. If this is correct, administration of aminophylline doses would be complicated by the need to hold TPN and provide flush solution after each aminophylline dose. Our experience with administering aminophylline over 30 minutes concurrently with TPN was that this was not problematic. We therefore examined the *in vitro* compatibility of aminophylline and TPN solutions used in our neonates over a 30-minute interval to see if our policy of allowing concurrent mixing of these products was appropriate.

METHODS TPN solutions (2.5 mL) were mixed with 1 mL of intravenous aminophylline 2.5 mg/mL in a glass vial. Three different TPN solutions used in our NICU were collected for the study, and five samples of each combination were prepared. Samples were watched for 60 minutes to see if precipitation occurred.

RESULTS Although the aminophylline and TPN solutions were not miscible, no turbidity or precipitation was observed.

CONCLUSIONS This study supports that aminophylline is physically compatible with neonatal TPN for 60 minutes.

KEYWORDS aminophylline, compatibility, parenteral nutrition, TrophAmine, TPN

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INTRODUCTION

Total parenteral nutrition (TPN) therapy in neonatal patients provides essential nutrition in the delicate time when growth is essential for development and survival. Patients receiving TPN are frequently receiving multiple medications, making venous access and compatibility of intravenous medications an important issue. TPN must be stopped for administration of incompatible medications, decreasing the amount of calories the patient receives. Additionally, flushes before and after medication administration increase total fluids without increasing caloric intake. For these reasons, determining compatibility of medications with TPN can be very useful for patient care.

ABBREVIATIONS NICU, Neonatal Intensive Care Unit; TPN, total parenteral nutrition

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During periods of critical illness many neonates develop acute renal failure. Aminophylline, a drug used in the past for chronic obstructive pulmonary disease in adults and apnea of prematurity in neonates, is useful as a treatment for acute renal failure.[1] Our institution uses 1 mg/kg/dose infused over 30 minutes every 12 hours in our neonatal population.[2] The compatibility of aminophylline with TPN is dependent upon the concentrations of calcium and phosphorous, as the drug is known to decrease the solubility of calcium phosphate salts by increasing pH. This can be a major concern in neonatal TPNs, as high doses of both calcium and phosphate are frequently used to promote bone maturation. Standard textbook references suggest that TPN and aminophylline are incompatible with some neonatal TPN solutions.[3,4] *In vitro* studies noting this incompatibility are limited.[5] However, this data was determined using different concentrations of aminophylline, calcium, and phosphate. We were previously unaware of this potential problem and have administered aminophylline at a Y-site with TPN for several years without apparent problems. Additionally we are reluctant to complicate fluid management further in our premature infants with renal failure. For these reasons, we examined the compatibility of neonatal TPN with aminophylline using a 60-minute time frame to simulate concurrent exposure time at a Y-site.

MATERIALS AND METHODS

Neonatal TPNs were prepared according to standard clinical practice. Amino acids (TrophAmine, Braun Medical Inc., Irvine, CA), dextrose, heparin, electrolytes, vitamins, and trace elements were added. Three TPN formulas, A, B and C, (Table) with different calcium phosphate products were sampled from current patients in the Neonatal Intensive Care Unit (NICU).

Aminophylline was prepared as a 2.5 mg/mL concentration by diluting 1 mL of a 25 mg/mL aminophylline solution (Hospira Inc., Lake Forest, IL) with 9 mL of D5W (Hospira Inc., Lake Forest, IL). Five samples of each TPN solution (A, B, and C) using a volume of 2.5 mL were mixed with 1 mL of the aminophylline 2.5 mg/mL solution in order to simulate the concentrations and mixture that would be present during our typical Y-site infusion. The samples were mixed by vortex for 1-2 seconds. Multiple observers inspected solutions macroscopically for precipitation at 1, 10, 30, and 60 minutes after mixture. Solutions were determined to be either clear, immiscible, or have particulate matter in them. Clear and immiscible solutions were assumed to be compatible.

Additionally, two samples of a high calcium phosphate product solution (solutions D and E) were prepared by adding additional calcium gluconate and potassium phosphate to an existing TPN. Aminophylline was added to solution D. These samples were observed until precipitation occurred.

RESULTS

TPN solutions A, B, and C were typical neonatal TPN solutions and were a clear yellow color. Aminophylline IV was a clear colorless solution. The aminophylline and TPN A, B, and C solutions were not miscible, but did not become turbid or precipitate when combined. Solution D had small amounts of precipitate by 60 minutes. Solution E showed immediate precipitation without addition of aminophylline, and time samples were not done. No visually obvious incompatibility was noted between aminophylline and typical TPN solutions used in our NICU.

DISCUSSION

This study is important because the use of aminophylline in neonates with renal failure and limited IV access requires a difficult balance between fluid intake and nutritional support that can be complicated by needing to pause TPN during aminophylline infusion, and by the using flush solutions after aminophylline administration to clear the line before restarting TPN. Our prior experience over several years indicated that infusing aminophylline over 30 minutes concurrently with the TPN solution was not associated with problems. It was only after a pharmacist noted the incompatibility in standard textbooks[3,4] that we questioned the safety of our current administration procedure.

Aminophylline is known to decrease the

Table. TPN Formulations

COMPONENTS	SOLUTION		
	A	B	C
Amino Acids	1.54 gm	2.36 gm	2 gm
Dextrose	10%	11.5%	15%
Heparin	20.4 units	42 units	24 units
Pediatric trace elements	0.088 mL	0.135 mL	0.2 mL
Selenium	1.32 µg	2.025 µg	3 µg
Zinc	0.088 mg	0.135 mg	0.2 mg
Molybdenum	0.11 µg	0.169 µg	0.25 µg
Pediatric Multivitamin	0.88 mL	1.35 mL	2 mL
Cysteine	61.6 mg	94.4 mg	80 mg
Ranitidine	0.88 mg	0.675 mg	2 mg
Levocarnitine	8.8 mg	0	20 mg
Sodium	0.44 mEq	1.69 mEq	3 mEq
Potassium	0.88 mEq	1.69 mEq	3.5 mEq
Calcium gluconate	0.83 mEq	2.57 mEq	2.3 mEq
Magnesium	0.13 mEq	0.2 mEq	0.3 mEq
Phosphorous	0.33 mmol	1.01 mmol	0.92 mmol
Chloride:Acetate	Maximum acetate	Maximum acetate	Approx. equal
Volume	40.8 mL	84 mL	48 mL
Calcium-Phosphate Product	36.45	54.64	86.25

Calcium-Phosphorous products were determined by the following equation:

$$\frac{[(2 \times \text{mmol/kg Phosphorous}) + \text{mEq/kg Calcium}] \times \text{weight in kg} \times 1000}{\text{volume in mL of TPN}}$$

solubility of calcium and phosphorous in TPN by raising the pH of the solution. Previous studies[5,6,7] have shown aminophylline to be compatible with adult TPNs.[5,6,7] Neonatal TPNs generally have a higher concentration of calcium and phosphate in order to promote bone maturation, thus there is a greater risk of calcium phosphate precipitation. Determining compatibility for neonatal TPNs by using data from adult TPNs, which have lower concentrations of calcium and phosphate, is not appropriate.

Two prior studies tested aminophylline compatibilities with neonatal TPNs.[8,9] Both used higher concentrations of aminophylline (25 mg/mL) than used at our institution. One study evaluated aminophylline as a continuous infusion, rather than as an intermittent infusion.[9] Since we administer a more diluted concentration of aminophylline 2.5 mg/mL concurrently with TPN, and doses are administered as intermittent infusions, it seemed reasonable that a more dilute drug concentration and shorter interval might avoid incompatibility problems, and conducting a compatibility test seemed appropriate.

We simulated the compatibility of aminophylline 2.5 mg/mL with several neonatal TPNs for an interval consistent with the physical mixing of these solutions in our clinical setting. We noted precipitation does not occur unless the calcium phosphate product in the TPN solution is elevated beyond 86, and even up to 100 provided the contact time is limited to 30 minutes. This exceeds the typical acceptable maximum for neonatal TPN solutions at either Women's Hospital or The University of North Carolina Hospitals. Our *in vitro* study did not support the need for separate administration of TPN and aminophylline infused over 30 minutes. We have not had any problems clinically while administering aminophylline with TPN, and the policy at our institution remains that aminophylline is compatible with TPN provided it is infused over 30 minutes.

There are several limitations to this study that may influence the reader's interpretation. The mixing of the solutions in a glass vial, rather than a Y-site infusion model requires extrapolation of the information to Y-site. We feel this is reasonable since mixing fluids that are stagnant should increase the likelihood of precipitation. Consequently, if precipitation did not occur in this model, it should not happen

with moving fluids. It is possible that mixing in glass, rather than plastic tubing, confers a different likelihood for precipitation. Another limitation is that drugs administered over 30 minutes in a Y-site setting may actually be administered over far longer periods of time so that continued contact may exist for hours after the end of the actual infusion. If this is the case, our 60-minute observation is too short. We have not observed a problem in the clinical setting, and the amount of aminophylline in contact with TPN would be more dilute as time passed, so our *in vitro* model in a stagnant setting would have misrepresented this clinical situation anyway. Our use of visual means for identifying precipitates may be challenged as inadequate for detecting problems. Our continued use of aminophylline administered as described earlier, without complications, is additional support that this administration approach is reasonable.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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