

Case Report

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Case Report

Successful and Safe Real-Time TDM-Guided Treatment of Invasive Pulmonary Aspergillosis Using Isavuconazole Administered by Enteral Tube

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Abstract: Invasive aspergillosis (IA) is an opportunistic infection affecting immunocompromised patients. Current clinical guidelines support the use of voriconazole for the treatment of IA, although this treatment is not free of interactions in this group of patients who are often treated with polytherapy; in these cases, isavuconazole may be a safe alternative with a lower risk of interactions. The oral route is commonly preferred to the parenteral route, but in patients who do not have access to the enteral route, the use of isavuconazole is limited to the parenteral route only, since the technical information sheet does not recommend the handling of tablets for enteral administration, stating that the capsules should not be chewed, crushed, dissolved or opened. This paper presents the case of a patient with diffuse large B-cell lymphoma with confirmed AI on treatment with isavuconazole by enteral tube. It is detailed here that isavuconazole concentrations are maintained when administered by enteral tube, as measured by therapeutic pharmacokinetic monitoring of its plasma concentrations. Administering isavuconazole by enteral tube was found to be a safe practice with monitoring of its plasma concentrations.

Keywords: isavuconazole; pharmacokinetics; enteral-tube

1. Introduction

Nowadays, patients with haematological malignancies are at increased risk for invasive fungal infections (IFI) [1,2], presenting high morbidity and mortality despite advances in therapy [2,3]. Knowing the possible risk factors allows early implementation of prevention, diagnosis and treatment strategies [2].

Most IFI are due to *Aspergillus* spp. with *Fumigatus* species being the majority. Invasive aspergillosis (IA) is a life-threatening opportunistic infection affecting immunocompromised patients, with an incidence of 0.8-2.3%, variable according to the underlying hematologic disease [4], and a mortality of 58% at 12 weeks [5,6]. The diagnosis of IA is based primarily on the presence of positive galactomannan antigen assay in blood or bronchoalveolar fluid (BAL) and/or compatible radiological images [7].

The available data do not support the prophylactic use of antifungals to prevent IA; however, it could be considered if deep and long-lasting immunosuppression is expected [8]. At present, clinical guidelines recommend first-line voriconazole therapy for IA [9–11] with a treatment duration of 6-12 weeks, depending on the degree and duration of immunosuppression [10,11].

In patients with haematological malignancies, polytherapy can lead to possible interactions, which can condition the success or failure of therapy. In this case, isavuconazole may be an alternative, particularly in the context of severe immunosuppression [10]. Clinical trials have demonstrated non-inferiority of isavuconazole to voriconazole, with a better safety profile and lower risk of interactions [12].

Isavuconazole is administered as a prodrug, at a loading dose of 200 mg every 8 hours (six doses), followed by a maintenance dose of 200 mg once daily, both intravenously and orally, due to its high bioavailability [13,14]. Oral absorption is not affected by food or gastric pH, allowing it to be administered without regard to meals [14]. It has high plasma protein binding, large volume of distribution and high elimination half-life, so that equilibrium concentrations will not be reached until at least 14 days after administration [13]. It is metabolized mainly by the hepatic route [13].

The oral route is commonly preferred to the parenteral route because it reduces the risk of complications such as infections or extravasations. The problem arises in patients who do not have access to the oral route, limiting the use of isavuconazole only to the parenteral route since the technical information sheet does not support the handling of the tablets for administration by enteral tube, stating that the capsules should not be chewed, crushed, dissolved or opened [15].

Regardless of the route of administration, it is essential to strictly control treatment with azoles in AI, with therapeutic drug monitoring (TDM) being an effective tool to optimize both the efficacy and safety of plasma levels [16].

A recent cost-effectiveness study compared treatment of IA with isavuconazole and voriconazole, concluding that isavuconazole is more cost-effective for a willingness- to-pay threshold of €25,000 per additional QALY [17]. This study does not refer to TDM of voriconazole, a strategy that seems to be more than endorsed in routine clinical practice for treatment optimization, with a therapeutic range of 1-4 mcg/mL [16]. However, there is still discrepancy in the usefulness of isavuconazole TDM [11,12,16,18,19]. What is clear is the marked increase in the cost of treatment of isavuconazole versus voriconazole, particularly the intravenous versus oral presentation.

2. Materials and Methods

2.1. Case Presentation

74-years-old male diagnosed in January 2023 with diffuse large cell non-Hodgkin's B lymphoma. The patient received first line of treatment with R-CHOP. After the second cycle of R-CHOP the patient presented mucositis and grade 4 neutropenia, which was treated with G-CSF.

On day +11 of the second cycle of R-CHOP, the patient went to the Emergency Department for thermometric fever of 38.6 °C, poor general condition with tachycardia and tachypnea. Laboratory test performed in the Emergency Department again showed grade 4 neutropenia, with elevated acute phase reactants (C-reactive protein, procalcitonin) and hyperlactacidemia, along with hypotension and tachycardia. After evaluation by Haematology, it was decided to admit him to the Intensive Care Unit (ICU) for septic shock with probable respiratory focus (condensation in the left lung base).

2.2. Treatment

After admission to the ICU he required noradrenaline to maintain blood pressure and antibiotic treatment. On day +2 of admission, intubation and connection to mechanical ventilation was performed due to respiratory failure. On the same day BAL galactomannan was detected positive for *Aspergillus*, with an index of 0.482 (positive for indexes higher than 0.20); therefore, treatment was started with IV voriconazole at a loading dose of 6 mg/kg c/12 h (two doses), with a maintenance of 4 mg/kg c/12h. In addition, ceftriaxone was started according to the antibiogram due to the presence of *Klebsiella oxytoca* in a bronchoaspirate sample (BAS). That same day nutritional support was started with individualized parenteral nutrition. On day +4 of treatment voriconazole beginning, TDM was performed. Voriconazole plasma concentrations were quantified by automated enzyme immunoassay. The follow-up of levels and dose adjustment is shown in Table 1.

3 days later, the patient was assessed by the Surgery Service for percutaneous endoscopic gastrostomy (PEG) placement, which was rejected until the patient was optimized; it was placed 7 days later. On the same day, tolerance to enteral nutrition was started, suspending individualized parenteral nutrition a few days later, and during this period the dose of voriconazole was adjusted according to TDM.

The patient progressed respiratory and a percutaneous tracheostomy was performed. On DAY +20 of voriconazol treatment, a new TDM was performed, obtaining an undetectable value, so the dose was increased, and a new TDM was performed 5 days later, in which the concentration was again undetectable. Given the instability of the patient`s concentrations, that same day it was decided to start treatment with isavuconazole 200 mg IV. After the first week of treatment, isavuconazole TDM was performed, in which an infratherapeutic level was obtained. Given the high half-life of the drug, the same dose was maintained, since equilibrium had not yet been reached. Isavuconazole plasma concentrations were quantified by an ultra-performance liquid chromatography system associated with an ultraviolet detector (UV/UPLC).

The patient progressed adequately and was discharged after 36 days with isavuconazol treatment on spontaneous respiration with oxygen through nasal goggles. Finally, three days later the patient was discharged from the ICU and admitted to the Haematology Department. That same day a new TDM of isavuconazole was performed, finding the levels within the range.

Table 1. Voriconazole and Isavuconazole TDM process.

Day	Dosage	Cmin	Recommendation
VORICONAZOLE			
16/03/23 (0)	400mg c/12 (x2) IV	-	-
17/03/23 (+1)	300mg c/12h IV	-	-
20/03/23 (+5)	300mg c/12h IV	10,1 mcg/mL	200mg c/12h IV
23/03/23 (+8)	200mg c/12h IV	6,8 mcg/mL	150mg c/12h IV
29/03/23 (+14)	150mg c/12h IV	2,9 mcg/mL	150mg c/12h IV
05/04/23 (+21)	150mg c/12h IV	undetectable	200mg c/12h IV
10/04/23 (+26)	200mg c/12h IV	undetectable	Change to isavuconazole
ISAVUCONAZOL			
17/04/23 (+33)	200mg c/24h IV	0,8 mcg/mL	200mg c/24h IV
24/04/23 (+39)	200mg c/24h IV	1,2 mcg/mL	200mg c/24h IV
03/05/23 (+49)	200mg c/24h IV	2,4 mcg/mL	200mg c/24h IV
10/05/23 (+56)	200mg c/24h IV	2,6 mcg/mL	200mg c/24h PEG
18/05/23 (+64)	200mg c/24h PEG	2,8 mcg/mL	200mg c/24h PEG
26/05/23 (+72)	200mg c/24h PEG	3,5 mcg/mL	200mg c/24h PEG
21/06/23 (+98)	200mg c/24h PEG	4,1 mcg/mL	200mg and 100mg PEG every other day
07/08/23 (+145)	200mg and 100mg PEG every other day	3,1 mcg/mL	200mg and 100mg PEG every other day

During the admission to the haematology unit, a multidrug-resistant *Pseudomonas aeruginosa* was isolated in sputum, so treatment with ceftazidime/avibactam was established for 10 days. Subsequently, ceftazidime was started again due to a new isolation of sensitive *Pseudomonas aeruginosa*, for 2 weeks more. During all this time, periodic isavuconazole TDM were performed, in which it can be observed how the concentration progressively increased.

Taking into account the clinical stability of the patient, and after a review of the available literature, on day +59 of isavuconazole treatment, it was decided to begin administering isavuconazole via enteral tube, at same dosage, performing periodic isavuconazole TDM.

3. Results

3.1. Ootcome and Follow up

Finally the patient was discharged on day +72 of isavuconazole treatment, with better general condition, administering medication through the PEG, and with enteral nutrition. Given the degree of immunosuppression of the patient, it was decided to maintain isavuconazole treatment for 16-20 weeks. During the entire admission no positive galactomannan was detected in any blood sample.

At the TDM on day +98 of isavuconazole treatment, it was observed that the isavuconazole concentration was beginning to accumulate, so it was decided to reduce the dose; and the suitability of the new regimen was checked with a new isavuconazole TDM on day +145. The patient completed treatment in mid-August 2023.

3.2. Investigation

The main investigation of this work is based on the evaluation of the evolution of the isavuconazole concentrations administered intravenously and subsequent administration by enteral tube, and finally the clinical response of the patient.

4. Discussion

The increased incidence of IA in patients with haematological malignancies, causes isavuconazole use progressively increase, and the potential interactions risk with voriconazole, in a group of patients who are usually treated with polytherapy.

The interindividual variability on isavuconazole concentrations exists, mainly due to the patient's creatinine clearance and body weight, which justifies TDM for the purpose of optimizing therapy [20]. At present, an optimal therapeutic range has not been established; however, it appears that achieving minimal concentrations ($C_{min} > 1 \mu\text{g/ml}$) has been associated with a higher likelihood of treatment success [16,21,22].

There is little evidence of administration of isavuconazole by enteral tube in adult patients with haematological malignancies. Table 2 gathers all the published evidence of isavuconazole administration via enteral tube.

Table 2. Evidence of isavuconazole administration by enteral tube.

Year	Author	Nº Patients	Type	Reference
2019	Adamsick	1	Lung transplant	23
2020	McCreary	19	Solid organ transplant (18) and hematopoietic progenitors (1)	27
2021	Spivey	14	Critical and non-critical	26
2021	Garner	1	Paediatric, LMA	24
2022	Dieringer	24	Solid organ transplant prophylaxis	25

Some isolated clinical cases have been published in which isavuconazole concentrations similar to the IV route were observed when administered by gastrostomy or jejunostomy [23], even in the paediatric population [24]. Dieringer et al. found no negative impact on isavuconazole concentrations associated with the administration by enteral tube in a group of 24 patients [25]. Previously, Spivey et al. had found higher isavuconazole concentrations when administered by gavage than by IV in critically ill and non-critically ill patients [26].

McCreary et al. published the only work that refers to any patient on isavuconazole treatment with hematologic malignancies. They included a cohort of 19 patients (18 with solid organ transplantation and 1 patient with hematopoietic progenitor transplantation for myelofibrosis). This patient received isavuconazole for the treatment of *A. calidoustus* [27].

All in all, isavuconazole TDM appears to be a key strategy to optimize long-term IA treatment in most patients, especially indicated in those with high body weight and critically ill patients [28]. Moreover, in patients with an enteral tube, the use of TDM is a safe strategy that supports the maintenance of isavuconazole concentrations by enteral tube, since TDM entails a lower cost than the treatment itself [16]. Another reason for the need for TDM is that it appears that the standard dose of isavuconazole is adequate for the treatment of IA caused by *A. fumigatus* with MICs $< 0.5 \text{ mcg/ml}$, but the likelihood of treatment success decreases as the MIC increases [20,29]. This is even more prominent in *Candida albicans* and *glabrata* infections [29].

The case presented describes the first patient with haematological malignancy in whom isavuconazole is administered by enteral tube, due to the presence of IA in BAL. It demonstrates the

stability of isavuconazole concentrations administered through PEG, performing periodic TDMs, even a slight accumulation of concentrations, as already pointed out by Spivey et al. beforehand²⁶. This practice led to a significant decrease in the economic impact compared to IV administration.

In view of the above, the integration of clinical pharmacology in multidisciplinary management is increasingly considered as part of patient care, with the aim of ensuring the achievement of the therapeutic objective in this scenario of uncertainty, also ensuring the efficiency of an increasingly frequent treatment.

5. Conclusions

The administration of isavuconazole through an enteral tube supplemented with periodic controls of its plasma concentrations through TDM, proved to be a safe and adequate practice.

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