Physical compatibility of various drugs with neonatal total parenteral nutrient solution during simulated Y-site administration

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Purpose. The physical compatibility of various drugs with neonatal total parenteral nutrient (TPN) solution during simulated Y-site administration was evaluated.

Methods. Study drugs were selected based on the lack of compatibility data with them and neonatal TPN solution and the frequency of use in a local neonatal unit. These drugs included amiodarone, caffeine citrate, clindamycin, enalaprilat, epinephrine, fluconazole, fosphenytoin sodium, hydrocortisone, metoclopramide, midazolam, pentobarbital, phenobarbital, and rifampin. Equal volumes of neonatal TPN solution or sterile water for injection were combined with study drugs or sterile water for injection at concentrations used clinically in neonates. Each test was performed in triplicate. The samples were examined via turbidimetric analysis and visually against light and dark backgrounds immediately after mixing and at 0.25, 0.5, 1, 2, and 3 hours after mixing. Analysis of variance was used to determine statistically significant differences between the test and control solutions.

Results. Many of the drugs studied exhibited no visual or turbidimetric evidence of incompatibility when combined with neonatal TPN solution for up to three hours in a simulated Y-site injection. Pentobarbital, phenobarbital, and rifampin formed visible precipitation immediately after mixing with the neonatal TPN solution.

Conclusion. Caffeine citrate, clindamycin, enalaprilat, epinephrine, fluconazole, fosphenytoin sodium, hydrocortisone, metoclopramide, and midazolam exhibited no visual or turbidimetric evidence of incompatibility when combined with a neonatal TPN solution for up to three hours in a simulated Y-site injection. Amiodarone, pentobarbital, phenobarbital, and rifampin were not compatible with the neonatal TPN solution and should not be coadministered via Y-site injection.

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Advances in medicine have led to the increased survival of neonates born at earlier gestational ages. These neonates require significant interventions to maintain life, often necessitating multiple drug therapies via i.v. infusion during the neonatal intensive care unit (NICU) stay. Several factors, including avoidance of early malnutrition in low-birth-weight neonates,[1] as well as complications from immature gastrointestinal tracts (e.g., necrotizing enterocolitis) may necessitate the use of parenteral nutrition during this critical time. Due to the size of these neonates, volume restrictions may necessitate the coinfusion of concentrated medication doses intravenously in conjunction with total parenteral nutrient (TPN) solutions. Knowledge of compatibility between commonly used medications and TPN solutions is essential to prevent product precipitation. This is of particular concern in a neonatal population, because precipitation in small arteries resulting in blood flow disruption and loss of i.v. access could be detrimental.

Since the composition and pH of neonatal TPN differ from that of adult or standard TPN solutions, the results from compatibility studies with such solutions cannot be extrapolated to admixtures with neonatal TPN solutions. In addition, the physical compatibility of many drugs commonly used in neonates with neonatal TPN solutions has not been fully elucidated.[2,3] The purpose of this study was to determine the

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Y-site compatibility of selected drugs with neonatal TPN solutions.

Methods

Study drugs were selected based on the lack of compatibility data with neonatal TPN solutions and their frequency of use in a neonatal unit. Drugs examined for physical compatibility with neonatal TPN solutions are listed in Table 1. The study took place over four days at room temperature (mean ± S.D. temperature of 21 ± 1.4 °C) under constant fluorescent lighting. The concentration of each study drug was determined using the maximum doses reported in the literature.[4,5] When drug doses were given in milligrams per kilogram of body weight, 8 kg was assumed as the maximum weight. This weight assumption was based on the history of patient weights at a local NICU. By using the maximum patient weight and drug doses, physical stability could be assessed at high concentrations for each drug. Higher concentrations of drugs are more likely to produce visual incompatibilities than lower concentrations; therefore, if drugs are compatible with neonatal TPN solutions at high concentrations, compatibility can be extrapolated to lower drug concentrations.[6] All study drugs were tested at commercially available strengths or were diluted to concentration with sterile water. Sterile water was used as the diluent to negate potential compatibility issues with the diluent and TPN solutions.

The neonatal TPN solution was composed of a stock concentration used at a local NICU minus lipids. Lipids were excluded due to their opacity and interference with visual and turbidimetric analyses. The components of the neonatal TPN solution are listed in Table 2.

Each study sample was mixed in a 1:1 ratio to simulate Y-site coinfusion as described by Allen et al.[7] and as performed in most compatibility studies.[8] Admixtures were observed over a three-hour period. A 2.5-mL sample of each study drug solution was combined with a 2.5-mL sample of neonatal TPN solution in a borosilicate test tube.[a] Three control solutions were assessed: (1) a 5-mL sample of sterile water for injection, (2) a 2.5-mL sample of sterile water for injection combined with a 2.5-mL sample of neonatal TPN solution, and (3) a 2.5-mL sample of sterile water for injection combined with a 2.5-mL sample of each study drug solution. A pipette[b] was used to withdraw each solution. Each test was performed in triplicate.

A laboratory turbidimeter[c] was used to measure the turbidity of each sample immediately after mixing and at 0.25, 0.5, 1, 2, and 3 hours after mixing. The samples were also examined with the unaided eye against light and dark backgrounds at each time point, and all observations

Table 1.
Drugs Tested for Physical Compatibility With Neonatal Parenteral Nutrient Solutions

Drug and Conc.[a]	Manufacturer	Lot	Expiration Date[b]	Simulated Y-Site Concentration (mg/mL)[c]
Amiodarone hydrochloride 50 mg/mL[d]	Bedford	918441	1/2008	16
Caffeine citrate 20 mg/mL[e]	BenVenue	LCJ18	3/2008	20
Clindamycin phosphate 150 mg/mL[d]	Hospira	37-385-EV	1/1/2008	24
Enalaprilat 1.25 mg/mL[d]	Baxter	05E124	5/2007	0.08
Epinephrine hydrochloride 0.31 mg/mL[d]	Hospira	33200DD	9/1/2007	0.0096
Fluconazole 2 mg/mL	Baxter	P185397	2/2008	2
Fosphenytoin sodium 50 mg/mL[f,g]	Parke-Davis	41453A	8/2006	50[g]
Hydrocortisone sodium succinate 125 mg/mL[d]	Pharmacia	33KYC	3/2009	25.6
Metoclopramide hydrochloride 5 mg/mL[d]	Sicor	06A106	1/2009	0.58
Midazolam hydrochloride 1 mg/mL[d]	Baxter	115037	11/2007	0.48
Pentobarbital sodium 50 mg/mL[f]	Abbott	298072721	6/1/2008	48
Phenobarbital sodium 130 mg/mL[d]	Baxter	025041	2/2008	64
Rifampin 60 mg/mL[d]	Bedford	696289	3/2007	Variable[h]
Sterile water for injection	Baxter	C67131	1/2007	Not applicable

[a]Concentration of commercially available product before dilution.
[b]Studies were conducted May 2006, before the expiration date for the drug lots used.
[c]Concentration before mixing with parenteral nutrient solution.
[d]Drug diluted with sterile water to reach desired concentration for purposes of the study; dilution with sterile water may not correspond to instructions for dilution in manufacturer's labeling.
[e]Equivalent to 10 mg/mL caffeine anhydrous.
[f]Brand name drug was used. For all others, generic formulations were used.
[g]Concentrations reported in phenytoin equivalents.
[h]Concentrations tested included 30 mg/mL, 15 mg/mL (1:2 dilution), 7.5 mg/mL (1:4 dilution), and 0.3 mg/mL (1:10 dilution).

were recorded. The turbidimeter was calibrated with a formazin standard[d] before beginning the study as outlined in the manual.[9] Test tubes were prepared, and sample turbidity was measured in accordance with the instructions provided by the manufacturer.[9] Turbidity in nephelometric turbidity units (NTU) and exact time of measurement were recorded for each sample reading. Accuracy of the turbidity measurements was verified using secondary turbidity standards provided with the turbidimeter. The four secondary turbidimeter standards[e] used were metal-oxide particle suspensions specifically formulated to 20, 200, 1000, and 4000 NTU for use with the turbidimeter.

Physical incompatibility was defined as the presence of any particulate matter, haze, turbidity, color change, or gas formation in the experimental group that differed from that seen in the control solutions based on visual or turbidimetric analysis.[10] A difference in measured turbidity of <0.5 NTU between the experimental group and control is generally accepted as compatible[11]; therefore, solutions with turbidity differences of ≥0.5 NTU were considered incompatible. Analysis of variance was used to determine statistically significant differences between the test and control solutions. The a priori level of significance was 0.05.

Table 2.
Composition of Neonatal Parenteral Nutrient Solution Tested

Component (per 350 mL)	Amount
Composition	
Trophamine	2 g
Dextrose	25% w/v
Sodium chloride	4 meq
Sodium acetate	4 meq
Potassium chloride	2 meq
Potassium acetate	2 meq
Potassium phosphate	2 meq
Magnesium sulfate	1 meq
Calcium gluconate	2 meq
Multivitamin[a]	2 mL
Trace elements[b]	0.1 mL
Electrolyte content	
Sodium	8.1 meq
Potassium	6 meq
Calcium	2 meq
Magnesium	1 meq
Phosphate	1.36 mM
Acetate	7.94 meq
Nutrient content	
Nitrogen	0.31 g
Protein	8 kcal
Carbohydrate	213 kcal
Lipids	0 kcal

[a]Infuvite Pediatric, Baxter Healthcare Corporation, Deerfield, IL.
[b]Multitrace-4 Neonatal, American Regent, Shirley, NY.

Results

Most of the drugs studied exhibited no visual or turbidimetric evidence of incompatibility when combined with neonatal TPN solution for up to three hours in a simulated Y-site injection (Tables 3 and 4). Pentobarbital, phenobarbital, and rifampin formed visible precipitants immediately after mixing with the neonatal TPN solution. The crystals in the pentobarbital and phenobarbital mixtures coarsened and continued to increase in volume during the three-hour observation period. The turbidity of the mixture containing rifampin and the neonatal TPN solution was above the measurable range. Dilutions of the solution (1:2 and 1:4) were made, and both diluted solutions exhibited turbidimetric evidence of incompatibility. The difference in turbidity of 1:10 mixtures of rifampin and neonatal TPN solution and of rifampin plus sterile water for injection was less than 0.05 NTU. The simulated Y-site concentrations of rifampin in the 1:4 and 1:10 sequential dilutions were 7.5 and 0.3 mg/mL, respectively. Although concentrations used in clinical practice usually fall between the two concentrations resulting from 1:4 and 1:10 sequential dilutions, rifampin should be considered incompatible with neonatal TPN solution.

The turbidity of the mixture containing amiodarone and the neonatal TPN solution was significantly greater than that of amiodarone plus sterile water for injection and of the neonatal TPN solution plus sterile water for injection. Although the mean ± S.D. difference in turbidity between these two admixtures (0.454 ± 0.036 NTU) was slightly less than the 0.5 NTU difference recommended in the literature as a benchmark for physical incompatibility,[11] the difference was statistically significant ($p < 0.001$), and amiodarone should be considered incompatible with neonatal TPN solution. It is important to note that the supplies used in this study were free from diethylhexyl phthalate plasticizers and therefore would not have caused an incompatibility with the amiodarone admixtures.[12]

Discussion

Pentobarbital and phenobarbital exhibited visual physical incompatibility and turbidimetric evidence of incompatibility when combined with the neonatal TPN solution. Rifampin and amiodarone were also found to be incompatible with the neonatal TPN solution.

The ability of this study to definitively determine Y-site compatibility of the studied medications with neonatal TPN solutions was limited by several factors. As lipids were purposefully excluded from the formulation studied due to opacity and potential interference with visual and turbidimetric analyses, coadministration of these medications with lipid products cannot be recommended. Since differences in the compatibility of drugs may be observed with neonatal TPN solutions whose composition differs from the one used in this study, caution should be taken in extrapolating compatibility results to other TPN formulations. Commercially available solutions and individualized formulations may not exhibit

Table 3.
Turbidity of Test Solutions and Control Solutions

Drug	Mean ± S.D. NTU[a]		
	Neonatal TPN Solution Plus Sterile Water for Injection	Drug Plus Sterile Water for Injection	Drug Plus Neonatal TPN Solution
Amiodarone hydrochloride	0.289 ± 0.034	0.196 ± 0.051	0.743 ± 0.034[b]
Caffeine citrate	0.287 ± 0.024	0.16 ± 0.021	0.22 ± 0.035
Clindamycin phosphate	0.327 ± 0.071	0.21 ± 0.024	0.29 ± 0.043
Enalaprilat	0.327 ± 0.071	0.144 ± 0.015	0.279 ± 0.023
Epinephrine hydrochloride	0.289 ± 0.034	0.145 ± 0.008	0.278 ± 0.023
Fluconazole	0.289 ± 0.034	0.138 ± 0.005	0.273 ± 0.013
Fosphenytoin sodium	0.312 ± 0.05	0.183 ± 0.02	0.297 ± 0.052
Hydrocortisone sodium succinate	0.289 ± 0.034	24.512 ± 102.195	0.451 ± 0.028
Metoclopramide hydrochloride	0.327 ± 0.071	0.185 ± 0.019	0.328 ± 0.083
Midazolam hydrochloride	0.287 ± 0.024	0.174 ± 0.13	0.294 ± 0.04
Pentobarbital sodium	0.287 ± 0.024	0.375 ± 0.591	19.134 ± 9.093[b]
Phenobarbital sodium	0.287 ± 0.024	0.48 ± 0.447	8.945 ± 6.62[b]
Rifampin	0.327 ± 0.071	0.287 ± 0.035	Not measurable[b,c]
Sterile water for injection	Not determined	0.164 ± 0.01	Not determined

[a]NTU = nephelometric turbidity units, TPN = total parenteral nutrient.
[b]$p < 0.05$ between the test and control solutions.
[c]Values were above the maximum measurable level (4000 NTU) for the specified turbidimeter.

similar compatibilities. Differences in pH can also cause incompatibilities between products, and the pH of the neonatal parenteral nutrition product used in this study was not examined. The chemical compatibility of these drugs with neonatal TPN should also be examined before recommending coadministration.

Conclusion

Caffeine citrate, clindamycin, enalaprilat, epinephrine, fluconazole, fosphenytoin sodium, hydrocortisone, metoclopramide, and midazolam exhibited no visual or turbidimetric evidence of incompatibility when combined with a neonatal TPN solution for up to three hours in a simulated Y-site injection. Amiodarone, pentobarbital, phenobarbital, and rifampin were not compatible with the neonatal TPN solution and should not be coadministered via Y-site injection.

Table 4.
Difference in Turbidity Between Experimental and Control Groups

Drug	Mean ± S.D. Difference in Turbidity (NTU)[a]
Amiodarone hydrochloride	0.454 ± 0.036[b]
Caffeine citrate	0.073 ± 0.015
Clindamycin phosphate	0.055 ± 0.063
Enalaprilat	0.056 ± 0.066
Epinephrine hydrochloride	0.018 ± 0.018
Fluconazole	0.022 ± 0.028
Fosphenytoin sodium	0.052 ± 0.055
Hydrocortisone sodium succinate	0.031 ± 0.02[c]
Metoclopramide hydrochloride	0.073 ± 0.075
Midazolam hydrochloride	0.019 ± 0.34
Pentobarbital sodium	18.85 ± 9.098[b]
Phenobarbital sodium	8.192 ± 6.72[b]
Rifampin	Not measurable[b,d]
Sterile water for injection	Not determined

[a]Difference between neonatal total parenteral nutrient (TPN) solution–drug and neonatal TPN solution–sterile water for injection unless otherwise noted. NTU = nephelometric turbidity units.
[b]$p < 0.05$ between the test and control solutions.
[c]Difference between drug–neonatal TPN solution and drug–sterile water for injection.
[d]Values were above the maximum measurable level (4000 NTU) for the specified turbidimeter.

[a]Borosilicate test tube, standard lab supply.
[b]Finnpipette adjustable-volume pipette, Thermo Fisher Scientific, Pittsburgh, PA.
[c]Model 2100N, Hach Company, Loveland, CO.
[d]StablCal, Hach Company.
[e]Gelex secondary standards kit for 2100N turbidimeter, Hach Company.

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