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Original Article

Simulated Y-Site Compatibility of Vancomycin and Piperacillin-Tazobactam

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ABSTRACT

Purpose: To evaluate the physical compatibility of vancomycin with piperacillin-tazobactam during simulated Y-site administration.

Methods: Vancomycin and piperacillin-tazobactam were tested using 2 different diluents: 0.9% sodium chloride and 5% dextrose for injection. Vancomycin concentrations of 2, 5, and 10 mg/mL were tested using 0.9% sodium chloride and 4 and 8 mg/mL in 5% dextrose. Piperacillin-tazobactam was diluted to 16, 30, 40, 80, and 100 mg/mL, representing common concentrations used clinically in hospitals, and concentrations were tested in both 0.9% sodium chloride and 5% dextrose for injection. Medications were reconstituted under USP <797> aseptic technique. Combinations were tested in duplicate and reverse order with control solutions. Compatibility testing for Y-site included visual inspection, inspection with a high-intensity monodirectional light source (Tyndall beam), turbidimeter for turbidity evaluation, pH, and microscopic viewing. Testing occurred immediately after mixing, 15 minutes, 60 minutes, and 4 hours. If inconsistencies were observed between samples, testing was repeated to confirm results. Solutions were deemed incompatible if any one test failed and compatible if all tests were accepted.

Results: When dextrose 5% for injection was used as the diluent, vancomycin 4 mg/mL was Y-site compatible with piperacillin-tazobactam 16, 30, and 40 mg/mL and incompatible with 80 and 100 mg/mL. Vancomycin 8 mg/mL was incompatible with all tested concentrations of piperacillin-tazobactam. When 0.9% sodium chloride was used as the diluents, Y-site compatibility was found with vancomycin 2 and 5 mg/mL and all tested concentrations of piperacillin-tazobactam. Vancomycin 10 mg/mL was incompatible with piperacillin-tazobactam 40, 80, and 100 mg/mL. Incompatibilities formed a white precipitate immediately on mixing.

Conclusion: Y-site incompatibility was greater for the tested concentrations of piperacillin-tazobactam and vancomycin when 5% dextrose was used as the diluent versus 0.9% sodium chloride. Y-site incompatibility was seen immediately in the form of a white precipitate on mixing.

Key Words—compatibility, piperacillin-tazobactam, vancomycin, Y-site, *Zosyn*

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Vancomycin hydrochloride is a tricyclic glycopeptide antibiotic used for the treatment of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*.[1] Piperacillin sodium-tazobactam sodium is a combination penicillin and beta-lactamase inhibitor used for the treatment of moderate to severe infections with coverage against gram-negative organisms including anaerobes and *Pseudomonas aeruginosa*.[2] Vancomycin and piperacillin-tazobactam are often used concomitantly as empiric therapy for infections in critically ill patients.

Traditionally piperacillin-tazobactam is infused over 30 minutes with a schedule of every 6 hours

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in patients with normal renal function. Piperacillin-tazobactam has been studied as an extended infusion of 4 hours 3 times a day. Several studies have emerged showing improved outcomes with extended-infusion piperacillin-tazobactam.[3,4] Specifically, critically ill patients with APACHE (Acute Physiology and Chronic Health Evaluation) score 17 and higher, patients with a history of organ transplant, and those with a prolonged intensive care unit stay demonstrated a decrease of in-hospital mortality with extended-infusion versus intermittent piperacillin-tazobactam.[3] Without compatibility information, it has been impossible to administer piperacillin-tazobactam extended interval infusion every 8 hours and vancomycin every 12 hours (the most common frequency of vancomycin) without either using 2 different lines or altering the administration schedule of one of the medications. Adjusting the administration schedule of vancomycin would be problematic, as it is routinely dosed using trough levels and the laboratory values would be inaccurate if the doses were not given on schedule. With this particular problem, having Y-site compatibility data between these 2 medications would be beneficial clinically for patients.

There are limited data on vancomycin and piperacillin-tazobactam compatibility at concentrations commonly used in the hospital. Vancomycin tested at 2 mg/mL in dextrose 5% for injection was Y-site compatible with piperacillin-tazobactam at most concentrations.[5-7] Vancomycin tested at 10 mg/mL in dextrose 5% was Y-site incompatible at most concentrations of piperacillin-tazobactam.[5-7] However, the most common concentration of vancomycin in Wesley Medical Center (Wichita, Kansas) is 3 to 5 mg/mL, and there has been no reported compatibility data for this concentration.

The purpose of this study was to evaluate Y-site compatibility of vancomycin with piperacillin-tazobactam diluted with either 0.9% sodium chloride or 5% dextrose at concentrations commonly used at Wesley Medical Center.

METHODS

All drugs were obtained from hospital stock. Vancomycin hydrochloride[a] was reconstituted with sterile water for injection[b] to yield a concentration of 50 mg/mL. Piperacillin-tazobactam[c] was reconstituted with either 0.9% sodium chloride for injection[d] or 5% dextrose for injection[e] (diluents were matched for consistency) to a concentration of 200 mg/mL of piperacillin.

The vancomycin reconstituted solutions were further diluted to concentrations of 2, 5, and 10 mg/mL in 0.9% sodium chloride for injection[f] and 4 and 8 mg/mL in 5% dextrose for injection[g]. Piperacillin-tazobactam was further diluted to 16, 30, 40, 80, and 100 mg/mL using 0.9% sodium chloride for injection or 5% dextrose for injection. The 5% dextrose diluent has been previously studied, however, 0.9% sodium chloride was the standard at Wesley Medical Center. All compounding was done using USP <797> standards.[8]

Previous studies have established that 2 drugs administered through Y-site mix in a 1:1 ratio.[9] This was simulated by mixing 5 mL of vancomycin hydrochloride with 5 mL piperacillin-tazobactam into an appropriately sized borosilicate glass, colorless vial with screw cap. The vials were triple washed in sterile water for irrigation[h] and rinsed with ethanol[i].[9] The sample solutions were filtered through a 0.2 micrometer filter[j] into the vials. This process was conducted in duplicate, reversing the order of addition between the 2 samples.[5] Control solutions were created by placing 10 mL of the reconstituted and diluted vancomycin hydrochloride and piperacillin-tazobactam at respective concentrations into vials individually.

The combined solutions were examined initially with the unaided eye in normal fluorescent light.[10] If at any time during testing combination medications were visually incompatible, testing was halted and incompatibility was recorded. Solutions were then examined using a high-intensity monodirectional light source[k] (Tyndall beam). The combined solutions were illuminated from below at the highest light intensity and viewed at a 90° angle against a white and dark background.[5] Incompatibility was defined as visual particulate matter, haze, or turbidity change from control solutions.[6] Inspections were performed immediately after mixing and at 15 minutes, 60 minutes, and 4 hours.

Turbidity was assessed with a laboratory-grade turbidimeter[m]. Calibration was performed using a StableCal calibration set[m]. Turbidity was assessed for each sample and the turbidimeter was returned to zero between each reading. Incompatibility was defined as an increase of 0.5 nephelometric turbidity units (NTU) or more from baseline.[5] Assessments were made immediately after mixing, 15 minutes, 60 minutes, and 4 hours.

Magnification and pH were assessed for each solution. Magnification was observed using a laboratory grade microscope[n] with an ocular set at 10 times

magnification.[11] Incompatibility was determined through visual particulate matter, haze, or turbidity change from control solution.[11] A calibrated laboratory grade pH meter[p] was used, and incompatibility was defined as a mean absolute change from the initial reading of greater than 1 pH unit over the 4-hour observational period.[10] Both assessments were made immediately after mixing and at 15 minutes, 60 minutes, and 4 hours.

RESULTS AND DISCUSSION

Vancomycin was clear, colorless, and free flowing when diluted with either 5% dextrose or 0.9% sodium chloride at any concentration. Piperacillin-tazobactam was clear, colorless to a slight yellow, and free flowing in both the 5% dextrose and 0.9% sodium chloride diluents. The piperacillin-tazobactam control appeared more turbulent than vancomycin in both diluents.

The control solutions were compatible upon visual inspection with the unaided eye and Tyndall beam. Visual particulate matter and haze were absent in all control solutions. Turbidity did not differ from baseline greater than 0.5 NTUs in the control solutions. Controls did not change greater than 1 pH unit throughout testing, and no visual incompatibility was found using a microscope.

When 0.9% sodium chloride was used as the diluent, most of the tested concentrations were compatible (**Table 1**). Incompatibility began to occur at 10 mg/mL vancomycin and with piperacillin-tazobactam concentrations higher than 30 mg/mL. The incompatible combinations formed immediate white cloudiness or wisps that quickly disappeared.

In 5% dextrose, vancomycin 8 mg/mL was incompatible with all tested concentrations of piperacillin-tazobactam, forming a white cloud and then dissipating. The white precipitant did not dissipate with piperacillin-tazobactam 16 mg/mL and vancomycin 8 mg/mL and was present 1 week after mixing. Vancomycin 4 mg/mL was compatible with all tested piperacillin-tazobactam concentrations except 80 and 100 mg/mL (**Table 2**).

The compatible combinations exhibited little change in measured turbidity throughout the study period (none exceeded 0.5 NTUs from baseline). Incompatible combinations that exhibited major turbidity changes did so upon mixing and thus were declared incompatible and not tested further. Solutions that were seen as compatible after mixing did not show any unusual precipitant, haze, or turbidity change through the microscope.

No solution was declared incompatible via pH change. Vancomycin was consistently more acidic than all other solutions tested. Combinations were in the 4 to 6 pH range, with no significant changes throughout testing.

The order of addition of medication affected the turbidity and overall compatibility of the drugs. For all concentrations and diluents used, the addition of piperacillin-tazobactam to vancomycin showed greater incompatibility than the addition of vancomycin to piperacillin-tazobactam. Vancomycin 10 mg/mL with piperacillin-tazobactam 40 mg/mL in normal saline and vancomycin 4 mg/mL with piperacillin-tazobactam 80 and 100 mg/mL in dextrose showed compatibility with vancomycin added to piperacillin/tazobactam but formed precipitant with reverse mixing and thus were declared incompatible.

CONCLUSION

The Y-site compatibility of vancomycin and piperacillin-tazobactam showed greater compatibility with 0.9% sodium chloride than with 5% dextrose. At the lowest tested concentration, vancomycin was compatible with all tested piperacillin-tazobactam

Table 1. Vancomycin and piperacillin/tazobactam Y-site compatibility in normal saline

Piperacillin-tazobactam concentrations	Vancomycin concentration		
	2 mg/mL	5 mg/mL	10 mg/mL
16 mg/mL	Compatible	Compatible	Compatible
30 mg/mL	Compatible	Compatible	Compatible
40 mg/mL	Compatible	Compatible	Incompatible
80 mg/mL	Compatible	Compatible	Incompatible
100 mg/mL	Compatible	Compatible	Incompatible

Table 2. Vancomycin and piperacillin/tazobactam Y-site compatibility in dextrose

Piperacillin-tazobactam concentrations	Vancomycin concentrations	
	4 mg/mL	8 mg/mL
16 mg/mL	Compatible	Incompatible
30 mg/mL	Compatible	Incompatible
40 mg/mL	Compatible	Incompatible
80 mg/mL	Incompatible	Incompatible
100 mg/mL	Incompatible	Incompatible

in both diluents. However, as the concentration increased, physical incompatibilities were exhibited including white precipitant and haze.

Patients being treated with piperacillin-tazobactam and vancomycin simultaneously now have more options for Y-site administration. This knowledge may also help hospitals with piperacillin-tazobactam administration.

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[a] Vancomycin hydrochloride, APP Pharmaceuticals, LLC, Schaumburg, IL; lot 6104818

[b] Sterile Water for Injection, USP, Hospira Inc, Lake Forest, IL; lot 21-511-DK

[c] Piperacillin-tazobactam single and bulk dose vials, APP Pharmaceuticals, LLC, Schaumberg, IL; lot 2K58TR; lot 2A02TW

[d] 0.9% Sodium Chloride Injection USP, Baxter Healthcare, Deerfield, IL; lot P290478

[f] 5% dextrose injection, USP, Baxter Healthcare, Deerfield, IL; lot C853572

[g] Combination 14.6% NaCl 50 mL vial, Hospira Inc, Lake Forest, IL; lot 06-029-DK and Sterile Water for Injection 2000mL, Hospira Inc, Lake Forest, IL; lot 20-059-JT

[h] Combination 70% Dextrose 2000mL, Hospira Inc, Lake Forest, IL; lot 19-091-JT and Sterile Water for Injection 2000mL, Hospira Inc, Lake Forest, IL; lot 20-059-JT

[i] Sterile water for irrigation, USP. Hospira; lot 17-317-4B-01

[j] Ethyl alcohol, 200 proof, Pharmco, Brookfield, CT; lot KJL01C

[k] Baxa, Englewood, CO; lot 2012-7909977

[l] IV Inspection station, Clean Air Technology, Canton, MI

[m] Hach 2100P turbidimeter, Loveland, CO

[n] Zeiss microscope, Thornwood, NY

[p] Orion Research Analog pH meter, model 301, Jacksonville, FL

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