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KETOCONAZOLE-INDUCED LIVER DAMAGE

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Abstract Five cases (four females, one male) of ketoconazole-related liver damage are presented, two of whom died. All patients received ketoconazole (400 mg/day) for various mycoses. In the four women the first signs of hepatotoxicity appeared after four weeks of therapy. One fatal case developed massive necrosis with fulminant liver failure and the other, submassive necrosis. In four cases cholestasis was a prominent finding. Biochemical evidence of biliary stasis may persist for several months, as occurred in the three surviving patients of our series. The two fatal cases continued receiving the drug in spite of its adverse effects. Consequently, repeated evaluation is recommended to detect early signs of liver involvement.

Resumen ***Injuria hepática inducida por ketoconazol.*** Se presentan 5 pacientes, 4 mujeres y 1 hombre, con toxicidad hepática por ketoconazol (Ke) 2 de los cuales tuvieron una evolución fatal. Todos los pacientes recibieron una dosis de 400 mg/día de Ke por diversos tipos de micosis superficiales. En las 4 mujeres los primeros signos de hepatotoxicidad aparecieron dentro del mes de iniciada la terapia. Los 2 casos fatales fueron del sexo femenino. Una de ellas presentó una necrosis hepática masiva con falla hepática fulminante mientras que la otra una necrosis submasiva. En 4 casos la colestasis constituyó la marca bioquímica e histológica más sobresaliente. Las evidencias bioquímicas de colestasis pueden persistir por tiempo prolongado a pesar de la suspensión de la droga como ha sido observado en los 3 pacientes que sobrevivieron. La continuidad de la ingesta de Ke después de la aparición de signos de hepatotoxicidad se asociaría con un peor pronóstico y por tal motivo sería recomendable evaluar a todos los pacientes en forma periódica durante la fase inicial del tratamiento.

Key words: ketoconazole, liver damage, hepatic failure, hepatic massive necrosis, hepatic submassive necrosis

Ketoconazole, an azole compound, is a widely used and highly effective antifungal agent[1, 2]. Side effects are uncommon, but can be significant and on rare occasions lethal drug-induced liver failure ensues[3, 4], as well as non-fatal liver injury[5, 7]. Fulminant liver failure is extremely infrequent and until 1997 we only found in the literature seven well documented cases[3, 5, 8, 9]. On the other hand, reports on pathology findings are scanty[8, 10]. This paper describes five cases of ketokonazole-related hepatotoxicity, two of whom died. In all patients liver biopsy was available.

Case reports

Case 1

Case 1 was a 61-year-old female with no history of disease or alcohol abuse, treated with ketoconazole (400 mg/day) since November 1989 for onychomycosis. A previous check-up (October 1989) found no abnormality. After 20 days of therapy she noted intense fatigue and on January 1990, also jaundice and choluria. However, she continued taking the drug for another 10 days, until she visited her physician. On January 23, 1990, jaundice, hypocholia, choluria, fatigue and flapping were observed. Laboratory studies revealed: bilirubin 8.5 mg%; AST, 168 IU/L, ALT, 132 IU/L, and prothrombin time (PT), 16 sec.

On February 2, 1990, the encephalopathy worsened and the patient was admitted into a critical care unit with fetor hepaticus and severe jaundice. The liver border was not palpable and percussive dullness was absent. No splenomegaly, collateral circulation or skin signs of chronic liver disease were detected. Laboratory studies showed: bilirubin 28.5 mg% (conjugate 23.6 mg%), alkaline phosphatase, 59 IU/L (N = 50 IU/L); PT 30 sec; glycemia 78 mg% and creatinine 1.1 mg%.

Three days later the encephalopathy improved but the severe coagulation disorder persisted. Hepatitis A and B virus markers, and antinuclear, smooth muscle, and mitochondria antibodies were negative. An anti-HCV test done retrospectively using bank serum was also negative. The ultrasonogram revealed reduced liver size and normal bile bladder and bile ducts.

Renal function deteriorated and a gastrointestinal tract bleeding due to congestive gastropathy supervened; the endoscopy showed grade I esophageal varices.

On March 1, the patient died. The post-mortem liver examination revealed hepatocyte necrosis with collapse of multiple acinary 3 zones. The necrotic areas were confluent, with por-

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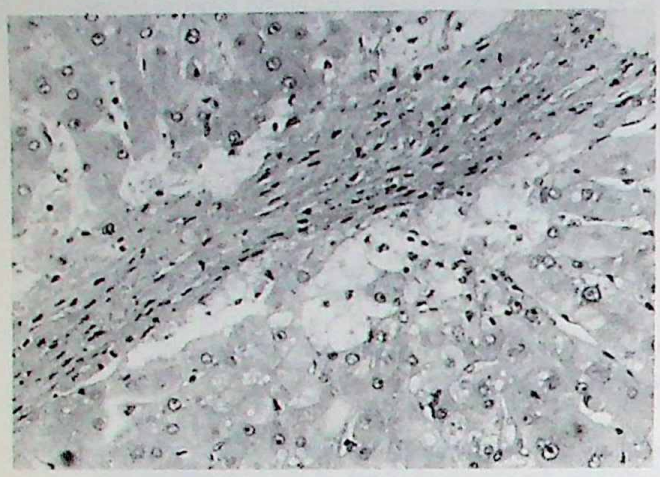

Fig. 1.– Case 1. Area of confluent necrosis in acinar zone 3. Paraseptal hepatocytes swollen and pale (cholate stasis), and foamy histiocytes (xanthomatus cells). (H & E stain, 250 x).

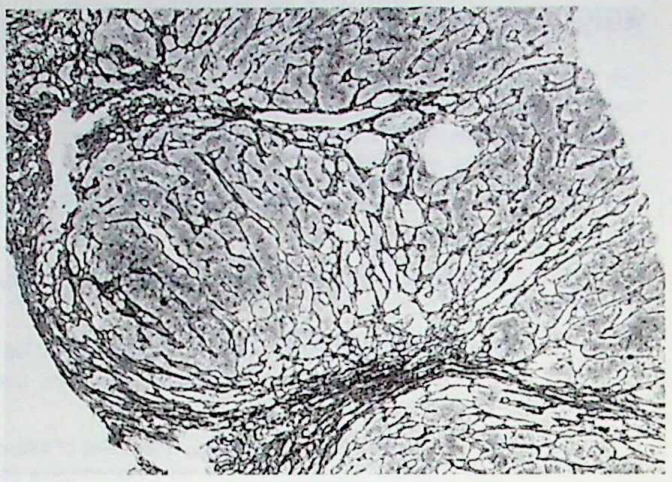

Fig. 3.– Case 1. Reticulum stain showing bridging due to the reticulum framework collapse, and nodular regeneration of the hepatocyte plates (25 x).

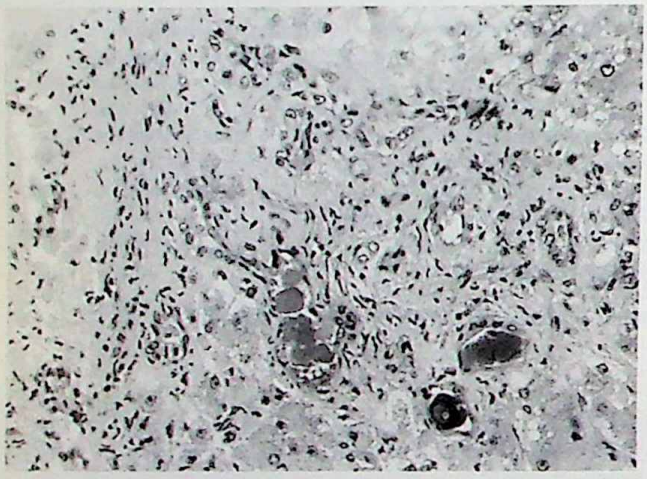

Fig. 2.– Case 1. A portal tract with severe ductular cholestasis. A confluent necrotic zone crosses the right side of the picture. (H & E stain, 100 x).

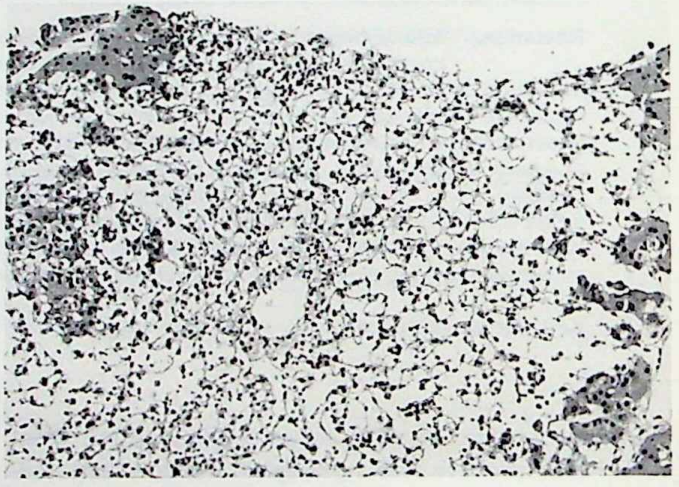

Fig. 4.– Case 2. Extensive necrosis around a centrilobular vein, and surviving hepatocytes at the periphery of the lobule. (H & E stain, 25 x).

tal-central and portal-portal necrotic bridges. Severe cholestasis with bile thrombi in ducts peripheral to portal bands and necrotic areas was seen, in addition to groups of periportal hepatocytes that displayed feathery degeneration (Fig. 1 and 2) and macrophages with cytoplasmic fat-laden vacuoles. Hepatocyte regeneration signs were focal and a mild portal and sinusoid inflammatory infiltrate with lymphocytes and polymor-phonuclear leukocytes, many of them eosinophils, was obser-ved. When reticulin and trichromic techniques were used, the architectural distortion produced by the confluent necrotic zones collapse and incipient cirrhosis due to collagen fiber deposition, was evident. The picture was then one of submassive liver necrosis with severe cholestasis and signs of progression to cirrhosis (Fig. 3).

Case 2

Case 2 was a 43-year-old female admitted on September 26, 1987 in stupor. The physical examination revealed good nutrition status, no fever, intense jaundice, ecchymosis on arms and legs, and hematomas. Reflexes were normal and a certain degree of muscular rigidity with cogged wheel sign was observed. Flapping was obvious. The liver size was reduced. The patient had a history of 10 years of adult celiac disease, controlled with diet. She also had a onychomycosis and vaginal fungal infection for the last 3 months, treated with ketoconazole (400 mg/day). The patient then presented with fatigue, increasing gastric intolerance, jaundice, choluria, and hipocholia and therefore, on August 6, 1987, the drug was discontinued. Laboratory studies showed: bilirubin 16.5 mg% (conjugate, 12.8 mg%); ALT, 1 600 IU/L; AST 740 IU/L; cholesterol 139 mg%, PT 15 sec; serum protein 6.8 mg%; albumin 3.9 g% and globulin 2.9 g%. Blood counts were normal. IgM anti-HAV and HBsAg were negative. Since then, the deterioration was progressive.

On September 26, 1987, encephalopathy with renal failure developed. Laboratory studies showed: AST 300 IU/L; ALT 410 IU/L; glycemia 140 mg%; PT 48 sec and ammonium 230 mg/dl. Screening for HBsAg, IgM anti-HAV, anti-CMV and anti-EB was negative. An anti-HCV done retrospectively using second generation ELISA with stored serum was negative. One day

before death the liver was not palpable and percussion was difficult; the patient had severe jaundice and was in coma. She developed epistaxis, gum bleeding and oligoanuria and on September 28, 1987, died. The post-mortem examination revealed massive liver necrosis, bile ducts proliferation and an inflammatory infiltrate composed of lymphocytes and polymorphonuclear leukocytes. The residual liver parenchyma showed hepatocyte regeneration (Fig. 4). The picture was consistent with fulminant hepatitis of several week's duration.

Case 3

Case 3 was a 65-year-old female admitted on June 1992 with jaundice, choluria and acholia, treated with ketoconazole (400 mg/day) for 3 months, for onychomycosis. She had lost almost 6 kg of weight in one month. She had no history of surgery, blood transfusions or alcohol abuse. Ten days before hospitalization laboratory examinations showed: bilirubin 4 mg%; AST 480 IU/L; ALT 560 IU/L; alkaline phosphatase 180 IU/L (N = 50 IU/L); gamma-glutamyl transpeptidase (G-GTP); 156 IU/L (N = 33 IU/L) and PT, 14 sec. Jaundice with flapping was obvious. Auditory and visual evoked potentials were consistent with hepatic encephalopathy. The ultrasonogram was normal. HAV, HBV and HCV markers were negative. A HCV RNA test using PCR excluded viremia. One week after admission the clinical and laboratory features improved. On day 15 a liver biopsy revealed perivenular cholestasis with canalicular bile plugs, isolated necrotic hepatocytes, and lipofuscin-laden macrophages in acinary zone 3. Portal inflammation was minimal. One month after ketoconazole was withdrawn, elevated levels of alkaline phosphatase (97 IU/L) and G-GTP (112 IU/L) persisted. Two months later HAV, HBV, and HCV markers were negative. After four months, all laboratory tests were normal.

Case 4

Case 4 was a 26-year-old male first seen on April 1993, who after one week on ketoconazole (400 mg/day) developed jaundice, choluria, and pruritus. Hepatomegaly, jaundice, and scratch lesions were noted. The spleen was not palpable. Laboratory studies revealed: bilirubin 8 mg% (conjugate 5 mg%); ALT 168 IU/L; AST 86 IU/L; cholesterol 200 mg%; PT 12 sec; serum protein 7.2 g%; albumin 4.1 g%, and gammaglobulin 1.2 g%. HAV, HBV, and HCV markers and PCR for HCV RNA were negative. Twenty days after ketoconazole was discontinued, a liver biopsy showed cholestasis with capillary thrombi in acinar zone 3. Hepatocyte ballooning with isolated cell necrosis and regeneration were seen. Portal Inflammatory infiltration was scanty and mixed, with lymphocytes and polymorphonuclear leukocytes (Fig. 5).

As increased levels of alkaline phosphatase and G-GTP persisted after two months without ketoconazole, and endoscopic retrograde cholangiography was performed, but no abnormality was detected. Viral markers and antinuclear, antimitochondria, and anti smooth muscle antibodies were negative. Ursodeoxycholic acid (600 mg/day) was prescribed and one year later, all laboratory tests were normal.

Case 5

Case 5 was a 52-year-old female first seen on May 1994, who after three months on ketoconazole (400 mg/day) developed epigastric discomfort, asthenia, jaundice, and pruritus. Laboratory studies revealed: bilirubin 15 mg%; PT 11 sec; ALT 700 IU/L, and AST 468 IU/L. Ketoconazole was withdrawn; antiHAV IgM, HBsAg, anti-HBc IgM, and PCR for HCV RNA were negative. The clinical status improved and on July 7, 1994, a bilirubin of 2.2/1.6 mg%, ALT of 23 IU/L, AST of 17 IU/L, alkaline phosphatase of 183 IU/L, and G-GTP of 23 IU/L were noted.

A liver biopsy showed little portal infiltration with lymphocytes and eosinophils with no invasion of the borderline plate. In acinar zones 3 disorganization of hepatocyte plates with prominent waxy pigment-laden macrophages was seen. Some hepatocytes had biliary pigment within their cytoplasm, but no canalicular bile plugs.No fibrosis was present. Those findings suggested resolving hepatitis with biliary stasis. All viral markers were negative. Eight months later the patients was asymptomatic and laboratory tests were normal.

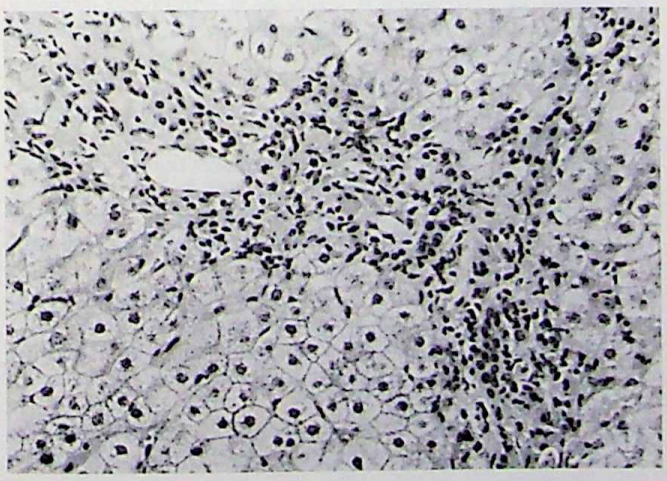

Fig. 5.– Case 4. Mild portal inflammation, with lymphocytes and polymorphonuclear leukocytes. There is a mild aggregate of ceroid-laden macrophages at the center of the tract. (H & E stain, 250 x).

Discussion

The first report on ketoconazole-induced liver damage was documented as early as 1981[11, 12]. On occasion, the cause-effect relationship was confirmed by rechallenge[6, 12, 13]. The incidence of ketoconazole hepatotoxicity is low and estimations ranged between 1/10 000 and 1/15 000[9, 14], but more recently it was shown that it may be as high as 1/2 000[15]. Although a review of 2 671 liver biopsies found 26 cases of drug-induced liver injury, only one of this serie was associated with ketoconazole[16].

Most patients are asymptomatic and only a minority has jaundice. Asymptomatic transaminase elevation occurs between 6 and 12% of the cases[15, 17]. This elevation is self limited and of short duration, but sometimes a biphasic elevation occur and normalization takes more time[18]. Liver damage due to ketoconazole does not seem to depend on the daily or accumulative dose, but generally, patients showing hepatic side-effects were taking the drug for more than 10 days[8, 9, 15]. Only one patient of our series was on ketoconazole therapy for a shorter period. He was not receiving other potentially hepatotoxic agent; all viral markers, including nested PCR for HBV and HCV were repeatedly negative during the follow-up and the ERCP showed a normal extra and intrahepatic

biliary tree. As the histopathology was suggestive of drug-induced hepatotoxicity, a causal relationship between ketoconazole and liver injury was assumed to be likely. In fact, some patients develop signs of toxic liver damage as soon as one or two days after therapy with ketoconazole begins[8, 19] but this event is highly uncommon. Elderly patients are more prone to liver dysfunction[15], but younger cases are also well documented[20]. Only one of our patients was under 40. Ketoconazole-induced hepatotoxicity is more frequent in women[15]. Our findings confirmed this notion. Men are also vulnerable to toxic reactions due to this drug, but to a much lesser extent[20].

The mechanism of ketoconazole-related liver injury is still unknown, but it seems to be idiosyncratic rather than immunoallergic[7, 17]. The absence of eosinophilia, skin rash, or hepatic granulomas in our patients favors this opinion, but a hypersensitivity component as contributive factor cannot be excluded. Usually, the hepatic side-effects of ketoconazole are self-limited, but sometimes, even when the drug is discontinued, the liver damage progresses[15, 21].

In contrast, if the drug is not withdrawn when symptoms of intolerance develop, the liver injury and the ultimate outcome may worsen[9]. Nevertheless, there are also reports describing resolution in patients who continue on ketoconazole[22].

In both of our patients with lethal outcome the drug was not interrupted until after several days of clear evidence of hepatotoxicity. In one patient with acute liver failure a orthotopic liver transplantation was successfully performed[23]. Cases of non-lethal ketoconazole-induced fulminant hepatitis are much more frequent[20, 24]. In one patient, therapy with corticosteroid seemed to be beneficial[25]. However, the subfulminant liver failure observed in one of our cases was never, to our knowledge, described before. Cholestasis seems to be an outstanding characteristic of ketoconazole hepato-toxicity[7, 10], but others[18] found a prevalence of necroinflammatory lesions. It was noted in about half of cases in some studies[8]. In our series, three patients presented with histological evidence of cholestasis associated with necroinflammatory lesions.

The biopsy findings in one of our fatal cases (Case 2) were similar to those already described[9]. Lakeb-Bakaar et al.[8] also described the marked ductular cholestasis. As they point out, this event is more common in sepsis, but in their cases it was probably related to the drug. In some non-fatal cases, Stricker et al.[15] found "beginning fibrosis". Presumably, patients with severe necrosis who survive may have residual structural damage-fibrosis or even lesions suggesting early cirrhosis.

Cholestasis does not seem to represent an unfavorable factor. In our series, only one of the two fatal cases had definite laboratory and pathology findings of severe cholestasis. Of the three surviving patients, on the other hand, one had cholestatic jaundice in spite of the favorable outcome.

In the future it will be necessary to compare in more detail the prevalence of hepatotoxic reactions to ketoconazole and the new oral antifungal azole derivatives[1, 26]. Recently it has been reported that fluconazole for example is much less hepatotoxic than ketoconazole[27, 28]. Mycoses, especially in certain immunodeficiencies, may have a very severe prognosis. Considering that a great number of patients have been treated with ketoconazole, a very effective drug, it is important to point out that hepatotoxicity due to this agent remains extremely rare.

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...creativity in science, as in the arts, cannot be organised. It arises spontaneously from individual talent. Well-run laboratories can foster it, but hierarchical organisation, inflexible, bureaucratic rules, and mountains of futile paperwork can kill it. Discoveries cannot be planned; they pop up, like Puck, in unexpected corners.

...creatividad en la ciencia, como en las artes, no puede ser organizada. Surge espontáneamente del talento individual. Laboratorios bien llevados pueden promoverla pero organizaciones arcaicas, reglas burocráticas, y montañas de expedientes pueden aniquilarla. Los descubrimientos no pueden ser planeados, suelen surgir, como Puck, en rincones inesperados.

Max Perutz

I wish I'd made you angry earlier. Cold Spring Harbor: Cold Spring Harbor Laboratory Press, 1998, p IX