Physical Compatibility of Micafungin With Sodium Bicarbonate Hydration Fluids Commonly Used With High-Dose Methotrexate Chemotherapy

Hospital Pharmacy
2018, Vol. 53(2) 125–127
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DOI: 10.1177/0018578717738391
journals.sagepub.com/home/hpx

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Abstract

Purpose: The purpose of this study was to determine the physical compatibility of micafungin with commonly used concentrations of sodium bicarbonate hydration fluids administered via a Y-site connected to a central venous catheter (Y-site/CVC). **Methods:** Micafungin sodium (evaluated concentration of 1.5 mg/mL) was combined in a 3:1 (vehicle:drug) ratio with the following commonly used hydration vehicles: 40 mEq/L sodium bicarbonate in 5% dextrose in water with ¼ normal saline (40SB-D5W-1/4NS), 75 mEq/L sodium bicarbonate in D5W (75SB-D5W), and 154 mEq/L sodium bicarbonate in D5W (154SB-D5W). A 3:1 ratio was used based on the flow rates (typically 125 mL/m²/h for bicarbonate-containing vehicles and 50 mL/h for micafungin) of the corresponding solutions in a clinical setting. Visual observations recorded to determine physical compatibility included visual inspection against different backgrounds (unaided, black, and white). Other physical observations were as follows: odor, evolution of gas, pH, and turbidity immediately recorded after mixing and at specified time points up to 2 hours. Evaluations at each time point were compared against baseline observation values at Time 0. **Results:** All combinations tested were found to be compatible up to 2 hours. Time points beyond 2 hours cannot be safely verified as compatible. **Conclusion:** Micafungin may be administered safely using a Y-site/CVC delivery system with all the vehicles tested in this study.

Keywords

intravenous therapy, oncology, drug/medical use evaluation, Y-site programs/incompatibilities

Introduction

The intravenous (IV) administration of a wide range of medications often utilizes acidic vehicles (eg, 0.9% sodium chloride, 5% dextrose in water). In contrast, there are also instances where the same medications may need to be administered with alkaline vehicles (eg, sodium bicarbonate) for a variety of reasons including treatment of metabolic acidosis, diabetic ketoacidosis, and chemotherapy regimens requiring alkalization of the urine to avoid nephrotoxicity of the agent. A specific example of the latter is high-dose methotrexate (HDMTX; ≥ 1000 mg/m²) used for acute lymphoblastic leukemia, non-Hodgkin's lymphoma, osteosarcoma, and breast cancer.^{1,2} The poor solubility in acidic urine of methotrexate and its metabolites results in increased toxicities and renal failure. To combat this or when alkalization of urine is required for other indications, intravenous hydration with sodium bicarbonate fluids is often used.

Prior to initiation of drug therapy, these patients often have a central venous catheter (CVC) inserted to administer

essential therapies, minimizing the need for repeated placement of a peripherally inserted central catheter (PICC). Specific therapies (including HDMTX) which often result in prolonged periods of neutropenia generally increase the risk of invasive fungal infections.³ Echinocandins such as micafungin are often utilized for the prevention and treatment of fungal infections. Simultaneous administration of sodium bicarbonate hydration fluids and micafungin through a Y-site/CVC would improve patient care by eliminating the need for PICC lines while maintaining alkalized urine. Micafungin is typically administered in 0.9% sodium

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Table 1. Physical Compatibility Results of Micafungin With Three different Vehicles.

Vehicle	pH range over 2-h observation period (delta)	Change turbidity (NTU)	Visual appearance	Odor	Evolution of gas	Result
40SB-D5W-1/4NS	8.4-8.6 (0.2)	0.29-0.39 (0.10)	Clear/colorless	None	None	Compatible
75SB-D5W	8.4-8.6 (0.2)	0.31-0.39 (0.08)	Clear/colorless	None	None	Compatible
154SB-D5W	8.4-8.7 (0.3)	0.31-0.48 (0.17)	Clear/colorless	None	None	Compatible

Note. Data represents changes or observations as compared with both vehicle comparator and Time 0 sample. 40SB-D5W-1/4NS: Sodium bicarbonate (40 mEq/L) with 5% dextrose in 0.225% hypotonic saline. 75SB-D5W: Sodium bicarbonate (75 mEq/L) with 5% dextrose in water. 154SB-D5W: Sodium bicarbonate (154 mEq/L) with 5% dextrose in water. Changes are over the 120-minute observation period relative to the initial reading (0 minute) time point. NTU = nephelometric turbidity units.

chloride (NS) or a 5% dextrose in water (D5W) vehicle. Currently, there is no physical compatibility data available for micafungin dosing via a Y-site/CVC with sodium bicarbonate. The purpose of this study is to determine the physical compatibility of sodium bicarbonate hydration fluids and micafungin via intravenous Y-site/CVC administration.

Materials and Methods

All drugs and vehicles were obtained from hospital stock and used prior to their expiration dates. Micafungin sodium (Astellas Pharma, Northbrook, Illinois; lot number 024260, Expiration date: 02/2019) was reconstituted with NS to produce a concentration of 10 mg/mL which was further diluted in NS to a final dose concentration of 1.5 mg/mL. These solutions were used immediately after preparation. The vehicle solutions (40SB-D5W-1/4NS, 75SB-D5W, and 154SB-D5W) were used as received from the hospital pharmacy. A stock 100 mL volume of each micafungin:vehicle combination was made by adding 1 part of freshly prepared micafungin to 3 parts of each vehicle. This stock was divided into aliquots of appropriate size for evaluation of each parameter. The 3 vehicles (40SB-D5W-1/4NS, 75SB-D5W, and 154SB-D5W) without micafungin added were used as comparators in this study.

Observations were conducted at room temperature under standard laboratory LED lighting for micafungin in each vehicle to determine physical compatibility at baseline (Time 0) and at 15, 30, 45, 60, 75, 90, 105, and 120 minutes after mixing. Recorded observations at each time point were compared with both the vehicle comparators and the time 0 evaluation of the mixture. Physical incompatibility was defined as visual detection of the formation of particles, crystals, cloudiness, evolution of gas or a noted change in the odor, or color.⁴ The visual observations conducted by 2 independent observers of each formulation in borosilicate glass included viewing the solution against matte black and nonglare white backgrounds as well as in the absence of a specific background. Turbidity was measured using a laboratory-grade turbidimeter (2100Q Turbidimeter, Hach, Loveland, Colorado) calibrated on each day of use using StablCal calibration standards (0.5, 1, 10, 20, 100 nephelometric turbidity units [NTU]) commercially available from Hach following

the manufactures instruction provided with the instrument. All measurements were made in reusable glass sample cells obtained from the manufacturer. A turbidity change of ≥ 0.5 NTU as compared with either the comparator or the time 0 baseline sample indicated physical incompatibility.⁵ Measurements of pH were made with pH meter (Ohaus Starter 2100, Parsippany, New Jersey) calibrated at pH 4, 7, and 10 using calibration buffer solutions on each day of use. Each sample and comparator was continuously stirred in borosilicate glass beakers during the measurement period. A pH change of ≥ 1.0 was set a priori as compared with the time 0 or comparator solution as an indication of physical incompatibility based on several previously published studies.⁶⁻⁹

Results and Discussion

Micafungin, when reconstituted to 10 mg/mL with NS and further diluted to 1.5 mg/mL with NS (final tested concentration) remained clear and colorless throughout the 2-hour observation period. Prior to mixing, all vehicles and control solutions were also clear and colorless throughout the observation period. Likewise, there were no significant changes in turbidity, pH, or odor in any of the vehicle controls.

When micafungin (1.5 mg/mL in NS) was mixed individually with each of the 3 vehicles evaluated (40SB-D5W-1/4NS, 75SB-D5W, 154SB-D5W), the resulting mixtures were observed to be compatible (Table 1) throughout the 2-hour observation period based on the predefined criteria. For each of the 3 mixtures, there were no observed changes in the visual assessments regarding color or clarity as determined by 2 independent observers. In addition, there was no evidence of crystal or precipitate formation as compared against the baseline or the vehicle comparators. Likewise, there was no detectable change in odor of the mixtures as compared with the baseline or controls. Changes in measured turbidity of the samples as compared with the vehicle comparators were all less than 0.5 NTU for the duration of the study. Actual measured turbidity values of the samples were in the range of 0.29 to 0.48 NTU, while those for the comparators were in the range of 0.13 to 0.26 NTU for each time point over the 2-hour observation period. Specific ranges for each mixture are shown in Table 1. The measured pH values of the samples as compared with the vehicle comparators also supported the samples being compatible.

The range of pH measurements for all samples and comparators were 8.4 to 8.7 and did not deviate from this at any time point throughout the 2-hour observation period.

Current literature and clinical practice recommend a NS or D5W vehicle for intravenously delivered micafungin. However, this study was designed to determine physical compatibility of micafungin in a basic vehicle to alkalize the urine in patients taking concomitant HDMTX. The chemical stability of micafungin in an alkaline pH aqueous solution has been reported in 2 forced degradation studies as part of the validation for stability indicating assays. Zhu et al¹⁰ reported a loss of 25.1% of a 2.5 mg/mL solution of micafungin in a 0.1 M NaOH solution (pH = 13) at room temperature after 1 hour. Briot et al¹¹ measured a 27% chemical degradation of a 2 mg/mL solution of micafungin also in a 0.1 M NaOH solution (pH = 13) after 30 minutes at room temperature. While both of these studies report significant chemical instability of micafungin in an alkaline solution, it should be noted that the pH was much higher (13 vs 8.4) and the time the micafungin is mixed with alkaline solution was much longer than what would occur in a clinical setting. Based on the flow rates and size and length of typical IV tubing used, the residence time of micafungin in our vehicles prior to entering the patient would not exceed 5 minutes. While this study did not address the chemical stability of micafungin in an alkaline solution, no significant loss of potency would be expected under the reported clinical parameters of use.

All 3 combinations of micafungin in various sodium bicarbonate-containing vehicles were deemed compatible physically based on our predefined criteria. Traditionally, Y-site compatibility studies for peripheral lines are conducted using a 1:1 ratio of the 2 solutions being evaluated.¹² To accurately simulate administration of micafungin with the various vehicles used in clinical practice, a volume ratio of the vehicle-drug relationship was determined. The basis for the 3:1 ratio of vehicle to micafungin is derived from the differential flow rates of the 2 solutions flowing into the Y-site. In our institution, the flow rate for the vehicle solutions is typically 125 mL/m²/h while micafungin is 50 to 100 mL/h. Based on the variable body surface area of the patients and the flow rate of micafungin, a 3:1 ratio was deemed to be appropriate. At any given time, the makeup of the combined medication solution will favor the vehicle because they typically have a greater flow rate than micafungin. However, the large difference in flow rates between micafungin and the vehicles mandated a change in the volume ratio.

The observed physical compatibility of the combinations evaluated in this work are likely influenced from the 3:1 ratio used in the study which results in a larger dilution effect on the micafungin as compared with a traditional 1:1 ratio evaluation. Physical compatibility of a 1:1 ratio of the vehicles evaluated in this study should not be extrapolated from these results.

Conclusion

The results of this study demonstrate the Y-site/CVC physical compatibility for up to 2 hour of micafungin sodium (1.5 mg/

mL in NS) with different concentrations of sodium bicarbonate hydration fluids administered to patients receiving HDMTX. These data support options for modified IV Y-site/CVC dosing modalities for these patients and should be useful in reducing the requirement of venous access or in cases of limited access.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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