Critical Care and Resuscitation 25 (2023) 1–5

Contents lists available at ScienceDirect

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj

Special Article

A protocol for an international, multicentre pharmacokinetic study for Screening Antifungal Exposure in Intensive Care Units: The SAFE-ICU study

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Keywords:
Antifungal agents
Dosing
Critically ill
Intensive care unit
Pharmacokinetics

A B S T R A C T

Objective: To describe whether contemporary dosing of antifungal drugs achieves therapeutic exposures in critically ill patients that are associated with optimal outcomes. Adequate antifungal therapy is a key determinant of survival of critically ill patients with fungal infections. Critical illness can alter an antifungal agents' pharmacokinetics, increasing the risk of inappropriate antifungal exposure that may lead to treatment failure and/or toxicity.

Design, setting and participants: This international, multicentre, observational pharmacokinetic study will comprise adult critically ill patients prescribed antifungal agents including fluconazole, voriconazole, posaconazole, isavuconazole, caspofungin, micafungin, anidulafungin, and amphotericin B for the treatment or prophylaxis of invasive fungal disease. A minimum of 12 patients are targeted for enrolment for each antifungal agent, across 12 countries and 30 intensive care units to perform descriptive pharmacokinetics. Pharmacokinetic sampling will occur during two dosing intervals (occasions): firstly, between days 1 and 3, and secondly, between days 4 and 7 of the antifungal course, collecting three samples per occasion. Patients' demographic and clinical data will be collected.

Main outcome measures: The primary endpoint of the study is attainment of pharmacokinetic/pharmacodynamic target exposures that are associated with optimal efficacy. Thirty-day mortality will also be measured.

Results and conclusions: This study will describe whether contemporary antifungal drug dosing achieves drug exposures associated with optimal outcomes. Data will also be used for the development of

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https://doi.org/10.1016/j.ccrj.2023.04.002

antifungal dosing algorithms for critically ill patients. Optimised drug dosing should be considered a priority for improving clinical outcomes for critically ill patients with fungal infections.

1. Introduction

To date, a substantial level of evidence has described altered dosing requirements of some antimicrobial agents in critically ill patients admitted to intensive care units (ICUs). Studies have clearly demonstrated that the altered pharmacokinetics (PK), common to different classes of antimicrobials, can frequently result in inappropriate drug exposures, particularly when conventional dosing regimens are used.[1–4] A multinational point-prevalence PK study, the Defining Antibiotic Levels in Intensive Care Unit Patients (DALI) study from the Working Group for Antimicrobial Use in the Infection Section of the European Society of Intensive Care Medicine (ESICM), has shown that inadequate antibiotic exposure in the ICU may be global and may have adverse consequences on patients' outcomes.[5] A recent multisociety Position Statement has further highlighted the available data.[6]

In addition to antibacterial drugs, the DALI Study also collected antifungal data in a small sample of patients receiving fluconazole (n = 15), anidulafungin (n = 9), and caspofungin (n = 7). The study indicated potential clinical risks from suboptimal dosing, with a high proportion of patients having inappropriate antifungal exposures (concentrations). For example, only 67% of patients receiving fluconazole had a therapeutic drug exposure.[7] Thus, the DALI study, like other recent antifungal PK studies,[8–10] supports a larger-scale investigation of the extent of suboptimal antifungal exposures and therefore inappropriate antifungal dosing in critically ill patients.

The overall objective of the Screening Antifungal Exposure in Intensive Care Units (SAFE-ICU) study is to describe whether contemporary dosing of antifungal drugs achieves therapeutic exposures (concentrations) in critically ill patients that are associated with optimal outcomes.

Specific objectives of the SAFE-ICU are:

1. To describe the interindividual variability of antifungal drug exposure in plasma and intra-abdominal fluid (when possible), including amongst patients from different institutions and geographic regions.
2. To describe the relationship between the observed antifungal drug exposure and different clinical covariates including the Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, admission diagnosis, hepatic and renal function, and the indication for antifungal prescription.
3. To identify whether achievement of prespecified exposures in plasma and/or intra-abdominal fluid is associated with improved clinical outcomes for different drugs/indications.
4. To use available PK data to develop population PK models for dosing simulations to identify optimised antifungal dosing in critically ill patients where necessary.

This article describes the SAFE-ICU study protocol.

2. Study design

The SAFE-ICU study is an open-label, prospective, international, observational pharmacokinetic study in adult medical/surgical ICUs. A minimum of 12 patients are targeted to ensure representation of the study population, across 12 countries and 30 ICUs. The study will progress simultaneously in all participating centres.

2.1. Participants

The study will comprise adult (≥18 years) critically ill patients from participating centres requiring ICU care, including both surgical and medical ICU patients. Patients who are prescribed any of the study systemic antifungal agents will be included, regardless of whether prescribed for treatment, pre-emptive treatment, or prophylaxis. Inclusion and exclusion criteria are described in Table 1.

2.2. Study outcomes

The primary endpoint for outcome assessment will be the attainment of antifungal exposures associated with optimal efficacy. These target exposures are described in Table 2 and where available are based on PK/PD data from clinical studies, are used as therapeutic drug monitoring targets,[6] or alternatively are from animal or *in vitro* studies upon which product information dosing is based. Patients will also be followed for up to 30 days after enrolment into the study to evaluate 30-day mortality.

2.3. Ethics approval

The study will be conducted in accordance with the ethical principles of human research outlined by the Declaration of Helsinki and the Good Clinical Practice guidelines and in line with the local regulatory statements for ethical conduct of research at each study site.

Table 1
Inclusion/exclusion criteria for the SAFE-ICU study.

Inclusion criteria
• Age ≥18 years
• Critically ill patients requiring ICU care
• Receiving enteral or intravenous therapy of the below-listed antifungals ✓ Fluconazole ✓ Voriconazole ✓ Posaconazole ✓ Isavuconazole ✓ Caspofungin ✓ Anidulafungin ✓ Micafungin ✓ Amphotericin B including prophylaxis indication and? antifungal therapy started in another unit (ward, operating room) for the same infectious episode
• Availability of suitable intravenous/intra-arterial access to facilitate sample collection
• Written informed consent has been obtained
Exclusion criteria
• Age < 18 years.
• Pregnancy
• Diagnosis with tuberculosis, human immunodeficiency virus, or hepatitis B or C
• Consent not obtained

ICU, intensive care unit; SAFE-ICU, Screening Antifungal Exposure in Intensive Care Units.

Table 2
Antifungal target exposures.

Antifungal agent	Clinical PK/PD target for efficacy
Fluconazole	AUC_{0-24}/MIC ≥55–100[6]
Voriconazole	Cmin ≥ 1–2 mg/L[6]
Posaconazole	Cmin >0.5 mg/L (prophylaxis)[6] Cmin >1 mg/L (treatment)[6]
Isavuconazole	Cmin between 2 and 4 mg/L[20,21]
Echinocandins (caspofungin, anidulafungin, micafungin)	AUC_{0-24}/MIC >3000[a], [6]
Amphotericin B	Cmax/MIC ≥ 4.5[22]

AUC_{0-24}, area under the plasma concentration–time curve from 0 to 24 h; MIC, minimum inhibitory concentration; Cmin, minimum observed plasma concentration; Cmax, maximum observed plasma concentration.
[a] In patients receiving micafungin for invasive candidiasis/candidemia.

The study protocol has been approved at national coordinating sites for the SAFE-ICU study in Australia (Royal Brisbane and Women's Hospital Human Research Ethics Committee – HREC/16/QRBW/292), Belgium (Medical Ethics Committee at Ghent University Hospital – B670201629117), United States of America (Ochsner Clinic Foundation Institutional Review Board – 2016.272.C), Portugal (Centro Hospitalar e Universitário de Coimbra – CHUC-062-16), France (Comité de Protection des Personnes Sud-Ouest et Outre-mer III – AM/CM/17.0355), Italy (Comitato Etico dell'Universita' "Sapienza" – Rif. 4571), and Malaysia (Kementerian Kesihatan Malaysia Medical Research & Ethics Committee – NMRR-16-2197-33201).

2.4. Safety considerations

As this study is observational without any treatment intervention, risks for participating patients will be limited and, if any, will be associated with blood samples or abdominal fluid sample collection. Any adverse events observed in participating patients will be assessed for any relationship to procedures of the study and will be recorded and reported to the local ethics committee, as well as the study coordination centre at the University of Queensland as soon as possible and within 72 h.

2.5. Blood samples collection

Blood samples will be collected from consenting patients on two occasions: firstly, during a dosing interval between the first and third day, and secondly, during a dosing interval between the fourth and seventh day of antifungal course in the ICU. On each sampling occasion, three blood samples (3 mL each) will be taken from established intravenous or intra-arterial access. The first sample (sample A) will be collected at 30 min post completion of intravenous infusion or after administration of the enteral dose of the drug; the second sample (sample B) between 3 and 6 h after the start of drug infusion or administration of enteral dose, and the last sample (sample C) within 30 min preceding the next scheduled dose. Exact time of each sample collection will be recorded in the case report form.

Immediately after collection, blood samples will be placed on ice and centrifuged within 6 h of collection to separate the plasma, which will be transferred to a labelled vial for frozen storage (at −20 °C for short-term storage or −80 °C for longer storage)[11–13] until distribution to the bioanalytical laboratory.

2.6. Abdominal fluid samples collection

When applicable, three abdominal fluid samples will be collected from indwelling drains on each sampling occasion. New drain bags will be attached to the indwelling catheter before each sampling time point. For the first and second samples (samples A and B), a new bag will be attached immediately after taking blood samples A and B, respectively; for the third sample (sample C), a new bag will be attached 2.5 h before the next dose administration. Sampling times will be scheduled 2 h after the new bags are attached, and the volume of abdominal fluid accumulated in the 2-h sample collection will be recorded. Samples will be collected into a labelled vial and will be placed on ice immediately after collection before being transferred for frozen storage (at −20 °C for short-term storage or −80 °C for longer storage)[11–13] until distribution to the bioanalytical laboratory.

2.7. Clinical data collection

The data collection process will be harmonised across study centres to ensure the quality of the data collected. A structured data collection sheet or case report form will be used for collecting patients' demographic and clinical data (Table 3) from their medical records. An electronic data collection tool using Research Electronic Data Capture (REDCap) (Vanderbilt University, Nashville, Tennessee, USA) will be developed, piloted, and validated to gather and store the collected data.

Table 3
Data collected in the case report form.

- Demographics
  - ✓ Date of birth
  - ✓ Sex
  - ✓ Height
  - ✓ Weight
- Admission details
  - ✓ Date of hospital admission
  - ✓ ICU admission diagnosis
  - ✓ Date and time of ICU admission
  - ✓ APACHE II score
  - ✓ SAPS II score
- Organ support
  - ✓ Invasive mechanical ventilation on days of sampling
  - ✓ Renal replacement therapy on days of sampling
- Microbiology
  - ✓ Site of infection
  - ✓ Yeast identified
- Type of antifungal therapy (empirical, pre-emptive, directed, prophylaxis)
- Antibiotics used to treat the current infectious episode that overlaps with the antifungal sampling periods.
- Clinical response (resolution, improvement, failure)
- Biological data
  - ✓ Albumin
  - ✓ Serum creatinine
  - ✓ AST/ALT
  - ✓ SOFA score
- Discharge
  - ✓ Date and time of ICU discharge
  - ✓ ICU discharge status
  - ✓ Date of death
  - ✓ Date and time of hospital discharge
  - ✓ Hospital discharge status
  - ✓ Vital status at 30 days
- Renal function data
  - ✓ Serum creatinine
- Pharmacokinetics data
  - ✓ Date the study antifungal commenced
  - ✓ Date of occasion
  - ✓ Dose number
  - ✓ Dosing frequency
  - ✓ Route of administration
  - ✓ Infusion duration
  - ✓ Time of dosing and sampling time points

APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SOFA, Sequential Organ Failure Assessment.

2.8. Drug assay

Each participating site will ship the samples frozen on dry ice to The University of Queensland, where they will be stored at −80 °C until analysis. Plasma and intra-abdominal fluid drug concentrations will be determined using chromatographic methods at the University of Queensland Centre for Clinical Research, The University of Queensland. These methods will be developed and validated in accordance with Food and Drug Administration's guidance for bioanalytical method validation.[14]

2.9. Statistical analysis

Descriptive statistics on demographic, clinical, and PK-/PD-related data will be performed using the statistical package SPSS version 28.0.1.0 (IBM Corp., Armonk, NY, USA) and presented as the number (%), mean ± standard deviation, or median (interquartile range), as appropriate. The achievement of the PK/PD targets will be performed by visual inspection of the results and comparison with the specified target exposures.

2.10. Statistical considerations

A targeted minimum of 12 patients for each drug is based on data from previous non-interventional pharmacokinetic studies in critically ill patients.[15–19] A higher number of patients will increase certainty about the currently unknown exposure variability between different ICUs and countries.

The data generated in the study will be summarised using descriptive statistics and subject to descriptive pharmacokinetic analysis. For this purpose, a noncompartmental analysis will be performed to describe the overall drug exposure using Phoenix® WinNonlin® software (Certara, St Louis, MO, USA). The noncompartmental PK results will underpin the primary outcome analyses.

For drugs where >10% of patients are identified to have non-therapeutic antifungal exposures, a nonlinear mixed-effects modelling approach, using NONMEM® (ICON plc, Dublin, Ireland), will be utilised for population PK analysis and dosing simulations. Development of population PK models will be performed using the first-order conditional estimation with interaction (FOCE-I) method to first determine the structural base model by fitting the concentration–time data to one, two, and three compartment models, using the Akaike information criterion; then testing of additive, proportional, or a combination of additive and proportional model to select the best fit statistical error model; followed by the selection and preliminary evaluation of potential covariates testing linear, power, and exponential function relationships as per standard covariate evaluation algorithms through forward addition ($p < 0.05$) and backward elimination ($p < 0.01$) in a stepwise fashion; and finally, model evaluation through statistical comparison of log likelihood and examination of diagnostic plots including goodness-of-fit plots and visual predictive check. After population PK analysis, Monte Carlo simulations will be performed using reported minimum inhibitory concentrations of the presumed or confirmed etiologic organisms, or specific minimum inhibitory concentrations if determined, to propose/confirm optimised drug doses for ICU patients.

3. Conclusion

The SAFE-ICU study will describe contemporary antifungal dosing regimens in a large cohort of ICU patients across the world and provide evidence on whether such dosing achieves therapeutic drug exposures. This study will lead to the development of evidence-based antifungal dosing guidelines that can be used to optimise clinical outcomes for critically ill patients receiving antifungal agents.

Funding

Funding for this study has been provided by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Royal Brisbane and Women's Hospital Research Foundation. Gilead Fellowship to Dr FB Sime.

Participating sites will not receive a per-patient payment. The University of Queensland (coordinating centre) will fund sample transport from the participating site and will also fund assaying of the samples.

CRediT authorship contribution statement

Jason A. Roberts: Conceptualization, Methodology, Writing - Original Draft, Supervision, Funding acquisition, Resources. Fekade Sime: Methodology, Investigation, Writing - Original Draft, Visualization Jeffrey Lipman: Conceptualization, Writing - Review & Editing María Patricia Hernández-Mitre: Writing - Review & Editing João Pedro Baptista: Project administration, Writing - Review & Editing Roger J. Brüggemann: Project administration, Writing - Review & Editing Jai Darvall: Project administration, Writing - Review & Editing Jan J. De Waele: Project administration, Writing - Review & Editing George Dimopoulos: Project administration, Writing - Review & Editing Jean-Yves Lefrant: Project administration, Writing - Review & Editing Mohd Basri Mat Nor: Project administration, Writing - Review & Editing Jordi Rello: Project administration, Writing - Review & Editing Leonardo Seoane: Project administration, Writing - Review & Editing Monica A. Slavin: Project administration, Writing - Review & Editing Miia Valkonen: Project administration, Writing - Review & Editing Mario Venditti: Project administration, Writing - Review & Editing Wai Tat Wong: Project administration, Writing - Review & Editing Markus Zeitlinger: Project administration, Writing - Review & Editing Claire Roger: Conceptualization, Methodology, Writing - Original Draft, Supervision

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgements

J.A. Roberts would like to acknowledge funding from the Australian National Health and Medical Research Council for a Centre of Research Excellence (APP2007007) and an Investigator Grant (APP2009736) as well as an Advancing Queensland Clinical Fellowship.

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