Compatibility of Caspofungin Acetate Injection with Other Drugs During Simulated Y-Site Coadministration

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ABSTRACT
The physical compatibility of caspofungin acetate injection with selected other drugs during simulated Y-site coadministration was evaluated by visual observation and turbidity measurement. Five-milliliter samples of caspofungin acetate 0.7 mg/mL in 0.9% sodium chloride injection were combined with 5 mL of 67 other drugs including antineoplastics, analgesics, anti-infectives, and supportive care drugs, undiluted or diluted in 0.9% sodium chloride injection or 5% dextrose injection, and with a parenteral nutrition admixture. Visual examinations were performed with the unaided eye in normal laboratory fluorescent light and with a Tyndall beam (high-intensity monodirectional light beam) to enhance visualization of small particles and low-level turbidity. The turbidity of each sample was measured as well. The sample mixtures were evaluated immediately and at 1 and 4 hours after preparation. Nineteen of the drugs tested and the parenteral nutrition admixture were incompatible with caspofungin acetate 0.7 mg/mL during the 4-hour observation period. The remaining drugs were compatible for at least 4 hours. Gross precipitation or turbidity changes visible in normal diffuse room light with the unaided eye occurred with 18 drugs and with the parenteral nutrition admixture. Microprecipitation of particulates not visible with the unaided eye occurred with cytarabine. The measured turbidity of the caspofungin acetate control solutions and the compatible test samples remained essentially unchanged throughout the observation period. In combination with caspofungin acetate, 48 drugs and a parenteral nutrition admixture were considered to be physically compatible. In contrast, 19 drugs with the parenteral nutrition admixture exhibited frank precipitation or microparticulate formation within 4 hours and should not be simultaneously administered via Y-site with caspofungin acetate.

INTRODUCTION
Caspofungin acetate (CANCIDAS; Merck & Co., Inc., Whitehouse Station, New Jersey) is a semisynthetic lipopeptide antifungal agent. The drug acts by inhibiting the synthesis of β(1,3)-D-glucan, an integral component of the fungal cell wall. Caspofungin acetate is active *in vitro* against several species of *Aspergillis* and *Candida*. The drug is indicated in the treatment of presumed fungal infections in febrile, neutropenic patients. It is indicated in *Candida* infections, including intra-abdominal abscess, peritonitis, infection of the pleural space, and esophageal candidiasis. Caspofungin acetate is also used to treat invasive aspergillosis in cases refractory to other treatments or in patients who cannot tolerate other medications. Caspofungin acetate is administered by slow intravenous infusion over 1 hour.[1]

Patients receiving caspofungin acetate infusion may be receiving many other parenteral drugs via Y-site coadministration, including anti-infectives, antiemetics, antineoplastics, steroids, analgesics, and other supportive care drugs. The potential exists during coadministration for development of physical incompatibilities of caspofungin acetate and other agents or components of their formulations.

The purpose of this study was to evaluate the physical compatibility of caspofungin acetate during simulated Y-site injection with 67 other drugs and a parenteral nutrition admixture by visual observation and turbidity measurement.

METHODS AND MATERIALS
Materials
Caspofungin acetate injection (Lots 0199U, 0421U, and 1567F; Merck & Co., Inc.) was supplied in 70-mg lyophilized single-use vials. The vial contents were reconstituted with 10 mL of 0.9% sodium chloride injection (Lot 34-012-JT; Hospira, Lake Forest, Illinois; or Lot J6S909; B. Braun, Bethlehem, Pennsylvania) removed from a 100-mL bag of the infusion solution. The reconstituted caspofungin acetate was added back to the 100-mL bags of 0.9% sodium chloride solution, yielding a 0.7-mg/mL caspofungin acetate solution used for this testing. The 67 drugs and parenteral nutrition admixture that served as secondary additives in this study are listed in Table 1. The secondary additives were tested undiluted, prepared in 0.9% sodium chloride injection, or prepared in 5% dextrose injection (Lot P198622; Baxter Healthcare, Deerfield, Illinois) for testing (see Table 1). Drug concentrations used for this testing were selected to represent the higher end of concentrations typically administered.

Allen et al reported that the mixing of an intravenous fluid in an administration set with a secondary additive from a Y-injection site occurs in a 1:1 ratio.[2] Therefore, a 5-mL sample of the caspofungin acetate 0.7 mg/mL solution was combined with a 5-mL sample of each of the other study drug solutions individually in colorless 15-mL borosilicate glass screw-cap culture tubes (Kimble, Division of Owens-Illinois, Toledo, Ohio) with polypropylene caps (Kimble, Division of Owens-Illinois) as described elsewhere.[3] Each of the sample solutions was passed through an appropriate 0.22-mcm filter (Millex-GV; Millipore Products, Bedford, Massachusetts) as it was introduced into the tube. Each caspofungin acetate/test drug combination was prepared in duplicate, the second trial reversing the order in which the drugs were added in the first trial.

Caspofungin acetate 0.7 mg/mL in 0.9% sodium chloride injection and the other test drug solutions each were diluted with an

equal volume of 0.9% sodium chloride injection to a concentration of 0.35 mg/mL to simulate test sample preparation. These dilutions served as controls. Incompatibility in the caspofungin acetate/test drug combinations was defined as any visible particulate matter, substantial haze or turbidity change from that in the controls, a color change, or gas evolution.

Table 1. Drugs Tested for Compatibility with Caspofungin Acetate 0.7 mg/mL in 0.9% Sodium Chloride Injection.

Drug	Manufacturer	Lot Number	Concentration[a]
Acyclovir sodium	Ben Venue	733396	7 mg/mL
Amikacin sulfate	Hospira	45-325-DK	5 mg/mL
Amiodarone hydrochloride	Sicor	06N216	4 mg/mL
Amphotericin B (colloidal)	X-Gen	5L6AB	0.6 mg/mL[b]
Amphotericin B lipid complex	Enzon Pharmaceuticals	6569A	1 mg/mL[b]
Amphotericin B liposomal	Astellas Pharma	042640AA	1 mg/mL[b]
Ampicillin sodium	American Pharmaceutical Partners	6F12AY	20 mg/mL
Aztreonam	Bristol-Myers Squibb	6B12498	40 mg/mL
Bumetanide	Bedford	957786	0.04 mg/mL
Carboplatin	Mayne Pharma	S041709	5 mg/mL
Cefazolin sodium	Cura Pharmaceuticals	C026083	20 mg/mL
Cefepime hydrochloride	Bristol-Myers Squibb	6C19179	20 mg/mL
Ceftazidime	GlaxoSmith Kline	A176	40 mg/mL
Ceftriaxone sodium	Orchid	C086014	20 mg/mL
Ciprofloxacin	Hospira	51-279-DK	2 mg/mL
Cisplatin	American Pharmaceutical Partners	201720	0.5 mg/mL
Clindamycin phosphate	Bedford	974322	10 mg/mL
Cyclosporine	Bedford	710699	5 mg/mL
Cytarabine	Mayne Pharma	S021982AA	50 mg/mL[c]
Daptomycin	Cubist	451653	10 mg/mL
Daunorubicin hydrochloride	Bedford	957972	1 mg/mL
Diltiazem hydrochloride	Hospira	50470DD	5 mg/mL[c]
Dobutamine hydrochloride	Hospira	44-287-DK	4 mg/mL
Dopamine hydrochloride	American Regent	5123	3.2 mg/mL
Doxorubicin hydrochloride	Bedford	954153	1 mg/mL
Epinephrine hydrochloride	Amphastar-IMS	DT029C7	0.05 mg/mL
Ertapenem	Merck	3918R	20 mg/mL
Etoposide phosphate	Sicor	06N614	5 mg/mL
Fentanyl citrate	Hospira	47-346-DK	0.05 mg/mL
Furosemide	American Regent	5475	3 mg/mL
Ganciclovir sodium	Roche	U2186	20 mg/mL
Gentamicin sulfate	Hospira	41-468-DK	5 mg/mL
Heparin sodium	Hospira	45-160-DK	100 units/mL[c]
Hydrocortisone sodium succinate	Hospira	43260DD	1 mg/mL
Hydromorphone hydrochloride	Baxter	037067	1 mg/mL
Ifosfamide	Baxter	5L163L	20 mg/mL
Imipenem-cilastatin	Merck	3967R	5 mg/mL
Insulin human regular	Novo Nordisk	SZF0177	1 unit/mL
Lansoprazole	TAP	48004RX	0.55 mg/mL
Levofloxacin	Janssen	6KB5500	5 mg/mL
Linezolid	Pharmacia & Upjohn	06105Z04	2 mg/mL[c]
Lorazepam	Hospira	39220DD	0.5 mg/mL
Magnesium sulfate	American Regent	5447	100 mg/mL
Melphalan hydrochloride	Cardinal Health	A502	1 mg/mL
Meperidine hydrochloride	Hospira	45625LL	10 mg/mL
Meropenem	AstraZeneca	MM0108	2.5 mg/mL
Methylprednisolone sodium succinate	Pharmacia & Upjohn	56PYD	5 mg/mL
Metronidazole	Baxter	P200337	5 mg/mL[c]
Midazolam hydrochloride	American Pharmaceutical Partners	402072	2 mg/mL
Milrinone lactate	Baxter	116097	0.2 mg/mL
Mitomycin	Bedford	1106707	0.5 mg/mL
Morphine sulfate	Baxter	116078	15 mg/mL[c]
Mycophenolate mofetil hydrochloride	Roche	H3057	6 mg/mL
Nafcillin sodium	Sandoz	140345	20 mg/mL
Norepinephrine bitartrate	Bedford	922401	0.128 mg/mL
Pantoprazole sodium	Wyeth	17283A	0.4 mg/mL
Parenteral nutrition admixture[d]	Mercy Health Center	None	
Phenylephrine hydrochloride	Baxter	163504	1 mg/mL
Piperacillin sodium/ tazobactam sodium	Wyeth	B45832	40/5 mg/mL
Potassium chloride	American Pharmaceutical Partners	402446	0.1 mEq/mL
Potassium phosphates	American Pharmaceutical Partners	141489	0.5 mmol/mL
Quinupristin/ dalfopristin	Monarch	A18640	5 mg/mL
Sulfamethoxazole/ trimethoprim	Sicor	06N102	4 + 0.8 mg/mL
Tacrolimus	Astellas Pharma	5A3118A	0.02 mg/mL
Tobramycin sulfate	Sicor	06E127	5 mg/mL
Vancomycin hydrochloride	Hospira	45-730Z7	10 mg/mL
Vincristine sulfate	Mayne Pharma	S057139AA	0.05 mg/mL
Voriconazole	Pfizer	A22281	4 mg/mL

[a]Tested in 0.9% sodium chloride injection unless stated otherwise; [b]Tested in 5% dextrose injection; [c]Tested undiluted; [d]Extemporaneously compounded at Mercy Health Center Pharmacy, Oklahoma City, Oklahoma. The specific formulation components and concentrations of the "2-in-1" parenteral nutrition admixture were not recorded.

Physical Stability

All sample combinations were examined visually with the unaided eye in normal laboratory fluorescent light. Combinations with no obvious visible incompatibility were examined further by using a Tyndall beam (high-intensity monodirectional light source; Dolan-Jenner Industries, Woburn, Massachusetts) as described elsewhere.[3] Inspections were performed during the first 15 minutes after the drugs were combined and at intervals of 1 and 4 hours after combination. The samples were stored at room temperature (approximately 23°C) under constant fluorescent light, except for the sodium nitroprusside samples, which were protected from light during the testing.

The samples were assessed for turbidity immediately after combination and at 1 and 4 hours after combination using a color-correcting turbidimeter (Model 2100AN; Hach Company, Loveland, Colorado) as described elsewhere.[4,5] Some drug products are inherently hazy. The use of the turbidimeter permits quantification of that haze and assessment of any changes, whether visually apparent or not. An incompatibility is defined as a substantial increase in measured turbidity. For relatively clear drug solutions such as caspofungin acetate diluted for infusion, an incompatibility has been defined as an increase in measured turbidity exceeding 0.5 nephelometric turbidity unit (NTU) that did not occur upon simple dilution alone.[3-5]

RESULTS AND DISCUSSION

Caspofungin acetate 0.7 mg/mL in 0.9% sodium chloride injection appeared in normal room light and when viewed using a Tyndall beam as a clear, colorless, free-flowing liquid. The initial 0.7 mg/mL solution was essentially without turbidity, having a very low measured turbidity near 0.1 NTU. When diluted to 0.35 mg/mL with an equal amount of 0.9% sodium chloride injection or 5% dextrose injection, in a manner identical to mixing with each of the secondary test drugs, the drug solution also had a measured turbidity of near 0.1 NTU.

A total of 48 drug combinations were determined to be compatible with caspofungin acetate 0.7 mg/mL in 0.9% sodium chloride injection. On visual inspection, these combinations appeared to be very similar in clarity to the caspofungin acetate solution diluted with an equal quantity of aqueous solution; their measured turbidities were similar.

Caspofungin acetate was physically incompatible with 19 of the drugs and the parenteral nutrition admixture (Table 2), exhibiting several observable changes including visible precipitation or turbidity formation (18 drugs and the parenteral nutrition admixture) or microparticulate formation (1 drug). Although microprecipitate formation was observed in this laboratory setting, it was not visually apparent in normal room light to the unaided eye. See Table 2 for incompatibilities observed in this study.

It should be noted that, in general, the timing, appearance, and extent or amount of physical incompatibility phenomena vary considerably. Consequently, any drug that has demonstrated a physical incompatibility with caspofungin acetate within 4 hours of mixing should be considered unacceptable for Y-site coadministration with caspofungin acetate at any time.

CONCLUSION

Caspofungin acetate 0.7 mg/mL in 0.9% sodium chloride injection is physically compatible for 4 hours at room temperature with 48 of the 67 drugs evaluated in this study during simulated Y-site administration. Nineteen drugs and a parenteral nutrition admixture mixed with caspofungin acetate resulted in unacceptable gross precipitation or microparticulate formation and should not be simultaneously administered via Y-site with caspofungin acetate.

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Table 2. Drugs Incompatible with Caspofungin Acetate 0.7 mg/mL in 0.9% Sodium Chloride Injection.

Drug	Remarks[a]
Amphotericin B colloidal	Gross yellow turbid precipitation formed immediately
Amphotericin B lipid complex	Gross yellow turbid precipitation formed immediately
Amphotericin B liposomal	Gross yellow-orange turbid precipitation formed immediately
Ampicillin sodium	Gross white turbid precipitation formed immediately
Cefazolin sodium	Gross white turbid precipitation formed immediately
Cefepime hydrochloride	Gross white turbid precipitation formed immediately
Ceftazidime	Gross white turbid precipitation formed immediately
Ceftriaxone sodium	Gross white turbid precipitation formed immediately
Clindamycin phosphate	Gross white turbid precipitation formed immediately
Cytarabine	Microparticulates[b] formed within 4 hours
Ertapenem	Gross white turbid precipitation formed immediately
Furosemide	Gross white turbid precipitation formed immediately
Heparin sodium	Gross white turbid precipitation formed immediately
Lansoprazole	Gross white turbid precipitation formed immediately
Methylprednisolone sodium succinate	Gross white turbid precipitation formed immediately
Nafcillin sodium	Transient turbidity appear upon mixing, becoming gross white turbid precipitation within 1 hour
Parenteral nutrition admixture	Gross white turbid precipitation formed immediately
Piperacillin sodium/ tazobactam sodium	Gross white turbid precipitation formed immediately
Potassium phosphates	Gross white turbid precipitation formed immediately
Sulfamethoxazole/trimethoprim	Gross white turbid precipitation formed immediately

[a]All observations were made in normal diffuse light with the unaided eye unless specified otherwise.
[b]Visible only with a Tyndall beam and measured using the light obscuration particle sizer/counter.