BRIEF REPORT

Toxicodynamics of Itraconazole: Implications for Therapeutic Drug Monitoring

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We explored concentration-toxicity relationships for itraconazole among 216 patients. Logistic regression revealed a progressive increase in the probability of toxicity with increasing concentrations of itraconazole. Classification and regression tree analysis suggested that 17.1 mg/L of itraconazole (measured using a bioassay) was the concentration level at which the population of patients was separated into 2 groups, each with a high and a low probability of toxicity.

Itraconazole is a broad-spectrum triazole antifungal agent that is still widely used for the management of fungal diseases [1–3]. Therapeutic drug monitoring (TDM) of itraconazole is advocated because of its variable pharmacokinetics and because of the clinically relevant concentration-effect relationships among patients [4, 5]. A range of adverse events are encountered [6]. We investigated the toxicodynamics of itraconazole to gain an improved understanding of the therapeutic index of this compound.

Methods. Patients treated with itraconazole for at least 3 weeks for prophylaxis or an *Aspergillus*-related syndrome and undergoing TDM during the period from March 2006 through January 2008 were identified from laboratory records at the Regional Mycology Laboratory of University Hospital of South Manchester. Both itraconazole capsules and suspension were administered according to local treatment protocols or as directed by the primary physician.

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Total itraconazole concentrations were measured using a bioassay as described elsewhere [7]. The limit of detection was 0.4 mg/L, and the dynamic range was 0.5–25.6 mg/L. The intra- and interassay coefficient of variation was <8% across the working range of the assay. Dosage adjustment was recommended if plasma itraconazole concentrations were <5 or >15 mg/L.

An adverse event was defined as being related to itraconazole use if (1) it had not been present before initiation of itraconazole therapy, (2) it occurred during itraconazole therapy, and (3) it resolved or improved with the cessation or reduction of itraconazole use. Multiple episodes of the same symptom in the same patient were recorded as only 1 episode for estimates of the overall incidence of adverse events, but were included in each of the adverse event categories.

The precise timing of itraconazole administration and specimen acquisition was not known for the majority of patients. For patients with an adverse event, the mean itraconazole concentration was calculated for the 3 months preceding the date that symptoms were first documented. This period represents a compromise between ensuring there were a sufficient number of samples to obtain a satisfactory estimate of mean drug concentrations and ensuring a meaningful temporal relationship between drug exposure and the development of symptoms. For patients in whom no adverse event occurred, the mean concentration between month 3 and month 6 of treatment was calculated. All drug concentrations were noted after the adverse events had been recorded, to minimize observation bias.

Statistical analyses were conducted using SYSTAT for Windows, version 11.0 (SPSS), and R (R Foundation for Statistical Computing). Concentration measurements above the upper limit of detection (ie, 25.6 mg/L) were assigned a value of 25.6 mg/L. Mean itraconazole concentrations from patients with and without adverse events were compared using the Student *t* test. The relationship between itraconazole level and the probability of toxicity was quantified using a longitudinal logistic regression analysis. An upper concentration boundary (ie, cutoff) that separated the study population based on the probability of toxicity was identified using classification and regression tree (CART) analysis. A receiver operator characteristic curve was constructed for the breakpoint, and its predictive performance was evaluated using the Fisher exact test.

Results. There were 216 patients who received 100–400 mg of itraconazole, and they provided a total of 952 individual serum samples; of these 216 patients, 121 (56%) were male. The average number of concentration measurements per patient was 4.4 (range, 1–21). The majority of patients had chron-

ic pulmonary aspergillosis ($n = 79$) or allergic bronchopulmonary aspergillosis ($n = 70$). There were only 41 solid organ transplant recipients who received itraconazole as prophylaxis, and there were only 4 patients with invasive aspergillosis. Most patients received itraconazole capsules ($n = 210$).

There were 99 patients (46%) who experienced an adverse event, and there were 23 asymptomatic patients (11%) with itraconazole concentrations of >15 mg/L; both of these groups of patients received a reduced dosage or had their therapy stopped. Forty-one patients (19%) received itraconazole as antifungal prophylaxis after solid-organ transplantation, in conjunction with cyclosporine or tacrolimus.

Of the 99 patients who experienced an adverse event, 73 experienced 1 symptom, 23 patients experienced 2 symptoms, and 3 experienced 3 symptoms. The most frequently observed adverse events were fluid retention (46 [21%] of 216 patients) and gastrointestinal intolerance (45 [21%] of 216 patients).

Of the 46 patients who experienced fluid retention, 43 (93%) had peripheral edema and 3 (7%) presented with other clinical features suggestive of congestive cardiac failure (reduced exercise tolerance and orthopnea). For the 3 patients who presented with other clinical features suggestive of congestive cardiac failure, the itraconazole concentrations were 22.1, 19.43, and 23.05 mg/L, respectively. For 1 of these 3 patients, an echocardiogram demonstrated a reduced left ventricular ejection fraction; for the other 2 patients, the echocardiogram was normal.

Gastrointestinal intolerance manifested as nausea and/or vomiting for 32 (15%) of the 216 patients and as abdominal pain, flatulence, and diarrhea for 13 (6%) of the 216 patients. For 5 patients (2%), liver function was abnormal, with a bilirubin level ⩾3 times the upper limit of normal; for 2 of the 5 patients, an associated elevation in the serum alkaline phosphatase level was ⩾3 times the upper limit of normal.

A number of less common adverse events were also observed. Sixteen patients (7%) developed a diffuse nonpruritic maculopapular rash during therapy that resolved 2–4 weeks after stopping itraconazole. Eight patients (4%) experienced headache without other neurological signs or symptoms. There were 11 patients (5%) who experienced peripheral neuropathy that manifested as a sensorimotor polyneuropathy affecting the hands and feet. Tremor was noted in 8 patients (4%). There were 21 patients (10%) who experienced sleep disturbance, with frequent waking, daytime somnolence, and associated low mood. Three patients reported dysgeusia. Clinical features of Cushing's syndrome were noted among 6 patients (3%) who were concomitantly receiving oral or inhaled corticosteroids. Increased dosages of insulin were required for 3 diabetic patients who received itraconazole coadministered with corticosteroids, and increased dosages of antihypertensive medication were required for 6 hypertensive patients who received itraconazole coadministered with corticosteroids.

Cessation of therapy was required for 72 of the 99 patients who experienced toxicity. Signs and symptoms of toxicity resolved with a 50% reduction in dose for 20 patients and with a 75% reduction in dose for 7 patients. Although gastrointestinal intolerance resolved rapidly when itraconazole therapy was stopped or when the dosage was reduced, the resolution of fluid retention, peripheral neuropathy, and tremor was protracted and took up to 6 months for some patients. Forty-five patients whose itraconazole therapy was stopped were administered alternative triazole antifungal therapy without recurrence of similar symptoms.

The mean plasma itraconazole concentration level (± standard deviation) was 16.0 ± 8.7 mg/L for patients who experienced at least 1 adverse event and 7.0 ± 5.9 mg/L for patients who did not experience any adverse events ($P < .001$). A longitudinal logistic regression model revealed a significant relationship between mean plasma itraconazole concentration level and the probability of any adverse event (figure 1).

CART analysis separated the population into 2 groups, each with a high and a low probability of toxicity with a breakpoint value of 17.1 mg/L. Mean concentration levels of <17.1 mg/L were observed in 152 patients, 31% of whom developed itraconazole toxicity. Mean concentration levels of ⩾17.1 mg/L were observed in 64 patients, 86% of whom developed toxicity. Determination of itraconazole concentration levels using a cutoff concentration of 17.1 mg/L was associated with a

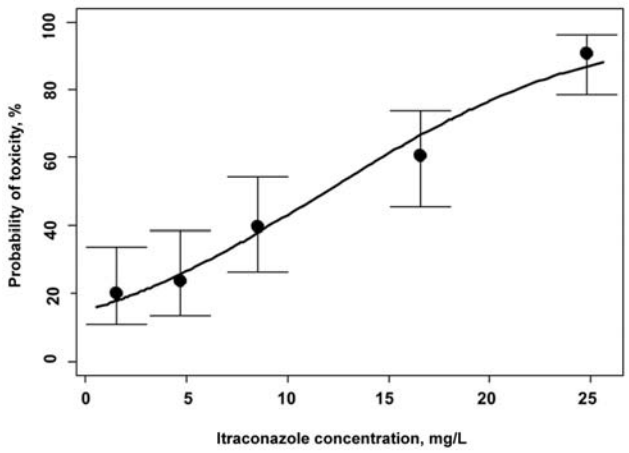

Figure 1. —Predicted probability of an adverse event vs. concentrations of itraconazole, from the logistic regression model. Data are mean values (95% confidence intervals) for the study population within 5 quintiles (determined by plasma itraconazole concentration level). The highest quintile includes values ⩾25.6 mg/L. The solid line represents a logistic regression model fitted to the measurements from each patient. The parameters for logistic regression are as follows: intercept, −0.111; coefficient, 0.151; odds ratio, 1.163 (95% confidence interval, 1.114–1.213; $P < .001$).

sensitivity and specificity of 53.9% and 92.1%, respectively, and a positive and negative predictive value of 85.9% and 69.1%, respectively, for predicting the subsequent development of toxicity. The area of the receiver operator characteristic curve was 0.86 and the predictive performance was statistically significant ($P < .001$).

Discussion. Despite the advent of newer triazoles, itraconazole remains a useful compound for the treatment of fungal diseases. Variability in itraconazole concentrations for patients receiving fixed dosages has an impact on therapeutic outcomes. Heretofore, the use of TDM for minimizing itraconazole-related toxicity has been limited by a lack of understanding of the toxicodynamics of this agent. Our study provides a foundation for dosing strategies that minimize toxicity.

Our study provides a quantitative relationship between itraconazole exposure and the probability of an adverse event. The logistic regression model shows that a concentration of 5 mg/L measured by bioassay (currently used in our laboratory as the lower bound for TDM) is associated with a probability of an adverse event of 26%. Higher itraconazole concentrations are associated with a progressively higher probability of toxicity. CART analysis suggests that 17.1 mg/L of itraconazole measured by bioassay may be an appropriate upper limit for TDM.

There are a number of caveats for the broad application of our findings. First, concentrations were measured using a bioassay rather than high-performance liquid chromatography (HPLC). The results from these techniques are not directly comparable, primarily because of the production of the active metabolite hydroxyitraconazole, which is detected by bioassay but not by HPLC. A study that correlated the results from these 2 assays showed that the bioassay generates concentrations that are ~7-fold higher than those generated by HPLC [8]. Second, our patient population predominantly consisted of ambulatory patients with chronic pulmonary aspergillosis. Relatively few patients received other medications that may have contributed to toxicity, either independently or via interaction with itraconazole. Importantly, however, this may be an issue for other specific patient groups (eg, bone marrow transplant recipients). Third, the impact of variables other than the itraconazole concentration on toxicity could not be assessed because sample sizes were insufficient within these subgroups. Fourth, we did not explore the possible relationship between itraconazole concentrations and the severity of toxicity, because the retrospective classification of symptom severity would have been associated with a high risk of interpretation bias. Nevertheless, symptoms were not life-threatening and all were reversible.

In conclusion, a range of adverse events may occur with the use of itraconazole. The probability of the occurrence of adverse events increases progressively with increasing concentrations of itraconazole. Our study provides a further indication for TDM as a means of individualizing dosing of itraconazole.

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