Assessment of the Physical Compatibility of Eravacycline and Common Parenteral Drugs During Simulated Y-site Administration

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ABSTRACT

Purpose: Eravacycline is a broad-spectrum, intravenous fluorocycline antibiotic approved for the treatment of complicated intra-abdominal infections in adults. A 60-minute infusion is recommended for each infused dose. Compatibility data that may allow convenient Y-site administration of eravacycline with other parenteral medications are unavailable. We aimed to determine the physical compatibility of eravacycline with other intravenous medications by simulated Y-site administration.

Methods: Eravacycline was reconstituted according to published prescribing information and diluted with 0.9% sodium chloride to a concentration of 0.6 mg/mL. Simulated Y-site administration was performed by mixing 5 mL of eravacycline with an equal volume of 51 other intravenous medications, including crystalloid and carbohydrate hydration fluids and 20 antimicrobials. Secondary medications were assessed at the upper range of concentrations considered standard for intravenous infusion. Mixtures underwent visual inspection and turbidity measurement immediately on mixture and at 3 subsequent time points (30, 60, and 120 minutes after admixture), and pH was measured at 60 minutes for comparison with the baseline value of the secondary medication.

Findings: Eravacycline was physically compatible with 41 parenteral drugs (80%) by simulated Y-site administration. Incompatibility was observed with albumin, amiodarone hydrochloride, ceftaroline fosamil, colistimethate sodium, furosemide, meropenem, meropenem/vaborbactam, micafungin sodium, propofol, and sodium bicarbonate.

Implications: Eravacycline for injection was physically compatible with most parenteral medications assessed. Pharmacists and nurses should be knowledgeable of the observed incompatibilities with eravacycline to prevent the unintentional mixing of incompatible intravenous medications. (*Clin Ther.* 2019;41:2162–2170)

Keywords: eravacycline, incompatible, intravenous administration, medication safety profile, multidrug resistance.

INTRODUCTION

Less than a century after the discovery of penicillin, inappropriate antibiotic use and suboptimal infection control practices have contributed to the rapid emergence of multidrug-resistant (MDR) bacteria worldwide.[1] In response to this threat, global efforts have been refocused on the development of new antibiotics.[2] The US Food and Drug Administration recently approved eravacycline, an intravenous fluorocycline antibiotic within the tetracycline class, for the treatment of complicated intra-abdominal infections (cIAIs) in adults.[3] The approval was based on achievement of noninferiority criteria when compared with ertapenem and meropenem in 2 pivotal Phase III trials.

Eravacycline has broad *in vitro* activity against gram-positive and gram-negative pathogens,[3]

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including anaerobes,[4,5] carbapenem-resistant Enterobacteriaceae,[6] and carbapenem-nonsusceptible *Acinetobacter baumannii* strains.[6,7] In the Phase III trials, microbiological and clinical cure were achieved in 32 (88.9%) and 13 (100%) eravacycline-treated patients with cIAIs caused by extended-spectrum β-lactamase–producing Enterobacteriaceae and third- and fourth-generation cephalosporin-resistant *A baumannii* strains, respectively.[8] These cures include 1 carbapenemase-producing Enterobacteriaceae strain[9] and 5 carbapenemase-producing *A baumannii* strains.[8] Pooling data from all clinical trials that included a comparator antibiotic, Lan et al[10] reported similar rates of clinical cIAI cure in eravacycline-treated patients (559/630 [88.7%]) compared with those who received a comparator (492/546 [90.1%]), as well as no differences in all-cause mortality or discontinuation attributable to adverse events.[10]

Multiple comorbid conditions are prevalent in patients with serious bacterial infections.[11] Therefore, it is likely that eravacycline-treated patients will require concomitant treatment with other intravenous medications, including other intravenous antibiotics. Simultaneous infusion can be accomplished by Y-site administration when compatibility data are available. In their absence, concerns for tolerability require placement of additional intravenous access catheters or careful staggering of dosage schedules to accommodate the higher-priority medication. The approved eravacycline dosage is 1 mg/kg of actual weight infused during 60 minutes every 12 hours.[3] However, there are currently no data on the compatibility of eravacycline and other parenteral medications when infused via Y-site to allow for convenient administration during each 1-hour infusion.

Because 2 drugs administered concomitantly via Y-site mix in a 1:1 ratio, an *in vitro* simulated Y-site study design can accurately be applied to address questions of physical compatibility.[12] Therefore, the purpose of this study is to determine the physical compatibility of intravenous eravacycline diluted for infusion with 20 intravenous antimicrobials and 31 other intravenous medications by simulated Y-site administration.

PATIENTS AND METHODS

Eravacycline for injection vials (lot P43022CA; Tetraphase Pharmaceuticals, Watertown, Massachusetts) were supplied by the manufacturer. Each vial was reconstituted with 5 mL of sterile water for injection (lot 90-087-JT; Hospira, Lake Forest, Illinois), resulting in a 10-mg/mL solution. Subsequent dilution with 0.9% sodium chloride for injection in a total volume of 50 mL (lot 95-023-JT; Hospira) or 250 mL (lot J8E024; B. Braun, Bethlehem, Pennsylvania) yielded a final concentration of 0.6 mg/mL, the upper range of appropriate final concentrations listed in published prescribing information.[3] Because the target concentration after calculation of a weight-based clinical dosage is 0.3 mg/mL, select medications determined to be incompatible with eravacycline 0.6 mg/mL were reassessed via mixing with eravacycline 0.3 mg/mL. All prepared eravacycline solutions were refrigerated (2°C–8°C) for a maximum of 24 hours before conducting compatibility assessments.

Selected concentrations of secondary drugs for analyses were those considered standard for clinically used intravenous admixtures or were near the upper limit of a specified concentration range. When necessary, the secondary agents were reconstituted according to manufacturers' instructions and/or diluted in 0.9% sodium chloride (lot 95-023-JT; Hospira) to achieve the desired test concentration. Certain secondary medications commercially available only in 5% dextrose were also included and tested directly from their admixture formulation. Before mixing with eravacycline, aluminum foil was used to protect secondary medications from light when the requirement was listed in the package insert.

To simulate 1:1 inline mixing of 2 intravenous fluids in an administration set with a Y-site injection site,[12] a 5-mL sample of eravacycline solution was combined with a 5-mL sample of each of the secondary intravenous medications in a colorless, 12-mL, borosilicate glass, screw-cap culture tube with polypropylene cap (Kimble Chase, Rockwood, Tennessee). Each test solution was passed through a 0.22-μm syringe filter (Millex-GV Durapore PVDF filter unit, lot R7EA03299; Merck Millipore Ltd, Cork, Ireland) as it was introduced into the culture tube to remove any particulates that may have originated during the preparation of medications before mixing with eravacycline. A larger size (Supor 25-mm 5-μm syringe filter; Baxter Healthcare, Deerfield, Illinois) was used for assessments with

albumin and propofol to prevent filtering the protein and oil phase out of the mixture, respectively. Each eravacycline-secondary medication combination was prepared in duplicate. In addition, the order of mixing was reversed in duplicate so that in total 4 vials that contained each eravacycline-secondary medication mixture were ultimately assessed.

All 10-mL sample mixtures were visually examined with the unaided eye under laboratory fluorescent light and against black and white backgrounds immediately after mixing and then 30, 60, and 120 minutes after mixing. These assessment time points were selected to encompass the recommended infusion time for eravacycline (60 minutes) and an additional 60 minutes to account for clinical scenarios that may arise in which the infusion time is extended. Tubes were gently inverted once before visual assessments. The beam generated by a red laser device (630−680 nm, <5 mW) was directed through the borosilicate culture tubes to test for the presence of a Tyndall effect to aid in visualization of suspended or mobilized particulate matter.[13]

Next, a laboratory-grade turbidimeter (model TL2350, Hach Company, Loveland, Colorado) was operated according to the manufacturer's instructions to record the turbidity of each sample immediately after each visual examination. Calibration was assessed before each day of use according to the manufacturer's recommendation, with standards ranging in turbidity from <0.01 nephelometric turbidity unit (NTU) to 7500 NTU (lot 9023, StablCal ampule kit; Hach Company). The turbidity of each drug sample was measured before mixing and then, for all sample mixtures, immediately on mixture and 30, 60, and 120 minutes after mixing. All sample mixtures were gently inverted 3 times to mobilize and uniformly distribute particulates that may have settled at the bottom of the culture tube before turbidity measurement. Samples were stored at room temperature under constant fluorescent light during the entire 120-minute assessment period.

For the purposes of all visual and turbidimetric comparisons, control solutions composed of 5 mL of diluted eravacycline solution (0.6 or 0.3 mg/mL) and 5 mL of 0.9% sodium chloride were assessed with the methods described above. Incompatibilities were defined as the appearance of any visible particulate matter, haze, color change, or change in measured turbidity of ≥0.5 NTU at any time point in any of the 4 culture tubes assessed for each secondary medication.[14,15]

The potential for incompatibility with propofol was assessed according to an alternative method as previously described.[16,17] In brief, propofol is an opaque white emulsion that renders turbidimetric measurement ineffective for delineation of physical drug incompatibilities.[17] Therefore, samples were prepared in 15-mL colorless, polypropylene plastic centrifuge tubes with polypropylene screw caps (lot 11577-912CB-912D; VWR International, Radnor, Pennsylvania). Four test mixtures were made (ie, in duplicate and reversing the order of drug addition) by mixing 5 mL of diluted eravacycline solution with 5 mL of propofol. Four sets of tubes (16 in total) were mixed at the same initial time, with each set prepared for assessment at 4 different time points: immediately after mixing and 30, 60, and 120 minutes after admixture. Samples designated for assessment at later time points were maintained at room temperature in normal laboratory fluorescent light. A visual assessment was made at each time point to record any obvious color changes or precipitate. Each set was centrifuged at 12,000 rpm for 15 minutes, which has been previously found to result in maximum phase separation,[17] at each designated time point. After centrifugation, each of the 4 tubes underwent a second visual examination. Incompatibility was defined by the formation of precipitate deposited at the bottom of the centrifugation tube (visible with the unaided eye or Tyndall beam) or evidence of a compromised emulsion. After centrifugation, an intact emulsion is described by a white plug of fat that separates and rises to the top of the tube. In the case of a broken emulsion, a layer of free oil forms on top of the sample, compromising the integrity of the fat plug.[14,16] A control solution that contained 10 mL of propofol was centrifuged at each time point for the purpose of comparison.

On mixture of 2 intravenous medications, significant alterations in the acid-base chemistry of either constituent may occur.[18] As such, sample pH was assessed to identify pH changes that may explain any observed incompatibilities. Before mixing, a 0.5-mL aliquot of each secondary intravenous medication was transferred to a borosilicate tube, and the pH was measured using a calibrated pH meter (Orion 320 PerpHecT LogR, Thermo Fisher Scientific,

Beverly, Massachusetts). Calibration was confirmed before each use at room temperature, which ranged from 21°C to 24°C. The pH of a 0.5-mL aliquot of each sample mixture pH was measured at the 60-minute assessment time point.

RESULTS AND DISCUSSION

A total of 41 tested secondary medications (80%) were physically compatible with eravacycline 0.6 mg/mL in 0.9% sodium chloride (Table I). Compatibility was confirmed with 5% dextrose and lactated Ringer's injection, allowing for convenient Y-site administration of scheduled eravacycline dosages in cases where these fluids were previously initiated as slow infusions. Congruent with the observed compatibility with 5% dextrose, no incompatibilities were noted for the 3 secondary medications assessed in a premix formulation diluted in 5% dextrose: ciprofloxacin, dopamine hydrochloride, and linezolid.

Table II provides a detailed description of the observed incompatibilities. The most common reason for incompatibility was a change in the turbidimetric measurement of $\geq$0.5 NTU. These changes were primarily observed in all 4 sample mixtures, with exceptions described in Table II, at each time point. A slight haziness was observed for all incompatible mixtures except those observed with amiodarone hydrochloride, which was clear to the unaided eye, and sodium bicarbonate, which was overtly cloudy. The slight haziness was apparent against a black background on close inspection, but the extent of the haze was such that it may be unnoticed in standard intravenous tubing; thus, the primary reason for these incompatibilities was the observed change in NTUs.

Eravacycline 0.3 mg/mL and 0.6 mg/mL solutions, when diluted in 0.9% sodium chloride, each appeared clear (ie, no haziness) and yellow, which is consistent with the description provided in published prescribing information.[3] No significant color changes were recorded as reasons for incompatibility because all mixtures retained the same shade of yellow when compared with the contents of the control tube. The single notable exception was for the mixture of eravacycline 0.6 mg/mL and albumin, for which each of the 4 tubes retained the golden shade of albumin when mixed with eravacycline.

The propofol mixtures with eravacycline 0.3 mg/mL and 0.6 mg/mL formed opaque, pale yellow solutions immediately after mixing. Particulates were not observed under fluorescent light or on inspection with the laser beam. After centrifugation, an off-white layer of fat (ie, the fat plug) was observed atop a pale-yellow aqueous phase. However, the integrity of the plug was compromised when gently tilting the tube to a 60° angle where the aqueous phase broke through to dissolve it. This observation was in contrast to the plug that formed in the tube containing 10 mL of propofol alone after centrifugation, which remained fully intact, even when tilting the tube to a 90° angle. Because of these alterations in appearance noted by visual inspection, eravacycline was determined to be physically incompatible with propofol. The baseline pH measurement of propofol was 8.14, whereas the mean mixture pH with eravacycline 0.6 mg/mL and 0.3 mg/mL was 7.04 and 7.07, respectively. Decreases in pH are known to destabilize the emulsion[19] and may have contributed to the changes observed.

Six of the 10 incompatibilities with eravacycline 0.6 mg/mL were repeated with the target concentration, 0.3 mg/mL. The secondary drugs reanalyzed at the lower concentration of eravacycline were ceftaroline fosamil, colistimethate sodium, furosemide, meropenem, propofol, and sodium bicarbonate. The reasons for incompatibility recorded with eravacycline 0.6 mg/mL were identical to those observed with eravacycline 0.3 mg/mL. These results suggest that, in the clinical setting, any medication observed to be physically incompatible with eravacycline should be considered incompatible regardless of the final eravacycline concentration.

For each of the 10 observed incompatibilities, pH changes are presented in Table III. The 3 mixtures with the most significant changes >1 pH unit were observed with micafungin sodium, furosemide, and propofol. However, none of these incompatibilities are explained by generation of a unionized, insoluble form of the drug. For example, micafungin is freely soluble in water as the sodium salt of the sulfate ester.[20] Because the only relevant acidic or basic group present is the weakly acidic phenol group (pK_a of approximately 9), a change in pH from 4.34 to 6.39 would not be expected to disrupt the predominant drug form in solution. On the other hand, the observed incompatibility with furosemide is seemingly concordant with the warning for precipitation in acidic solutions in published

Table I. Parenteral drugs assessed for physical compatibility with eravacycline 0.6 mg/mL in 0.9% sodium chloride.

Drug	Concentration Tested	Manufacturer (Lot)	Compatibility Result
Albumin*	25%	Baxalta (CB042432)	Incompatible
Amiodarone hydrochloride	2 mg/mL	Mylan (180626)	Incompatible
Aztreonam	20 mg/mL	Bristol-Myers Squibb (AAV6912)	Compatible
Bumetanide*	0.25 mg/mL	Hospira (76005DD)	Compatible
Calcium chloride	20 mg/mL	Hospira (90267DK)	Compatible
Calcium gluconate	20 mg/mL	Fresenius Kabi (6017543)	Compatible
Cefepime hydrochloride	40 mg/mL	WG Critical Care (107797C)	Compatible
Ceftaroline fosamil	12 mg/mL	Forest Pharmaceuticals (0001D67)	Incompatible
Ceftazidime	40 mg/mL	PremierPro Rx (107209C)	Compatible
Ceftazidime and avibactam sodium	40 + 10 mg/mL	GlaxoSmithKline (Q309)	Compatible
Ceftolozane sulfate and tazobactam sodium	20 + 10 mg/mL	Merck (SP1413)	Compatible
Ciprofloxacin†	2 mg/mL	Claris (A0B0688)	Compatible
Cisatracurium besylate	0.4 mg/mL	Abbvie (87250DD)	Compatible
Colistimethate sodium	4.5 mg/mL‡	Fresenius Kabi (6119954)	Incompatible
Dexmedetomidine hydrochloride*	0.004 mg/mL	Hospira (90240DD)	Compatible
Dextrose, hydrous in water*	5%	Hospira (84010JT)	Compatible
Diltiazem hydrochloride*	5 mg/mL	Akorn (121238A)	Compatible
Dobutamine hydrochloride	4.1 mg/mL	Hospira (84239DK)	Compatible
Dopamine hydrochloride†	0.8 mg/mL	Baxter (P384891)	Compatible
Epinephrine	0.016 mg/mL	BPI Labs (18287)	Compatible
Esmolol hydrochloride*	10 mg/mL	Fresenius Kabi (6017922)	Compatible
Fentanyl citrate*	0.05 mg/mL	West-Ward (098375)	Compatible
Fluconazole[e]	2 mg/mL	Sagent (60827)	Compatible
Furosemide	3 mg/mL	Fresenius Kabi (6017090)	Incompatible
Gentamicin sulfate	5 mg/mL	Fresenius Kabi (6116971)	Compatible
Heparin sodium	1000 U/mL	Sagent (104813N)	Compatible
Hydromorphone hydrochloride	1 mg/mL	Akorn (051078A)	Compatible
Imipenem and cilastatin sodium	5 + 5 mg/mL	Fresenius Kabi (0002D75)	Compatible
Insulin, human regular	1 U/mL	Eli Lilly (C938643D)	Compatible
Lactated Ringer's solution*	NA	B. Braun (J8K258)	Compatible
Levofloxacin	5 mg/mL	AuroMedics (CLF180001)	Compatible
Linezolid†	2 mg/mL	Pfizer (18H09416)	Compatible
Magnesium sulfate	100 mg/mL	Fresenius Kabi (6017780)	Compatible
Meropenem	20 mg/mL	Fresenius Kabi (4B18F20)	Incompatible
Meropenem and vaborbactam	8 + 8 mg/mL	Facta Farmaceutici (0001D8)	Incompatible
Metronidazole§	5 mg/mL	Baxter (P387431)	Compatible
Micafungin sodium	4 mg/mL	Astellas (A00004911)	Incompatible
Midazolam hydrochloride	1 mg/mL	Hospira (91025 PK)	Compatible
Morphine sulfate	1 mg/mL	West-Ward (037416)	Compatible
Nicardipine hydrochloride	0.1 mg/mL	Exela (PMXL1809)	Compatible
Norepinephrine bitartrate	0.032 mg/mL	Claris (17136C)	Compatible

Table I. (*Continued*)

Drug	Concentration Tested	Manufacturer (Lot)	Compatibility Result
Octreotide acetate	0.004 mg/mL	Fresenius Kabi (6119595)	Compatible
Pantoprazole sodium	0.4 mg/mL	Pfizer (420579)	Compatible
Phenylephrine hydrochloride	1 mg/mL	Avadel (00032A)	Compatible
Piperacillin sodium and tazobactam sodium	40 + 5 mg/mL	Fresenius Kabi (7C13TR)	Compatible
Propofol*	10 mg/mL	Fresenius Kabi (16MK2291)	Incompatible
Sodium bicarbonate*	1 mEq/mL	Fresenius Kabi (6018169)	Incompatible
Tobramycin sulfate	5 mg/mL	Fresenius Kabi (6018285)	Compatible
Vancomycin hydrochloride	5 mg/mL	Alvogen (YV822)	Compatible
Vasopressin	1 U/mL	Par Pharmaceutical (325085)	Compatible
Vecuronium bromide*	1 mg/mL	Teva (31325712B)	Compatible

NA = not applicable.
* Use of undiluted drug product.
† Commercial preparation prepared in 5% dextrose.
‡ Concentration expressed in terms of colistin.
§ Commercial preparation diluted in 0.9% sodium chloride.

prescribing information.[21] However, when incompatibility was confirmed with eravacycline 0.3 mg/mL, the pH of the initial furosemide solution was 7.33, and the pH of the sample mixtures at 60 minutes ranged from 7.35 to 7.43 in the presence of confirmed precipitation. The reason for visible precipitation is unclear and may be related to the eravacycline component of the mixture.

There were 4 strongly acidic solutions with pH <4 documented before mixture. These solutions were vancomycin hydrochloride (pH 3.35), midazolam hydrochloride (pH 3.10), diltiazem hydrochloride (pH 3.94), and vecuronium bromide (pH 3.83). No change in pH or a minor increase (<1 pH unit) was noted for these solutions when mixed with eravacycline. Therefore, the mixing of these physically compatible formulations does not pose a patient tolerability concern relative to the acidity of the mixture.

Incompatibilities between eravacycline and other tested antimicrobials occurred in 5 of 20 assessments (25%). In patients assessed to be at risk for MDR or polymicrobial infections, prescribers may prefer combination antimicrobial regimens, especially for empirical treatment. Although it is unfortunate from a convenience standpoint that meropenem, meropenem/vaborbactam, ceftaroline fosamil, colistimethate sodium, and micafungin were incompatible with eravacycline, these findings do not preclude combination treatment as long as the medications are administered through separate intravenous access catheters or treatment schedules are properly staggered.

This study did not assess for potential chemical incompatibilities that may compromise the antimicrobial efficacy of eravacycline or contribute to other drug-related problems. For instance, the physical compatibility observed between eravacycline and solutions that contain divalent cations (ie, lactated Ringer's solution, calcium gluconate, calcium chloride, magnesium sulfate) should be interpreted with caution. The concern for reduced effectiveness of tetracycline antibiotics caused by metal chelation is primarily reported in the context of decreased absorption after oral dosing.[22] The clinical significance of the interaction is unclear. It is known, however, that the affinity of tetracyclines for metal cations is pH dependent.[23] In this study, the pH range observed among any tube that contained a mixture of eravacycline and a divalent cation-containing salt (ie, lactated Ringer's solution, calcium gluconate, calcium chloride, magnesium sulfate) was 4.37 to 6.06. It is plausible that in this acidic

Table II. Description of physical incompatibilities with eravacycline 0.6 mg/mL in 0.9% sodium chloride.

Drug	Time of Assessment After Mixing, min*			
	0 (Immediate)	30	60	120
Albumin	Turbidity increase (>6 NTU)	Turbidity increase (>6 NTU)	Turbidity increase (>6 NTU)	Turbidity increase (>6 NTU)
Amiodarone hydrochloride	Turbidity increase (>0.5 NTU) in 2 of 4 tubes	Turbidity increase (>0.5 NTU) in 3 of 4 tubes	Turbidity increase (>0.5 NTU) in 4 of 4 tubes	Turbidity increase (>0.5 NTU) in 2 of 4 tubes
Ceftaroline fosamil	No changes relative to control	No changes relative to control	No changes relative to control	Turbidity increase (>0.5 NTU) in 2 of 4 tubes
Colistimethate sodium	Clear (yellow solution)	Turbidity increase (>7 NTU); Tyndall effect	Turbidity increase (>15 NTU); Tyndall effect	Turbidity increase (>26 NTU); Tyndall effect
Furosemide	Turbidity increase (>6 NTU); Tyndall effect	Turbidity increase (>8 NTU); Tyndall effect	Turbidity increase (>9 NTU); Tyndall effect	Turbidity increase (>9 NTU); Tyndall effect
Meropenem	Turbidity increase (>1 NTU) in 3 of 4 tubes	Turbidity increase (>5 NTU); Tyndall effect	Turbidity increase (>9 NTU); Tyndall effect	Turbidity increase (>13 NTU); Tyndall effect
Meropenem and vaborbactam	Turbidity increase (>1 NTU) in 2 of 4 tubes; Tyndall effect in 3 of 4 tubes	Turbidity increase (>12 NTU); Tyndall effect	Turbidity increase (>16 NTU); Tyndall effect	Turbidity increase (>21 NTU); Tyndall effect
Micafungin sodium	Turbidity increase (>6 NTU); Tyndall effect	Turbidity increase (>9 NTU); Tyndall effect	Turbidity increase (>10 NTU); Tyndall effect	Turbidity increase (>11 NTU); Tyndall effect
Propofol	Compromised emulsion	Compromised emulsion	NA	NA
Sodium bicarbonate	Turbidity increase (>77 NTU); Tyndall effect; cloudy	Turbidity increase (>85 NTU); Tyndall effect; cloudy	Turbidity increase (>83 NTU); Tyndall effect; cloudy	Turbidity increase (>83 NTU); Tyndall effect; cloudy

NA = not assessed; NTU = nephelometric turbidity unit.
* Changes observed in all 4 tubes unless otherwise noted.

environment, the tetracycline ring was protonated at the typical site of chelation,[24] thereby preventing formation of the insoluble metal complex.

Practitioners and nurses who administer intravenous medications should be aware that the chemistry of physical compatibilities is complex,[18] and compatibility may be formulation specific or concentration dependent. Although commonly available formulations and concentrations were selected for this study, intravenous tubing downstream from a Y-site should always be inspected for particulate matter after the coinfusion of any combination of intravenous medications to optimize patient tolerability. Moreover, use of a syringe filter in this *in vitro* study of drug compatibility, which is consistent with methods previously published by others,[25,26] does not necessarily mandate clinical use of an in-line filter during Y-site administration of

Table III. Test solution pH for incompatible combinations of eravacycline and parenteral drugs.

Drug	pH		
	Before Mixing With Eravacycline (0.6 mg/mL)	60 min After Mixing With Eravacycline (0.6 mg/mL)*	Absolute Difference
Albumin	7.05	6.93	−0.12
Amiodarone hydrochloride	4.49	5.39	0.90
Ceftaroline fosamil	4.95	5.29	0.34
Colistimethate sodium	7.68	7.75	0.07
Furosemide	8.05	6.92	−1.59
Meropenem	7.96	7.91	−0.05
Meropenem and vaborbactam	7.99	7.86	−0.13
Micafungin sodium	4.34	6.39	2.05
Propofol	8.14	7.04	−1.10
Sodium bicarbonate	7.98	8.22	0.24

* Mean pH in all 4 tubes.

eravacycline; such requirements should always be assessed on a case-by-case basis.

CONCLUSIONS

Eravacycline was physically compatible with 41 parenteral drugs (80%) by simulated Y-site administration. Incompatibilities occurred with albumin, amiodarone hydrochloride, furosemide, propofol, and sodium bicarbonate. Antimicrobial incompatibilities included ceftaroline fosamil, colistimethate sodium, meropenem, meropenem/vaborbactam, and micafungin sodium. Because intravenous incompatibilities place critically ill patients at risk for various organ dysfunctions,[27] these findings should be used to safeguard against coinfusion of the aforementioned medications with eravacycline.

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DISCLOSURES

D.P. Nicolau and J.L. Kuti serve on advisory boards and the speakers' bureau for Tetraphase Pharmaceuticals. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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