Effects of Fluconazole Administration in Critically Ill Patients

Analysis of Bacterial and Fungal Resistance

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Hypothesis: The administration of fluconazole in intensive care unit (ICU) patients leads to the emergence of bacterial and fungal resistance.

Design: Retrospective analysis of 2 patient cohorts: (1) critically ill patients treated in surgical, trauma, and medical ICUs between June 1997 and January 1999 who did and did not receive fluconazole; and (2) ICU patients with fungal infections and sensitivity testing results from June 1994 to December 1998.

Setting: University-affiliated tertiary care hospital.

Patients: The first cohort included 99 ICU patients with documented microorganism culture(s) who were treated with (n = 50) or without (n = 49) fluconazole; the second cohort included 38 patients with Candida species infection, identification, and antifungal susceptibility testing.

Results: Mortality (40% vs 20%; P = .03) and hospital length of stay (33.8 vs 25.6 days; P = .04) were higher in the patients treated with fluconazole compared with patients not treated with fluconazole. The ICU length of stay was also higher in patients treated with fluconazole (23.7 vs 15.1 days; P = .009). An increase in bacterial resistance occurred in patients after fluconazole treatment as opposed to bacterial resistance of patients who were treated for bacterial microorganism(s) without fluconazole (16% vs 4%; P = .049). Comparison of patient populations with Candida species identification before and after December 1997 showed an increase in Candida species resistance to fluconazole (11% vs 36%; P = .16), respectively. Fungal strains were dominated by a combination of Candida albicans and Candida glabrata in both populations (60% [before 1998] vs 82% [after 1998]), with an emergence of Candida non-albicans species tolerant to fluconazole. The amount of fluconazole administered and the number of patients receiving fluconazole treatment in the ICUs has also increased when comparing both periods.

Conclusions: Comparison of critically ill patient populations with and without fluconazole treatment found increased mortality and longer hospital and ICU lengths of stay in the fluconazole-treated group. This group also had higher bacterial pathogen resistance to antibiotics after fluconazole administration compared with bacterial resistance of patients without fluconazole treatment. Our results warrant concern regarding worsening bacterial infections, increased mortality, and an increase in Candida resistance to fluconazole from increased use in ICU patients, with a shift in yeast infection that is more difficult to treat.

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PATIENTS AND METHODS

This study consists of 2 cohorts from Rhode Island Hospital, Providence, which is a 480-bed tertiary care hospital affiliated with Brown University. The first cohort includes critically ill patients from the surgical, trauma, and medical ICUs from June 1997 through January 1999. These patients were divided into 2 groups to determine the effects of fluconazole therapy in critically ill patients. The first subset of patients were patients with documented bacterial pathogen culture(s) who did not receive fluconazole (group 1). The second subset of patients were patients with documented bacterial pathogen culture(s) who received fluconazole (group 2). Group 2 patients were selected in a blinded, randomized fashion by the Rhode Island Hospital Pharmacy; group 1 was a randomly selected age-matched cohort control of patients in the same ICU sites during the same study period. The dose and duration of antifungal therapy were noted for patients receiving fluconazole. The hospital, microbiological infection, sensitivity, and clinical records were reviewed and the severity of illness was measured by the Acute Physiology and Chronic Health Evaluation III (APACHE III). APACHE III score was determined on admission to the ICU for both subsets of patients. Data were analyzed in terms of age, sex, admitting diagnosis and disease severity, hospital and ICU length of stay, surgery, and mortality (Table 1). Increased bacterial resistance was defined as a bacterial pathogen with sensitivity to a particular antibiotic that subsequently became resistant in terms of growth to the same antibiotic during one hospitalization.

The second cohort included 38 patients treated in ICUs at our institution (Rhode Island Hospital) from June 1994 through December 1998. The patients were selected to determine if Candida isolates were more resistant to fluconazole and to determine if increasing fluconazole-resistant Candida species coincided with increasing fluconazole administration in the ICUs. The patients had Candida species infection and antifungal susceptibility test results from the Fungus Testing Laboratory of the University of Texas Health Science Center at San Antonio, which included minimum inhibitory concentration of fluconazole in all patients and amphotericin B in most patients. Fluconazole-tolerant Candida species were defined as a minimum inhibitory concentration of 16 µg/mL or greater. To analyze and compare the sensitivity profile, patients were divided into 2 populations by date of final report: before and after January 1, 1998 (Table 2). This date was selected because of the significant yearly increase in both the total milligram use of fluconazole in the ICUs and the milligrams of fluconazole administered per critically ill patient. The total number of patients receiving fluconazole and the amount of administered fluconazole to ICU patients during the same period were obtained by the Rhode Island Hospital Information Services (Table 3).

The analysis of a data set (Table 1) of variables was used to explore hypotheses relating to fluconazole use and the predictors of mortality. We used χ² and independent-sample t tests to seek univariate relationships between the control group (group 1) and the fluconazole group (group 2) and patient mortality vs nonmortality. We used multivariate logistic regression to find predictors of in-hospital mortality. All statistical analyses were performed with Stata 5.0 software (Stata Corporation, College Station, Tex).

All research was conducted in accordance with the institutional review board committee of Rhode Island Hospital.

RESULTS

Patients in groups 1 and 2 had documented microorganism culture(s). Group 1 included ICU patients without fluconazole treatment and group 2, those with fluconazole treatment. Patients in both groups were of similar age (64.7 vs 60.3 years; P = .26). There were significantly fewer males in group 2 (46% vs 67%; P = .03). Both groups had similar rates of surgery (59% vs 58%; P = .91). Hospital length of stay (33.8 vs 23.6 days; P = .04) and ICU length of stay (23.7 vs 15.2 days; P = .009) were significantly longer for the fluconazole-treated patients compared with the non–fluconazole-treated group (Figure 1).

The number of fungal infection sites was higher in group 2 (1.22 vs 0.27 sites; P = .001) (Figure 2). The number of different bacterial infections was similar in both groups (2.41 vs 2.34; P = .81); however, the number of different antibiotics administered was higher in the fluconazole-treated patients (3.6 vs 4.2 in group 1; P = .006) (Figure 3). Importantly, an increase in bacterial resistance occurred after fluconazole treatment compared with...
the sensitivity profile of bacterial resistance of patients without fluconazole treatment (16% vs 4%; *P* = .049) (Figure 4). Five different pathogens in group 2 had increased bacterial resistance (*Pseudomonas aeruginosa*, 4 of 8; *Staphylococcus* species, 3 of 8; *Klebsiella*, 1 of 8; *Xanthomonas*, 1 of 8; *Enterobacter*, 1 of 8). Six of 8 patients had one pathogen with increased resistance whereas 2 patients had 2 pathogens with increased resistance. Group 1 had 2 patients with 1 pathogen each with increasing bacterial resistance (*P aeruginosa* and *Staphylococcus aureus*).

The APACHE III scores were similar (42.2 vs 38.0; *P* = .17) in both groups. The percentage of patients with diabetes mellitus was higher in group 2 (26% vs 14% in group 1; *P* = .15) but was not statistically significant. The use of glucocorticoids during hospitalization in group 2 was higher (40% vs 8%; *P* = .001) (Table 1). The prevalence of diabetes mellitus and glucocortocoid use was analyzed independently to determine their effect on mortality. Glucocorticoid use was associated with increased...
mortality (47% for patients receiving steroids vs 14% for patients not receiving steroids; \( P = .001 \)) whereas diabetes was not statistically related to increased mortality (27% for patients with diabetes vs 17% for patients without diabetes; \( P = .29 \)). Analysis of all patients receiving glucocorticoids in groups 1 and 2 (ie, 24 of 99 patients) produced an overall mortality rate of 58%, with an increased rate when analyzing both glucocorticoid and fluconazole administration in the same hospitalization (65%).

The hospital mortality rate was higher in the fluconazole-treated patients (40% vs 20% in group 1; \( P = .03 \)) (Figure 5). A logistic regression analysis for mortality is presented in Table 4. The model \( (\chi^2 = 47.51, P<.001; \) log likelihood, 36.96) retained 4 variables: hospital length of stay, number of antibiotics, APACHE III score, and glucocorticoid use. The results show that the odds ratio of mortality increases by 0.91 for every 1-day hospital length of stay, 1.54 for every 1-unit increase in the number of different antibiotics, 1.09 for every 1-unit increase in APACHE III score, 6.00 for the use of glucocorticoids, and 3.25 for the use of fluconazole.

A comparison of the 38 patients with \textit{Candida} species infection, identification, and antifungal susceptibility testing was done before (population 1) and after (population 2) January 1, 1998. Fungal strains were dominated by the combination of \textit{Candida albicans} and \textit{Candida glabrata} in populations 1 and 2 (39% vs 82%), respectively. Population 2 had more fluconazole-tolerant species than population 1 (36% vs 11%; \( P = .16 \)). Population 1 had resistance to \textit{C. albicans} and \textit{Candida krusei}, and population 2 had resistance to \textit{C. glabrata} and \textit{Candida tropicalis} (Table 2). The number of patients receiving fluconazole and grams of fluconazole administered (oral and intravenous) per year in the ICU has increased from 1994 to 1998 (Table 3). The average number of patients receiving fluconazole in the ICUs between 1994 and 1997 was lower than the number of patients receiving fluconazole in 1998 (191.5 vs 235 patients) as was the total grams of fluconazole administered per year (383.18 vs 543.4 g/y) and milligrams per ICU patient (2000.30 vs 2312.34 milligrams per patient) (Table 3).

The incidence of both nosocomial and community-acquired fungal infections has increased dramatically in the United States during the past 2 decades. This has resulted in both increased mortality and hospitalizations. Nosocomial fungal infection rates have increased from 2.0 to 3.8 infections per 1000 patients discharged between 1980 and 1989.6 Fungal infection incidence in critically ill patients has also increased and the importance of fungi as a pathogen in the ICU as an increasing prevalent problem is exemplified by the fact that candidemia rates are dramatically higher in high-risk, critical care units than in other parts of the hospital. A prospective study of medical and surgical ICUs documented an incidence of candidemia of 1 patient per 500 admissions.12 Among patients with systemic fungal infections, mortality rates are higher than 50%.2

Antifungal agents available for candidiasis include amphotericin B, the polyenes, fluconazole and itraconazole, the triazoles, and fluocytosine, the pyrimidine compound.13 Amphotericin B remains the drug of choice at doses of 0.6 to 1.0 mg/kg per day in critically ill patients with suspected or documented candidiasis because of its broad spectrum of activity against most \textit{Candida} species (all species except \textit{Candida lusitaniae}). However, the high incidence of the dose-limiting infusion-related side effects and nephrotoxicity of amphotericin B in a population with a preexisting renal failure has led to extensive fluconazole use. Fluconazole has been an attractive an-
tifungal agent because it causes relatively few side effects compared with amphotericin B and because it can be administered orally or intravenously. Fluconazole has antifungal activity against *C. albicans* as well as *Cryptococcus neoformans* and *Coccidioides immitis*. Unlike amphotericin B, fluconazole in vitro activity against other *Candida* species (*C. glabrata*, *C. tropicalis*) has been suboptimal. Several studies have also demonstrated resistance to fluconazole among patients treated for candidemia or for prophylaxis in patients with the acquired immunodeficiency syndrome. Resistant fungal infections have often been the same genotype as the isolate from the initial fluconazole-treated patient. In a study of candidemic patients, 13% of these patients were already receiving antifungal treatment as empirical treatment for neutropenia and fever or as prophylaxis. Sixty-two percent of these patients received fluconazole before fungemia developed and 76% of the isolates were *Candida non-albicans* species, including *C. krusei*, *C. glabrata*, and *Candida parapsilosis*. Another study has shown increasing use of fluconazole in ICUs, with a resulting increase in fluconazole-tolerant isolates and a shift in *Candida* species to *Candida non-albicans*. 

The results of our study confirm those of previous studies and delineate the role of fluconazole in the treatment of critically ill patients. The groups of patients studied were from the same period and were similar in age, rate of surgery, and APACHE III score. There were fewer male patients in the fluconazole-treated group (group 2). Both hospital and ICU lengths of stay were increased for patients administered fluconazole.

Both groups had similar numbers of bacterial infections per patient; however, the group receiving fluconazole had an increase in the number of different antibiotics administered per patient. Infection rates were higher for the fluconazole-treated group in terms of both fungal infection sites (1.22 vs 0.27 sites) and more bacterial resistance after fluconazole administration compared with patients without fluconazole treatment (16% vs 4%). The critical care units are an area where antibiotic resistance problems are most likely to be encountered because of the intensity of antibiotic use. Antibiotic resistance often is due to multiple-antibiotic usage and prolonged administration, and the antibiotics used in the ICUs often have high resistance potential. These groups had a similar number of bacterial infections; however, increased bacterial resistance was demonstrated in the fluconazole-treated patients after administration. This could be because fluconazole is not a bacteriostatic or bactericidal agent or because the different number of antibiotics used, which was higher in the fluconazole-treated patients, caused increased bacterial resistance.

The prevalence of glucocorticoid use and diabetes mellitus was higher in the fluconazole-treated group. When both characteristics were examined independently with respect to mortality, only glucocorticoid use had a statistically significant impact on mortality. Analysis of all patients administered glucocorticoids demonstrated significant mortality with an increased mortality rate in patients administered glucocorticoids with concomitant fluconazole use. Mortality was also increased in the fluconazole-treated group compared with the non–fluconazole-treated group (40% vs 20%). Mortality was analyzed in a logistic regression model and the significant findings showed an increased odds ratio of mortality with increased hospital length of stay, number of antibiotics, APACHE III score, glucocorticoid use, and fluconazole use. Noncontributory variables to this model were the presence or absence of a fungal infection and age. The clinical significance of these results illustrates the consequence that fluconazole treatment has on patient mortality (3.25 increased odds ratio with respect to mortality with fluconazole use, Table 4). With respect to ICU and hospital length of stay, the group treated with fluconazole had statistically significant increases in both. This finding could represent the causal effect of fluconazole treatment on critically ill patients; however, this may only be an association of fluconazole administration to a more unhealthy patient group.

This study also evaluated the use of fluconazole in all ICU patients from our institution and in patients with *Candida* species infection and antifungal susceptibility testing results over the past 4 years. When these patients were divided into 2 populations by date, our results indicated an increase in fungal resistance after December 1997 compared with prior to December 1997 (36% vs 11%). During the same period, fluconazole administration in ICU patients demonstrated trends toward an increase in the number of patients per year and milligrams per patient (Table 3). As stated in previous studies, *Candida* species have not only become more fluconazole tolerant but a shift in fungal flora has also occurred. These studies also noted increasing fluconazole use in their institutions.

There are several limitations to our study. In our initial cohort analysis, the number of patients (n = 99) selected was small regarding both evaluating critically ill patients and patients with *Candida* species infection identification and sensitivity. By Fisher exact test, the finding of increasing resistant *Candida* isolates only approaches significance (*P* = .16). Even though both groups of critically ill patients were similar in regard to age, surgery, and APACHE III score, there were differences in sex and pre-morbid contributors to chronic illness. Group 2, the fluconazole-treated patients, had fewer males and a higher prevalence of glucocorticoid use and diabetes mellitus. The impact of glucocorticoid use on mortality raises the question of whether the death of critically ill patients is from its use or the pre-morbid conditions of those patients reviewed. Importantly, analysis of patients administered glucocorticoids with fluconazole had a higher mortality rate compared with the patients administered glucocorticoids without fluconazole (65% vs 25%). Furthermore, the mortality of ICU patients who did not receive glucocorticoids with or without fluconazole was not significantly different from that of patients receiving both glucocorticoids and fluconazole (23% vs 20%). Therefore, the independent addition of glucocorticoids to pre-existing fluconazole administration in this study statistically increased the mortality rate from 23% to 65% (*P* = .007). Finally, as this is a retrospective review, our data do not permit us to state whether fluconazole administration is causally related or
merely associated with the increased mortality and lengths of stay seen in group 2 patients.

Fungal infections in critically ill patients are an increasingly prevalent problem and are due to many factors, including severity of illness, multiple-antibiotic administration, and the use of intravascular devices and life-support systems. However, the extensive use of fluconazole over the past several years in critically ill patients warrants concern. Its universal administration appears to be associated with the emergence of fluconazole-resistant Candida species and possibly increased bacterial resistance to antibiotics after treatment. Despite its few toxic effects, in this study, patients treated with fluconazole demonstrated increased mortality when compared with patients not treated with fluconazole. These results illustrate that the prophylactic use of fluconazole may have adverse effects, especially in critically ill patients and in patients receiving glucocorticoids. Rather than empirically treating patients with fluconazole, our results suggest that fluconazole therapy should be instituted only when fungal infection or colonization occurs. Fluconazole therapy is indicated in stable patients with C. albicans colonization or culture-proven infection only. Unstable patients with suspected or documented multisite fungal infection should receive amphotericin B. The problems of inappropriate antifungal therapy may also be corrected if antifungal susceptibility testing becomes routine. This study confirms that fluconazole treatment warrants restriction to the appropriate patients in the ICUs due to its adverse effects.

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**REFERENCES**