

Critically-III Recipients of Weight-Based Fluconazole Meeting Drug-Induced Liver Injury Network (DILIN) Criteria

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Abstract

Purpose: Fluconazole-associated liver injury is estimated to occur in <10% of patients; however, the effect of weight-based fluconazole dosing on liver injury has not been assessed. This study evaluated how often patients met Drug Induced Liver Injury Network (DILIN) criteria when receiving fluconazole daily doses of <6mg/kg versus ≥6mg/kg.

Methods: This multi-center, retrospective cohort study was performed in critically-ill fluconazole recipients hospitalized from January 2009 to December 2012. It included patients who received ≥3 fluconazole doses with ≥1 dose administered in the intensive care unit. Patients were excluded if they were pregnant, presented with acetaminophen toxicity, received fluconazole within 1 week of liver transplantation, or missed >1 fluconazole dose during therapy. We compared liver function tests (LFTs) upon fluconazole initiation to peak LFTs within 2 weeks after fluconazole discontinuation using DILIN criteria. The Fisher's exact test was used to detect differences in the primary outcome of patients meeting DILIN criteria by weight-based dosing as well as in subgroups of patients with kidney dysfunction, liver disease, septic shock, and those receiving a loading dose.

Results: Two-hundred and forty-eight of 767 patients met inclusion criteria; 90% had a documented fungal infection or received empiric therapy for suspected invasive candidiasis. Of the 199 patients receiving <6 mg/kg of fluconazole, 55% met DILIN criteria versus 46.9% of the 49 patients in the ≥6 mg/kg cohort (p=0.20). Only 14.5% of patients meeting DILIN criteria also met the definition for hepatocellular damage. In analysis of subgroups, 77.3% of patients with cirrhosis and 76.3% with septic shock met DILIN criteria (p<0.001 for both compared to those without these conditions).

Conclusions: Weight-based fluconazole dosing did not affect the number of critically-ill recipients who met DILIN criteria. However, DILIN criteria may overestimate the incidence of fluconazole-associated liver injury in critically-ill patients.

Background

A meta-analysis of ten randomized, controlled trials, including 697 patients, evaluated the incidence of hepatotoxicity with fluconazole when used for treatment of invasive fungal infections.¹ Ten percent of patients had increased liver transaminases, of which only 0.7% discontinued fluconazole. However, the definition of hepatotoxicity varied greatly between each included study. The DILIN has developed standardized definitions to identify cases of drug-induced liver injury. At this time, studies have not systematically evaluated the effect of weight-based fluconazole dosing on liver injury.

Purpose

Primary Objective: To evaluate the incidence of patients meeting DILIN criteria with weight-based fluconazole dosing (<6mg/kg vs. ≥6mg/kg) in an ICU population.

Secondary Objective: To assess the affect of the following characteristics on development of fluconazole-associated drug induced liver injury (DILI): renal dysfunction (CrCl<50 mL/min), cirrhosis, septic shock, and patients receiving a loading dose of fluconazole.

Methods

This is a multicenter, retrospective cohort study of ICU patients at University Hospital or Audie L. Murphy Veterans Affairs Hospital. Patients included received fluconazole for ≥3 days with ≥1 dose given in the ICU. Serum creatinine and liver function panel were collected the day of or day prior to fluconazole initiation and ≥1 follow-up lab within 2 weeks of discontinuation. If available, labs collected on days 3, 7, and weekly thereafter were included.

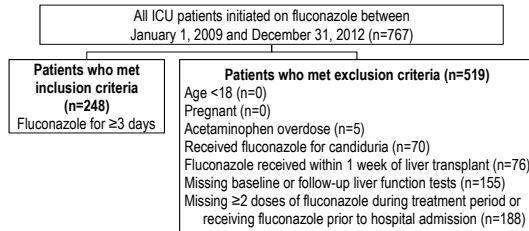


Table 1. Drug-Induced Liver Injury Definition²

- AST or ALT >5x ULN or >5x baseline abnormal value, or
- Alkaline phosphatase (ALP) >2x ULN (or pretreatment baseline if baseline level is abnormal), or
- Total serum bilirubin level >2.5 mg/dL along with elevated AST or ALT or ALP, or
- INR >1.5 with elevated AST or ALT or ALP

Type of Injury

- Hepatocellular R ≥ 5
- Cholestatic R ≤ 5
- Mixed R <2 or R <5

NOTE: R = (ALT/ULN)/(alkaline phosphatase/ULN)

Statistics

Statistical analysis with JMP® 10.0 (SAS Corporation, Cary, NC)

- Nominal data analyzed using Chi-squared or Fisher's exact, as appropriate.
- Continuous variables tested for normality using the Shapiro-Wilk W Test.
- Non-parametric continuous data analyzed using the Wilcoxon rank sum.

Results

Table 2. Baseline Characteristics

	Fluconazole <6 mg/kg (n=199)	Fluconazole ≥6 mg/kg (n=49)
Age, years	57 (49-64)	56 (46.5-64)
Weight, kg ^a	80.3 (69.4-97.6)	59.1 (50.8-64.3)
Height, cm ^a	172.7 (162.6-180.0)	167.6 (157.5-172.5)
Creatinine clearance, mL/min ^a	59.8 (30.7-92.8)	76.0 (46.8-121.0)
Average maintenance dose, mg ^a	222 (200-400)	400 (400-508)
Weight based average dose, mg/kg ^a	3.44 (2.52-4.56)	7.18 (6.53-8.81)
Weight based loading dose, mg/kg ^a	6.01 (4.50-8.40)	14.6 (11.8-19.1)

NOTE. Data is for Median (IQR).

^ap<0.05

Table 3. Baseline Characteristics of Subgroups

	Fluconazole <6 mg/kg	Fluconazole ≥6 mg/kg
Creatinine Clearance (CrCl) <50 mL/min ^a	84 (42.4%)	13 (26%)
Cirrhosis ^a	79 (39.7%)	9 (18.3%)
Sepsis at ICU admission	138 (69.3%)	37 (75.5%)
Septic Shock	60 (30.1%)	20 (40.8%)
Number of patients receiving loading dose (LD)	45 (23%)	6 (12%)
Number of patients receiving LD >12 mg/kg ^a	0 (0.0%)	5 (10.2%)

NOTE. Data is for number (%) of patients.

^ap<0.05

While 90% of patients included in the study were on fluconazole for empiric treatment or had a documented fungal infection, less than 20% received fluconazole ≥6 mg/kg.

Table 4. Number of Patients Meeting DILIN Criteria and Type of Injury

	Fluconazole <6 mg/kg	Fluconazole ≥6 mg/kg
Patients meeting DILIN criteria ^a	110 (55%)	23 (46.9%)
Hepatocellular	31 (28.1%)	5 (21.7%)
Mixed	14 (12.7%)	3 (13.0%)
Cholestatic	65 (59.1%)	15 (65.2%)

NOTE. Data is for number (%) of patients.

^ap=0.20

Table 5. Number of Patients Meeting DILIN Criteria by Subgroups

	Fluconazole <6 mg/kg	Fluconazole ≥6 mg/kg
CrCl <50 mL/min	52 (61.90%)	8 (61.54%)
Cirrhosis	60 (75.95%)	8 (88.89%)
Sepsis at ICU Admission	78 (56.52%)	17 (45.95%)
Septic Shock ^a	51 (85.00%)	10 (50.00%)
Loading Dose Received	23 (51.11%)	2 (33.33%)

NOTE. Data is for number (%) of patients.

^ap<0.05

Discussion

This multicenter, retrospective cohort study suggests that there is no increased risk of patients meeting DILIN criteria with higher doses of fluconazole. However, in this study, 50% of patients met the DILIN criteria. This high rate of possible DILI may be because the definition evaluates increases in ALP, total serum bilirubin, and INR. However, previous literature shows fluconazole-induced liver injury with primary increases in AST and ALT which indicates a hepatocellular pattern of damage.³

Currently, there are no standardized tools currently available to evaluate DILI in ICU patients. If clinicians use DILIN criteria in the ICU, it may lead to an overestimation of DILI which may result in inappropriate discontinuation of necessary drugs or inappropriate dosage reduction.

It is noteworthy that a large number of patients did not receive fluconazole ≥6mg/kg. The overall average weight of the patients in our study was 76 kg and the overall average maintenance dose of fluconazole was 350 mg/day (about 4.6mg/kg overall). Furthermore, the median average maintenance dose was only 400 mg in the ≥6mg/kg dose group. This finding may indicate that similar doses were given to all patients, regardless of weight. Patients were more likely to be placed in the ≥6mg/kg group if they were of lower weight.

Limitations

- 1) Exclusion of 155 patients due to missing labs. This limitation was minimized by including patients with baseline labs the day of or day prior to fluconazole initiation and ≥1 follow-up lab within two weeks of discontinuation.
- 2) DILIN excluded patients with previous liver or bone marrow transplant, underlying liver disease defined as autoimmune liver disease, or sclerosing cholangitis. However, only a small number of patients met this criteria and labs were only followed for up to two weeks after fluconazole discontinuation.

Conclusion

Clinicians should be cautious of using DILIN criteria in the ICU setting because it may overestimate hepatotoxicity. DILIN criteria should be followed with causality assessment in patients and investigation into other causes of elevated LFTs in the ICU setting. Investigations for more specific scales in ICU patients need to be created and validated. Retrospective studies should be conducted applying these criteria to biopsy-confirmed cases of drug-induced liver injury in critically-ill patients where true sensitivity and specificity tests can be performed.

References

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