Compatibility of Ceftazidime-Avibactam, Ceftolozane-Tazobactam, and Piperacillin-Tazobactam with Vancomycin in Dextrose 5% in Water

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ABSTRACT

Objectives: The compatibility of vancomycin with existing and novel β -lactam/ β -lactamase inhibitors at clinically relevant concentrations in 5% dextrose in water has not been fully explored to date.

Methods: Vancomycin concentrations tested ranged from 5 to 20 mg/mL. Ceftazidime-avibactam was tested at 8, 20, and 40 mg/mL, ceftolozane-tazobactam at 15 mg/mL, and piperacillin-tazobactam at 28 mg/mL. Compatibility of drug admixtures were tested via both simulated and actual y-site infusion. For the simulated y-site compatibility assessment, 1:1 mixtures of each respective drug were analyzed over 24 hours. Actual y-site infusion followed a 4-hour extended-infusion protocol, with aliquots tested hourly for 4 hours. At all time points, the compatibility of each admixture was determined using 6 different methods: visual, microscopic, Tyndall beam, nephelometric, pH, and microbiologic bioassay assessment. If any admixture failed any one of these 6 assays, it was considered incompatible. Any combination deemed incompatible was filtered through a 0.22 μ m filter and reanalyzed to assess impact of particle size.

Results: There were no differences in compatibility categorizations between simulated and actual y-site infusion. There were no changes in compatibility over the time course of any experiment. Ceftazidime-avibactam at 8 mg/mL was incompatible with vancomycin at 5 mg/mL. The maximum compatible vancomycin concentrations were 5 mg/mL and 10 mg/mL with 20 and 40 mg/mL of ceftazidime-avibactam, respectively. Ceftolozane-tazobactam 15 mg/mL was compatible with vancomycin concentrations up to 10 mg/mL. The maximum compatible vancomycin concentration with piperacillin-tazobactam 28 mg/mL was 5 mg/mL. None of the β -lactam/ β -lactamase inhibitors tested were compatible with 15 or 20 mg/mL of vancomycin. None of the admixtures considered incompatible by other methods displayed any decrease in antimicrobial activity as assessed by bioassay. After filtration, all admixtures originally deemed incompatible maintained their visual turbidity and microscopic particulate matter.

Conclusions: Ceftazidime-avibactam prepared at the lowest concentration recommended in the package insert is incompatible with vancomycin. Ceftolozane-tazobactam did not display incompatibility until vancomycin concentrations above 10 mg/mL were tested. Piperacillin-tazobactam at a typical extended-infusion concentration is compatible with vancomycin in D5W. To our knowledge, this is the first study to assess compatibility of antibiotic admixtures via direct measurement of antimicrobial activity. The lack of any decrement in antibacterial activity of any apparently incompatible admixture and maintenance of incompatibility after passage through a 0.22 μ m filter may suggest a lack of clinically relevant adverse effects when co-administered. Future compatibility studies should incorporate appropriate methods to accurately assess both efficacy and safety of co-administered drug products.

Key Words— ceftazidime-avibactam, ceftolozane-tazobactam, compatibility, dextrose, piperacillin-tazobactam, vancomycin

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It is well documented that the administration of effective antimicrobial therapy reduces mortality in patients with severe sepsis and septic shock and that the timeliness of antimicrobial therapy for infected patients is of paramount importance.^{1,2} The 2012 Surviving Sepsis Guidelines recommend initial antimicrobial therapy broad enough to cover all likely pathogens,³ and recent data indicate that vancomycin is the most widely used parenteral antimicrobial in US acute care hospitals, followed closely by piperacillin-tazobactam.⁴ Despite the prevalence of their empiric use and the understood need to administer timely antimicrobial therapy, vancomycin and piperacillin-tazobactam are typically regarded as incompatible for y-site administration. Although recent reports have challenged this notion of incompatibility,^{5,6} these studies often use only one diluent or examine drug concentrations rarely used in clinical practice. As such, many institutions continue to avoid their concomitant administration, forcing clinicians to choose which antibiotic to administer first in situations of limited vascular access. This choice may unnecessarily delay the administration of effective antimicrobial therapy. In addition to piperacillin-tazobactam, 2 novel β -lactam/ β -lactamase inhibitor combination antibiotics have recently been approved. These agents, ceftazidime-avibactam and ceftolozane-tazobactam, have spectrums of activity broad enough to cover all likely pathogens even in patients with a history of infection with multidrug-resistant pathogens.^{7,8} Currently, no information regarding the compatibility of these agents with other antimicrobials is available.^{9,10} In addition to the potential negative impact of delaying antimicrobial therapy, the concurrent administration of incompatible drug products in vivo has resulted in adverse events.¹¹⁻¹⁴ As such, it is vitally important to establish both the efficacy and safety of co-administered drug products for their use in human patients. The objective of this study was to assess the compatibility of ceftazidime-avibactam, ceftolozane-tazobactam, and piperacillin-tazobactam with vancomycin at various concentrations in dextrose 5% in water (D5W).

MATERIALS AND METHODS

Drug Preparation

Antibiotics were reconstituted per manufacturer's instructions. Vancomycin^a was diluted in D5W^b to final concentrations of 5, 10, 15, and 20 mg/mL. Ceftazidime-avibactam^c was diluted in D5W to 8, 20, and 40 mg/L based on suggested administration concentrations in the package insert. Ceftolozane-tazobactam^d was diluted in D5W to a

final concentration of 15 mg/mL per package insert. Piperacillin-tazobactam^e was diluted in D5W to a final concentration of 28 mg/mL, the current standard extended-infusion administration concentration at University of Illinois Hospital and Health Sciences System. Phenytoin^f was provided in solution at 50 mg/mL, which was then diluted to 5 mg/mL in D5W for use as a positive control as it is known to form a precipitate when mixed with vancomycin.¹⁵ D5W alone was used as a negative control for all experiments.

Simulated Y-site Compatibility

Previous reports indicate that mixing of fluids in a y-site administrative set occurs in a 1:1 ratio.¹⁶ To simulate y-site compatibility, a 1 mL aliquot of each drug to be tested was mixed with a 1 mL aliquot of vancomycin at each respective concentration in separate clear glass test tubes. Each experiment was repeated in reverse addition order and performed in triplicate. After mixing, simulated y-site compatibility was assessed via 6 different methods at 0, 1, 2, 3, 4, and 24 hours. Admixtures were stored at room temperature under fluorescent light. Admixtures were considered incompatible if any one of the 6 methods yielded a positive result at any time point. To ensure incompatibility was not a result of bacterial contamination, an aliquot of any drug admixture deemed incompatible was passed through a 0.22-micron syringe filter and reanalyzed. Aliquots of each incompatible drug admixture were also plated on tryptic soy agar plates containing 5% sheep's blood and incubated for 24 hours to ensure lack of bacterial growth.

Actual Y-site Compatibility

To more accurately mimic clinical drug administration conditions, any drug combination that was categorized as incompatible in the simulated y-site experiment was then infused into a collection beaker via y-site administration setup with B. Braun Outlook 400es and 100es infusion pumps^g. Two milliliter aliquots were collected from the end of the infusion tubing at 0, 1, 2, 3, and 4 hours and evaluated via the same 6 methods and criteria. All drugs were infused over 4 hours to maximize the contact time between the 2 agents.

Method 1: Visual Evaluation

After preparation and mixing, each vancomycin β -lactam/ β -lactamase inhibitor combination was visually observed against light and dark backgrounds at 0, 1, 2, 3, 4, and 24 hours. Incompatibility was defined as any turbidity, visible particulate formation, or color change.

Method 2: Tyndall Light Scattering

Immediately after visual evaluation, each test tube containing the drug admixture was subjected to a high-intensity mono-directional light source (Tyndall beam) at a 90° angle in front of a white and a black background at 0, 1, 2, 3, 4, and 24 hours. Drug admixtures that prevented the light source from passing through the admixture and appearing on the background were considered incompatible.

Method 3: Microscopic Evaluation

To distinguish incompatibilities not visible to the naked eye, microscopic analyses were also performed at 0, 1, 2, 3, 4, and 24 hours. A 10 μ L drop of each drug admixture was visualized under an EVOS XL core microscope^h at 10X and 20X magnification and assessed for precipitation and/or crystallization as compared to the negative control.

Method 4: Nephelometric Evaluation

To accurately quantify the degree of turbidity, a 200 μ L aliquot of each drug admixture was placed in a 96-well round bottom plate and analyzed for absorbance at 620 nm on a BioTek Synergy H1 multi-mode readerⁱ at 0, 1, 2, 3, 4, and 24 hours. Admixtures that exhibited a nephelometric turbidity unit (NTU) increase of greater than 50% compared to the single drug in D5W were considered incompatible.

Method 5: pH Evaluation

The pH of each drug combination was determined immediately after mixing using Fisher brand pH test papers with a range of 0-14. Any change in pH greater than 1 pH unit at 1, 2, 3, 4, or 24 hours compared to time 0 led to these drugs being categorized as incompatible.

Method 6: Bioassay Evaluation

So as to assess the antibacterial activity of each β -lactam/ β -lactamase inhibitor-vancomycin drug admixture, bioassays utilizing *Escherichia coli* ATCC 25922 and a clinical bloodstream isolate of methicillin-resistant *Staphylococcus aureus* (MRSA) as test organisms were performed. A 4 mm cork borer was used to create a well in the center of cation-adjusted Mueller-Hinton II (Becton, Dickinson and Company, Franklin Lakes, NJ) agar plates. A 50 μ L aliquot of each single drug solution or admixture to be tested from each collection time point was then loaded into the 4 mm well. Finally, a 100 μ L suspension of the bacterial strain at a concentration of 1.0×10^8 CFU/mL was lawned onto the surface of the plate and

Figure 1. Bioassay to determine antibacterial efficacy of antibiotic admixture. 50 μ L aliquot of antibiotic alone and in admixture is placed in well and allowed to diffuse through Mueller-Hinton agar plate. Susceptible bacteria are seeded on plate and inhibitory radius is measured after 24 hours incubation. Inhibitory zone of admixture is then compared to the single agent alone in dextrose 5% water.

incubated for 24 hours in ambient air at 35°C. MRSA was used to test the antibacterial activity of vancomycin while the *E. coli* was used to test antibacterial activity of the ceftazidime-avibactam, ceftolozane-tazobactam, and piperacillin-tazobactam. After incubation, radii of inhibitory zones were measured using a dial Manostat caliper (Figure 1). Any decrease in the inhibitory radius of 2 drug admixtures of more than 10% compared to the single drug was considered incompatibility.

RESULTS

Results of all 6 compatibility assays at all time points for all drug admixtures at pre-specified concentrations are summarized in Table 1. There were no differences in compatibility categorizations between simulated and actual y-site infusion. All incompatibilities were evident immediately upon admixing, and no appreciable change was noted over time. Ceftazidime-avibactam at 8 mg/mL was determined to be incompatible with vancomycin at 5 mg/mL by both nephelometric analysis and cloudy precipitate formation that was visually (Figure 2) and microscopically (Figure 3) observable. Interestingly, increasing the concentration of ceftazidime-avibactam to 20 or 40 mg/mL restored compatibility with vancomycin 5 mg/mL. When the vancomycin concentration was increased to

Table 1. Compatibility results for combinations of vancomycin and selected β -lactam/ β -lactamase inhibitors

Evaluation method							
	Visual	Micro- scopic	Tyndall beam	Nephelo- metric	pH	Bioassay	Conclusion
Vancomycin 5 mg/mL							
+ceftazidime-avibactam 40 mg/mL	C	C	C	C	C	C	C
+ceftazidime-avibactam 20 mg/mL	C	C	C	C	C	C	C
+ceftazidime-avibactam 8 mg/mL	I	I	C	I	C	C	I
+ceftolozane-tazobactam 15 mg/mL	C	C	C	C	C	C	C
+piperacillin-tazobactam 28 mg/mL	C	C	C	C	C	C	C
Vancomycin 10 mg/mL							
+ceftazidime-avibactam 40 mg/mL	C	C	C	C	C	C	C
+ceftazidime-avibactam 20 mg/mL	I	I	I	I	C	C	I
+ceftazidime-avibactam 8 mg/mL	I	I	I	I	C	C	I
+ceftolozane-tazobactam 15 mg/mL	C	C	C	C	C	C	C
+piperacillin-tazobactam 28 mg/mL	I	I	I	I	C	C	I
Vancomycin 15 mg/mL							
+ceftazidime-avibactam 40 mg/mL	I	I	I	I	C	C	I
+ceftazidime-avibactam 20 mg/mL	I	I	I	I	C	C	I
+ceftazidime-avibactam 8 mg/mL	I	I	I	I	C	C	I
+ceftolozane-tazobactam 15 mg/mL	I	I	I	I	C	C	I
+piperacillin-tazobactam 28 mg/mL	I	I	I	I	C	C	I

Note: C = compatible; I = incompatible.

Figure 2. Visual compatibility assessment. Upon mixing, vancomycin 5 mg/mL and ceftazidime-avibactam 8 mg/mL (B) demonstrated a visually identifiable increase in turbidity when compared to dextrose 5% water alone (A) but not to the degree of the vancomycin-phenytoin positive control (C).

Figure 3. Microscopic evaluation of incompatibility. Upon mixing, vancomycin 5 mg/mL and ceftazidime-avibactam 8 mg/mL (B) demonstrated a microscopically identifiable precipitate when compared to dextrose 5% water (A). The precipitate differed, however, from the obvious crystallization in the vancomycin-phenytoin positive control (C).

10 mg/mL, incompatibility was observed with ceftazidime-avibactam at 20 mg/mL but not at 40 mg/mL. When vancomycin was increased again to 15 mg/mL, incompatibility was observed with all 3 concentrations of ceftazidime-avibactam. Ceftolozane-tazobactam 15 mg/mL was compatible with vancomycin at 5 and 10 mg/mL in all assays but incompatible at 15 mg/mL. The maximum compatible vancomycin concentration with piperacillin-tazobactam 28 mg/mL in D5W was 5 mg/mL. At 10 mg/mL of vancomycin, 4 of the 6 methods resulted in incompatibility with piperacillin-tazobactam 28 mg/mL.

None of the admixtures displayed any notable changes in pH over the course of the experiment. The majority of the incompatibility categorizations were based on positive results in the visual, microscopic, Tyndall beam, and nephelometric assessments. It is important to note that none of the admixtures considered incompatible by other methods displayed any decrease in antimicrobial activity as assessed by bioassay. When compared to the single agent alone, there were no changes greater than 1 mm in the inhibitory radii of any drug admixture regardless of concentration and time of the experiment. The vancomycin-phenytoin positive control admixture also did not display any loss of vancomycin activity against the MRSA strain utilized.

DISCUSSION

This is the first study to evaluate the compatibility of 2 recently approved β -lactam/ β -lactamase inhibitor combination agents with the most commonly used parenteral antibiotic in the United States. Applying conventional definitions, vancomycin at 5 mg/mL was incompatible with the least concentrated dilution of ceftazidime-avibactam recommended in the package insert (8 mg/mL). When prepared at the most concentrated dilution recommended (40 mg/mL), ceftazidime-avibactam was compatible with vancomycin concentrations up to 10 mg/mL in D5W. Preparing ceftazidime-avibactam in the most concentrated form recommended by the package insert may therefore be advantageous for y-site compatibility, in decreasing delivered fluid volume, and facilitating extended-infusion dosing regimens.¹⁷ Ceftolozane-tazobactam at the recommended dilution according to the package insert was compatible with vancomycin concentrations up to 10 mg/mL in D5W.

In this study, piperacillin-tazobactam at a concentration typically used for extended infusion administration was compatible with vancomycin at 5 mg/mL

in D5W but incompatible at concentrations 10 mg/mL and higher. A previous study evaluated the compatibility of vancomycin and piperacillin-tazobactam in D5W.⁶ Wade et al found that vancomycin at 4 mg/mL was compatible with piperacillin-tazobactam at concentrations ranging from 16 to 100 mg/mL whereas vancomycin at 8 mg/mL was incompatible with all tested concentrations of piperacillin-tazobactam. Concentrations between 4 and 8 mg/mL of vancomycin were not tested in this study, despite the package insert recommendation not to exceed 5 mg/mL of vancomycin.¹⁸ Our study provides a welcomed addition to the literature for institutions currently utilizing 5 mg/mL of vancomycin with piperacillin-tazobactam in D5W.

The use of a multitude of supporting methodologies allowed us to more confidently assess the compatibility or incompatibility of each respective drug admixture. While the visual, microscopic, Tyndall beam, nephelometric, and pH evaluations provided a designation of incompatibility similar to much of the current literature, none of these tests were able to assess the potential clinical ramifications of the apparent incompatibility. High-performance liquid chromatography (HPLC) is a more laborious and expensive tool that has been used previously to evaluate the compatibility of drug combinations by evaluating decreases in drug concentrations over time.¹⁹ Yet HPLC still does not provide any information in regard to the maintenance or loss of antibacterial activity of the drugs in question. This is particularly important in the case of antimicrobial admixtures, as any loss of activity due to precipitation could have a deleterious impact on patient outcomes. The use of a bioassay in these experiments provided a consistent, inexpensive, and simple way to directly measure the activity of each drug admixture and, in particular, the admixtures determined to be incompatible by other methods. Relying solely upon methodologies commonly seen in previous literature, all of the admixtures displaying even the slightest turbidity would have simply been categorized as "incompatible." While our results that relied on visual assessment reiterate previously published data, the bioassay results demonstrate that the impact of visual turbidity on the activity of these antimicrobials may potentially be clinically insignificant. Furthermore, all of the admixtures that were filtered through a 0.22 micron filter retained their visually turbid appearance and incompatibility categorization. Given that circulating human erythrocytes and leukocytes can range between 6 and 12 μ m in diameter,^{20,21} it is unclear whether the

particle size causing the turbidity in the admixtures would cause injury to the patient during intravenous administration. Furthermore, specific guidelines, such as those from the US and European Pharmacopoeia, recommend assessing for clinically relevant particulate matter in preparations by counting only particles that are larger than 10 μm .^{22,23} Finally, it has been demonstrated that drugs deemed incompatible can in fact be administered safely to patients, even those at high risk of adverse events such as pediatric patients in the intensive care unit.²⁴ This disconnect between research and clinical practice is possibly due to the over simplistic methods and antiquated conventional definitions used to delimit incompatibilities in previous in vitro studies. It is essential that future studies addressing the issue of compatibility incorporate appropriate assays to assess both the potential efficacy and safety of drug admixtures. Furthermore, the clinical impact of administering drug admixtures deemed "incompatible" based on conventional definitions needs to be thoroughly explored in order to not unnecessarily preclude their co-administration, particularly in the case of antimicrobials.

There were limitations to our study. The definitions of incompatibility by various methods were based on previous literature and clinical judgment, but were somewhat arbitrary in nature. To our knowledge there are no validated methods by which to assess clinically relevant NTU or pH changes. Also, the results of our study apply only to the specific brands and lots of antimicrobials used in these experiments.

CONCLUSION

Ceftazidime-avibactam at the lowest concentration recommended in the package insert is incompatible with vancomycin. Ceftolozane-tazobactam did not display incompatibility until vancomycin concentrations exceeded 10 mg/mL. Piperacillin-tazobactam at a typical extended-infusion concentration is compatible with vancomycin ≤ 5 mg/mL in D5W. None of the tested admixtures, even those deemed incompatible by other methods, demonstrated any decrease in antimicrobial activity. All precipitates formed in this study were smaller than 0.22 μm and therefore may not be injurious to humans, although further research is needed to confirm lack of adverse effects.

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^aVancomycin hydrochloride for injection, Hospira Inc., Lake Forest, IL, Lot 490268E03

^bDextrose 5% water for injection, Baxter Healthcare Corporation, Deerfield, IL, Lot Y011254

^cAvycaz for injection, Forest Pharmaceuticals Inc., Cincinnati, OH, Lot Z598

^dZerbaxa for injection, Merck and Co. Inc, Whitehouse Station, NJ, Lot SP1354

^ePiperacillin and Tazobactam for injection, Sandoz Inc., Princeton, NJ, Lot 5T06TQ

^fPhenytoin sodium, West-Ward Pharmaceuticals, Eatontown, NJ, Lot 095331

^gB. Braun Medical Inc., Bethlehem, PA

^hThermo Fisher Scientific, Waltham, MA

ⁱBioTek Instruments, Inc., Winooski, VT

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