

CASE REPORT

Voriconazole for pulmonary aspergillosis: a case report underlining the necessity of drug monitoring

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Abstract

Voriconazole is commonly used for the treatment of invasive pulmonary aspergillosis. Recent guidelines strongly advise routine therapeutic drug monitoring for patients receiving voriconazole. We present a case with subtherapeutic voriconazole serum levels caused by drug interactions and genetic polymorphisms.

Introduction

Voriconazole is commonly used for the treatment of invasive pulmonary aspergillosis (IPA).^[1] Recent guidelines strongly advise routine therapeutic drug monitoring (TDM) for patients being treated with voriconazole.^[2] We present a case where voriconazole was used in a setting of near-drowning and suspicion of subsequent IPA. The voriconazole serum levels were strongly divergent, underlining the importance of routine TDM for voriconazole, aiming at serum concentrations between 1.5-2 and 6 mg/l.

Case

A 29-year-old homeless patient known with alcohol and drug abuse was admitted to our intensive care unit (ICU) after a cardiac arrest. The patient had been found in a pond and had nearly drowned. During resuscitation, orotracheal intubation was performed and because of his decreased consciousness after return of spontaneous circulation, invasive mechanical ventilation was started. Initial computed tomography imaging of the lungs showed bilateral ground glass opacities, most probably due to pulmonary oedema, signs of aspiration, in particular in the left lower lobe, and bronchiectasis affecting the right upper lobe.

Because of the submersion in combination with the imaging results, a bronchoscopy was performed, showing food scraps on both sides which were removed successfully. Bronchoscopy showed no signs of fresh water aspiration.

The patient was treated according to the targeted temperature management protocol for attenuation of postanoxic encephalopathy, but after stopping sedatives myoclonic seizures were seen. The patient was treated with high doses of antiseizure drugs (propofol, midazolam, levetiracetam, phenytoin, clobazam and ultimately thiopental), but after cessation of thiopental, generalised myoclonus returned.

Since the patient had been found in a pond in a setting of near-drowning and ingestion of contaminated water has been associated with IPA,^[3] the patient was treated with intravenous voriconazole (two loading doses of 6 mg/kg followed by 4 mg/kg bid), even though the EORTC criteria^[2] of proven or probable IPA were not fulfilled (due to a lack of host factors and clinical criteria). A galactomannan test (Platelia Aspergillus Antigen Assay, Bio-Rad, Hercules, United States) on bronchoalveolar lavage (BAL) fluid was positive (optical density index of 4.5). Fungal cultures of BAL fluid remained negative and consequently, antifungal susceptibility testing was not possible. When voriconazole was started, the patient was also receiving levetiracetam, midazolam, norepinephrine, paracetamol, piperacillin/tazobactam, propofol, sufentanil (all intravenously), ascorbic acid, thiamine and vitamin B complex (all orally), nadroparin prophylaxis and standard decontamination of the digestive tract.

Serum voriconazole concentrations were measured during treatment and are shown in *table 1* and *figure 1*. The first concentration measurement was performed after five administrations of voriconazole, including two loading doses of 6 mg/kg. Because of two subtherapeutic concentrations on day 8 and 10, the voriconazole dose was increased from 4 mg/kg bid to 6 mg/kg bid, but concentrations remained low on day 13. On day 14, the voriconazole treatment was discontinued because of low clinical suspicion of IPA.

TDM was also performed for valproate, phenytoin and clobazam (*table 1*). Because of consistently low serum concentrations of

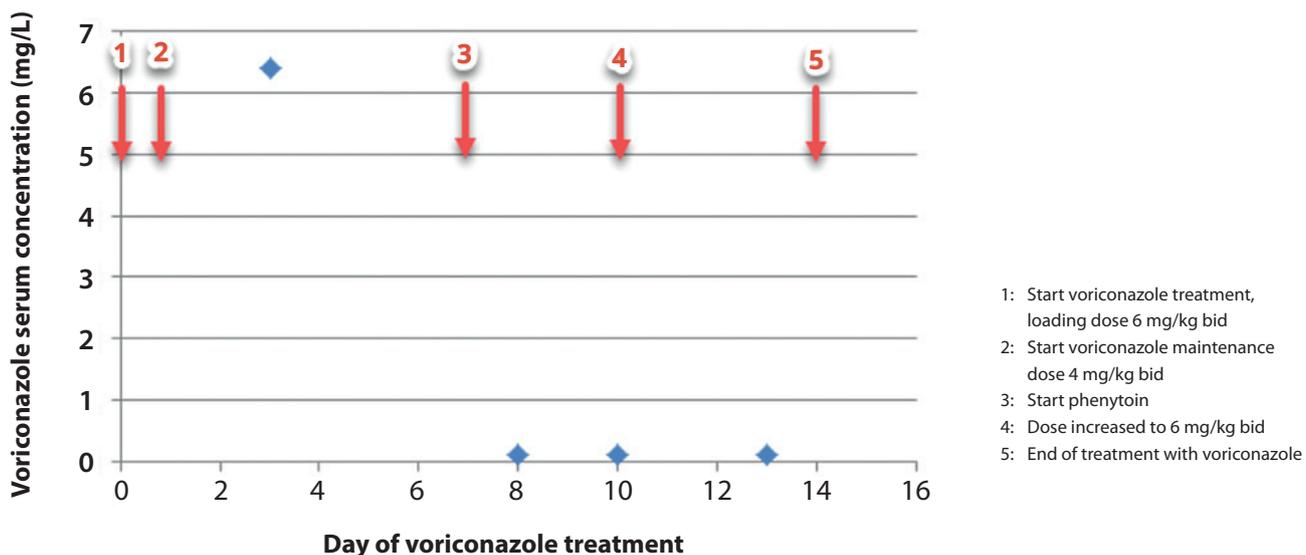


Figure 1. Voriconazole serum concentrations during treatment

all the drugs measured, the patient’s DNA coding for CYP2C9, CYP2C19, CYP2D6 and CYP3A4 was analysed for mutations. Ultra-rapid metabolism for CYP2D6 (*1/*2xN), increased metabolism for CYP2C19 (*1/*17) and normal metabolism for CYP2C9 (*1/*1) and CYP3A4 (*1/*1) were found.

After 16 days in the ICU, life-sustaining treatment (i.e. invasive mechanical ventilation) was withdrawn considering the very poor prognosis of this severe postanoxic encephalopathy. The patient was discharged to the neurology ward. Surprisingly, the patient regained consciousness and slowly recovered with ability to speak again and further motor recovery. After a hospitalisation of four months, the patient was discharged for further rehabilitation.

Discussion

Voriconazole serum concentrations are variable, both intra- and inter-individually.^[4] In a randomised trial, voriconazole TDM reduced drug discontinuation due to adverse events and improved treatment response in invasive fungal disease.^[5]

In recent years, measurement of voriconazole serum concentrations is increasingly performed to assure efficacy and to avoid toxicity in the treatment of invasive fungal infections. Both the ESCMID-ECMM-ERS guideline^[2] and the Dutch guideline for the management of invasive fungal infections^[6] recommend monitoring of azole serum concentrations. According to the Dutch guideline, voriconazole concentrations are to be assessed two to three days after first administration and repeated once or twice weekly, aiming at serum concentrations between 1.5-2 and 6 mg/l.

Many factors can be important when interpreting voriconazole plasma concentrations. First, target values for voriconazole are based on trough concentrations^[2,6] and serum samples should be collected right before administration of the next dose. In this case, the first voriconazole concentration may have been measured right after administration of voriconazole, rendering correct interpretation impossible. Second, voriconazole is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4 and CYP2C9.^[7] Any other medication with the potential to inhibit or induce these enzymes may have an important interaction with voriconazole treatment. This patient was started on phenytoin on day 7 which is known to induce CYP2C19, CYP3A4 and CYP2C9 and therefore decrease voriconazole serum concentrations.^[8] At the time, there was no automatic warning for this interaction in the Dutch national

Table 1. Therapeutic drug measurements during hospital admission

Drug and day of treatment	Concentration (mg/l)	Target concentration (mg/l)
Voriconazole day 3	6.4	1.5-6
Voriconazole day 8	<0.2	1.5-6
Voriconazole day 10	<0.2	1.5-6
Voriconazole day 13	<0.2	1.5-6
Valproate day 15	8	40-100
Phenytoin day 7	<1.5	8-20
Phenytoin day 10	<1.5	8-20
Clobazam day 9	0.101 (clobazam) 0.263 (desmethylclobazam)	0.03-0.4 0.3-3.0

medication monitoring system, this was added a few months after this case took place. The interaction was recognised later during admission because of a low serum voriconazole concentration on day 10, when phenytoin and voriconazole had been co-administered for three days. However, as induction of CYP enzymes takes several days to weeks to reach its full effect and serum levels were already low on day 8, this is probably not the only explanation. Finally, voriconazole pharmacokinetics may be influenced by a patient's genetic makeup. Because of consistently low serum concentrations of several drugs (table 1), the patient's DNA was analysed for polymorphisms in genes coding for CYP enzymes. A CYP2C19 *1/*17 genotype was found. It is uncertain how voriconazole treatment is influenced by this polymorphism. However, case reports and small studies showed increased clearance and lower serum concentrations,^[9,10] which can be overcome by TDM-based dose escalation of voriconazole.

In conclusion, this case illustrates the importance of TDM in patients treated with voriconazole. There is a high degree of variation in patients' serum voriconazole concentrations. Since clinical effect is closely related to serum concentrations, TDM should be performed for every patient treated with voriconazole. In case of divergent voriconazole serum levels drug interactions, timing of blood samples and genetic polymorphisms should be taken into account.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

Informed consent

Informed consent was obtained from the patient presented in this case report.

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