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Evaluation of the Implementation of a Voriconazole Pharmacokinetic Monitoring Program in Hematological Patients

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Abstract

Background: Invasive Fungal Infections (IFI) is a significant cause of morbidity and mortality in patients with hematological malignancies. Voriconazole is widely used for the prophylaxis and treatment of IFIs. However, its efficacy and safety are influenced by factors such as nonlinear pharmacokinetics, genetic polymorphisms, hepatic metabolism, and drug interactions. Pharmacokinetic (PM) monitoring is an essential tool to optimize voriconazole therapy.

Objectives: This study aimed to evaluate the impact of the implementation of a voriconazole MF program on drug safety and dosing optimization in hematological patients.

Methods: A prospective study was conducted in hospitalized patients with hematological malignancies who received voriconazole between January and December 2023. Inclusion criteria included adults under therapy with both oral and intravenous voriconazole, with at least one plasma level determination. Voriconazole levels were measured using the ARK Voriconazole II Assay, and dose adjustments were made based on predefined therapeutic ranges (1-4 mcg/mL). Statistical analyzes were performed with SPSS v28, applying non-parametric tests.

Results: A total of 42 blood samples from 32 patients were analyzed. Most patients (71.42%) received oral voriconazole. Therapeutic levels (1-4 mcg/mL) were reached in 57.14% of the samples, while 28.57% were supratherapeutic and 9.52% were infratherapeutic. Weight was significantly associated with voriconazole levels (p=0.032), while age and route of administration were not. Adverse events were observed in 17 cases, 82% in patients with supratherapeutic levels, including hepatotoxicity, neurotoxicity and renal alterations. The pharmacist's recommendations led to dose modifications in 40.47% of cases, with an acceptance rate of 88.10% by physicians.

Conclusions: Implementation of voriconazole MF has proven to be a viable strategy to improve safety. It was observed that 82% of adverse effects occurred in patients with levels greater than 4 mcg/mL, highlighting the value of monitoring as a predictive tool. Furthermore, the intervention of hospital pharmacists had high acceptance (88%), which supports the importance of their role in optimization.

Keywords: Voriconazole • Pharmacokinetic monitoring • Hematological malignancies • Antifungal therapy • Pharmacokinetics • Safety

Introduction

Pharmacokinetic Drug Monitoring (PM) has the potential to improve treatment efficacy and minimize adverse effects, especially in patients with hematological malignancies. Invasive Fungal Infections (IFI) has increased in incidence in recent years. Data from more than 120 countries include findings that annually, more than 2 million people develop invasive aspergillosis in the setting of chronic obstructive pulmonary disease, intensive care, lung cancer, or hematologic malignancies, with crude annual mortality between 30% and 85% [1,2]. Antifungal drugs for treatment and prophylaxis are essential components in the management and prevention of IFIs in hematological patients. However, they may lose effectiveness due to drug interactions, variable pharmacokinetics, and the development of resistance. MF has emerged as a valuable strategy to address these challenges, especially in triazole therapy [1,3].

One of the most used drugs to treat fungal infections is voriconazole. Immunocompromised patients, including those with hematologic malignancies, are at risk for these diseases. Integrating FM into clinical practice is one of the most valuable tools that pharmacists can offer both for the treatment and prevention of IFIs, contributing to safer, more effective and personalized therapies.

Voriconazole is a second-generation triazole approved in Spain for the treatment of invasive aspergillosis, candidemia in non-neutropenic patients, invasive diseases caused by *Candida* (including *Candida krusei*) resistant to fluconazole, serious infections caused by *Scedosporium* spp. and *Fusarium* spp., and as prophylaxis of serious fungal diseases in high-risk *Hematopoietic Stem Cell Transplants* (HSCT) (4). The efficacy of voriconazole is well documented, but it is important to recognize that several factors may influence its plasma concentration. These include oral bioavailability, nonlinear pharmacokinetics, and hepatic metabolism, genetic polymorphisms in CYP2C9 and CYP2C19, and drug interactions due to its metabolism in CYP3A4. Given these complexities, MF should be implemented in most hospitals for hematological patients [3,4]. Plasma concentrations of drugs have been shown to play a crucial role in both efficacy and toxicity. Voriconazole trough concentrations greater than 1 mcg/mL have shown similar efficacy to concentrations greater than 5.5 mcg/mL. Additionally, voriconazole concentrations greater than 5.5 mcg/mL have been associated with neurological and hepatic toxicities [5-7].

Despite growing evidence supporting the benefits of voriconazole MF, implementation of this practice in real-world clinical settings remains limited. This study aims to provide the first results on the implementation of voriconazole MF in hematological patients in our hospital, evaluating its impact on safety.

Methodology

In this prospective study, we reviewed patients hospitalized with hematologic malignancies during the period January to December 2023 who had at least one voriconazole blood determination. The inclusion criteria for our study were patients with hematological malignancy, over 18 years of age and being treated with voriconazole, either orally or intravenously. We collected all

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possible patients who met these criteria during that period.

Hematology patients receiving voriconazole during hospitalization received routine drug monitoring as part of their standard care. All clinical and laboratory data were collected, ensuring strict compliance with anonymity protocols. The study was approved by the Clinical Research Ethics Committee of our hospital, adhering to the fundamental principles of the Declaration of Helsinki.

Voriconazole monitoring was generally performed on the third day of treatment, once the patient had received the loading dose and subsequent maintenance doses, reaching steady state (after 48 h). In cases where a loading dose was not administered, drug monitoring was requested seven days after initiation. Blood collection was performed 30 minutes before the administration of the next dose. The time of the last dose of voriconazole administration and the exact time of blood sample collection were routinely recorded. The monitoring levels were requested by the doctors in the Hematology Service department or by the hospital pharmacists. Subsequently, the blood sample was sent to the Clinical Analysis department of the city's reference hospital. The analytical determination was performed using the ARK Voriconazole II Assay [8], which uses a homogeneous enzyme immunoassay technique for the quantitative determination of voriconazole in human serum using automated analyzers. The detection limits of the analytical device were 0.5–16.0 µg/mL. The result was obtained between 48 and 72 hours after sending the sample and was recorded electronically in the analysis program (Modulab®). Once the analytical results were obtained, we proceeded to prepare a pharmacokinetic report indicating the appropriateness of the dosage or whether a dosage adjustment was required. In addition, said report is attached to the electronic prescription program (MIRA®).

The standard oral dosing regimen consists of a loading dose of 400 mg twice daily on the first day, followed by 200 mg twice daily. For intravenous administration, a loading dose of 6 mg/kg twice daily is administered, followed by 4 mg/kg twice daily. All doses are based on the patient's actual body weight.

At our institution, we adhere to a conservative therapeutic range of voriconazole between 1 mcg/mL and 4 mcg/mL. This range is based on the recommendations of the Antifungal Susceptibility Subcommittee of the Clinical and Laboratory Standards Institute [9,10] as well as our internal protocol. Dose adjustments were made according to the patient's clinical status, in consultation with the treating physicians, and guided by our dose modification guidelines [10]. These dose adjustment guidelines are as follows (Table 1) [3,10,11].

If the level of the voriconazole drug was within the therapeutic range, we recommended re-monitoring a week later or according to the patient's symptoms. However, if the drug level was not within the therapeutic range, dose adjustment was performed and we recommended re-monitoring after 72 hours.

Our statistical analysis was carried out using SPSS v28. We checked for non-normality in our sample, so we decided to use non-parametric tests for independent samples, such as the Kruskal-Wallis test. A p-value <0.05 was considered significant. All data were collected in an Excel® database.

Results

Our first results during a year of study, after the implementation of the program, a total of 42 blood samples from 32 patients with hematological diseases were analyzed. Baseline and admission characteristics are represented in Table 2. All patients received treatment with voriconazole, either oral or intravenous. Of the 42 samples, 30 samples (71.42%) were obtained during oral therapy, while 12 samples (28.57%) were obtained during intravenous therapy.

Fungal species were isolated in 37.50% of the microbiological samples, and the majority of the results (58.00%) were caused by *Aspergillus fumigatus*. The indication for voriconazole could be both prophylaxis and treatment. For treatment, there are three non-exclusive strategies: empirical treatment for febrile neutropenic patients, preventive treatment (based on early laboratory and radiological diagnostic tests), and targeted first-line treatment (for proven or probable IFI) [12]. Table 3 shows the number of patients and the corresponding percentage.

During the monitoring process, 24 samples (57.14%) were found to be within the therapeutic range of voriconazole (1-4 mcg/mL). Furthermore, 12

Table 1. Voriconazole dose adjustment guide according to blood levels.

Voriconazole Levels (mcg/mL)	Interventions
0.0–0.6	Increase dose 100 mg
0.7–0.9	Increase dose 50 mg
01-Apr	Level in range. No changes
4.1–5.5	Reduce dose 50 mg
5.6–7.9	Stop one dose and reduce subsequent doses by 25%
>8	Stop one dose and reduce subsequent doses by 50%

Table 2. Description of the patients.

		N= 32 pacientes
Characteristics of the Patients	Median age	62 años (41-69)
	Masculine	55%
	Female	45%
Weight	Low weight (< 60 kg)	17%
	Average weight (=60 and <80 kg)	58%
	High weight (>or = 80 kg)	25%
Monitoring Indications	Starting with loading dose	91%
	Start without loading dose	9%
Diagnosis	Acute myeloid leukemia	41%
	Myelodysplastic syndrome	23%
	B cell lymphoma	17%
	Burkitt lymphoma	6%
	T cell lymphoma	6%
	Brain lymphoma	6%
		N=42 muestras
Route of Administration	Intravenous	28.57 % (12)
	Oral	71.42 % (30)

Table 3. Indications of voriconazole and isolated species.

Fungal Species	% (N)
Aspergillus fumigatus	58.00% (7)
Aspergillus flavus	16.66% (2)
Aspergillus glaucus	8.33% (1)
Candida krusei	8.33% (1)
Candida albicans	8.33% (1)
Indication of voriconazole	
Prophylaxis	23.00%
Empirical treatment	29.50%
Advance treatment	10.00%
Targeted treatment	37.50%

samples (28.57%) exceeded the upper limit of the therapeutic range, with concentrations varying between 4.17 and 12.17 mcg/mL. Furthermore, 4 samples (9.52%) presented subtherapeutic levels, with concentrations ranging from 0.4 to 0.78 mcg/mL. It is worth mentioning that 2 samples (4.76%) gave erroneous results due to problems in the analytical technique (Figure 1).

After determination of plasma levels, hospital pharmacists provided various recommendations to the clinical team regarding voriconazole dosage adjustments. Among the recommendations, 59.53% suggested maintaining the same dose. In 9.52% of cases, the recommendation was to increase the dose by 50 mg every 12 hours, while in 11.90% of cases, the recommendation was to reduce the dose by 50 mg every 12 hours. Furthermore, in almost 20% of the recommendations, due to supratherapeutic levels, we recommend suspending a dose and reducing the following doses by the corresponding percentage according to the level. It should be noted that 88.10% of the recommendations made by the hospital pharmacists were accepted by the doctors (Figure 2).

We decided to analyze whether there were significant differences between voriconazole levels, route of administration, age and weight. The results showed that there were no significant differences between voriconazole levels and age or route of administration, with $p = 0.253$ and 0.180, respectively. However, we found statistically significant differences between voriconazole levels and patient weight ($p = 0.032$). To find out in which group the difference existed (low, medium or high), we performed the Mann-Whitney U test between two groups, but applying the Bonferroni correction, where α was 0.0167, instead of 0.05. Our results showed that heavier patients had higher blood levels of voriconazole.

In our study, a total of 17 adverse events were documented, and we classified these events based on the corresponding voriconazole concentrations found in the blood samples. In Figure 3, we classify the adverse events found in our patients. Adverse events associated with supratherapeutic concentrations (>4 mcg/mL, ranging between 4.17 and 9.37 mcg/mL) were 82.36% (14 events) and included: hallucinations, hepatotoxicity, delirium, renal failure, and hypokalemia. Within the therapeutic range (1-4 mcg/mL), a total of 3 (17.64%) adverse events were observed in our study, all of them hepatotoxicity (Figure 3).

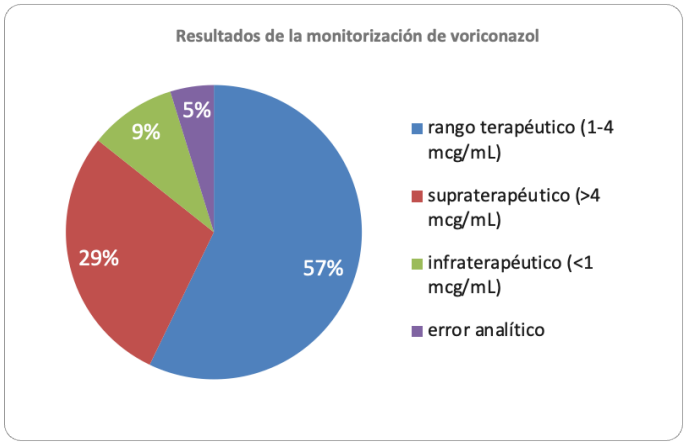

Figure 1. Diagram of voriconazole monitoring results.

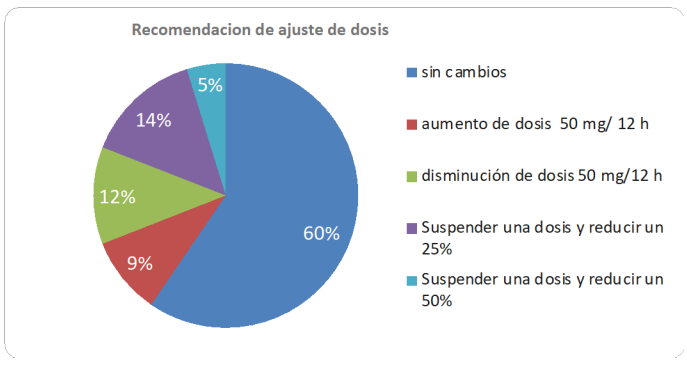

Figure 2. Dose adjustment recommendation diagram.

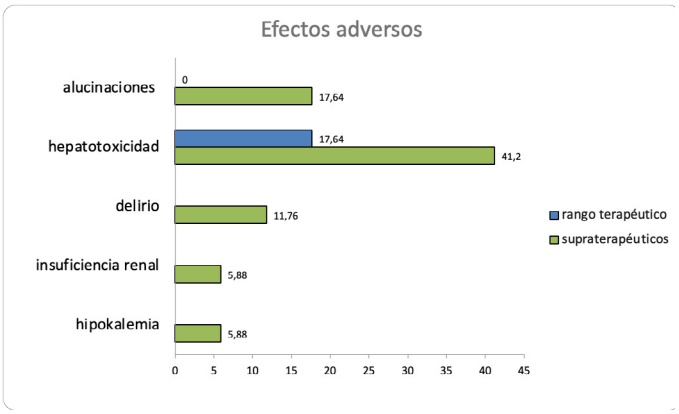

Figure 3. Classification of adverse effects in our study.

These findings indicate that the majority of adverse events were associated with supratherapeutic concentrations of voriconazole.

Discussion

Implementation of voriconazole pharmacokinetic monitoring at our institution has posed challenges, including standardization of procedures, continuing education for clinical staff, and the need to determine levels at an outside facility. However, early results indicate that this approach not only improves treatment safety, but also optimizes dosing, minimizing complications related to drug concentrations outside the therapeutic range. Initial results from the implementation of voriconazole MF at our institution indicate that, through appropriate dose adjustments based on plasma levels, better control of therapeutic concentrations has been achieved and we can improve our

management in reducing adverse events, particularly those associated with supratherapeutic concentrations.

In a study carried out in hematological patients like ours, no correlation was found between weight, kidney function, bilirubin levels and age. For these reasons, it is difficult to predict the concentration of voriconazole without monitoring its concentrations [13]. However, in our study, we found statistically significant differences between voriconazole levels and patient weight, with heavier patients having higher voriconazole levels.

The association between clinical response to voriconazole and serum concentrations has been demonstrated mainly by retrospective analyzes and some prospective evaluations. These studies have shown that drug levels between 0.72 mcg/mL and 2.2 mcg/mL are linked to a lower risk of treatment failure [1,5,14,15]. Furthermore, a systematic review and meta-analysis on this topic concluded that, based on current evidence, a threshold of ≥ 1 mcg/mL is the best predictor of treatment response [16]. A retrospective study in patients with hematological diseases identified the success of treatment with voriconazole at concentrations greater than 2 mcg/mL [13].

Voriconazole has several side effects: hepatotoxicity, dermatological toxicity, neurotoxicity, ocular toxicity, bone toxicity and others such as nephrotoxicity or cardiovascular toxicity [3]. Effects such as neurotoxicity and hepatotoxicity have been associated with supratherapeutic levels [13,15]. A meta-analysis concluded that voriconazole levels greater than 6.0 mcg/mL were the best predictor of toxicity [16]. Visual disturbances are dose-related and include blurred vision, photophobia, or altered perception. This toxicity is temporary and resolves without interrupting therapy [3]. Hepatotoxicity presents as elevated transaminases and hyperbilirubinemia. Some data suggest that this toxicity is related to supratherapeutic levels, and discontinuation of treatment may result in normalization [3]. Rash, pruritus and photosensitivity are manifestations of dermatological toxicity. In prolonged exposures, cases of squamous cell carcinoma and melanoma have been reported [17,18]. Neurological toxicity, such as agitation, dizziness, confusion, and anxiety, has been reported as symptoms of neurotoxicity and appears to be associated with concentrations greater than 5.5 mcg/mL [5]. Periostitis and elevated serum fluoride concentrations have been reported in cases of prolonged use. Discontinuation seems to normalize this condition [3,19].

Our single-center prospective study has several limitations. One of the limitations is the small size of the cohort we present, but in the near future we will try to expand it as we improve our FM program. The other limitation corresponds to the barriers to implementing the voriconazole MF program in our center. The processing laboratory is outside our hospital, causing us a 2 to 3 day delay in obtaining serum voriconazole concentration and making subsequent dose adjustments.

For patients with trough concentrations less than 1 mcg/mL, dose adjustments should be considered to achieve higher voriconazole concentrations to improve effectiveness. In cases where patients experience side effects such as hallucinations or visual disturbances, drug monitoring should be strongly considered. Additionally, further research is needed to establish a consensus on drug monitoring practices and define a therapeutic range for voriconazole. This will help optimize treatment results and ensure safe and effective use of the medication. Therefore, therapeutic drug monitoring should be considered for all hematological patients as soon as steady state is achieved to optimize efficacy outcomes and minimize the risk of toxicity symptoms.

Conclusion

The results of this pilot study in our center demonstrate that the implementation of voriconazole MF in hematological patients is a viable strategy that improves treatment safety. By monitoring drug levels, we ensured that most concentrations were within the therapeutic range, to ensure clinical success. Our findings serve as a basis for future research and the expansion of this practice in our institution and in hospitals with similar characteristics. 82% of the adverse effects we found in our patients were in those who had voriconazole concentrations above 4 mcg/mL. That is why MF serves as a predictive tool to anticipate adverse events. The intervention of hospital pharmacists in the monitoring of voriconazole, with 88% acceptance of the recommendations, encourages us to continue carrying out this activity and improve our monitoring program.

References

1. Boyer, Johannes, Martin Hoenigl and Lisa Kriegl. "Therapeutic drug monitoring of antifungal therapies: Do we really need it and what are the best practices?." *Expert Rev Clin Pharmacol* 17 (2024): 309-321.
2. Denning, David W. "Global incidence and mortality of severe fungal disease." *Lancet Infectious Diseases* 24 (2024): e428-e438.
3. Chau, Maggie M., Kathryn Daveson, Jan-Willem C. Alffenaar and Amanda Gwee, et al. "Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy and haemopoietic stem cell transplant recipients, 2021." *Int Med J* 51 (2021): 37-66.
4. https://www.ema.europa.eu/en/medicines/human/EPAR/voriconazole-accord
5. Pascual, Andres, Thierry Calandra, Saskia Bolay and Thierry Buclin, et al. "Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes." *Clin Infect Dis* 46 (2008): 201-211.
6. Miyakis, Spiros, Sebastiaan J. Van Hal, John Ray and Deborah Marriott. "Voriconazole concentrations and outcome of invasive fungal infections." *Clin Microbiol Infect* 16 (2010): 927-933.
7. Troke, Peter F., Hans P. Hockey and William W. Hope. "Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients." *Antimicrob Agents Chemother* 55 (2011): 4782-4788.
8. https://arktdm.com/products/antifungal/voriconazole/pdfs/ARK_VoriconazoleII_Assay_Rev03_June_2018.pdf
9. Wayne, P. "Clinical and Laboratory Standards Institute: Reference method for broth dilution antifungal susceptibility testing of yeasts; approved standard." CLSI document M27-A3 and Supplement S3 (2008): 6-12.
10. Perreault, Sarah, Dayna McManus, Anthony Anderson and Tiffany Lin, et al. "Evaluating a voriconazole dose modification guideline to optimize dosing in patients with hematologic malignancies." *J Oncol Pharm Pract* 25 (2019): 1305-1311.
11. John, Jamie, Angela Loo, Shawn Mazur and Thomas J. Walsh. "Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients." *Expert Opin Drug Metab Toxicol* 15 (2019): 881-895.
12. Llamas, J. Carlos Vallejo and Isabel Ruiz-Camps. "Invasive fungal infection in hematologic patients." *Enferm Infecc Microbiol Clin* 30 (2012): 572–579.
13. Ueda, Koki, Yasuhito Nannya, Keiki Kumano and Akira Hangaishi, et al. "Monitoring trough concentration of voriconazole is important to ensure successful antifungal therapy and to avoid hepatic damage in patients with hematological disorders." *Int J Hematol* 89 (2009): 592-599.
14. Park, Wan Beom, Nak-Hyun Kim, Kye-Hyung Kim and Seung Hwan Lee, et al. "The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: A randomized controlled trial." *Clin Infec Dis* 55 (2012): 1080-1087.
15. Dolton, Michael J., John E. Ray, Sharon C-A. Chen and Kingsley Ng, et al. "Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring." *Antimicrob Agents Chemother* 56 (2012): 4793-4799.
16. Luong, Me-Linh, Mona Al-Dabbagh, Andreas H. Groll and Zdenek Racil, et al. "Utility of voriconazole therapeutic drug monitoring: A meta-analysis." *J Antimicrobial Chemotherapy* 71 (2016): 1786-1799.
17. Miller, Daniel D., Edward W. Cowen, Josephine C. Nguyen and Timothy H. McCalmont, et al. "Melanoma associated with long-term voriconazole therapy: A new manifestation of chronic photosensitivity." *Arch Dermatol* 146 (2010): 300-304.
18. McCarthy, Kate L., E. Geoffrey Playford, David FM Looke and Michael Whitby. "Severe photosensitivity causing multifocal squamous cell carcinomas secondary to prolonged voriconazole therapy." *Clin Infect Dis* 44 (2007): e55-e56.
19. Gerber, Bernhard, Roman Guggenberger, David Fasler and Gayathri Nair, et al. "Reversible skeletal disease and high fluoride serum levels in hematologic patients receiving voriconazole." Blood 120 (2012): 2390-2394.

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