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No Increased Risk of Ketoconazole Toxicity in Drug–Drug Interaction Studies

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Abstract

In July 2013 the U.S. Food and Drug Administration (FDA) released a safety announcement regarding the use of ketoconazole and its adverse drug reactions. The FDA report advised against the use ketoconazole tablets as a first-line treatment for any fungal infections because of the risk of potentially serious drug–drug interactions and liver and adrenal gland complications. The European Medicines Agency (EMA) also proposed to limit the use of oral ketoconazole in fungal infections because of the same risk of harmful effects and interactions. In addition, the FDA also advised against the use of oral ketoconazole in drug interaction studies, in which it has been extensively used as an index inhibitor of drug metabolism. The aim of this investigation was to evaluate the risks of ketoconazole-induced hepatotoxicity described by the FDA and EMA in published drug interaction studies with ketoconazole and compare these data with the toxicity reported for ketoconazole when used as antifungal treatment. In the drug interaction studies (2355 participants; healthy volunteers and patients; median treatment duration, 6 days), only 40 participants were reported to have increased liver transaminase activity (1.7%), and no deaths were reported or associated with ketoconazole. In studies investigating ketoconazole treatment, patients were treated for 276 days (median), and 5.6% of patients had elevated liver enzyme activity. Because of the short treatment period in drug interaction studies the risk of drug-induced hepatic injury is considered very low. As such, we recommend that ketoconazole remain a safe CYP3A index inhibitor for use in drug interaction studies with healthy volunteers.

Keywords

CYP3A inhibition, ketoconazole, hepatic toxicity, adverse events

The management of invasive fungal infections improved significantly with the introduction of ketoconazole in 1981, as did tolerability and adverse effects, compared with amphotericin B.[1,2] Triggered by the observation of the clinically significant terfenadine–ketoconazole drug interaction and after the introduction of fluconazole and itraconazole, the clinical utility of ketoconazole as an systemic antifungal treatment changed. Ketoconazole became widely used as a prototypic CYP3A inhibitor in vitro and in vivo, especially to establish the "worst-case" scenario for CYP3A-mediated interactions.[1,2]

The first reports of adverse drug reactions (ADRs) for the broad-spectrum antimycotic drug ketoconazole occurred in 1982, reported in the United States and other countries.[3] The liver was the organ most affected by ketoconazole exposure. The effect of treatment with ketoconazole ranged from asymptomatic transient irregularities of liver enzyme activity to potentially fatal acute hepatic necrosis. Serious ADRs are usually rare.[4]

The recent European Medicines Agency (EMA)–approved Summary of Product Characteristics[5] for ketoconazole lists the following adverse effects (and frequency):

Very common (≥1/10): liver function tests abnormal, hepatic enzyme increased.

Common (≥1/100 to <1/10): adrenal insufficiency, nausea, abdominal pain, vomiting, diarrhea, pruritus, rash.

Uncommon: (≥1/1,000 to <1/100): thrombocytopenia, allergic conditions including anaphylactic shock, anaphylactoid reaction and anaphylactic reaction, and angioedema, headache, dizziness, somnolence, urticaria, alopecia, asthenia, platelet count decreased.

In July 2013 the U.S. Food and Drug Administration (FDA) released a safety announcement regarding adverse reactions and drug-induced liver injury (DILI) related to ketoconazole exposure.[6] In its report the FDA advised avoiding the use of ketoconazole tablets as a first-line treatment for any fungal infections because of the risk of clinically serious drug–drug interactions and adverse effects related to hepatic and adrenal gland complications. The EMA also recommended a

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restriction on the use of oral ketoconazole in the management of fungal infections because of the risk of ADRs such as drug interactions, liver toxicity, and adrenal insufficiency.[7,8]

Moreover, by the end of 2013 the FDA also recommended against the use of ketoconazole in drug–drug interaction studies,[9] although in the current draft guideline on "Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations,"[10] the use of ketoconazole as an inhibitor of CYP3A is still recommended. A recently published analysis of 53 drug–drug interaction (DDI) studies (2005–2015) including 971 healthy volunteers with systemic ketoconazole exposure reported no enhanced risk of ketoconazole-related toxicity.[11] Furthermore, there is an ongoing discussion concerning the optimal alternative to replace ketoconazole as an index inhibitor for CYP3A-mediated metabolism for use in DDI studies.[12,13]

The aim of the present investigation was to evaluate the risks of ketoconazole-induced hepatotoxicity as identified by the FDA and EMA in 2013 in all published DDI studies conducted using ketoconazole and compare these data with the incidence of toxicity reported during antifungal ketoconazole treatment.

Methods

A literature search was carried out by screening PUBMED for the terms *ketoconazole* ("ketoconazole"[MeSH Terms] OR "ketoconazole"[All Fields]). Found were 8129 articles; randomized clinical trials, longitudinal studies, case reports, and literature reviews were included until September 2015.

All titles and abstracts from the 8129 articles were read and divided into several groups accordingly:

- "In vivo" interactions with ketoconazole
  Case reports
  Original research studies
  Literature reviews
- Toxicity related to ketoconazole use
  Case reports
  Original research studies
  Literature reviews
- Ketoconazole pharmacokinetic studies

All available full-text articles were analyzed according to study population (healthy volunteers or patients), number of participants per study, the substrate used (and its dose), and the ketoconazole dose and length of treatment period. The total dose of ketoconazole was calculated and the number of treatment days with a 400-mg standard daily dose. In addition, area under the plasma concentration–time curve (AUC), peak plasma concentration (C_{max}), clearance (CL), and terminal elimination half-life ($t_{1/2}$) of the substrate with and without ketoconazole coadministration were recorded; safety reports and laboratory values indicative of liver injury including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity were extracted when recorded. C_{max} and AUC ratios of the substrates were calculated as measures of exposure during ketoconazole coadministration divided by exposure without ketoconazole. Descriptive statistical parameters were obtained using Prism 6.0 (GraphPad Software, La Jolla, California).

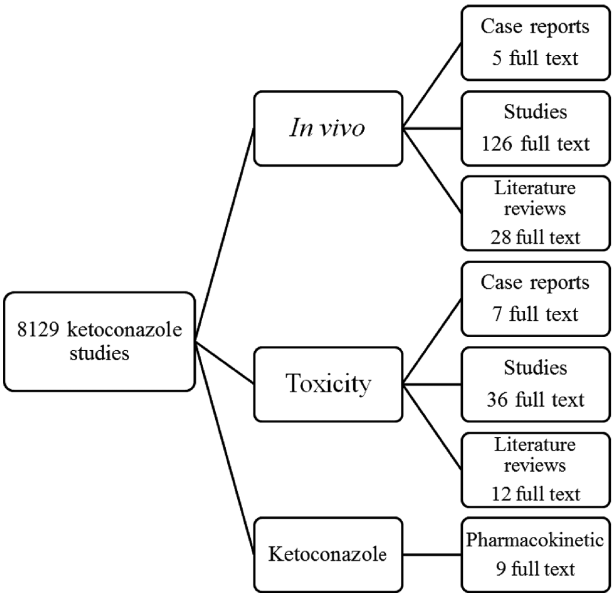

Figure 1. Summary of the total ketoconazole studies.

Results

From the 8129 articles found, 358 reported were selected and divided into the groups accordingly (Figure 1). Of these 224 full-text articles were acquired. The articles used are listed in the supplement.

DDI Studies

In the 126 articles of the group "in vivo" ketoconazole interaction studies, AUC values extracted from 120 articles were evaluated. A total of 161 studies were analyzed because there was more than 1 study reported per article (several substrates tested or different ketoconazole doses compared). From these studies 106 used a single dose of the substrate, 55 studies employed a multiple dose, and 27 studies used both single- and multiple-dose regimens in the study design. In 10 studies a single oral dose of ketoconazole was used, whereas in 151 studies a multiple-dose regimen of ketoconazole was employed. From 9 studies calculation of AUC ratios (AUCRs) of the "victim" drug was not possible, in 6 studies no AUC values for the victim drug

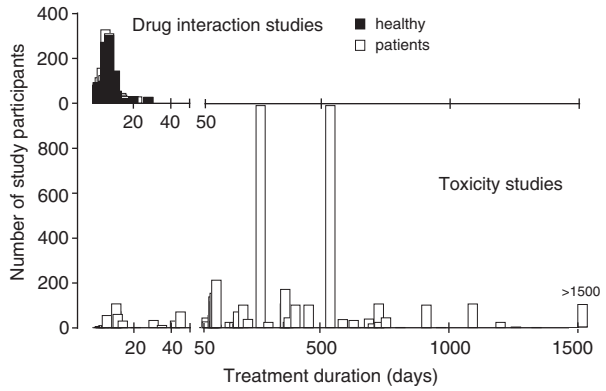

Figure 2. Treatment duration of ketoconazole treatment (normalized to 400 mg/day) in drug interaction and treatment studies.

were provided, and in 3 studies incomplete values (only ketoconazole AUC or only the victim drug's AUC) were provided. The majority of DDI studies were performed in healthy volunteers (82.5%), and only 17.5% were carried out in patients with the target indication or renal impairment. In total, 2355 participants were exposed to ketoconazole in the drug interaction studies captured in this analysis.

The duration of ketoconazole administration varied considerably in the 151 drug interaction studies, shown in Figure 2 (range, 2–29 days; median, 6 days). In most cases ketoconazole was administered for 5 days; the second most common duration of administration used in these studies was 7 days. The administered doses of ketoconazole varied among 400 mg once daily (79 studies), 400 mg twice daily (1 study), 400 mg 3 times daily (1 study), 200 mg once daily (40 studies), 200 mg twice daily (34 studies), 200 mg 3 times daily (1 study), 100 mg once daily (2 studies), 100 mg twice daily (1 study), and 600 mg once daily (2 studies). In some of the studies more than 1 dose of ketoconazole was tested (eg, 400 mg once daily and 200 mg once daily).

From the 161 interaction studies, 152 reported AUC values, and the AUCR of the victim drug with and without ketoconazole coadministration was calculated. The highest AUCR was approximately 60.0 for L-771,688, a strong and highly selective experimental α_1-adrenoceptor antagonist with demonstrated effects on clinical urodynamics.[14] All drugs with an AUCR above 2.0 (moderate to strong inhibition) are presented in Figure 3.

Toxicity Reported in Interaction Studies

Of the 126 articles reporting drug interaction studies, 20 did not report or describe any ADRs, and 3 articles reported ADRs without adequate details of the event, leaving 103 articles available for analysis. From the 103 articles, 32 did not report any details of liver function tests, 49 reported no changes in the laboratory values throughout the study (without providing any specific data), 3 explicitly reported no events of hepatic toxicity,[15–17] 1 article stated there were no ADRs attributable to ketoconazole,[17] and 18 articles reported changes in the laboratory values of ALT and AST activity; however, only 5 provided data on ALT and/or AST activity of study participants (Table 1).

The mean total dose of ketoconazole administered per study was 2767 mg (median, 2400 mg). The highest total cumulative dose of ketoconazole administered to healthy volunteers was 11.2 g (400 mg/day for 28 days), and no serious ADRs were reported in this study.[18] The highest total cumulative dose administered to patients with advanced prostate carcinoma was 16.8 g (400 mg 3 times daily for 14 days), and there were no reported episodes of hepatotoxicity, although fatigue and weakness were reported, and it the severity was reported to increase with higher ketoconazole doses.[16]

Three studies in healthy volunteers reported an episode of increased transaminase activity. In 1 study 15 healthy volunteers were administered ketoconazole 200 mg twice daily for 9 days, and 1 participant withdrew from the study because of increased transaminase activity[19]; in another study 42 healthy volunteers received ketoconazole 400 mg once daily for 9 days, and 2 participants withdrew prematurely because of elevated hepatic enzyme activity and headache.[20] One participant was reported to have abnormal laboratory tests including elevated liver function tests after ketoconazole administration and before taking the study drug (L-771,688), which was considered unrelated to the study. The participant was found to be infected with the hepatitis C virus.[14]

In a clinical trial involving patients 1 participant of 13 cancer patients receiving 400 mg ketoconazole/day for 4 days was reported to have elevated total bilirubin serum concentrations without a history of liver disease.[21]

To account for different ketoconazole dosing regimens the treatment duration of a standardized dose of 400 mg/day of ketoconazole was calculated. Healthy participants were administered ketoconazole for a median of 6 days, with 5 days the most often used administration duration, followed by 7 days. For the drug interaction studies involving patients the median duration of ketoconazole treatment was 5 days, with 3 days the most common period of ketoconazole administration.

Toxicity During Therapy Studies With Ketoconazole

Fifty-five articles that reported studies in which ketoconazole was used as an antifungal treatment were analyzed—36 of these article were clinical studies, 12 were literature reviews, and 7 were case reports. In some

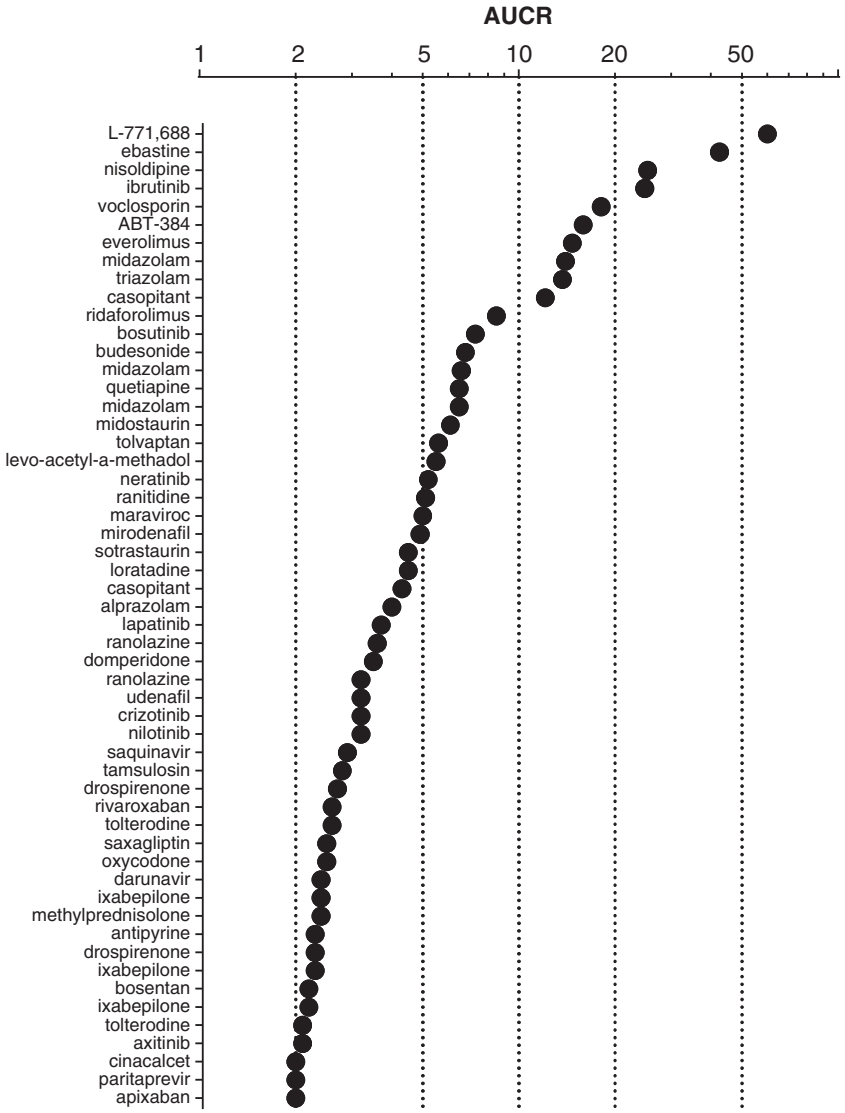

Figure 3. AUC ratios (AUCRs) of the victim drug with and without ketoconazole extracted from the screened literature; only AUCRs greater than 2 (moderate to strong inhibition) are shown.

cases there was more than 1 study per article (different periods of administration or different ketoconazole doses), providing a total of 80 studies included in this analysis. The total number of patients treated with ketoconazole was 4427, and the duration of ketoconazole treatment and/or the dose given was provided in 72 studies.

The duration of ketoconazole treatment was highly variable (see Figure 2). The median ketoconazole treatment duration was 276 days, and the median total cumulative dose of ketoconazole administered was 73 g.

In 1 study ketoconazole was reported to be used for a period of 3650 days (10 years, 51 patients) coadministered with cyclosporine in kidney transplant patients.[22] In this study the ketoconazole dose regimen was 100 mg/day, and in some patients the daily dose was reduced to 50 mg/day. This study includes a control group that did not receive ketoconazole treatment. The total ketoconazole dose administered was typically 365 g (when taken as 100 mg daily).

The adverse effects observed and reported in this study were:

- Abnormal liver function tests in 25.5% of the ketoconazole-treated group (n = 51) and 30.6% of the control group (n = 49);
- Transient elevation of hepatic transaminases, which was associated with high blood concentrations of cyclosporine and normalized with dose adjustment (4 patients in the ketoconazole-treated group);

Table 1. All Studies With Reported ALT and AST Values in Ketoconazole Drug Interaction Studies

Author, Year	Number of Participants	ALT (U/L)	AST (U/L)
Engels, Mathot, Loos, van Schaik, Verweij, 2006[38]	7 (cancer patients)	Baseline 20 U/L No mention during or after the study	Baseline 25 U/L No mention during or after the study
Xu et al, 2015[39]	22 (healthy volunteers)	1 subject ≤ 144 U/L Decreased once ketoconazole was stopped	–
Kovarik, Huang, Slade, Sfikas, Chandler, 2009[40]	17 (healthy volunteers)	1 subject 74 U/L (normal range, 3–60 U/L) 2 months after the study, 18 U/L	–
Lee et al, 1995[41]	13 (cancer patients)	1 subject 479 IU/mL On day 20 of treatment with ketoconazole	1 subject 535 IU/mL On day 20 of treatment with ketoconazole
Tham et al, 2006[42]	29 (cancer patients)	Average data Control, 21 U/L Ketoconazole, 29 U/L	Average data Control 33 U/L Ketoconazole 34 U/L

- Persistent mildly increased bilirubin concentrations and serum transaminase activity (n = 2 patients);
- 5 Patients were withdrawn from therapy because of viral hepatitis;
- 16 Patients discontinued ketoconazole therapy at different times (6–72 months) for reasons including hepatic dysfunction (n = 5), antituberculostatic drugs (n = 4), pregnancy (n = 5), noncompliance with immunosuppressive medication (n = 1), and development of cancer (n = 1).[22]

The highest cumulative ketoconazole dose administered to patients with hormone-refractory prostate cancer was 1296 g over a period of 1440 days.[23] In this study 38 patients received ketoconazole 300 mg 3 times daily together with 30 mg of hydrocortisone. The duration of treatment varied between 3 and 48 months, and the median was 6 months. The following adverse effects were reported: nausea (13.2%), fatigue (10.6%), diarrhea (2.6%), visual disturbance (2.6%), and abnormal liver function tests (2.6%; ALT and AST activity values not provided), and 6 patients (15.8%) were reported to have discontinued ketoconazole therapy because of "intolerable adverse effects."[23] At the end of the study 12 patients were reported to survive (the median age was approximately 73 years).

Allergic reactions after a single oral dose of ketoconazole have been reported.[24] A female patient with dermatomycosis of the breasts was prescribed ketoconazole, and according to the patient, she had not previously experienced an allergic reaction except for contact dermatitis to miconazole. Shortly (45 minutes) after administration of ketoconazole, the patient reported being dizzy and collapsed several times. During the examination severe angioedema and pronounced erythema of the face, hands, and feet were found. After sufficient supportive treatment all symptoms resolved the next day.[24] A male patient also received a single dose of ketoconazole (200 mg). He also had not previously experienced an allergic reaction to ketoconazole and reported not currently taking other medication. After 30 minutes the patient reported swelling of the hands and feet and itching. Clinical examination revealed severe angioedema of the face, hands, and feet. Gastrointestinal complaints and pronounced dyspnea were also present but gradually resolved. After supportive treatment the patient recovered within 2 hours.[24]

From the 55 articles analyzed, only 4 actually reported ALT and AST values, 4 articles reported ALT values only (Table 2), 18 articles described abnormal liver function tests without providing any values, 11 studies reported no changes in hepatic function, and 18 articles did not mention hepatic function.

Two articles reported ALT and AST activity at the beginning of ketoconazole treatment and reported no changes throughout the 2 years of follow-up.[25,26]

Discussion

According to a report from the FDA, ketoconazole should not be used in drug interaction studies because the typical dosage (200–400 mg daily for 5 days) has been associated with liver injury.[9] The decision of the FDA was based on data from the FDA Adverse Event Reporting System (FAERS), which is not easily accessible to the public, and epidemiological data of the General Practice Research Database from 1999,[27] in which 2 of 1052 patients with prescribed ketoconazole reported drug-induced liver injury (nonfatal outcome).

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