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A pharmacokinetic analysis of posaconazole oral suspension in the serum and alveolar compartment of lung transplant recipients☆

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ABSTRACT

Invasive fungal infections cause significant morbidity and mortality after lung transplantation. Fungal prophylaxis following lung transplantation is not standardised, with transplant centres utilising a variety of regimens. Posaconazole is a broad-spectrum antifungal triazole that requires further investigation within the setting of lung transplantation. This prospective, single-centre, observational study explored the pharmacokinetics of posaconazole oral suspension (POS) in the early perioperative period following lung transplantation in 26 patients. Organ recipients were scheduled to receive 400 mg POS twice daily for 6 weeks as primary antifungal prophylaxis. Therapeutic drug monitoring (TDM) of serum posaconazole levels was performed in accordance with local clinical protocols. Bronchoalveolar lavage fluid (BALF) was sampled during routine bronchoscopies. Posaconazole levels were measured both in serum and BALF using mass spectrometry. Posaconazole levels were highly variable within lung transplant recipients during the perioperative period and did not achieve 'steady-state'. Serum posaconazole concentrations positively correlated with levels within the BALF ($r = 0.5527$; $P = 0.0105$). Of the 26 patients, 10 failed to complete the study for multiple reasons and so the trial was terminated early. Unlike study findings in stable recipients, serum posaconazole levels rarely achieved steady-state in the perioperative period; however, they do reflect the concentrations within the airways of newly transplanted lungs. The role of POS as primary prophylaxis in the perioperative period is uncertain, but if used TDM may be helpful for determining attainment of therapeutic levels.

1. Introduction

Invasive fungal infections (IFIs) cause significant morbidity and mortality following lung transplantation [1]. Invasive aspergillosis complicates 3–15% of lung transplants, with a mortality rate between 52% and 55% [2]. The optimal approach for fungal prophylaxis following lung transplantation has not been universally agreed. Antifungal agents used include echinocandins (such as caspofungin), polyenes (amphotericin B) and triazoles (itraconazole, voriconazole and posaconazole). Itraconazole therapy is complicated by variable gastrointestinal absorption, toxicity and emerging resistance; voriconazole is often limited by side effects such as hepatic toxicity, photosensitivity and long-term concerns regarding increased risk of skin cancers; caspofungin therapy must be administered intravenously making long-term use impractical; and amphotericin-associated nephrotoxicity can be particularly problematic for patients who concurrently receive calcineurin inhibitors. Posaconazole is a triazole antifungal agent with broad-spectrum activity. Currently posaconazole is most commonly used as second-line therapy in lung transplant recipients who are intolerant to voriconazole [3]. Few data are available on the efficacy and safety of posaconazole oral suspension (POS) in this population and this may account for posaconazole currently being used predominantly as a second-line agent. POS may be better tolerated with a lower incidence of resistance, but more data are required on safety and efficacy within this patient population.

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There are no published data on the time required to achieve steady-state serum concentrations of POS immediately following lung transplantation. There are two published studies examining POS in lung transplant patients. One showed that cardiothoracic transplant patients ($n = 17$) with trough blood posaconazole levels consistently >0.5 μg/mL were more likely to have a successful outcome [4]. Another study looked at short-term dosing (400 mg twice daily for a week) and demonstrated sustained blood and alveolar compartment concentrations during the 24-h period after the last dose in 12 lung transplant recipients [5]. Critical illness is known to disrupt the pharmacokinetics of many drugs, and these studies in stable lung transplant recipients may not translate into patients in the intensive care unit (ICU) immediately after transplantation [6]. The pharmacokinetics of prophylactic regimens require further specific study in the early post-transplant recovery phase.

No data exist on the relationship between serum and alveolar posaconazole levels over an extended treatment period. Data on the differences between patients transplanted for cystic fibrosis (CF) versus those transplanted for diseases other than CF are lacking. This is a clinically important question due to concern regarding drug absorption differences between CF and non-CF populations post-transplant and thus merits study.

The aim of this study was to answer two questions: (i) how long is required to achieve steady-state posaconazole concentrations in the serum of lung transplant recipients? and (ii) is there an association between bronchoalveolar lavage (BAL) posaconazole levels and concurrent serum posaconazole levels?

2. Methods

2.1. Trial protocol

This study was registered at ClinicalTrials.gov (http://www.clinicaltrials.gov) and was approved both by the Bristol Research Ethics Committee (UK). All patients provided written confirmation of their informed consent prior to undergoing lung transplantation (Fig. 1). Inclusion criteria for study enrolment were: scheduled to undergo lung transplantation at Harefield Hospital (Harefield, UK); able to take oral/nasogastric medication; and ≥18 years old. Exclusion criteria were: treatment with posaconazole within 14 days before transplant; and history of reactions to posaconazole or its related compounds.

Twenty CF and twenty non-CF recipients were to be studied, and patients were scheduled to receive the first dose of POS within 12 h of leaving the operating theatre. The default dose of POS for all patients was 400 mg if taken twice daily, co-prescribed with a high-fat supplement (Calogen® 30 mL twice daily) to increase drug absorption. In keeping with our standard practice, the dose was changed to 200 mg four times a day (each dose taken with 15 mL of Calogen®) in patients with serum posaconazole concentrations below prophylactic concentrations (repeated levels <0.5 μg/mL) as this has been shown to increase drug absorption [7]. Routine practice at this centre is to prescribe nebulised amphotericin B (Fungizone®) as prophylaxis until hospital discharge and this was also continued for all study patients, in addition to the trial stock of posaconazole.

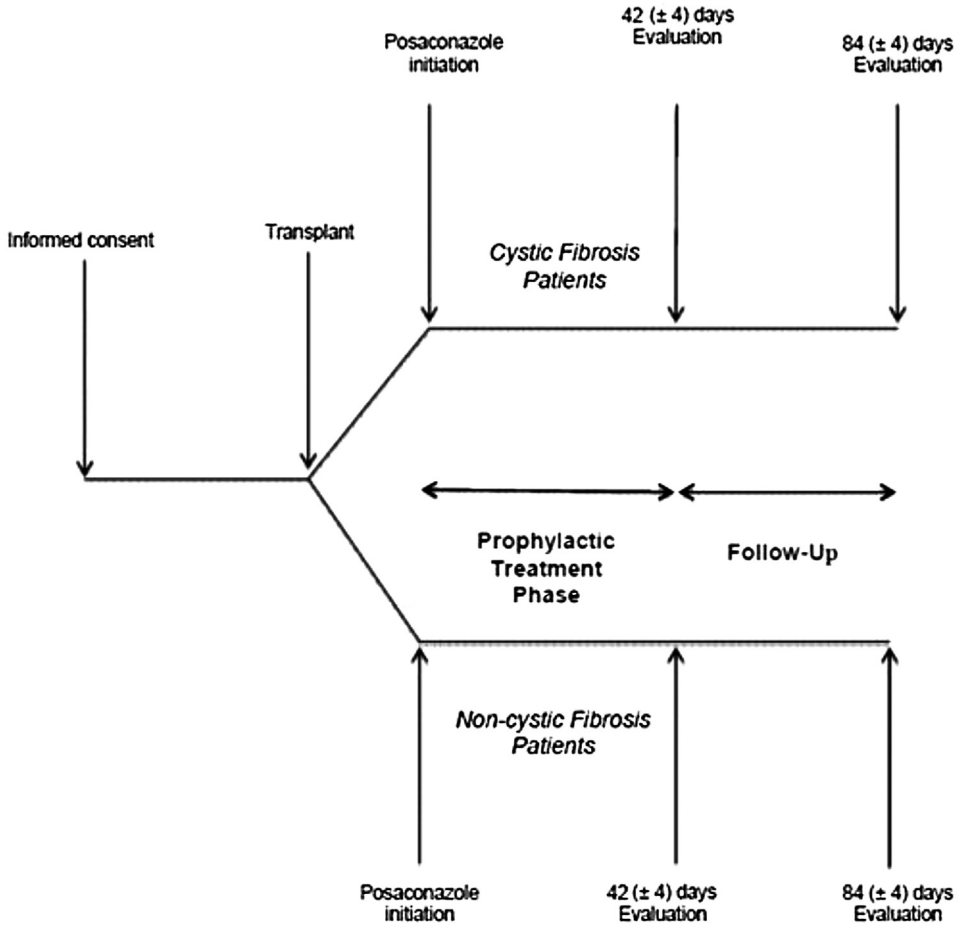

Fig. 1. Study design.