Original Article

Y-Site Compatibility of Vancomycin and Piperacillin/Tazobactam at Commonly Utilized Pediatric Concentrations

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Abstract

Background: Vancomycin and piperacillin/tazobactam are common empiric antibiotics in hospitalized pediatric patients. Studies evaluating intravenous (IV) compatibility at various concentrations show inconsistent results.

Objective: The objective of this study was to determine the Y-site compatibility of vancomycin 10 mg/mL and piperacillin/tazobactam 112.5 mg/mL.

Methods: Vancomycin (10 g vial) was reconstituted using sterile water for injection (SWFI) and diluted with 5% dextrose in water (D5W) to a final concentration of 10 mg/mL in an evacuated IV bag. Piperacillin/tazobactam (40.5 g vial) was reconstituted and diluted with SWFI to a final concentration of 112.5 mg/mL (100 mg/mL piperacillin) in an evacuated IV bag. Both antibacterial stock solutions were then stored in a refrigerator at 4°C (39.2°F). Initial solution appearances, including color, clarity, and particulates, were documented. Diluted solutions were mixed in a quantity of 3 mL of each vancomycin and piperacillin/tazobactam in glass test tubes. Subsequent evaluation included pH assessment and visual evaluation with unaided eye, magnifying glass, high-beam light, and via Spec-20 turbidimeter. Solution mixtures were evaluated upon mixing and again at 30 minutes, 1 hour, and 4 hours after mixing.

Results: Initial combination of vancomycin and piperacillin/tazobactam resulted in a milky precipitate, visible to the unaided eye, which dissipated 15 seconds after mixing. No precipitate was visualized via any method at any additional time point. Turbidimetry and pH readings did not demonstrate differences from baseline measurements.

Conclusions: A combination of vancomycin 10 mg/mL and piperacillin/tazobactam 112.5 mg/mL demonstrated precipitation immediately upon mixing. Co-infusion of vancomycin and piperacillin/tazobactam via Y-site should be considered incompatible.

Key Words—*compatibility, infusions, intravenous, piperacillin/tazobactam, vancomycin*

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Vancomycin hydrochloride and piperacillin sodium/tazobactam sodium (PT) are 2 antibacterials commonly used within pediatric institutions. They are often used together in children to treat a variety of suspected or proven infections due to their broad spectrum of bacterial coverage. Simultaneous intravenous (IV) medication administration in pediatric patients can be complicated by limited IV

access. The IV medication concentrations used in pediatric facilities may differ from those used in adult populations making extrapolating compatibility data difficult. Published vancomycin and PT compatibility data, describing varying concentrations of each drug, demonstrate inconsistent results.^{1–3} There are no published data regarding Y-site compatibility of vancomycin 10 mg/mL and PT 112.5 mg/mL, which are the standard

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concentrations used at our institution. The objective of this study was to evaluate the Y-site compatibility of vancomycin 10 mg/mL and PT 112.5 mg/mL.

METHODS

HEPA-filtered lab benches were powered on for a minimum of 30 minutes before the study began. Stock solutions of vancomycin and PT were compounded as follows. Two 10-g vials of vancomycin hydrochloride for injection (APP Pharmaceuticals, lot 6101799) were each reconstituted with 95 mL of sterile water for injection (SWFI). Contents of each vancomycin vial were then diluted with 900 mL of 5% dextrose in water (D5W) in an empty 1000 mL *Intravia* container (Baxter) for a final vancomycin stock solution concentration of 10 mg/mL. Two 40.5-g PT vials (Hospira, lot 503B010) were each reconstituted with 152 mL of SWFI. Contents of each PT vial were then diluted with 360 mL SWFI in an empty 1000 mL *Intravia* container (Baxter) for a final PT stock solution concentration of 112.5 mg/mL. Upon compounding completion, one container each of vancomycin and PT were labeled and stored in a 4°C (39.2°F) refrigerator and given a 7-day shelf-life concordant with the storage policy within our institution. The remaining container was used immediately for testing.

Four test tubes containing 3 mL each of vancomycin 10 mg/mL and PT 112.5 mg/mL were created and assessed at 0 minutes (initial mixing), 30 minutes, 1 hour, and 4 hours. Five control solutions (deionized [DI] water, D5W, SWFI, vancomycin 10 mg/mL, and PT 112.5 mg/mL) of 6 mL were created as baseline measurements. Each control consisted of one test tube with 6 mL of control solution. Data was collected for each control and the mixtures. Physical stability was assessed using visual inspection that included unaided eye against a white background (UAWB), unaided eye against a black background (UABB), high beam light using a 4-cell *Maglite* against a white background (HBWB), high beam light against a black background (HBBB), a 4.0 diopter (D) magnifying glass against a white background (MGWB), and a magnifying glass against a black background (MGBB).⁴⁻⁸ The pH of each test tube was determined using alkalacid test paper. Absorbance was measured using a Spectronic 20D+ (Thermo Fisher Scientific, Waltham, Massachusetts). The Spectronic 20 was calibrated with a test tube of DI water set at 700 nm wavelength with a constant absorbance of 0.000. An absorbance value of >0.01 was considered to be evidence of turbidity.^{7,9}

At 7 days after initial reconstitution but prior to shelf-life expiration, the procedures were repeated

with the remaining vancomycin and PT stock solutions.

RESULTS

None of the controls contained visual precipitate during any of the time checks at either time point of the study. Air bubbles were common in all test tubes throughout the study. Bubbles were easily visually distinguished from precipitate formation. DI water was read with an absolute absorbance of 0.000 throughout the entire experiment. All solutions yielded a litmus color of either yellow or orange, indicating a pH of 6, weakly acidic, or a pH of 8, weakly alkaline, respectively. Vancomycin and PT control solutions had slightly variable absorbance levels (Table 1). Visual inspection, pH, and absorbance of the control solutions were comparable at each observation time on days 1 and 7, making their comparison against variable (combination) solutions appropriate (Table 1).

During initial vancomycin and PT mixing at 0 minutes, precipitate formation was observed in all 4 tubes with all visual inspection methods. Precipitation was most evident with the unaided eye. Precipitation dissipated within 15 seconds of mixing. Precipitation also occurred when the methods were repeated on day 7. No further precipitation was observed over the course of the 4-hour time frame in variable or control solutions.

Spectrometry results for vancomycin and PT combinations were similar to those from control solutions (Table 2). All absorbance readings for the combination solutions were similar at 0 minutes, 30 minutes, 1 hour, and 4 hours, with no absorbance differences of greater than 0.05 as compared to control solutions. Litmus readings resulted as yellow or orange in all cases, with a majority of yellow readings.

DISCUSSION

Transient precipitate formed immediately upon mixing of vancomycin 100 mg/mL and PT 112.5 mg/mL,

Table 1. Control solutions at time 0 (upon initial mixing)

	Visual inspection	Spectrometry	
	Days 1 & 7	Day 1	Day 7
Vancomycin	No precipitate	0.010	0.029
Piperacillin/tazobactam	No precipitate	0.009	0.006
Sterile water for injection	No precipitate	0.014	0.001
Dextrose 5% in water	No precipitate	0.009	0.001
Deionized water	No precipitate	0.001	0

Table 2. Visual and spectrometry data for vancomycin and piperacillin/tazobactam combinations on days 1 and 7

Day 1	Visual inspection (all methods)				Spectrometry			
	0 h	0.5 h	1 h	4 h	0 h	0.5 h	1 h	4 h
Vanc + PT 1	Small precipitate	None	None	None	0.015	0.014	0.015	0.013
Vanc + PT 2	Mild precipitate	None	None	None	0.009	0.008	0.014	0.012
Vanc + PT 3	Mild precipitate	None	None	None	0.012	0.014	0.008	0.014
Vanc + PT 4	Cloudy	None	None	None	0.015	0.009	0.009	0.008
Day 7								
Vanc + PT 1	Air bubbles	None	None	None	0.116	0.02	0.02	0.039
Vanc + PT 2	Milky precipitate	None	None	None	0.005	0.003	0.001	0.001
Vanc + PT 3	Milky precipitate	None	None	None	0.002	0.04	0.031	0.049
Vanc + PT 4	None	None	None	None	0.002	0	0.005	0.001

Note: h = hours; PT = piperacillin/tazobactam; Vanc = vancomycin.

suggesting that the 2 drugs at these concentrations when mixed via Y-site are incompatible. The observed precipitation completely dissolved in solution by 15 seconds after mixing. Trissel and colleagues mixed vancomycin and PT in a number of other concentrations and similarly demonstrated an immediate transient precipitate formation leading the authors to conclude that the 2 drugs were incompatible.¹⁻³ Different concentrations and combinations of concentrations were used in those studies (vancomycin 2 mg/mL, 10 mg/mL, and 20 mg/mL; PT 1.125 mg/mL, 11.25 mg/mL, 45 mg/mL, 56.25 mg/mL, and 225 mg/mL), and results suggested that compatibility may be concentration-dependent.¹⁻³ An additional factor to be considered when evaluating differences in reported Y-site compatibilities for PT is the reformulation of *Zosyn* by its manufacturer in 2005.¹⁰ Two stabilizing excipients, ethylene diamine tetraacetic acid disodium salt (EDTA disodium) and sodium citrate, were incorporated in order to decrease particulate formation following reconstitution.¹¹ This change resulted in expanded Y-site compatibility with lactated Ringer's solutions, amikacin, and gentamicin and may explain discrepant compatibility reports in the literature.^{3,10} Of note, the product used in the current study (piperacillin sodium and tazobactam sodium injection, powder, for solution; APP Pharmaceuticals LLC) does not contain the aforementioned additives.¹² These differences may explain discrepancies from previously reported Y-site compatibilities between PT and vancomycin.³

Our study was limited in determining the amount of precipitation within each vial. Although spectroscopy was utilized to ensure precipitation was not missed

by visual inspection, turbidimetric readings may not be the most effective way to assess precipitation of medications.⁷

Immediate formation of precipitate that was viewable with all visual inspection methods, however, supports the immediate incompatibility of the 2 drugs at those concentrations.

Although overall vancomycin 10 mg/mL and PT 112.5 mg/mL compatibility seems plausible at 30 minutes and beyond, the initial mixing resulted in a milky white precipitate. Therefore, vancomycin 10 mg/mL and PT 112.5 mg/mL should be considered incompatible for co-administration via Y-site infusion. This result adds to currently limited and variable compatibility information for vancomycin and PT.

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(Continued from page 43)

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