Compatibility of Micafungin Injection with Other Drugs During Simulated Y-Site Co-Administration

Abstract

The objective of this study was to evaluate the physical compatibility of micafungin injection with selected other drugs during simulated Y-site co-administration. Physical stability was assessed by both visual observation and turbidity measurement. Micafungin in 0.9% sodium chloride injection was combined with each of 48 other drugs, including antineoplastics, analgesics, anti-infectives, and supportive care drugs undiluted or diluted in 0.9% sodium chloride injection, and with a parenteral nutrition admixture. Visual examinations were performed with the unaided eye in fluorescent light and by using a Tyndall beam, and the turbidity of each sample was measured. The samples were evaluated immediately after mixing and again 1 and 4 hours after preparation. Twenty-nine of the drugs tested were found to be compatible for at least 4 hours. The measured turbidity of the micafungin control solutions and the compatible test samples remained essentially unchanged throughout the study. The other 19 drugs exhibited frank precipitation, microparticulate formation, or unacceptable increases in turbidity within 4 hours of mixture with micafungin and thus should not be administered simultaneously via Y-site with micafungin.

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Introduction

Micafungin (Mycamine; Astellas Pharma US, Inc., Deerfield, Illinois) is a new semisynthetic lipopeptide antifungal agent. The drug acts by inhibiting the synthesis of 1,3-β-D-glucan, an integral component of the fungal cell wall. Micafungin is active *in vitro* against several species of *Candida*. The drug is indicated in the treatment of esophageal candidiasis as well as the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. Micafungin is administered by intravenous infusion after dilution in 0.9% Sodium Chloride Injection USP or in 5% Dextrose Injection USP.[1]

Patients who receive micafungin infusion may be receiving many other parenteral drugs via Y-site co-administration, including anti-infectives, antiemetics, antineoplastics, steroids, analgesics, and other supportive care drugs. The potential exists for the development of physical incompatibilities during such Y-site co-administration of micafungin injection with these other agents or components of their formulations.

The purpose of this study was to evaluate the physical compatibility of micafungin during simulated Y-site injection with 48 other drugs and with a parenteral nutrition admixture by visual observation and turbidity measurement.

Methods

Micafungin injection (Lot 0010; Astellas Pharma US, Inc.) was supplied in 50-mg lyophilized single-use vials. The vials were reconstituted with 5 mL of 0.9% Sodium Chloride Injection USP (Lot P160630; Baxter Healthcare Corporation, Deerfield, Illinois), yielding a 10-mg/mL solution. The reconstituted micafungin was added to 50-mL polyvinylchloride bags of 0.9% Sodium Chloride Injection USP (Lot PS170449; Baxter Healthcare Corporation) to achieve a concentration of 1.5 mg/mL in 0.9% sodium chloride injection, the concentration used in the treatment of esophageal candidiasis.[1] The 48 other drugs and a parenteral nutrition admixture that were studied are listed in Table 1. These drugs were tested undiluted, diluted in 0.9% sodium chloride injection, or diluted in 5% dextrose injection (Lot P160630; Baxter Healthcare Corporation) for testing (see Table 1). Drug concentrations used for this testing were selected to represent the higher end of normal administration concentrations and were approved by Astellas Pharma US, Inc., prior to this testing.

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, 5-mL samples of the micafungin 1.5 mg/mL solution were combined with a 5-mL sample of each of the other study drug solutions individually in colorless 15-mL

Table 1. Drugs Tested for Compatibility with Micafungin 1.5 mg/mL in 0.9% Sodium Chloride Injection USP.

Drug	*Manufacturer*	*Lot Number*	*Concentration*[a]
Albumin, human	ZLB Biopharma	04319-00087	25%[b]
Aminophylline	American Regent	4021	2.5 mg/mL
Amiodarone HCl	Baxter	4251-18	4 mg/mL
Bumetanide	Bedford	155353A	0.04 mg/mL
Calcium chloride	Abbott	15-079-EV	40 mg/mL
Calcium gluconate	American Reagent	5084	40 mg/mL
Carboplatin	Baxter	04D14NB	5 mg/mL
Cisatracurium besylate	Abbott	Z11953A	0.5 mg/mL
Cyclosporine	Bedford	710699	5 mg/mL
Diltiazem HCl	Baxter	05B128	5 mg/mL[b]
Dobutamine HCl	Abbott	12-420-DK	4 mg/mL
Dopamine HCl	American Regent	2036	3.2 mg/mL
Epinephrine HCl	Abbott	192103A	0.05 mg/mL
Eptifibatide	Schering	YB126A1	0.75 mg/mL[b]
Esmolol HCl	Baxter	3291-02	10 mg/mL
Etoposide	Sicor	04L611	0.4 mg/mL
Fenoldopam mesylate	Baxter	3H028A	0.08 mg/mL
Furosemide	American Regent	5221	3 mg/mL
Heparin sodium	Abbott	25-194-DK	100 units/mL[b]
Hydromorphone HCl	Baxter	025085	0.5 mg/mL
Insulin, human, regular	Novo Nordisk	PZF0230	1 unit/mL
Labetalol HCl	Abbott	256553B	2 mg/mL
Lidocaine HCl	Abbott	25-447-DK	10 mg/mL
Lorazepam	Abbott	194303A	0.5 mg/mL
Magnesium sulfate	American Regent	4546	100 mg/mL
Meperidine HCl	Abbott	Z15103A	10 mg/mL
Mesna	American Pharmaceutical Partners	141128	20 mg/mL
Midazolam HCl	American Pharmaceutical Partners	343270	2 mg/mL
Milrinone lactate	Bedford	569607	0.2 mg/mL
Morphine sulfate	American Pharmaceutical Partners	114071	15 mg/mL[b]
Mycophenolate mofetil HCl	Roche	U3057	6 mg/mL[c]
Nesiritide	Scios	R0003A	0.006 mg/mL[c]
Nicardipine HCl	ESP Pharma	064034	1 mg/mL
Nitroglycerin	American Regent	5116	0.4 mg/mL
Norepinephrine bitartrate	Bedford	04C130	0.128 mg/mL
Octreotide	Novartis	S0023	0.005 mg/mL
Ondansetron HCl	GlaxoSmithKline	C113718	1 mg/mL
Phenylephrine HCl	Baxter	05C120	1 mg/mL
Phenytoin sodium	Hospira	21500LL	50 mg/mL[b]
Potassium chloride	Abbott	15-416-DK	0.1 mEq/mL
Potassium phosphates	American Pharmaceutical Partners	141489	0.5 mMol/mL
Rocuronium bromide	Organon	3579900116	1 mg/mL
Sodium nitroprusside	Abbott	25 938Z7	2 mg/mL
Sodium phosphates	American Regent	5042	0.5 mMol/mL
Tacrolimus	Fujisawa	5A3094A	0.02 mg/mL
Theophylline	Abbott	25-147-JT	4 mg/mL[b]
TPN admixture[d]	Mercy Health Center	None	[d]
Vasopressin	American Regent	5085	1 unit/mL
Vecuronium bromide	Bedford	732269	1 mg/mL[b]

[a]Tested in Sodium Chloride 0.9% Injection USP unless stated otherwise.
[b]Tested undiluted.
[c]Tested in Dextrose 5% Injection USP.
[d]Extemporaneously compounded at Mercy Health Center Pharmacy, Oklahoma City, Oklahoma. The TPN admixture had the following composition: Aminosyn 15% - 29.75 mL; dextrose 70% - 37.50 mL; sterile water for injection - 33.65 mL; sodium chloride 4 mEq/mL - 1.18 mL; potassium chloride 2 mEq/mL - 1.05 mL; potassium phosphate 3 mMol/mL - 0.35 mL; magnesium sulfate 50% - 0.16 mL; calcium gluconate 10% - 1.37 mL.

HCl = hydrochloride
TPN = total parenteral nutrition
USP = United States Pharmacopeia

borosilicate glass screw-cap culture tubes (Kimble, Division of Owens-Illinois, Toledo, Ohio) with polypropylene caps (Kimble) as described elsewhere.[3] Each of the sample solutions was passed through a 0.22-µm filter (Millex-GV; Millipore Products, Bedford, Massachusetts) as it was introduced into the tube. Each combination was prepared in duplicate, reversing the order of drug addition between the two samples.

Micafungin injection 1.5 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 0.75 mg/mL to simulate test sample preparation. These dilutions served as controls. Incompatibility in the micafungin-test drug mixtures was defined as any visible particulate matter, substantial haze, or turbidity change from that in the controls, a color change, or gas evolution.

All samples were examined visually with the unaided eye in normal laboratory fluorescent light. Combinations with no obvious visual 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 over the first 15 minutes after sample preparation and at intervals of 1 and 4 hours after sample preparation. 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 turbidity of the samples also was assessed immediately after preparation and at 1 and 4 hours after preparation by using a color-correcting turbidimeter (Model 2100AN; Hach Company, Loveland, Colorado) as previously described.[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. Incompatibility is defined as development of a substantial increase in measured turbidity. For relatively clear drug solutions such as micafungin diluted for infusion, 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

On visual inspection, micafungin 1.5 mg/mL in 0.9% Sodium Chloride Injection USP appeared in normal room light and when viewed using a Tyndall beam as a clear, colorless, free-flowing liquid. The initial 1.5 mg/mL solution was essentially without turbidity, having a very low measured turbidity near 0.325 NTU. When diluted to 0.75 mg/mL with an

Table 2. Drugs Incompatible with Micafungin 1.5 mg/mL in 0.9% Sodium Chloride Injection USP.

Drug	*Remarks*[a]
Albumin, human	Measured haze increased immediately
Amiodarone HCl	Gross white milky precipitate formed immediately
Cisatracurium besylate	Gross flocculent precipitate formed immediately
Diltiazem HCl	Gross flocculent precipitate formed immediately
Dobutamine HCl	Gross cloudy white precipitate formed immediately
Epinephrine HCl	Microparticulates[b] formed within 4 hours
Insulin, human, regular	Measured haze increased and microparticulates[b] formed within 4 hours
Labetalol HCl	Gross cloudy white precipitate with layering formed immediately
Meperidine HCl	Milky white precipitate with layering formed immediately
Midazolam HCl	Gross white flocculent precipitate formed immediately
Morphine sulfate	White precipitate formed immediately
Mycophenolate mofetil HCl	Gross cloudy white precipitate formed immediately
Nesiritide	Small amount of microparticulates[b] formed immediately
Nicardipine HCl	Gross yellowish-white precipitate formed immediately
Octreotide	Small amount of microparticulates[b] formed within 4 hours
Ondansetron HCl	Gross white flocculent precipitate formed immediately
Phenytoin sodium	Measured haze increased within 1 hour
Rocuronium bromide	Gross white flocculent precipitate formed immediately
Vecuronium bromide	Gross white flocculent precipitate formed immediately

[a]All observations were made in normal diffuse light with the unaided eye unless specified otherwise.
[b]Visible with a Tyndall beam only.

HCl = hydrochloride
USP = United States Pharmacopeia

equal amount of 0.9% Sodium Chloride Injection USP, in a manner identical to mixing with each of the secondary test drugs, the drug solution had a measured turbidity of near 0.2 NTU.

A total of 29 drugs/combinations were determined to be compatible with micafungin injection 1.5 mg/mL in 0.9% Sodium Chloride Injection USP. These combinations appeared to be very similar in clarity to the micafungin diluted with an equal volume 0.9% sodium chloride injection solution and exhibited similar measured turbidities.

Micafungin injection was physically incompatible in combination with 19 of the drugs (Table 2); the mixtures exhibited several observable changes including visible precipitation or turbidity formation (13 drugs) or increases in measured haze and microparticulate formation (6 drugs). Although changes in turbidity and microprecipitate formation were observed, they were not usually visually apparent. No order-of-addition compatibility determination differences were found for any of the micafungin drug combinations.

It should be noted that physical compatibility phenomena, in general, commonly exhibit differences and variations in the timing, appearance, and extent or amount of physical incompatibility. Consequently, any drug that has demonstrated a physical incompatibility with micafungin within 4 hours of mixing should be considered unacceptable for Y-site co-administration with micafungin at any time.

Conclusion

Micafungin injection 1.5 mg/mL in 0.9% sodium chloride injection is physically compatible for 4 hours after simulated Y-site co-administration at room temperature with 29 of the 48 drugs and the parenteral nutrition admixture evaluated in this study. Combination with 19 drugs resulted in unacceptable gross precipitation, microparticulate formation, visible turbidity, or increase in measured haze; these drugs should not be administered simultaneously via Y-site with micafungin solutions.

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