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

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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 \( \beta(1,3) \)-D-glucan, an integral component of the fungal cell wall. Caspofungin acetate is active in vitro against several species of Aspergillus 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.

Patients receiving caspofungin acetate infusion may be receiving many other parenteral drugs via Y-site coadministration, including anti-infectives, anti-neoplastics, 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. 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.

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

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 anti-neoplastics, 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.
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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Lot Number</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir sodium</td>
<td>Ben Venue</td>
<td>733396</td>
<td>7 mg/mL</td>
</tr>
<tr>
<td>Amikacin sulfate</td>
<td>Hospira</td>
<td>45-325-DK</td>
<td>5 mg/mL</td>
</tr>
<tr>
<td>Amiodarone hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B (colloidal)</td>
<td>X-Gen</td>
<td>5L6AB</td>
<td>0.6 mg/mL</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>Enzon</td>
<td>6569A</td>
<td>1 mg/mL</td>
</tr>
<tr>
<td>Amphotericin B liposomal</td>
<td>Astellas Pharma</td>
<td>042640AA</td>
<td>1 mg/mL</td>
</tr>
<tr>
<td>Ampicillin sodium</td>
<td>American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Bristol-Myers</td>
<td>6B12498</td>
<td>40 mg/mL</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>Bedford</td>
<td>957786</td>
<td>0.04 mg/mL</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Mayne Pharma</td>
<td>S014709</td>
<td>5 mg/mL</td>
</tr>
<tr>
<td>Cefazolin sodium</td>
<td>Cura</td>
<td>C026083</td>
<td>20 mg/mL</td>
</tr>
<tr>
<td>Cefepime hydrochloride</td>
<td>Bristol-Myers</td>
<td>6C19179</td>
<td>20 mg/mL</td>
</tr>
<tr>
<td>Cefazidine</td>
<td>GlaxoSmith</td>
<td>A176</td>
<td>40 mg/mL</td>
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<td>Ceftriaxone sodium</td>
<td>Orchid</td>
<td>C086014</td>
<td>20 mg/mL</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Hospira</td>
<td>51-279-DK</td>
<td>2 mg/mL</td>
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<tr>
<td>Cisplatin</td>
<td>American</td>
<td>201720</td>
<td>0.5 mg/mL</td>
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<tr>
<td>Clindamycin sulfate</td>
<td>Bedford</td>
<td>974322</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Bedford</td>
<td>71069B</td>
<td>5 mg/mL</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Mayne Pharma</td>
<td>S0211982AA</td>
<td>50 mg/mL</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Calibra</td>
<td>451655</td>
<td>10 mg/mL</td>
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<td>Daunorubicin hydrochloride</td>
<td>Bedford</td>
<td>957972</td>
<td>1 mg/mL</td>
</tr>
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<td>Diltiazem hydrochloride</td>
<td>Hospira</td>
<td>50470DD</td>
<td>5 mg/mL</td>
</tr>
<tr>
<td>Dobutamine hydrochloride</td>
<td>Hospira</td>
<td>44-287-DK</td>
<td>4 mg/mL</td>
</tr>
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<td>Dopamine hydrochloride</td>
<td>American</td>
<td>5123</td>
<td>3.2 mg/mL</td>
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<tr>
<td>Doxorubicin hydrochloride</td>
<td>Bedford</td>
<td>954153</td>
<td>1 mg/mL</td>
</tr>
<tr>
<td>Epinephrine hydrochloride</td>
<td>Amaphar-IMS</td>
<td>DT029C07</td>
<td>0.05 mg/mL</td>
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<tr>
<td>Ertapenem</td>
<td>Merck</td>
<td>3918R</td>
<td>20 mg/mL</td>
</tr>
<tr>
<td>Etoposide phosphate</td>
<td>Sicon</td>
<td>06N614</td>
<td>5 mg/mL</td>
</tr>
<tr>
<td>Fentanyl citrate</td>
<td>Hospira</td>
<td>47-346-DK</td>
<td>0.05 mg/mL</td>
</tr>
<tr>
<td>Furosemide</td>
<td>American</td>
<td>5475</td>
<td>3 mg/mL</td>
</tr>
<tr>
<td>Ganciclovir sodium</td>
<td>Roche</td>
<td>U2186</td>
<td>20 mg/mL</td>
</tr>
<tr>
<td>Gentamicin sulfate</td>
<td>Hospira</td>
<td>41-468-DK</td>
<td>5 mg/mL</td>
</tr>
<tr>
<td>Heparin sodium</td>
<td>Hospira</td>
<td>45-160-DK</td>
<td>100 units/mL</td>
</tr>
<tr>
<td>Hydrocortisone sodium</td>
<td>Hospira</td>
<td>43260DD</td>
<td>1 mg/mL</td>
</tr>
</tbody>
</table>

*Tested in 0.9% sodium chloride injection unless stated otherwise; †Tested in 5% dextrose injection; ‡Tested undiluted; §Temporarily 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. 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. 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 demonstrated to be a useful way to define incompatibility. 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 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 microparticulate formation was observed in this laboratory testing, 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.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B colloidal</td>
<td>Gross yellow turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>Gross yellow turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Amphotericin B liposomal</td>
<td>Gross yellow-orange turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Anaplasticin sodium</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Cefazolin sodium</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Cefepime hydrochloride</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Ceftriazone sodium</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Clindamycin phosphate</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Microparticulates formed with 4 hours</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Eurosemide</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Heparin sodium</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Methylprednisolone sodium succinate</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Nafcillin sodium</td>
<td>Transient turbidity appear upon mixing, becoming gross white turbid precipitation within 1 hour</td>
</tr>
<tr>
<td>Parenteral nutrition admixture</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Piperacillin sodium/tazobactam sodium</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Potassium phosphates</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td>Gross white turbid precipitation formed immediately</td>
</tr>
</tbody>
</table>

All observations were made in normal diffuse light with the unaided eye unless specified otherwise.

Table 2 for incompatibilities observed in this study.

REFERENCES


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