Fluconazole Pharmacokinetics in Burn Patients

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The pharmacokinetics of fluconazole in nine adult patients with severe (30 to 95% total body surface area) burns were studied. There was no significant difference in half-life ($t_{1/2}$), clearance (CL), or volume of distribution ($V$) over time in five patients on days 3 and 8 of the study ($P > 0.05$). Combined parameter estimates (means ± standard deviations) for all nine patients for the two study periods were as follows: $t_{1/2}$, 24.4 ± 5.8 h; CL, 0.36 ± 0.09 ml/min/kg; and $V$, 0.72 ± 0.12 liters/kg. These estimates of $t_{1/2}$ and CL in burn patients were approximately 13% shorter and 30% more rapid, respectively, than the most extreme estimates reported for other populations.

Fluconazole is a broad-spectrum triazole antifungal agent that has emerged as a suitable alternative to amphotericin B in the treatment of a wide variety of superficial and systemic fungal infections (16, 20). Prophylactic use of fluconazole has also been established in the management of various immunocompromised patient subsets (16). However, no study to date has documented the efficacy of fluconazole in preventing fungal sepsis in patients with severe thermal injury, despite the high morbidity and mortality associated with this complication (9, 12, 18, 19, 25, 26, 28). In addition, the potential for alterations in fluconazole’s pharmacokinetic disposition within this particular patient subset has not been investigated (2). The objective of the present study was to characterize the pharmacokinetic profile of fluconazole over time in patients with extensive thermal injury. It was conducted in conjunction with an ongoing prospective, randomized, double-blind, placebo-controlled clinical trial of fluconazole for the prevention of fungal sepsis in burn patients.

Patients over 18 years old who had been admitted to the Firefighters Regional Burn Center at the Regional Medical Center at Memphis, Tennessee, with thermal injuries covering at least 30% of their total body surface areas (TBSA) were eligible for enrollment in the study. Patients who had received immunotherapy or cytotoxic chemotherapy within 1 month preceding study entry, or anticipated the use of any of these therapies during the course of the study, were excluded, as were pregnant women. The protocol was approved by the Institutional Review Board at the University of Tennessee, Memphis, and written, informed consent was obtained from the patients or their legally authorized representatives. Patients began the protocol as soon as possible after informed consent was obtained.

Patients were randomly assigned to one of two groups by a random-number table. One group of patients received 400 mg of fluconazole intravenously every 24 h (infused over 2 h), while the other group received a placebo (0.9% sodium chloride) of equal volume. Patients were continued on fluconazole or the placebo until all wounds had healed or been grafted, until the patient was discharged from the hospital, until the adverse side effect was suspected, or until any cultures indicating an invasive fungal infection were returned from the laboratory. Fluid and electrolyte management, drug therapy, and monitoring of the study patients were in accordance with standard burn intensive care unit practices. Medical investigators, nursing staff, and patients were blinded as to their study group assignment. The pharmacy investigators responsible for the pharmacokinetic aspect of the study were not blinded to the randomization schedule and consequently did not participate in any part of the efficacy assessments during the study.

Blood samples were collected in nonanticoagulant (red-top) collection tubes before and at 1, 3, 6, 12, and 22 h following administration of the study drug on days 3 and 8 of treatment. The rationale for waiting until the third day of dosing was to avoid spurious estimates during the first 48 h following the study patients’ burns, when major fluid-restorative therapy was in progress. Blood samples were obtained from an indwelling arterial catheter whenever possible. Alternatively, samples were obtained from an indwelling venous catheter. Each sample was allowed to clot and was promptly centrifuged, and the serum was harvested, transferred to glass test tubes, and then stored at −70°C until assayed. In order to avoid compromising the blinded study design among the nursing staff and medical investigators, blood samples were obtained from the patients receiving the placebo as well as the patients receiving fluconazole. Two 24-h urine collections corresponding with the days of blood sampling were obtained for the determination of creatinine clearance (CL$_{\text{Cr}}$). The last available measured serum creatinine concentration before the end of the 24-h collection period was used in the calculation of CL$_{\text{Cr}}$.

A quantitative assay of the fluconazole concentrations in serum was performed by means of high-performance liquid chromatography according to the method of Flores-Murrieta et al. (10), with minor modifications. Chromatography was performed in the reverse-phase mode with a μBondapak C$_{18}$ column (3.9 by 300 mm; Waters Corporation, Milford, Mass.) with a mobile phase of acetonitrile and phosphate buffer (25:75, vol/vol). Fluconazole and the internal standard UK-930 were detected by ultraviolet absorbance at 260 nm.
were detected by a UV absorbance detector set at a wavelength of 210 nm. The precision and accuracy of the assay were measured at 2, 6, and 12 µg of the drug/ml, with a 50-ng/ml limit of detection. The within-day variation was 5.2% or less, with the relative error of the mean concentration being less than ±2.5% for the concentrations tested. The between-day variation was 3.8% or less, with the relative error of the mean concentration being less than ±2.5% for the tested concentrations.

One- and two-compartment models were fit to each patient’s fluconazole concentration-time data on study days 3 and 8 after visual inspection of the data. In weighting of the data, a variance proportional to the model estimates was assumed, with an initial estimate of coefficient of variance of 10%. ADAPT II software (Biomedical Simulations Resource, University of Southern California, Los Angeles) was used to estimate fluconazole pharmacokinetics for each patient by the maximum-likelihood estimation procedure (7). Drug administration was modeled as a zero-order input (e.g., 2-h infusion), with all infusion periods prior to the blood sampling incorporated into the pharmacokinetic model. Pharmacokinetic parameters were calculated by standard methods (15). The trapezoidal rule was used to estimate the fluconazole area under the concentration-time curve for each data set (15).

Descriptive statistics were used to summarize patient demographics. Data are reported as means ± standard deviations (SD) unless otherwise specified. A two-tailed, paired Student’s t test was used to compare the pharmacokinetic parameter estimates obtained for data from day 3 with estimates for data from day 8. Simple linear regression was used to assess the relationships between variables of interest. A P value less than 0.05 was considered significant for all statistical tests.

Ten patients (7 men and 3 women; age range, 24 to 65 years) with second- and third-degree thermal injuries covering 30 to 95% of their TBSA were enrolled in the study. Patient characteristics are listed in Table 1. One patient (patient 5) had extremely labile blood pressure requiring continuous pressor therapy following admission and was omitted from further analysis. This patient expired on study day 8. Patient 2 experienced hypotension requiring pressor therapy on study day 7 and subsequently developed acute renal failure on study day 8. Patient 10 developed acute renal failure beginning on study day 4. Therefore, data on patients 2 and 10 from study day 8 were omitted from the study analysis. In each of these instances, the blood sampling strategy was inadequate for accurately characterizing the prolonged elimination of fluconazole that was observed. Finally, study day 8 samples were not obtained from patients 3 and 7 due to their discharge from the burn center on study days 4 and 6, respectively. In summary, drug concentrations were obtained for all patients on study day 3 and for five of the patients on study day 8. All but two patients had therapy initiated on day 2 of their hospitalization. Patients 7 and 9 had fluconazole therapy initiated on the days of their admission to the burn center. The mean (SD) daily fluconazole dose administered to all patients was 5.1 (0.83) mg/kg of actual body weight.

Tables 2 and 1 list individual fluconazole pharmacokinetic parameter estimates and $\text{Cl}_{\text{CR}}$ measurements, respectively, in the study patients after initial $(n = 9)$ and multiple $(n = 5)$ doses. One-compartment pharmacokinetic estimates are provided since fitting a two-compartment model to the data did not appreciably improve the fit for the majority of patients based on the Akaike information criterion (7). There were no significant changes in volume of distribution ($V$), clearance (CL), or half-life ($t_{1/2}$) between study days 3 and 8 ($P > 0.05$), suggesting relative stability in pharmacokinetic parameter estimates over time in burn patients. Measured concentrations observed at the 1-h postinfusion sampling time on study day 3 ranged from 8.2 to 18.6 µg/ml. Correspondingly, the 22-h-postinfusion sampling time concentrations on study day 3 ranged from 4.3 to 10.1 µg/ml. There was no significant correlation between CL or $t_{1/2}$ and percentage of TBSA burned for the nine study patients ($P > 0.05$). Similarly, no significant correlation between CL or $t_{1/2}$ and $\text{Cl}_{\text{CR}}$ was observed at a $P$ value of < 0.05. However, the correlation between CL and $\text{Cl}_{\text{CR}}$ approached significance ($P = 0.09, r = 0.51$).

The findings of the present study are the first characterization of fluconazole’s pharmacokinetics in patients with severe thermal injury. Estimates of fluconazole’s $t_{1/2}$ in healthy volunteers and patients with normal renal function have ranged from 28 h (11) to 34.2 h (6) following doses of 25 to 400 mg. This is comparable to the shorter mean $t_{1/2}$ of 24.4 h in the burn patients from the present study. $V$ estimates from previously published fluconazole studies have ranged from 39 liters (11) to 45.8 liters (24), with reported CLs ranging from 11.4 ml/min (6) to 21.0 ml/min (21). While the mean $V$ for fluconazole in burn patients (56 liters) was slightly higher than those in previous reports, CL was substantially greater (27.5 ml/min).

The tendencies for decreased $t_{1/2}$ and increased CL and $V$
for fluconazole in burn patients are consistent with several pharmacokinetic studies of other antimicrobials in this patient population. Among the most extensively studied are the amino-glycosides, for which the $t_{1/2}$ was relatively shorter in at least five studies of burn patients (17, 23–29–31). A shorter $t_{1/2}$ was also observed in a pharmacokinetic study of vancomycin in burn patients (14). Increased CL has been documented for vancomycin (22), ceftazidime (27), and ticarcillin (1) in thermal-injury patients. A surprising finding of the present study was the lack of a statistically significant correlation between 24-h measured CL$_{CR}$ and fluconazole CL, considering that approximately 73% of fluconazole is excreted unchanged in the urine (8). In the cases of four other agents that have high degrees of renal elimination, i.e., vancomycin (5), imipenem (3), aztreonam (13), and piperacillin (4), CL$_{CR}$ was reasonably well correlated with drug clearance ($r > 0.75$). Possible explanations for this discrepancy include the relatively small number of patient data sets included in the present analysis (a type II statistical error) and/or limitations in obtaining reliable CL$_{CR}$ estimates for critically ill patients undergoing dynamic physiologic changes following burn injury. Regardless, since there was a trend toward a correlation between CLPEA and CL$_{CR}$, until a superior alternative is identified, the latter should continue to be used as a general bedside guide for dosing in burn patients, based on the manufacturer’s published recommendations.

In summary, fluconazole pharmacokinetics in burn patients appear to differ from those in healthy volunteers or other patient populations. Estimates of fluconazole’s $t_{1/2}$ were 13% shorter and its CL was 30% greater than the most extreme values previously published. Thus, moderate and aggressive daily doses of fluconazole in the prophylaxis and treatment, respectively, of fungal infections in burn patients are recommended.

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REFERENCES