



Brief Report

Characterization and real-live results of nebulized voriconazole: A single-center observational study

Maria Larrosa-García*, Sònia Terradas Campanario, Aurora Fernández Polo, Carme Cañete Ramírez, Alba Pau Parra and David Company Herrero

Pharmacy Department, Vall d'Hebron University Hospital, Barcelona, Spain

ARTICLE INFO

Article history:

Received 1 March 2023

Accepted 14 July 2023

Available online 21 August 2023

Keywords:

Voriconazole

Nebulizer

Fungal lung disease

Aspergillosis

Compounding

ABSTRACT

Objective: Pulmonary administration of voriconazole involves advantages, including optimization of lung penetration and reduction of adverse effects and interactions. However, there is scarce evidence about its use and there are no commercial presentations for nebulization. We aim to characterize a compounded voriconazole solution for nebulization and describe its use in our center.

Method: This is a retrospective observational study including patients who received nebulized voriconazole to treat fungal lung diseases (infection or colonization). Voriconazole solution was prepared from commercial vials for intravenous administration.

Results: The pH and osmolarity of voriconazole solutions were adequate for nebulization. Ten patients were included, 9 adults and a child. The dosage was 40 mg in adults and 10 mg in the pediatric patient, diluted to a final concentration of 10 mg/ml, administered every 12–24 h. The median duration of treatment was 139 (range: 26–911) days. There were no reported adverse effects and the drug was not detected in plasma when nebulized only.

Conclusion: Voriconazole nebulization is well-tolerated and it is not absorbed into the systemic circulation; further research is needed to assess its efficacy.

© 2023 Sociedad Española de Farmacia Hospitalaria (S.E.F.H). Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Caracterización y resultados del uso de voriconazol nebulizado en vida real: estudio observacional unicéntrico

RESUMEN

Objetivo: La administración pulmonar de voriconazol implica ventajas, incluyendo la optimización de la penetración pulmonar y la reducción de los efectos adversos e interacciones. Sin embargo, la evidencia sobre su utilización es escasa y no existen presentaciones comerciales específicas para nebulización. Nuestro objetivo es caracterizar las soluciones de voriconazol elaboradas para nebulización y describir su uso en nuestro centro. **Método:** Estudio observacional retrospectivo incluyendo pacientes que reciben voriconazol nebulizado para el tratamiento de enfermedades pulmonares (infecciones fúngicas o colonizaciones). La solución de voriconazol se preparó a partir de los viales comerciales para la administración intravenosa.

Resultados: El pH y la osmolaridad de las soluciones de voriconazol fueron adecuados para su nebulización. Se incluyeron diez pacientes, nueve adultos y un niño. La dosis fue de 40 mg en adultos y 10 mg en el paciente pediátrico, diluido a 10 mg/ml, administrados cada 12–24 horas. La duración mediana del tratamiento fue de 139 (rango: 26–911) días. No se reportaron efectos adversos y no se detectó voriconazol en plasma cuando se administró únicamente vía nebulizada.

Conclusiones: La nebulización de voriconazol es bien tolerada y no se absorbe hacia la circulación sistémica. Son necesarios más estudios de investigación para evaluar su eficacia.

© 2023 Sociedad Española de Farmacia Hospitalaria (S.E.F.H). Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Palabras clave:

Voriconazol

nebulizador

enfermedad pulmonar fúngica

aspergillosis

formulación magistral

* Corresponding author at: Pg. de la Vall d'Hebron, 119, 08035 Barcelona, Spain.

E-mail address: maria.larrosa@vallhebron.cat (M. Larrosa-García).

Introduction

Aspergillus spp. can cause different diseases, depending on the host immune system status. Invasive pulmonary aspergillosis (IPA) is a serious disease affecting patients with prolonged neutropenia, transplant recipients, and those receiving long-term treatment with high doses of corticosteroids, among others.¹ Even antifungal prophylaxis is indicated in vulnerable patients, an increase of fungal infections prevalence and severity has been observed. Lung transplant (LT) recipients are especially vulnerable to IPA, a prevalence of 6.5% and mortality rate of 52% has been reported in this population.² Other non-immunosuppressed patients, such as those with cystic fibrosis (CF), can be affected by *Aspergillus* spp.; it has been reported that more than 50% of respiratory cultures from CF patients in a year were positive and about 10% of the patients developed allergic bronchopulmonary aspergillosis, related to airway damage and respiratory function alterations.³ Even if azole treatment has shown positive results in CF, treating *Aspergillus* spp. colonization in this population remains controversial due to the need of long treatments related to drug interactions, toxicity, and the emergence of antifungal resistance.

Voriconazole is the primary treatment for IPA; it is available in oral and intravenous pharmaceutical forms. Other antifungal drugs such as amphotericin, isavuconazol, itraconazole, posaconazole, and echinocandins can be added to the treatment or used as alternatives in case of treatment failure.⁴ IPA management usually involves long systemic antifungal treatments that lead to high rates of adverse events including liver, kidney, and medullar toxicities; moreover, these therapies are usually involved in major drug–drug interactions with clinical implications and their pharmacokinetic profile is difficult to predict due to pharmacogenetic diversity among the population.⁵ Finally, treatment efficacy depends on the drug distribution to the lung and the epithelial lining fluid that coats the bronchoalveolar epithelium; however, it has been observed that the distribution of antifungal drugs to the biophase might be limited by their physicochemical properties in some cases.⁶

In this context, antifungal administration through the pulmonary route has been suggested in order to ensure therapeutic concentrations of drug in the biophase and increase treatment efficacy, avoid adverse events, and prevent drug–drug interactions. Even if there are not commercial antifungal pharmaceutical presentations for pulmonary administration currently, vials of liposomal amphotericin B and amphotericin B deoxycholate for intravenous administration have been widely used for nebulization in prophylaxis and treatment of pulmonary aspergillosis; this approach has been proved to be safe and effective.⁷

There is little evidence about voriconazole administration via nebulization. The goal of this study is to characterize the compounded voriconazole solution for nebulization and describe the use of nebulized voriconazole in our center.

Method

Study design

We conducted a retrospective study including patients treated with nebulized voriconazole in Vall d'Hebron University Hospital, a third referral hospital in Barcelona, Spain.

Voriconazole solution

Voriconazole solution for nebulization was prepared in vertical laminar flow microbiological safety cabinet in the Pharmacy Department, following the Good Manufacturing Practice and dispensed as monodose polypropylene syringes ready to use. Different brands of voriconazole were used, depending on the availability (Table 1). Voriconazole solution was compounded according to available literature.⁸ An osmometer (A2O, Advanced Instrument INC) and a pH meter (Testo 206) were used to characterize the solution.

Clinical data collection and analysis

Patients' data were collected from the time of antifungal treatment initiation until nebulized voriconazole was stopped due to recovery, death, or other reasons using electronic medical records. Information about antifungal treatment was obtained from the prescription software used in our center. Samples used to identify fungal pathogens included sputum, bronchoalveolar lavage, or aspirate or tracheal aspirate.

Voriconazole concentration in plasma was determined in the Biochemistry Department using high-performance liquid chromatography (HPLC) with fluorescence.

Descriptive statistics are expressed as medians and range (minimum–maximum) or absolute numbers (percentages) for categorical variables.

Results

Voriconazole solution compounding and characterization

Voriconazole vials containing 200 mg of powder for solution for infusion were diluted with 19 ml of sterile water for injection; syringes containing 40 mg of voriconazole in 4 ml were obtained. Voriconazole powder from Teva[®] was diluted in sodium chloride 0.9%, instead of sterile water for injection, in order to reach an acceptable osmolarity. Characterization of the compounded voriconazole solutions is shown in Table 1, all of them were considered appropriate for nebulization based on published literature.^{9–13}

It was estimated that the voriconazole solution was chemically stable for 30 days refrigerated (2–8 °C) and 90 days frozen (–20 °C).^{8,10} Biological stability was calculated based on the Good Manufacturing Practice in Hospital Pharmacy Services,¹⁰ since it was shorter, it defined the voriconazole solution valid period as 9 days refrigerated and 45 days frozen. Syringes generally kept refrigerated, they were only frozen when dispensed in the outpatients pharmacy.

Patients' characteristics

A total of 10 patients were treated with nebulized voriconazole during the study period; data is shown in Table 2. There were 9 adults and 1 pediatric patient; the median age was 35 (5–69) and all of them were male. Five patients were affected by CF and 8 had received at least 1 LT, the median time from LT was 7 (0–84) months (3 CF patients had received LT).

Table 1

Physical properties of different brands of voriconazole powder diluted in 19 ml of sterile water for injection.

Commercial product	Voriconazole concentration in water for injection solution (mg/ml)	pH	Osmolarity (mOsm/kg)
Voriconazole Normon [®] 200 mg powder for solution for infusion	10	5	313
Voriconazole Accord [®] 200 mg powder for solution for infusion	10	4.97	359
Voriconazole Kern [®] 200 mg powder for solution for infusion	10	7	503
Voriconazole Teva [®] 200 mg powder for solution for infusion	10	6.28	69 (563 ^a)

^a Osmolarity when diluted with sodium chloride 0.9%.

Table 2 Patients' basal characteristics and nebulized voriconazole treatment description.

Age (years)	Comorbidities	Time from LT	Fungal pathogen	Antifungal treatment indication	Treatment site	Justification for voriconazole nebulization initiation	Dosage	Voriconazole powder for infusion brand	Other treatments	DOT	Outcome
35	CF	3 m	- <i>Scedosporium prolificans</i>	Respiratory distress	- Hospital ward - Outpatient treatment	- Lack of response to oral voriconazole	- 40 mg/24 h - 40 mg/12 h	- Kern®	- Voriconazole (oral)	122	- Clinical, radiological, and microbiological response
21	CF	NT	- <i>Aspergillus citrinoterreus</i> - <i>Aspergillus terreus</i> (R to amphotericin and voriconazole)	Fungal colonization	- Hospital ward - Outpatient treatment	- Symptomatic liver toxicity to systemic azoles	- 40 mg/12 h - 40 mg/24 h - 40 mg/w	- Kern® - Normon®	- Isavuconazole (oral)	>420	- Resolved liver toxicity - Fungal colonization remains present - Nebulized voriconazole treatment continues and it is well-tolerated
35	CF	0 d	- <i>Scedosporium prolificans</i> (multi-drug R, S to voriconazole)	LT fungal prophylaxis after isolation of <i>S. prolificans</i> in the graft preservation fluid	- Hospital ward - Outpatient treatment - ICU	- Need of topical antifungal prophylaxis after LT active against <i>Scedosporium prolificans</i> R to amphotericin	- 40 mg/12 h	- Kern®	- Micafungin (neb)	>170	- Successful LT - Nebulized voriconazole treatment continues and it is well-tolerated
69	Non-specific interstitial pneumonia	4 y	- <i>Aspergillus flavus</i> (R to amphotericin)	Bronchitis	- Hospital ward - Outpatient treatment	- Lack of response to amiodulafungin - Symptomatic toxicity to azoles (dizziness, myopathy).	- 40 mg/12 h - 40 mg/24 h	- Accord®	- Isavuconazole (oral)	911	- <i>Aspergillus flavus</i> is still present in bronchoalveolar lavage - After voriconazole treatment, <i>Aspergillus flavus</i> showed resistance to this treatment and treatment was changed to nebulized liposomal amphotericin - Microbiological response - Oral treatment was stopped due to visual and liver toxicity - Nebulized voriconazole treatment continues and it is well-tolerated
60	Idiopathic pulmonary fibrosis	1 m	- <i>Scedosporium apiospermum</i> complex	Colonization	- Outpatient treatment	- Combination of nebulized and systemic treatment to readily reach therapeutic voriconazole concentration in the lung.	- 40 mg/12 h	- Kern®	- Voriconazole (oral)	>156	- Patient died due to graft failure
65	Chronic obstructive pulmonary disease	7 m	- <i>Aspergillus fumigatus</i> - <i>Aspergillus flavus</i>	Respiratory distress	- Hospital ward	- Avoiding clinically relevant drug-drug interaction among systemic azoles and sirolimus	- 40 mg/12 h	- Kern®	- None	26	- Patient died due to graft failure
64	Chronic obstructive pulmonary disease	NT	- <i>Purpureocillium lilacinus</i> (multi-drug R; S to voriconazole, posaconazole, and isavuconazole)	Respiratory distress	- Hospital ward	- Symptomatic toxicity to systemic azoles - Kidney failure - Avoiding clinically relevant drug-drug interaction among systemic azoles and sirolimus.	- 40 mg/12 h	- Teva®	- None	30	- Patient died, <i>P. lilacinus</i> was not found in the last bronchoalveolar lavage
18	CF	NT	- <i>Scedosporium apiospermum</i> complex (multi-drug R, S to voriconazole, posaconazole, isavuconazole, and micafungin)	Colonization	- Outpatient treatment	- Symptomatic toxicity to systemic azoles (rash)	- 40 mg/48 h - 40 mg/24 h	- Teva® - Kern® - Normon®	- Posaconazole (oral)	>840	- Colonization remained - Nebulized voriconazole treatment continues and it is well-tolerated

(continued on next page)

Table 2 (continued)

Age (years)	Comorbidities	Time from LT	Fungal pathogen	Antifungal treatment indication	Treatment site	Justification for voriconazole nebulization initiation	Dosage	Voriconazole powder for infusion brand	Other treatments	DOT	Outcome
30	CF	7 and 0 d ^a	- <i>Aspergillus flavus</i> complex (R to amphotericin) - <i>Aspergillus terreus</i> complex (R to amphotericin)	Surgery complications after second LT	- ICU	- Lack of response to previous treatments	- 40 mg/24 h	- Kern®	- Isavuconazole (IV) - Micafungin (IV) - Liposomal amphotericin (IP)	28	- Patient died due to IPA
5	Interstitial pneumopathy	9 m	- <i>Aspergillus flavus</i> complex (R to amphotericin)	Respiratory distress	- P-ICU	- Lack of response to previous treatments.	- 10 mg/24 h	- Normon®	- Liposomal amphotericin (neb) - Isavuconazole (IV) - Amidulafungin (IV)	81	- Microbiological response - Nebulized voriconazole treatment continues and it is well-tolerated

CF: cystic fibrosis, LT: lung transplantation, NT: no transplantation, d: days, w: weeks, m: months, y: years, R: resistant, S: susceptible, DOT: days of treatment, ICU: intensive care unit, IPA: invasive pulmonary aspergillosis, P-ICU: pediatric intensive care unit, neb: nebulized, IV: intravenous, IP: intrapleural.
^a 7 years from the first and 0 days from the second LT.

Fungi detected were mainly *Aspergillus* spp. (5; 50%), being *A. flavus* the most common (4; 40%), followed by *Scedosporium* spp. (4; 40%). Respiratory distress was present in 6 patients (6; 60%), there were 2 cases of fungal colonization (2; 20%) and 1 asymptomatic patient. One patient received nebulized voriconazole as fungal prophylaxis after LT after multi-resistant *Scedosporium prolificans* had been isolated from the graft transportation fluid.

Nebulized voriconazole treatment

Nebulized voriconazole treatment was mainly initiated in the hospital wards (5; 50%), but it also started in the intensive care unit (3; 30%) or outpatient (2; 20%). The main reasons for treatment initiation were lack of response to antifungals (4; 40%) and systemic treatment toxicity (4; 40%); other reported reasons were avoiding clinically relevant drug-drug interactions (2;20%), post-LT prophylaxis (1;10%), and booster oral voriconazole effect (1; 10%).

The voriconazole dose used was 40 mg (4 ml of the 10 mg/ml solution) in adults and 10 mg (1 ml of the 10 mg/ml solution) in the pediatric patient. It was administered using jet nebulizers every 12 or 24 h, only patients with CF and fungal colonization receiving outpatient treatment used lower frequencies (Table 2). Nebulized voriconazole was used as monotherapy in 2 cases (2; 20%), it was combined with systemic therapy in 7 cases (7; 70%), and used in combination with nebulized micafungin in 1 case (1; 10%). The median duration of treatment was 139 (26–911) days; short treatments correspond to patients who died, whereas long treatments were used in colonized patients.

Tolerance and pharmacokinetics

We estimate that 13.762 voriconazole nebulizations have been administered. There were no reported adverse events. There was 1 case of mild pruritus that did not require treatment withdrawal in a patient who had a history of skin toxicity related to systemic voriconazole.

Voriconazole plasma levels were measured according to clinicians' criteria. There were 11 voriconazole plasma measurements for 6 patients; it was undetectable in 9 plasma samples from the 4 patients receiving voriconazole by pulmonary route of administration only and 2 patients receiving systemic voriconazole had plasma levels within the goal range.

Clinical outcomes

Three patients died during the study. One patient died due to graft failure and another due to IPA, in the third case of death, fungi were not detected in the last bronchoalveolar lavage available.

Two patients affected by CF who suffered fungal lung colonization did not have exacerbations requiring antifungal treatment or hospitalization during the time of the study. One patient receiving nebulized voriconazole as prophylaxis after LT had an adequate clinical evolution during the follow-up. There were 3 cases of microbiological response and voriconazole resistance was developed in 1 case.

Discussion

Our study retrospectively describes the use of nebulized voriconazole to treat IPA in a third referral hospital. Compounded voriconazole solution for nebulization characteristics are adequate for nebulization, it is well-tolerated and voriconazole is not absorbed into systemic circulation even in long treatments.

This study has been performed in the real-world setting, allowing the inclusion of complex patients who represent the potential target population of this treatment. Even if the sample of patients is limited, determination of serum concentration of voriconazole has allowed us to evaluate the rate of voriconazole absorption and the great length of some of the treatments have provided reliable information about safety.

Literature available about the use of nebulized voriconazole in humans is scarce. Jolle et al. have reported the use of nebulized voriconazole in combination with oral treatment in a young patient with CF to treat a severe pulmonary infection caused by *Scedosporium apiospermum*, they concluded that it was safe and effective.¹⁴ Hilberg et al. published a series of 3 cases of IPA caused by *Aspergillus* spp. successfully treated with inhaled voriconazole monotherapy (40 mg every 12–24 h).¹⁵ Authors reported an adequate tolerability to voriconazole nebulization, as our results confirm. The efficacy reported by these case reports is better than we observed in our study; however, authors' conclusions should be taken cautiously since there might be a bias towards publishing only cases with positive outcomes. This study has some limitations. First, since it is a retrospective study, voriconazole plasma concentration was not consistently measured in all patients, so there is missing information. Second, different excipients contained in each voriconazole brand could have an impact on treatment toxicity and absorption, even if we did not detect any differences. Third, patients included were highly complex and some of them were sedated; thus, our capacity to detect adverse events might have been restricted. Finally, due to the limited sample and the absence of a control group, it is not possible to draw conclusions about treatment effectiveness.

In conclusion, our study has shown that voriconazole solution is suitable for nebulization, it is well-tolerated, and it is not absorbed into the systemic circulation even in long treatments. Therefore, the pulmonary route of administration could be an interesting option to treat complex pulmonary infections and/or colonizations when preferred treatments are not efficient, there is toxicity due to systemic treatment or there is risk of drug–drug interactions. Further research is needed in order to assess voriconazole nebulization efficacy to treat specific clinical situations.

Contribution to literature

Voriconazole solution is well-tolerated and it is not absorbed into systemic circulation when nebulized.

It could be an interesting strategy to treat fungal lung diseases; further research is needed to assess its efficacy.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest. This research received no specific grant from any funding agency in the public,

commercial, or not-for-profit sectors. This work was presented as a communication in the 65th Congress of the European Association of Hospital Pharmacists (EAHP), Wien, March 2022.

References

1. El-Baba F, Gao Y, Soubani AO. Pulmonary aspergillosis: what the generalist needs to know. *Am J Med.* 2020;133(6):668–74.
2. Kabir V, Maertens J, Kuypers D. Fungal infections in solid organ transplantation: an update on diagnosis and treatment. *Transplant Rev (Orlando).* 2019;33(2):77–86.
3. Warris A, Bercusson A, Armstrong-James D. *Aspergillus* colonization and antifungal immunity in cystic fibrosis patients. *Med Mycol.* 2019;57:S118–26.
4. García-Vidal C, Alastruey-Izquierdo A, Aguilar-Guisado M, Carratalà J, Castro C, Fernández-Ruiz M, et al. Executive summary of clinical practice guideline for the management of invasive diseases caused by *Aspergillus*: 2018 update by the GEMICOMED-SEIMC/REIPI. *Enferm Infecc Microbiol Clin.* 2019;37(8):535–41.
5. Wang T, Zhu H, Sun J, Cheng X, Xie J, Dong H, et al. Efficacy and safety of voriconazole and CYP2C19 polymorphism for optimized dosage regimens in patients with invasive fungal infections. *Int J Antimicrob Agents.* 2014;44(5):436–42.
6. Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. *Clin Microbiol Rev.* 2014;27(1):68–88.
7. Monforte V, Ussetti P, Gavalda J, Bravo C, Laporta R, Len O, et al. Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B for *Aspergillus* infection prevention in lung transplantation. *J Heart Lung Transplant.* 2010;29(5):523–30.
8. Tolman JA, Nelson NA, Son YJ, Bosselmann S, Wiederhold NP, Peters JL, et al. Characterization and pharmacokinetic analysis of aerosolized aqueous voriconazole solution. *Eur J Pharm Biopharm.* 2009;72(1):199–205.
9. 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.
10. Guía de buenas prácticas de preparación de medicamentos en servicios de farmacia hospitalaria. MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD; 2014. Available at: https://www.sefh.es/sefhpdfs/GuiaBPP_JUNIO_2014_VF.pdf.
11. Dupuis A, Tournier N, Le Moal G, Venisse N. Preparation and stability of voriconazole eye drop solution. *Antimicrob Agents Chemother.* 2009;53(2):798–9.
12. Sahraoui L, Chiadmi F, Schlatter J, Toledano A, Cisternino S, Fontan JE. Stability of voriconazole injection in 0.9% sodium chloride and 5% dextrose injections. *Am J Health Syst Pharm.* 2006;63(15):1423–6.
13. Adams AI, Morimoto LN, Meneghini LZ, Bergold AM. Treatment of invasive fungal infections: stability of voriconazole infusion solutions in PVC bags. *Braz J Infect Dis.* 2008;12(5):400–4.
14. 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.
15. Hilberg O, Andersen CU, Henning O, Lundby T, Mortensen J, Bendstrup E. Remarkably efficient inhaled antifungal monotherapy for invasive pulmonary aspergillosis. *Eur Respir J.* 2012;40(1):271–3.