International Journal of Antimicrobial Agents 45 (2015) 192–195

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Short Communication

Pharmacokinetics of fluconazole in critically ill patients with acute kidney injury receiving sustained low-efficiency diafiltration

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ARTICLE INFO

Article history:
Received 12 June 2014
Accepted 29 August 2014

Keywords:
Pharmacokinetics
Fluconazole
Renal replacement therapy
Sustained low-efficiency diafiltration
Extended daily diafiltration
Critically ill patients

ABSTRACT

Fluconazole is a widely used antifungal agent in critically ill patients. It is predominantly (60–80%) excreted unchanged in urine. Sustained low-efficiency diafiltration (SLED-*f*) is increasingly being utilised in critically ill patients because of its practical advantages over continuous renal replacement therapy. To date, the effect of SLED-*f* on fluconazole pharmacokinetics and dosing has not been studied. The objective of this study was to describe the pharmacokinetics of fluconazole in critically ill patients with acute kidney injury receiving SLED-*f* and to compare this with other forms of renal replacement therapy. Serial blood samples were collected at pre- and post-filter ports within the SLED-*f* circuit during SLED-*f* and from an arterial catheter before and after SLED-*f* from three patients during one session. Fluconazole concentrations were measured using a validated chromatography method. Median clearance (CL) and 24-h area under the concentration–time curve (AUC_{0-24}) were 2.1 L/h and 152 mg·h/L, respectively, whilst receiving SLED-*f*. Moreover, 72% of fluconazole was cleared by a single SLED-*f* session (6 h) compared with previous reports of 33–38% clearance by a 4-h intermittent haemodialysis session. CL and AUC_{0-24} were comparable with previous observations in a pre-dilution mode of continuous venovenous haemodiafiltration. The observed rebound concentration of fluconazole post SLED-*f* was <2%. Although a definitive dosing recommendation is not possible due to the small patient number, it is clear that doses >200 mg daily are likely to be required to achieve the PK/PD target for common pathogens because of significant fluconazole clearance by SLED-*f*.

1. Introduction

Fluconazole is a widely used triazole antifungal agent for prophylaxis, pre-emptive and empirical therapy, and treatment of known or suspected *Candida* spp. infections in intensive care units (ICUs). Acute kidney injury (AKI) is a common complication in ICU patients, with an incidence as high as 42% in patients with severe sepsis or septic shock, depending on the definition used [1]. Renal replacement therapy (RRT) is the commonly employed treatment for AKI. Although continuous renal replacement therapy (CRRT) is commonly used in the ICU, hybrid techniques including sustained low-efficiency dialysis/diafiltration (SLED/SLED-*f*), also known as slow low-efficiency dialysis or extended daily dialysis/diafiltration (EDD/EDD-*f*), are being increasingly utilised in ICUs as a more convenient alternative to CRRT [2].

Although no single RRT modality has been shown to be superior to others with respect to clinical outcomes, SLED-*f* is being increasingly used because of its practical advantages and cost savings over CRRT [2]. However, these advantages present a new set of challenges for drug dosing. Drug dosing in SLED-*f* may be more difficult and challenging compared with CRRT and intermittent

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http://dx.doi.org/10.1016/j.ijantimicag.2014.08.013
0924-8579/

haemodialysis (IHD) owing to variations in clearance during and after SLED-*f* because of its intermittent nature and the dynamic physiological changes in critically ill patients compared with chronic renal failure patients, respectively. This is further compounded by the paucity of pharmacokinetic studies available to rationalise antifungal dosing in patients receiving SLED-*f* [2]. Moreover, membrane types, flow rates and the duration of SLED-*f* treatment used in different studies have not been sufficiently uniform to inform clinicians as to how they may adapt dosing for their setting. In addition, given the common use of high-flux filters during SLED-*f*, drug dosing recommendations based on older practices and equipment may result in suboptimal dosing. Owing to an increasing incidence of *Candida* spp. infections, use of fluconazole, use of SLED-*f* in ICUs and lack of fluconazole dose sufficiency studies in SLED-*f*, the objective of this study was to describe the pharmacokinetics of fluconazole during SLED-*f* and to compare the results with those reported in other forms of RRT.

2. Materials and methods

This was a prospective, open-label, pharmacokinetic study conducted at the ICU of The Queen Elizabeth Hospital (Adelaide, Australia). Critically ill patients who met the following criteria were eligible for inclusion: (i) age ≥18 years; (ii) present in the ICU and undergoing/planned to undergo SLED-*f*; (iii) arterial line in situ or planned insertion; (iv) indwelling urinary catheter in situ or planned insertion; and (v) informed consent from the patient or the substitute decision-maker. Patients who met one or more of the following criteria were excluded: (i) known or suspected allergy to triazole antifungal agents; and (ii) pregnancy.

2.1. Fluconazole administration and sample collection

Fluconazole (200 mg) was administered as an intravenous infusion over 60 min at 4–6 h prior to initiation of SLED-*f*. One patient received 200 mg twice daily, whereas the other two patients received 200 mg daily. Blood samples were collected at pre- and post-filter ports within the SLED-*f* circuit during SLED-*f* and from the arterial catheter before and after the SLED-*f* treatment period. The aim was to collect blood samples before initiation of the infusion and at 60, 120, 240 and 300 or 360 min following commencement of the infusion; during SLED-*f*, at 60, 120, 180, 240, 300 and 360 min (SLED-*f* completion); post SLED-*f* at 30, 60, 120 min and prior to next dose where possible. Ultrafiltration samples were not able to be collected due to use of an online water inlet and outlet system common to SLED-*f* circuitry.

2.2. Sustained low-efficiency diafiltration prescription

SLED-*f* was performed in all patients using a 4008S haemodialysis machine (Fresenius Medical Care, Bad Homburg, Germany) with an AV600S Ultraflux® Polysulfone® filter (1.4 m^2 surface area; Fresenius Medical Care). A standardised prescription consisted of haemodiafiltration with target duration of 6–8 h (with 12 L/h of blood and dialysate flow and 3.96 L/h of pre-dilution). The biochemical composition of the dialysate and bicarbonate-based replacement fluid was set according to the patient's biochemistry. Data on the precise times for SLED-*f* commencement and cessation, due to blood clotting on the filter or the end of treatment, were recorded. Vascular access in all patients was achieved via a double-lumen catheter inserted in either the internal jugular or the femoral vein.

2.3. Assay

Plasma concentrations of fluconazole were analysed with a high-performance liquid chromatography (HPLC) system (Shimadzu Corp., Kyoto, Japan) with electrospray mass spectrometer detector (LC/MS–MS) (API 2000™; Applied Biosystems, Foster City, CA). Briefly, the method was as follows: 300 μL of plasma was mixed with 50 μL of internal standard (voriconazole 1 μg/mL) and was precipitated with 150 μL of 10% trichloroacetic acid. The samples were centrifuged at 12 000 × *g* for 6 min at 4 °C after thoroughly vortexing for 30 s. Analytes were separated through an Agilent ZORBAX Eclipse XDB-c18 (2.1 mm × 150 mm, 3.5 μm particle size) (Agilent Technologies Inc., Santa Clara, CA) by gradient elution using mobile phase A (water containing 0.1% formic acid) and mobile phase B (methanol containing 0.1% formic acid) with a total flow rate of 0.3 mL/min and were detected by an electrospray positive-ionisation mode of tandem mass spectrometry. Mass-to-charge ratios (m/z) in multiple-reaction monitoring were 307.3/127 for fluconazole and 349.9/224 for the internal standard.

The calibration curve was linear over the concentration range 0.1–20 mg/L. The intraday and interday coefficients of variation were validated to be within 10% at low, medium and high concentrations of the calibration range. Assays were validated and conducted using criteria from the US Food and Drug Administration (FDA) guidance on bioanalysis [3].

2.4. Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis for the data was performed. The maximum concentration in plasma (C_{max}) and the time to reach C_{max} after drug administration were obtained directly by visual examination of concentration–time data. The area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$) was calculated by the log-linear trapezoidal rule until the time of the last quantifiable plasma concentration and then extrapolated to infinity using the quotient of the last measurable concentration to the terminal phase rate constant (β). The terminal elimination rate constant (β) was estimated from the slope of the terminal exponential phase of the logarithmic plasma concentration–time profile. The elimination half-life ($t_{1/2\beta}$) was determined as $0.693/\beta$. Clearance (CL) was determined as dose/$AUC_{0-\infty}$.

The dialyser clearance (CL_{dial}) was estimated from concentrations before (C_{in}) and directly after (C_{out}) the SLED-*f* filter as $CL_{dial} = (Q_{in} \cdot C_{in} - Q_{out} \cdot C_{out})/C_{in}$, where the plasma flow in (Q_{in}) and out (Q_{out}) of the dialyser were estimated using the blood flow, haematocrit and ultrafiltration rate. The rebound concentration ($C_{rebound}$) was estimated from concentrations immediately after SLED-*f* completion (SLED-*f* C_{min}) and maximum measured concentration after SLED-*f* (SLED-*f* C_{max}) as $C_{rebound}$ = (SLED-*f* C_{min} − SLED-*f* C_{max})/SLED-*f* C_{max}. The fraction of drug removed by the dialyser was estimated using AUC as $(AUC_{without\ SLED\text{-}f} - AUC_{with\ SLED\text{-}f})/AUC_{without\ SLED\text{-}f}$.

3. Results

Three AKI patients with anuria (urine output <100 mL) were recruited. Two patients had received fluconazole for 10 days and the other for 5 days prior to enrolment into the study. All three patients received SLED-*f* for 6 h with fluid removal of 0.40 ± 0.08 L/h. Total effluent flow achieved in this study was 16.36 ± 0.08 L/h. Blood samples were collected post completion of SLED-*f* for only two patients because a 12-hourly dosing regimen was chosen by the treating team in the third patient, making it impossible to further describe elimination-phase concentrations.