



BRIEFS ORIGINALS

Bilingual edition English/Spanish

Physicochemical characterization of micafungin and anidulafungin for its nebulized administration

Caracterización fisicoquímica de micafungina y anidulafungina para su administración mediante nebulización

Laura Gómez-Ganda, Sonia Terradas-Campanario, David Company-Herrero

Pharmacy Service. Vall d'Hebron University Hospital. Barcelona, Spain.

Author of correspondence

Laura Gómez Ganda
Hospital Universitario Vall d'Hebron
Passeig de la Vall d'Hebron, 119-129,
08035, Barcelona. Spain.

Email:
laura_gomez@vhebron.net

Received 13 February 2019;
Accepted 3 May 2019.

DOI: 10.7399/fh.11226

How to cite this paper

Gómez-Ganda L, Terradas-Campanario S, Company-Herrero D. Physicochemical characterization of micafungin and anidulafungin for its nebulized administration. Farm Hosp. 2019;43(5):163-5

Abstract

Objective: To determine by experimentation whether micafungin and anidulafungin possess physicochemical properties suitable for nebulization.

Method: pH, osmolality, viscosity, density and chloride content were determined by pH monitoring, osmometry, viscometry, densitometry and potentiometry in two samples of different concentrations, 5 and 10 mg/mL each echinocandin.

Results: The results obtained for micafungin solution were: pH 5.80 (0.14), osmolality 293.33 (1.53) mOsm/kg, chloride content 134.67 (0.58) mmol/L and density 1,009.4 (0.1) kg/m³; while for 10 mg/mL solution: osmolality 342.00 (1.00) mOsm/kg, chloride content 139.67 (0.58) mmol/L and density 1,014.5 (0.2) kg/m³. The results obtained for 5 mg/mL anidulafungin were: pH 4.22 (0.01), osmolality 464.67 (2.52) mOsm/kg, chloride content 137.00 (0.00) mmol/L and density 1,016.5 (0.2) kg/m³; while for 10 mg/mL solution: osmolality 656.33 (1.15) mOsm/kg, chloride content 132.00 (0.00) mmol/L and density 1,029.8 (0.4) kg/m³.

Conclusions: pH, osmolality, chloride content and density values proved to be suitable for proper tolerability by nebulization.

Resumen

Objetivo: Determinar experimentalmente si micafungina y anidulafungina poseen propiedades fisicoquímicas adecuadas para su nebulización.

Método: Se determinó el pH, la osmolalidad, la viscosidad, la densidad y el contenido en cloruros mediante pH-metría, osmometría, viscosimetría, densitometría y potenciometría, respectivamente, en dos muestras de diferente concentración, 5 y 10 mg/ml, de cada equinocandina.

Resultados: Para la solución de micafungina 5 mg/ml los resultados obtenidos fueron: pH 5,80 (0,14), osmolalidad 293,33 (1,53) mOsm/kg, contenido en cloruros 134,67 (0,58) mmol/l y densidad 1.009,4 (0,1) kg/m³; y para la solución de 10 mg/ml: osmolalidad 342,00 (1,00) mOsm/kg, contenido en cloruros 139,67 (0,58) mmol/l y densidad 1.014,5 (0,2) kg/m³. Para la solución de anidulafungina 5 mg/ml los resultados obtenidos fueron: pH 4,22 (0,01), osmolalidad 464,67 (2,52) mOsm/kg, contenido en cloruros 137,00 (0,00) mmol/l y densidad 1.016,5 (0,2) kg/m³; y para la solución de 10 mg/ml: osmolalidad 656,33 (1,15) mOsm/kg, contenido en cloruros 132,00 (0,00) mmol/l y densidad 1.029,8 (0,4) kg/m³.

Conclusiones: Los valores de pH, osmolalidad, contenido en cloruros y densidad resultaron adecuados para una correcta tolerabilidad mediante nebulización.

KEYWORDS

Micafungin; Anidulafungin; Antifungal; Nebulized;
Scedosporium; *Scopulariopsis*.

PALABRAS CLAVE

Micafungina; Anidulafungina; Antifúngico; Nebulizado;
Scedosporium; *Scopulariopsis*.



Los artículos publicados en esta revista se distribuyen con la licencia
Articles published in this journal are licensed with a
Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.
<http://creativecommons.org/licenses/by-nc-sa/4.0/>
La revista Farmacia no cobra tasas por el envío de trabajos,
ni tampoco por la publicación de sus artículos.

Introduction

In critical or immunosuppressed patients, such as lung transplant patients, systemic fungal infections can carry serious clinical consequences^{1,4}.

Possible fungal infections affecting these patients include species of the genus *Aspergillus* sp. In immediate post-lung transplantation these infections primarily affect respiratory tract and include ulcerative tracheobronchitis and anastomotic infections. Current guidelines prescribe triazole as a first-line treatment and advise the possibility of associating a nebulized antifungal as an adjuvant treatment⁵. Said association would prove to be beneficial, considering that these patients do not usually reach appropriate drug concentrations in lung with parenteral administration, due to the tissue penetration being low in lung. Most of the patients undergo mechanical ventilation, which produces an alteration in pharmacokinetic parameters of the active substance⁶.

There is a growing tendency of infections caused by fungal species in addition to *Aspergillus* sp, whose response to conventional antifungal treatment is very limited, as *Scedosporium* sp or *Scopulariopsis* sp, among others. For infections disseminated by *Scedosporium* sp, voriconazole in monotherapy or either combined with an intravenous echinocandin and/or terbinafine is prescribed^{7,8}. However, the optimal antifungal for *Scopulariopsis* sp is unknown.

In situations where clinical response to antifungal agents of choice is either ineffective or adverse effects occur, and the source of infection is located in the respiratory tract, antifungal drugs may be considered via nebulization.

Currently, literature on nebulization of anti-infective agents is limited, and most have not authorized this route of administration. There is published literature on nebulization of conventional and liposomal amphotericin B, pentamidine, nystatin, posaconazole, voriconazole, itraconazole, caspofungin and micafungin^{1,3,4,7,9-12}. Published studies on nebulization of micafungin were aimed exclusively at characterizing drug particles released through various nebulizers^{3,10}.

The administration of anti-infective drugs through nebulization, combined with intravenous treatment, may provide an alternative in cases where there is little diffusion across biological membranes as well as a high concentration of drug in the respiratory tract is required to facilitate control on the source of infection⁹.

In addition, drug nebulization allows reaching local high concentrations with minimal systemic exposure, which generally translates into greater efficiency and fewer systemic side effects^{1,4,6,7,9-12}. Thus, it could be administered via nebulization in monotherapy whenever local action is required or when a patient has adverse effects on intravenous administration².

Literature suggests that, in order to achieve optimal nebulization, physicochemical properties of active substance, the nebulizer system used and the patient's physical and clinical conditions must be taken into account^{1,4}.

Physicochemical properties such as pH, osmolality, chloride ion concentration, density and particle size of the drug affect the efficacy, as well as the tolerability of nebulization (Table 1). Furthermore, the presence of sodium edetate excipients, benzalkonium chloride, phenols and sulfites can cause poor tolerability^{4,11}.

Studies so far show that extreme pH values, osmolality and lack of chlorides in preparations of nebulization may cause coughing and/or bronchoconstriction^{4,11,13}.

The volume of drug to be administered must be adequate to ensure proper viscosity. Drug dissolution in small volumes lead to a high viscosity, which could make nebulization difficult and could as well cause blockage or damage to the nebulizer, while solution in larger volumes would result in a reduced viscosity that could increase nebulization time^{6,11}.

Particles size, expressed as mass median aerodynamic diameter (MMAD), must lie in the range of 1-5 µm, allowing adequate access to the site of action. Particles exceeding 5 µm MMAD are deposited in the upper airways, while those with less than 1 µm MMAD can be expelled during exhalation⁴.

The dose to be administered by nebulization of anti-infectives that do not have authorization via nebulization is established empirically in cases where previous pharmacokinetic studies have not been carried out.

Tabla 1. Physicochemical recommended values for proper nebulization and tolerability

Physicochemical parameter	Recommended value range
Mass median aerodynamic diameter	1-5 µm ^{1,4,9}
pH	2.6-10.0 ^{4,7,13}
Osmolality	150-1,200 mOsm/kg ⁴
Chloride ions	31-300 mmol/L ¹
Nebulization volume	4-5 mL ^{10,11}

The aim of this study focuses on experimentally assessing whether micafungin and anidulafungin antifungals could present adequate tolerability via nebulization, since its data sheet only provides the intravenous route.

Methods

To perform the analytical determinations, we started from commercial presentations by Mycamine® (micafungin) and Ecalta® (anidulafungin) 100 mg concentrated powder for perfusion solution. They were prepared from those two different concentrations of each echinocandin, 5 mg/mL and 10 mg/mL, using 0.9% of sodium chloride as diluent.

Osmolality determinations and chloride content in triplicate were performed for each of the samples in the hospital's Biochemistry Department. Osmolality was determined through automated osmometer Advanced Instruments INC® A2O, employing the freezing point reduction technique. The chloride content was determined through potentiometry with the Beckmann Coulter® AU5800.

pH determination was conducted in the Pharmacy Service by pH meter Testo 206®, also in triplicate, with only a concentration of 5 mg/mL, as it is an independent concentration variable.

Viscosity and density were determined by the Drug Development Service in the School of Pharmacy and Food Sciences of the University associated with the hospital through the Brookfield CAP 2000® viscometer and Anton Paar® densitometer respectively, and in triplicate for each of the concentrations of both echinocandins.

Results

The results obtained, expressed as mean ± standard deviation for samples of micafungin 5 mg/mL and 10 mg/mL and anidulafungin 5 mg/mL and 10 mg/mL are shown in table 2.

The viscosity of the samples could not be determined as they were aqueous solutions with a very similar viscosity as the water's.

Discussion

The pH and osmolality values obtained in micafungin and anidulafungin samples in the studied concentrations, as well as the chloride content, are within the ranges accepted for a correct tolerability via nebulization^{1,4,7,13}. The density values obtained are similar to the value of water density (1,000 kg/m³). Thus, aerosolization in the nebulizer would be suitable¹. Therefore, the studied physicochemical characteristics indicate that its distribution through nebulization may be suitable. Reconstitution of micafungin and anidulafungin was performed using 0.9% sodium chloride, since according to the data sheet, both were stable and, thus, chloride ions were added to the solution.

In addition, the data sheet indicates that the employed presentations do not contain any excipient (sodium edetate, benzalkonium chloride, phenols and sulfides) in connection with the production of cough and/or bronchoconstriction.

This is the first reported study that determines micafungin physicochemical properties: pH, osmolality, chloride content and density for nebulization. In addition, this is the first study on anidulafungin physicochemical characterization to administer through nebulization. Density values and chloride content obtained for both echinocandins are similar to the results published in Wong-Beringer et al. study on characterization of caspofungin,

Tabla 2. Results obtained in echinocandins samples

Drug	Concentration (mg/mL)	pH	Osmolality (mOsm/kg)	Chloride content (mmol/L)	Density (kg/m ³)
Micafungin	5	5.80 ± 0.14	293.33 ± 1.53	134.67 ± 0.58	1.009.4 ± 0.1
	10	5.80 ± 0.14	342.00 ± 1.00	139.67 ± 0.58	1.014.5 ± 0.2
Anidulafungin	5	4.22 ± 0.01	464.67 ± 2.52	137.00 ± 0.00	1.016.5 ± 0.2
	10	4.22 ± 0.01	656.33 ± 1.15	132.00 ± 0.00	1.029.8 ± 0.4

while the difference in pH and osmolality is higher, but are within the recommended ranges¹.

The studied concentrations would allow administration of appropriate volumes for nebulization of a 50 mg dose, used in Shi *et al.* and Alexander *et al.*'s studies^{9,10}. In said studies where the release of micafungin solution at a concentration of 10 mg/mL was characterized, MMAD were obtained within the established values. Therefore, a significant proportion of the drug would reach deep airways. These results improve the chances of using micafungin via nebulization.

Unlike amphotericin B deoxycholate or liposomal, currently there are no published studies evaluating the efficacy, safety and tolerability of micafungin and anidulafungin through nebulization. One example is the study of Monforte *et al.*, which showed a local distribution in the lungs of liposomal amphotericin B and an adequate tolerability after a 25 mg administration¹⁴. It was also noted that suitable drug levels are maintained for at least 14 days after administration¹⁴.

As for the study's limitations, it should be highlighted that results would only be valid for the used trademarks. To ensure effective dissemination of the drug in the lung, it would also be necessary to determine other physical factors, such as particle size, type of nebulizer as well as the patient's physical and clinical characteristics.

The micafungin and anidulafungin solutions described in this study would be suitable for nebulization and they can be used in events of

complex respiratory fungal infections caused by susceptible species. They could be administered, either in conjunction with intravenous therapy to intensify the treatment or in monotherapy when the intravenous route is not possible or adequate.

Funding

No funding.

Conflict of interests

No conflict of interests.

Presentation in Congresses

Presentation in poster format at the 63rd National Congress of the Spanish Society of Hospital Pharmacy (SEFH). Palma de Mallorca. November 8 to 10, 2018.

Contribution to scientific literature

This is the first study to physicochemically characterize micafungin and anidulafungin for nebulization. Nebulization would treat respiratory infections caused by susceptible microorganisms.

Bibliography

- Wong-Beringer A, Lambros MP, Beringer PM, Johnson DL. Suitability of caspofungin for aerosol delivery: physicochemical profiling and nebulizer choice. *Chest*. 2005;128(5):3711-6. DOI: 10.1378/chest.128.5.3711
- Holle J, Leichsenring M, Meissner PE. Nebulized voriconazole in infections with *Scedosporium apiospermum*—case report and review of the literature. *J Cyst Fibros*. 2014;13(4):400-2. DOI: 10.1016/j.jcf.2013.10.014
- McConville JT, Overhoff KA, Sinswat P, Vaughn JM, Frei BL, Burgess DS, *et al.* Targeted high lung concentrations of itraconazole using nebulized dispersions in a murine model. *Pharm Res*. 2006;23(5):901-11. DOI: 10.1007/s11095-006-9904-6
- Le J, Ashley ED, Neuhauser MM, Brown J, Gentry C, Klepser ME, *et al.* Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2010;30(6):562-84. DOI: 10.1592/phco.30.6.562
- Husain S, Sole A, Alexander BD, Aslam S, Avery R, Benden C, *et al.* The 2015 International Society for Heart and Lung Transplantation Guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients: Executive summary. *J Heart Lung Transplant*. 2016;35(3):261-82.
- Ehrmann S, Chastre J, Diot P, Lu Q. Nebulized antibiotics in mechanically ventilated patients: a challenge for translational research from technology to clinical care. *Ann Intensive Care*. 2017;7(1):78. DOI: 10.1186/s13613-017-0301-6
- Solé A, García-Robles AA, Jordá C, Cases Viedma E, Mancheno N, Poveda-Andrés JL, *et al.* Salvage therapy with topical posaconazole in lung transplant recipients with invasive *Scedosporium* infection. *Am J Transplant*. 2018;18(2):504-9. DOI: 10.1111/ajt.14580
- Mensa J, Gatell JM, García-Sánchez JE, Letang E, López-Suñé E, Marco F. Guía terapéutica antimicrobiana. 28ª ed. Barcelona: Antares; 2018.
- Shi S, Ashley ES, Alexander BD, Hickey AJ. Initial characterization of micafungin pulmonary delivery via two different nebulizers and multivariate data analysis of aerosol mass distribution profiles. *AAPS PharmSciTech*. 2009;10(1):129-37. DOI: 10.1208/s12249-009-9185-6
- Alexander BD, Winkler TP, Shi S, Ashley ES, Hickey AJ. Nebulizer delivery of micafungin aerosols. *Pharmacotherapy*. 2011;31(1):52-7. DOI: 10.1592/phco.31.1.52
- Clemente Bautista S, Fernández Polo A, Gil Luján G, Cabañas Poy MJ, Oliveras Arenas M, Hidalgo Albert E. Anti-infectives administration by inhalation. *Farm Hosp*. 2007;31(2):73-136. DOI: 10.1016/S1130-6343(07)75722-7
- Vaughn JM, Wiederhold NP, McConville JT, Coalson JJ, Talbert RL, Burgess DS, *et al.* Murine airway histology and intracellular uptake of inhaled amorphous itraconazole. *Int J Pharm*. 2007;338(1-2):219-24. DOI: 10.1016/j.ijpharm.2007.02.014
- Lowry RH, Wood AM, Higenbottom TW. Effects of pH and osmolality on aerosol-induced cough in normal volunteers. *Clin Sci (Lond)*. 1988;74(4):373-6.
- Monforte V, Ussetti P, López R, Gavalda J, Bravo C, de Pablo A, *et al.* Nebulized liposomal amphotericin B prophylaxis for *Aspergillus* infection in lung transplantation: pharmacokinetics and safety. *J Heart Lung Transplant*. 2009;28(2):170-5. DOI: 10.1016/j.healun.2008.11.004