USE OF NEBULIZED VORICONAZOLE: A SINGLE-CENTER REAL-LIVE STUDY

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Abstract

Voriconazole is the primary treatment for invasive pulmonary aspergillosis (IPA) and it has been used to treat patients colonized by Aspergillus spp. The pulmonary route could increase drug concentration in the biophase, reduce drug-drug interactions (DDI) and minimize adverse events (AE); however, there is scarce evidence about its use and there are no commercial voriconazole formulations for nebulization. The goal of this study is to characterize the compounded voriconazole solution for nebulization and describe its use in our center. This is a retrospective observational study including all patients treated with nebulized voriconazole to treat pulmonary fungal infections or colonizations. Voriconazole solution was prepared from commercial vials for intravenous administration. The pH and osmolarity of voriconazole solutions were adequate for nebulization, the dosage was 40 mg in adults and 10mg in the paediatric patient, administered every 12-24h. The median duration of treatment was 139 (26-911) days, there were no reported adverse effects related to voriconazole nebulization and the drug was not detected in plasma when used through the pulmonary route only. There were 3 cases of death, one case of voriconazole resistance, 3 cases of microbiological response, 2 cases of colonization without exacerbation and one case of successful prophylaxis. Voriconazole nebulization is well-tolerated and the drug is not absorbed into the systemic circulation. Further research is needed to assess voriconazole nebulization efficacy in specific clinical situations.

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, transplantat 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 (2), a prevalence of 6.5% and mortality rate of 52% has been reported in this population (3). 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 (4,5). 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, itraconazole, posaconazole and echinocandines can be added

to the treatment or used as alternatives in case of treatment failure (6). 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 (7,8). 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 (9).

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 a safe and effective (10).

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.

METHODS

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 Hospital Pharmacy Department, following the Good Manufacturing Practice and dispensed as monodose syringes ready to use. Different brands of voriconazole were used, depending on the availability (Table 1).

Voriconazole solution was compounded according to available literature (11). 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 was 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 (min-max) 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 19ml of sterile water for injection; syringes containing 40 mg of voriconazole in 4ml were obtained. Voriconazole powder from Teva® was diluted in sodium chloride 0.9% 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 (12-17).

It was estimated that the voriconazole solution was chemically stable for 30 days refrigerated (2-8^{o}C) and 90 days frozen (-20^{o}C) (11, 13). Biological stability was calculated based on the Good Manufacturing Practice in Hospital Pharmacy Services (13), since it was shorter, it defined the voriconazole solution valid period as 9 days refrigerated and 45 days frozen.

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 one paediatric 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 one LT, the median time from LT was 7 (0-84) months (3 CF patients had received 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 two cases of fungal colonization (2; 20%) and one 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 DDI (2;20%), post LT prophylaxis (1;10%) and booster oral voriconazole effect (1; 10%).

The voriconazole dose used was 40 mg in adults and 10mg in the paediatric patient. It was administered using jet nebulizers every 12 or 24 hours, 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 mycafungin 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 AE. There was one 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 two 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 was 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 three cases of microbiological response and voriconazole resistance was developed in one 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 (18). 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 hours) (19). 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 AE 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.

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 DDI. Further research is needed in order to assess voriconazole nebulization efficacy to treat specific clinical situations.

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The authors confirm that the data supporting the findings of this study are available within the article.

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

*Osmolarity when diluted with sodium chloride 0.9%.

Table 1. Physical properties of different brands of voriconazole powder diluted in 19ml of sterile water for injection.

Age (years)	**Comorbidities**	**Time from LT**	**Fungal pathogen**	**Antifungal treatment indication**	**Treatment site**	**Justification for voriconazole nebulization initiation**	**Dosage**	**Voriconazole powder for solution for infusion brand**	**Other treatments**	**DOT**
35	CF	3 m	*Scedosporium prolificans*	Respiratory distress	Hospital ward Outpatient treatment	Lack of response to oral voriconazole	40mg/24h 40mg/12h	Kern®	Voriconazole (oral)	122

21	CF	NT	*Aspergillus citrinoterreus* - *Aspergillus terreus* (R to amphotericin and voriconazole)	Fungal colonization	Hospital ward Outpatient treatment	Symptomatic liver toxicity to systemic azoles	40mg /12h 40mg/24h 40mg 3/w	Kern® Normon®	Isavuconazole (oral)	1-120
35	CF	0 d	*Scedosporium prolificans* (multidrug R, S to voriconazole)	LT fungal prophylaxis after isolation of *S. prolificans* in the graft preservation fluid	Hospital ward Outpatient treatment ICU	Need of topical antifungal prophylaxis after LT active against *Scedosporium prolificans* R to amphotericin	40mg/12h	Kern®	Micafungin (neb)	>170

69	Nonspecific4 y interstitial pneumonia	*Aspergillus flavus* (R to amphotericin)	Bronchitis	Hospital ward Outpatient treatment	Lack of response to anidulafungin Symptomatic toxicity to azoles (dizziness, myopathy).	40mg/12h 40mg/24h	Accord®	Isavuconazole (oral) 31

60	Idiopathic pulmonary fibrosis	1 m	*Scedosporium apiospermum complex*	Colonization	Outpatient treatment	Combination of nebulized and systemic treatment to readily reach therapeutic voriconazole concentration in the lung.	40mg/12h	Kern®	- Voriconazole (oral)	>156
65	Chronic obstructive pulmonary disease	7 m	*Aspergillus fumigatus* - *Aspergillus flavus*	Respiratory distress	Hospital ward	Avoiding clinically relevant drug-drug interaction among systemic azoles and sirolimus	40mg/12h	Kern®	None	26

64	Chronic obstructive pulmonary disease	NT	*Purpureocillium lilacinus* (multi-drug R; S to voriconazole, posaconazole and isavuconazole)	Respiratory distress	Hospital ward	Symptomatic toxicity so systemic azoles Kidney failure Avoiding clinically relevant drug-drug interaction among systemic azoles and sirolimus.	10mg/12h	Teva®	None	30
18	CF	NT	*Scedosporium apiospermum complex* (multi-drug R, S to voriconazole, posaconazole, isavuconazole and micafungin)	Colonization	Outpatient treatment	Symptomatic toxicity to systemic azoles (rash)	10mg/48h 40mg /24h	Teva® Kern® Normon®	Posaconazole (oral)	840
30	CF	7 y / 0 d*	*Aspergillus flavus complex* (R to amphotericin) *Aspergillus terreus complex* (R to amphotericin)	Surgery complications after second LT	ICU	Lack of response to previous treatments	40mg/24h	Kern®	Isavuconazole (IV) Micafungin (IV) Liposomal amphoterin (IP)	28

5	Interstitial neumopathy	9 m	*Aspergillus flavus complex* (R to amphotericin)	Respiratory distress	P-ICU	Lack of response to previous treatments.	10mg/24h	Normon®	Liposomal amphotericin (neb) Isavuconazole (IV) Anidulafungin (IV)	81

***** 7 years from the first and 0 days from the second LT.

Table 2. Patients' basal characteristics and nebulized voriconazole treatment description (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, P-ICU: pediatric intensive care unit, neb: nebulized, IV: intravenous, IP: intrapleural).