Intrapulmonary Penetration of Voriconazole in Patients Receiving an Oral Prophylactic Regimen

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Voriconazole penetrated well into the pulmonary epithelial lining fluid (ELF) in lung transplant patients receiving oral prophylaxis. The ELF concentrations exceeded those of the plasma, with an average ELF-to-plasma ratio of 11 (±8). A strong association between plasma and ELF concentrations (r² = 0.95) was noted.

Adequate drug penetration to the infection site is crucial for antimicrobial therapeutic optimization. The lungs are the most common site of primary infection in cases of invasive aspergillosis (9, 14). Voriconazole has become a preferred agent for the treatment of invasive aspergillosis (3). Despite its widespread use in the management of pulmonary aspergillosis, the intrapulmonary penetration of voriconazole has not been reported in humans. Voriconazole is used routinely as antifungal prophylaxis in some lung transplant centers; this offers an opportunity to study the intrapulmonary penetration of the drug, since lung transplant recipients routinely undergo surveillance bronchoscopy (5, 7).

This was a prospective observational pilot study. The subjects were lung transplant patients, ≥18 years of age, who had received at least six oral doses of voriconazole prior to a scheduled bronchoscopy. The Institutional Review Board approved the study, and all patients provided written informed consent prior to participation.

Voriconazole treatment (6 mg/kg of body weight intravenously every 12 h for 2 doses followed by 200 mg orally twice daily) was initiated immediately after transplant and continued for approximately 4 months as standard clinical care. Bronchoalveolar lavage (BAL) was performed at 2, 4, and 8 weeks posttransplant in all patients during the voriconazole prophylaxis period. A blood sample and an aliquot of pooled BAL supernatant were acquired for study purposes during one of these procedures.

Total (free and protein-bound) voriconazole concentrations were measured in the plasma and BAL supernatant by a modified high-performance liquid chromatography-electrospray ionization mass spectrometry technique (13, 18). Authentic voriconazole (UK-109,496) and an internal standard (UK-103,446) were provided by Pfizer Global Research and Development (Sandwich, United Kingdom). The standard curves were linear (r² = 0.99) over a concentration range of 0.05 to 6.0 µg/ml for the plasma and 0.001 to 0.5 µg/ml for the BAL. Interday coefficients of variation were <12.6%.

The concentrations of urea in the serum and BAL supernatant were measured, separately, by a colorimetric method (serum, Vitros 950 [Ortho Clinical Diagnostics, Rochester, NY]; BAL, Urea Nitrogen Reagent [Teco Diagnostics, Anaheim, CA], respectively). The volume of epithelial lining fluid (ELF) recovered in the BAL aspirate and the concentration of voriconazole in the ELF were calculated based on the urea dilution method as previously reported (1, 2, 12). A two-tailed Spearman’s rank correlation test was applied to test for a relationship between plasma and ELF concentrations.

Twelve patients were enrolled in the study, with BAL and blood samples successfully collected from 11 patients (Table 1). All study patients were receiving multiple concomitant medications at the time of bronchoscopy, none of which has been documented to impact the plasma concentration of voriconazole (11).

The average volumes instilled and recovered during the BAL procedure were 116 ± 11 ml and 64 ± 14 ml, respectively. The average calculated ELF volume recovered was 1.4 ± 0.7 ml, or 2% of the total lavage fluid recovered. At the time of bronchoscopy, 2/12 patients had minimal acute rejection, and 1/12 patients had severe acute rejection.

The total voriconazole concentration in the ELF exceeded that in the plasma in all patients studied, with a mean ELF-to-plasma concentration ratio of 11 ± 8 (Table 2). A strong association between plasma and ELF concentrations (r² = 0.95; P < 0.0001) was observed. No differences in pulmonary penetration based on the type of lung transplantation or acute or chronic rejection status at the time of bronchoscopy were noted.

To our knowledge, this is the first report of the intrapulmonary penetration of voriconazole in humans. Although based on a limited sample size, our data reveal that voriconazole achieves substantial lung penetration. The physiological basis for the higher concentration of voriconazole in the ELF than that in the plasma is unknown and warrants further evaluation.

The highest voriconazole ELF concentrations were observed in patients sampled at 5 to 6 h postdose (Table 2). Since
voriconazole reportedly peaks in the plasma at 2 to 3 h following oral dosing, this may indicate a lag time in the attainment of peak pulmonary concentrations (11). A wide degree of variability in ELF and plasma voriconazole concentrations between patients was observed (Table 2). This was expected, based on the nature of this type of study, the limited sample size, and the use of different BAL sampling time points in relation to drug administration. Furthermore, a large degree of interpatient pharmacokinetic variability is known to be associated with voriconazole due to its nonlinear pharmacokinetics and genetic polymorphism of cytochrome P-450 enzymes that metabolize voriconazole (11, 15).

The ELF concentration of an antibacterial agent is considered to be a “best estimate” of the concentration at the site of extrapulmonary bacterial infection (4, 8). However, the site of intrapulmonary infection of Aspergillus spp. is not well defined, and the clinical relevance of antifungal ELF concentrations is unknown. In vitro studies demonstrate a propensity for the conidia of Aspergillus fumigatus to invade and germinate in human pneumocytes (6, 17). Thus, the sites of pulmonary aspergillosis likely include not only the ELF but also alveolar macrophages, pulmonary epithelial cells, and the interstitial fluid of lung tissue.

The voriconazole ELF concentration achieved with the prophylactic regimen exceeded both the MIC\textsubscript{50} (0.25 μg/ml) and the MIC\textsubscript{90} (1.0 μg/ml) previously reported for Aspergillus spp. (10, 16) at the time of bronchoscopy in all but two patients. The ELF concentration in subject 9 fell below the MIC\textsubscript{90} midway through the dosage interval. The clinical relevance of drug exposure in relation to the MIC of a fungal pathogen at the site of infection is unknown at this time. Further pharmacodynamic and clinical studies are required to identify clinically relevant antifungal concentrations at the site of infection.

The volume of ELF recovered in the BAL aspirate is calculated based on the premise that the urea concentration in the blood and ELF is in equilibrium. Although the ELF volume recovered in the current study (1.4 ± 0.7 ml) was consistent with that reported in healthy subjects (1.7 ± 0.2 ml), a larger proportion of BAL fluid was determined to be ELF (2% versus 1%, respectively) (12). It is unclear whether urea contamination of the BAL fluid from other sources contributed to an overestimation of ELF volume or whether our results depict differences in lung transplant patients compared to healthy subjects. Nonetheless, an overestimation of ELF volume would result in an underestimation of the ELF voriconazole concentration based on a dilutional effect (12). Finally, it must be noted that total voriconazole concentrations (free and protein bound) were measured in both the plasma and BAL supernatant. Free-drug concentrations in these compartments may be less than those reported here.

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REFERENCES


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Mean (SD) 66 (44) 11 (8)

a NA, not available; SD, standard deviation.
b A plasma sample was not obtained from one patient.
c This patient received 200 mg twice daily for 22 doses followed by 200 mg once daily for 5 doses.


