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# Multiport Y-site Compatibility Studies of a Parenteral Nutrition Solution with Routinely Used Pediatric CVICU Medications

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## Abstract

**Purpose:** Determine physical compatibilities through multiport Y-site simulations of various combinations of routinely used medications in a pediatric cardiovascular intensive care unit (CVICU) with a lipid-free total parenteral nutrition (TPN) vehicle.

**Methods:** Twelve multi-medication product combinations each in their primary vehicle were evaluated in ratio mixtures that reflect various volumes and flow rates commonly used in the pediatric CVICU. The evaluated medications included epinephrine, vasopressin, milrinone, and calcium gluconate (collectively termed Base 4) with furosemide, esmolol, amiodarone, and dexmedetomidine individually and in various combinations with the Base 4. Observations recorded include: visual observations against various backgrounds (unaided, black, and white), odor, evolution of gas, pH, and turbidity immediately after mixing and at specified time points up to 4 hours. Evaluations at each time point were compared against baseline observation values at Time 0 as well as against the TPN and vehicle-only controls of each combination.

**Results:** Of the twelve combinations tested, eleven were found to be compatible over the full four-hour study period. One combination, Base 4 + amiodarone, was found to be incompatible due to an increase in the turbidity beyond recommended levels. All combinations that contained amiodarone had a definitive increase in measured turbidity over the time course of the study.

**Conclusion:** The majority of commonly used medications in pediatric CVICU evaluated in this study may be safely administered along with TPN via multiport Y-site device. Co-administration of amiodarone through a multiport IV Y-site with other medications evaluated in this study should be avoided in clinical practice.

**Keywords:** Multi-Y site compatibility, pediatric, cardiovascular intensive care, parenteral nutrition, physical compatibility

## Introduction

Pediatric cardiac patients admitted to the cardiovascular intensive care unit (CVICU) could require numerous medications to maintain proper cardiac function [1]. An increase in the number of intravascular (IV) medications dictates the need for additional access points. This requirement has the potential to increase the risk of infection, hypervolemia, phlebitis, and extravasation. Pediatric patients' small size often limits the number of viable access points available to administer appropriate IV medications. For some patients, it becomes necessary to simultaneously administer the necessary medications in the same IV line with total parenteral nutrition (TPN) [2-8]. Temporarily stopping a medication or a TPN in order to administer another medication is one utilized modality to circumvent compatibility issues, however, this practice could potentially result in poor patient outcomes due to the needed continuous administration of necessary medications or nutrition [9,10]. With limited IV access, multiport IV lines provide another treatment modality to allow for multiple medications to be administered through a single line. These multiport IV lines contain as many as seven or more insertion ports with the primary line running a main vehicle. The multiple ports on either side allow for delivery of other medications typically by a syringe pump or serve as a port for IV dosing. However, infusing several medications and vehicles concurrently within the same IV line via a multiport device can lead to the development of drug incompatibilities that can affect the patient. Examples of these include formation of particles, cloudy precipitate, and potential chemical reactions between drugs, which can render them inactive. Therefore, healthcare workers are hesitant to infuse multiple medications in the same port due to the lack of data that exist [9,11]. The purpose of this project is to determine the physical compatibility of a standard mixture of medications: epinephrine, vasopressin, milrinone, and calcium gluconate, collectively known as the Base 4, commonly used in a pediatric CVICU with furosemide, esmolol, amiodarone, and dexmedetomidine in various combinations within a lipid-free TPN vehicle.

## Materials and Methods

**Medications and vehicles:** Data on the medications used in this study are presented in Table 1. The composition of the lipid-free TPN solution is given in Table 2, and the evaluated medication combinations (C1-C12), final concentrations, and the vehicles used are listed in Table 3.

**Evaluated combinations and controls:** Simulation of administered medications with the lipid-free TPN solution in a multiport Y-site device was conducted by first determining the volume ratio of lipid-free TPN to total medication volume administered to pediatric CVICU patients. This ratio was based on the approximate percentage that each component (lipid-free TPN and total dosed medications) represented of the total dosed volume. Because dose rates vary significantly between patients and between differently dosed medications, typical values for each were used in determining the ratio. The ratio used in this study was 80/20 lipid-free TPN/total medication volume infused, which was based on commonly reported rates clinically used in the pediatric patient population in the CVICU. The largest difference in flow rates is between the lipid-free TPN solution and the dosed medications, rather than between different medications. Therefore, the 20% portion was made up of an equal volume of each evaluated medication. This is also consistent with traditional Y-site studies in determining compatibility of only two medications, which use an equal volume (50/50) of the evaluated medications [12-14]. Two separate experimental controls consisted of (a) the baseline observation values measured upon mixing (Time 0) of each drug combination and (b) lipid-free TPN + Base 4 vehicles of D5W, 0.9% NaCl, and deionized water (Table 1). A final volume of 100 mL was prepared (80 mL lipid-free TPN plus 20 mL of the total medications infused) for each of the combinations (C1-C12) listed in Table 3.

**Order of addition and time points:** Each medication within the 20 mL ratio volume was added in equal parts in the same order

**Table 1:** Medications Evaluated for Physical Compatibility.

| Medication | Manufacturer (Lot #) | Expiration | Stock Concentration (Vehicle) | Test Concentration (Vehicle) |
|---|---|---|---|---|
| Epinephrine | Amphastar (DT000G6) | 6/2018 | 1 mg/mL (SWFI) | 16 µg/mL (NS)[a] |
| Vasopressin | Par Sterile Products (802173) | 2/2018 | 20 units/mL (SWFI) | 0.2 units/mL (D5W)[b] |
| Milrinone | Hospira (64209KL) | 4/2018 | 0.2 mg/mL (D5W) | 200 µg/mL (D5W)[b] |
| Calcium Gluconate | Fresenius Kabi (6011459) | 3/2017 | 100 mg/mL (SWFI) | 100 mg/mL (SWFI)[c] |
| Furosemide | Letco (1502110214) | 2/2018 | Bulk | 1 mg/mL (D5W)[b] |
| Esmolol | Baxter (Y006775) | 12/2017 | 20 mg/mL (NS) | 20 mg/mL (NS)[a] |
| Amiodarone | APP Pharmaceuticals (6012060) | 8/2017 | 50 mg/mL (SWFI) | 6 mg/mL (D5W)[b] |
| Dexmedetomidine | Hospira (67110DD) | 7/2018 | 4 µg/mL (NS) | 4 µg/mL (NS)[a] |

[a]NS = normal saline (0.9% sodium chloride), [b]D5W = 5% dextrose in water, [c]SWFI = sterile water for injection

**Table 2:** Components of the Lipid-Free Total Parenteral Nutrition Vehicle.

| Component | Amount in TPN |
|---|---|
| Sterile Water | 315.79 mL |
| Dextrose 70% in Water | 82.5 g |
| Amino Acid 10% (Trophamine) | 10.08 g |
| Magnesium sulfate 4.06 mEq/mL | 1.83 mEq |
| Heparin 1000 units/mL inj | 550 units |
| Levocarnitine 100 mg/mL inj | 36.67 mg |
| Pediatric Multivitamin inj | 3.97 mL |
| Selenious Acid Special Dilution 20 mcg/mL | 7.33 mcg |
| Trace Minerals Cr-Cu-Mn-Zn | 1.1 mL |
| NaCl 4 mEq/mL inj | 1.83 mEq |
| KCl 2 mEq/mL | 7.33 mEq |

**Table 3:** Combinations and Physical Compatibility Testing Results.

| Combination[a] | Visual Assessments | | | Odor Change | Average pH | pH Change[b] | | Average Turbidity (NTU) | Turbidity Change[b] (NTU) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unaided | Black Background | White Background | | | Time 0 | Vehicle | | Time 0 | Vehicle |
| Control: TPN + Base 4 Vehicles | Clear yellow | Clear yellow | Clear yellow | None | 5.56 | 0.03 | N/A | 1.00 | 0.17 | N/A |
| C1 (Base 4) | Clear yellow | Clear yellow | Clear yellow | None | 5.60 | -0.27 | -0.04 | 0.85 | 0.01 | -0.20 |
| C2 (Base 4 + F) | Clear yellow | Clear yellow | Clear yellow | None | 5.57 | 0.02 | 0.01 | 0.96 | 0.12 | -0.09 |
| C3 (Base 4 + E) | Clear yellow | Clear yellow | Clear yellow | None | 5.53 | 0.01 | -0.03 | 0.89 | -0.19 | -0.16 |
| C4 (Base 4 + A) | **Crystals (120 mins)** | **Crystals (120 mins)** | **Crystals (120 mins)** | None | 5.55 | -0.01 | 0.02 | 1.82 | 0.35 | **0.77** |
| C5 (Base 4 + D) | Clear yellow | Clear yellow | Clear yellow | None | 5.58 | -0.11 | 0.00 | 0.94 | -0.08 | -0.12 |
| C6 (Base 4 + F + E) | Clear yellow | Clear yellow | Clear yellow | None | 5.55 | -0.01 | -0.01 | 0.90 | -0.05 | -0.15 |
| C7 (Base 4 + F + A) | Clear yellow | Clear yellow | Clear yellow | None | 5.55 | -0.04 | -0.01 | 1.32 | 0.11 | 0.27 |
| C8 (Base 4 + F + D) | Clear yellow | Clear yellow | Clear yellow | None | 5.57 | 0.03 | 0.01 | 0.95 | 0.00 | -0.10 |
| C9 (Base 4 + E + D) | Clear yellow | Clear yellow | Clear yellow | None | 5.53 | 0.01 | -0.03 | 0.90 | -0.02 | -0.15 |
| C10 (Base 4 + A + D) | Clear yellow | Clear yellow | Clear yellow | None | 5.58 | -0.17 | -0.02 | 1.29 | 0.16 | 0.24 |
| C11 (Base 4 + F + E + D) | Clear yellow | Clear yellow | Clear yellow | None | 5.55 | 0.01 | -0.01 | 0.91 | -0.05 | -0.14 |
| C12 (Base 4 + F + A + D) | Clear yellow | Clear yellow | Clear yellow | None | 5.56 | 0.01 | 0.00 | 1.22 | 0.13 | 0.17 |

[a]Base 4 = Epinephrine (16 µg/mL) in NS, Vasopressin (0.2 units/mL) in D5W, Milrinone (200 µg/mL) in D5W, Calcium gluconate (100 mg/mL) in SWFI. F = Furosemide (1 mg/mL) in D5W, E = Esmolol (20 mg/mL) in NS, A = Amiodarone (6 mg/mL) in D5W, D = Dexmedetomidine (4 µg/ml) in NS. [b]Change in either pH or turbidity is relative to either Time 0 or the vehicle-only control

according to its respective combination: epinephrine, vasopressin, milrinone, calcium gluconate, furosemide, esmolol, amiodarone, and dexmedetomidine. Combinations were assessed for physical compatibility at baseline (Time 0), 5, 15, 30, 45, 60, 120, and 240 minutes. Time points were selected in order to detect any early compatibility issues during medication contact times in multiport Y-site and IV tubing prior to entering the patient, as well as any trends in observed data over a longer time period.

**Physical compatibility:** Each of the medication combinations (Table 3) were assessed for physical compatibility through visual assessment and changes in odor at each time point by two independent observers. Visual tests were conducted at each time point using unaided,

black, and white backgrounds. Visual detection of the formation of particles, crystals, or cloudiness or a noted change in the odor constituted physical incompatibility. Additionally, turbidity was measured at each time point using a turbidimeter (2100Q Tubidimeter, Hach, Loveland, CO, USA) calibrated according to the instructions at 10, 100, and 800 NTU. Furthermore, pH measurements were made with pH meters (Ohaus Starter 2100, Parsippany, NJ) calibrated at pH 4, 7, and 10 using calibration buffer solutions. A turbidity change of ≥ 0.5 NTU denotes a physical incompatibility as defined by Trissel and Bready [13]. Additionally, a pH change of ≥ 1.0 as compared to baseline or to control was determined to be a physically incompatible result [15,16]. Lastly, gas formation was assessed at each time point as a means to identify any potential changes in the chemical properties of each solution.

## Results

The results of the physical compatibility observations made for the 12 medication combinations in a lipid-free TPN vehicle evaluated in our multiport Y-site study are presented in Table 3. Only one evaluated combination – C4 (Base 4 + amiodarone) – failed physical compatibility based on the defined evaluation criteria. The measured turbidity upon mixing (Time 0) had an observed increase of 0.63 NTU as compared to the vehicle control. Additionally, the turbidity continued to increase as a function of time throughout the evaluated time points (Figure 1). This combination also failed visual inspection due to crystalline precipitate and particle formation after 120 minutes (Table 3), independently detected by two separate observers. Other combinations containing amiodarone (C7, C10, and C12) were found to meet the physical compatibility criteria described above, however, it was noted that the measured turbidity values for these combinations continued to increase as a function of time (Figure 2). There were no significant changes in the pH or odor of any of the combinations evaluated relative to either the Time 0 value or the vehicle control. Likewise, there was no evidence of gas evolution in either of the controls or the combinations evaluated.

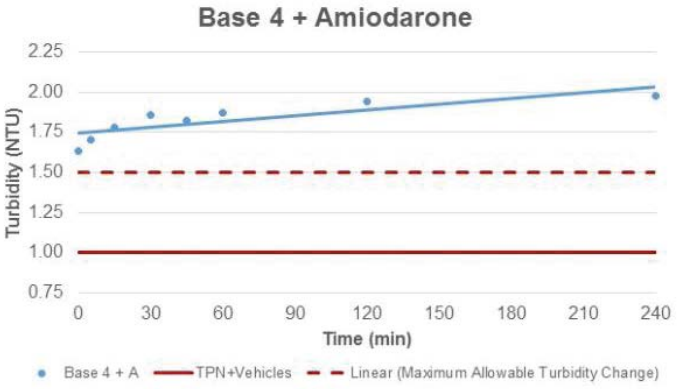


**Figure 1:** Turbidity results of the base 4+ amiodarone.

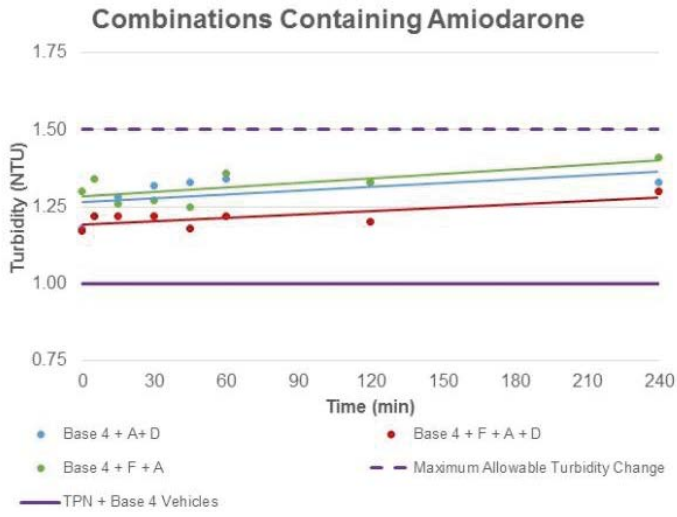


**Figure 2:** Turbidity results of the combinations containing amiodarone.

## Discussion

Traditional Y-site compatibility studies are used to assess the physical compatibility of two medications when mixed together in equal volumes at each drug's dosing concentration. In acute care settings, multiple IV medications administered at different rates with different vehicles are often required, necessitating multiple venous access points. The risk of multiple medications inducing hypervolemia and the increased number of access points required are issues within an adult population. However, the concern is greater with pediatric patients due to their inability to tolerate higher intravenous volumes and their limited number of IV insertion sites. This can be further complicated due to chronic illness, prematurity, and prolonged hospitalization which are issues that are frequently seen in the pediatric population. Pediatric CVICU patients, more specifically, neonates are prone to volume overload due to an extreme inflammatory response after cardiopulmonary bypass. This results in markedly increased morbidity and mortality of this patient population [17-20]. Up to 40% of patients develop acute kidney injury early in the postoperative course, necessitating judicious fluid management [17,18,21]. To alleviate these potential issues, this work is the first of its kind to our knowledge to systematically evaluate multiple medications used in a pediatric CVICU for IV compatibility. In contrast to traditional Y-site studies, this work also takes into account the actual lipid-free TPN: total medication ratio being infused to the patient. While it is not feasible to evaluate every possible flow rate, our design utilized commonly used rates found in a pediatric CVICU setting for the drugs being evaluated.

Of the four combinations that contained amiodarone, only one, C4 (Base 4 + amiodarone), exceeded the predefined compatibility criteria and was deemed incompatible. The remaining three combinations that contained amiodarone (C7, C10, and C12) were observed to fall within the defined criteria for compatibility. This is most likely due to the dilution of amiodarone from the increased vehicle volume encountered when more than one medication is mixed with the Base 4. An increasing positive slope in turbidity was observed in all combinations containing amiodarone, despite the additional volume of vehicle from other medications (Figure 2). These data suggest the potential for incompatibility at later time points for amiodarone-containing combinations. Based on these data, we recommend using a separate IV line for amiodarone administration when dosed in combination with other medications evaluated in this study. No trends as a function of time were noted for any of the remaining parameters evaluated.

It should also be noted that further evaluation of results of existing literature data from traditional Y-site studies of many of the same medications evaluated in our study initially show conflicting compatibility results with our data. For example, a previous experiment with esmolol hydrochloride 10 mg/mL in D5W is reported as physically incompatible with milrinone lactate 0.2 mg/mL in D5W [22]. Chalmers et al. deemed amiodarone hydrochloride 6 mg/mL in D5W with calcium gluconate 10 mg/mL in D5W physically compatible based on visual criteria, while amiodarone hydrochloride 3 mg/mL in D5W with calcium gluconate 40 mg/mL in D5W was physically incompatible due to opaque precipitate formation [23,24]. Similarly, amiodarone hydrochloride and calcium gluconate showed uncertain results in the literature [23,24]. Furosemide also showed varying and incompatible results with some of the other medications in the literature, including vasopressin, milrinone, esmolol, and amiodarone. Again, the concentrations of medications were both higher in these experiments and the vehicles varied in composition [23,25]. The basis for the noted discrepancy in comparing the data comes not only from differences in the drug concentrations and the vehicles evaluated, but also from the presence of the lipid-free TPN vehicle and the ratio of total drug to

vehicle. The instances where our data showed compatibility of multiple medications in contrast to a two-drug combination from traditional Y-site studies is most likely due to the vehicle: drug ratio used in this study. The resulting dilution effect made our experimental combination physically compatible based on previously defined criteria.

An intentional design of this study included the absence of lipids, calcium, and phosphate in the compounded TPN vehicle. Lipids were excluded from the vehicle due to difficulty detecting turbidity changes and visual inspection for possible precipitate formation. Additionally, use of lipid-containing TPN is not a common practice in the institution we collaborated with as part of this study. Calcium was eliminated from the TPN formulation due to the presence of calcium gluconate (100 mg/mL) in the Base 4 medication group. Phosphate is routinely excluded from TPN solution to eliminate the possibility of precipitation with the calcium gluconate infusion. TPN makeup also differs between health-systems and between individual patients, making it difficult to evaluate a universal TPN solution applicable to all clinical situations. It should be noted that different results may be obtained with different TPN formulations. Lastly, this study was conducted at only one TPN vehicle: drug (80:20) ratio, therefore valid results for other ratios should not be extrapolated from these data.

## Conclusion

This study provides laboratory data on physical compatibility for multiport Y-site administration of commonly used medications in a pediatric CVICU in various combinations. The results conclude that separate IV access lines should be used when infusing amiodarone in clinical practice due to the physical incompatibility noted by visual and turbidity changes of the Base 4 + amiodarone combination. Additionally, it is recommended amiodarone be administered in a separate and individual line when dosed with any of the medication combinations evaluated in this study.

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