

Flutamide-induced hepatotoxicity during treatment of acne - A case report*

*Hepatotoxicidade pela flutamida em paciente sob tratamento para acne - Relato de caso**

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Abstract: Flutamide is a non-steroidal anti-androgenic drug used in the treatment of prostate cancer, acne and hirsutism. Some cases of severe flutamide-induced hepatotoxicity have been reported in the literature. We report the case of a 21-year-old female who presented with a significant increase of aminotransferase levels during the treatment of acne with flutamide, which resolved completely after discontinuation of the drug. We discuss the diagnosis, the risk/benefit ratio, and conclude that monitoring liver function tests is mandatory and that the drug should be discontinued if an increase in aminotransferase levels occurs, due to the possibility of severe liver dysfunction.

Keywords: Acne vulgaris; Flutamide; Hepatitis, toxic

Resumo: A flutamida é agente antiandrogênico não esteróide usado no tratamento do câncer de próstata, da acne e do hirsutismo. Alguns casos de hepatotoxicidade grave têm sido apresentados na literatura com seu uso. Relata-se o caso de uma paciente com 21 anos de idade, que apresentou significativa elevação das aminotransferases durante o tratamento para acne com flutamida, completamente resolvida após a descontinuação da droga. Discute-se o diagnóstico, a relação risco/benefício e conclui-se que a monitoração com exames que avaliem o fígado é imperativa e que a droga deve ser suspensa se houver elevação de aminotransferases, dada a possibilidade de disfunção hepática grave.

Palavras-chave: Acne vulgar; Flutamida; Hepatite tóxica

INTRODUCTION

Flutamide is a non-steroidal anti-androgenic drug used in treatment of prostate cancer, and it is also prescribed to treat acne,¹ alopecia and hirsutism.² The incidence of flutamide-induced hepatotoxicity is < 0.18%. However, severe cases have been reported.² Hepatotoxicity is probably due to an idiosyncratic mechanism² or a mechanism involving the cytochrome

P450. In individuals with prostate cancer, a reduction of the CYP1A2 activity (the major enzyme involved in the activation of flutamide) promoting liver injury is suggested.³

Acute hepatitis in young patients during the treatment of acne with flutamide was reported,^{4,5} progressing to encephalopathy and coagulopathy.⁵ The objective of the present study is to report a case of oral flutamide-induced hepatotoxicity for the treatment of acne.

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CASE REPORT

A 21-year-old female patient, with body mass index (BMI) of 20.55 was referred by a dermatologist. She started to take oral flutamide (250mg/day) for the treatment of acne eight months before. She took the medication for five months, then discontinued the treatment for one month and restarted the same dose two months ago, totaling up seven months of treatment. She discontinued the medication ten days before her visit to Endocenter because of increased levels of aminotransferases - aspartate aminotransferase (AST) = 1762, reference value (RV) < 50U/L; alanine aminotransferase (ALT) = 1862, RV < 65U/L - and bilirubins - total bilirubin (TB) = 2.61; direct bilirubin (DB) = 0.77; indirect bilirubin (IB) = 1.84. The patient was asymptomatic. She denied the use of alcohol, risk factors for viral hepatitis, and past history of jaundice or liver disease. Four months before (in the fifth month on flutamide), she concomitantly took the anorectic drug sibutramine hydrochloride (15mg/day) for one month, having lost 2kg of her body weight. The patient had no past surgical history or blood transfusion and no family history of hepatobiliary disease. Her physical examination was normal, she had no symptoms, jaundice or any other sign of liver damage.

Laboratory tests: Laboratory tests: Her blood count showed red blood cells = 4,140,000/mm³, hemoglobin = 11.1g/dL, hematocrit = 32.7%; total white blood cells = 6,100/mm³, neutrophils = 56%, absolute neutrophil count = 3,416, eosinophils = 4%, basophils = 0, lymphocytes = 34%, monocytes = 6%; platelets = 322,000/mm³. Blood glucose, BUN, creatinine, cholesterol, triglycerides, and TSH were normal. Protein electrophoresis showed total protein (TP) = 6.8g/dL; albumin = 3.3g/dL, with normal alpha 1, alpha 2, and beta; gamma = 1.7g/dL (RV<1.6g/dL). Initial prothrombin time and activity (PTA) = 15", and 62%. Anti-HAV IgM was negative, and anti-HAV IgG was positive. HbsAg, anti-HBc IgM, and anti-HBc IgG were negative, as well as anti-HCV, anti-HEV IgM, and

IgG. Anti-smooth muscle antibodies, anti-mitochondria, anti-DNA, and anti-nuclear factor (ANF) were negative, as well as serology for dengue, cytomegalovirus, and Epstein-Barr. Ultrasonography of the abdomen was normal. The results and progression of biochemical tests are shown in table 1.

To assess causality, the Maria&Victorino⁶ scale was used, and the score obtained was 14 to 17, equal to probable. In the clinical follow-up, the patient was advised to keep her daily activities, with normal diet, and no medications. Aminotransferase levels gradually decreased and returned to normal values on the 71st day after drug discontinuation (Table 1). No clinical or other laboratory test alterations were observed.

DISCUSSION

The liver is the main organ for the metabolism of almost every drug. Liver injury may potentially occur secondary to usage of most substances. The most frequent manifestation is acute hepatitis, usually reversible, with hepatocellular necrosis or cholestasis, ranging from moderate biochemical alterations to acute liver failure. Chronic manifestations are less common and include chronic hepatitis, chronic cholestasis, fatty liver disease with steatohepatitis, fibrosis/cirrhosis, granulomatous or venoocclusive disease, peliosis hepatis, and benign or malignant neoplasia.⁷

In the majority of cases, the diagnosis of drug-induced hepatitis is based on circumstantial evidences. To establish a causal relation, several criteria are used, such as exclusion of other causes, improvement of clinical manifestations after drug discontinuation, and associated risk factors. Although no golden standard for the diagnosis exists, scales for causality assessment may be applied, such as that of the Council for International Organizations of Medical Sciences (CIOMS), and Maria & Victorino scale, which make the interpretation of findings easier.⁷

TABLE 1: Results and progression of laboratory tests after flutamide discontinuation

Test	Day 0 Result/(RV)	Day 11 Result/(RV)	Day 27 Result/(RV)	Day 71 Result/(RV)	Day 170 Result/(RV)
AST	1762U/L (≤ 50)	537U/L (≤ 50)	81U/L (≤ 50)	41U/L (≤ 50)	40U/L (≤ 50)
ALT	1862U/L (≤ 65)	840U/L (≤ 65)	94U/L (≤ 65)	48U/L (≤ 65)	52U/L (≤ 65)
GGT	-	149U/L (≤ 40)	82U/L (≤ 40)	32U/L (≤ 40)	33U/L (≤ 40)
TB	2.61mg/dL	1.79mg/dL	-	0,82mg/dL	0,88mg/dL
BD	0.77mg/dL	0.69mg/dL	-	0,40mg/dL	0,41mg/dL
IB	1.84mg/dL	1.10mg/dL	-	0,42mg/dL	0,47mg/dL
PTA	-	15" 62%	14" 70%	12"100%	12"100%
AP	-	109U/L (≤ 105)	101U/L (≤ 105)	-	91U/L (≤ 105)

Day 0 = flutamide discontinuation (RV) = reference value

The Maria & Victorino scale expresses the probability of a diagnosis of drug-induced liver injury using a final result or score, obtained after the inclusion and scoring of information comprising temporal relationship between drug intake and the onset of clinical manifestations, exclusion of other causes, extrahepatic manifestations, recurrence of clinical manifestation after re-exposure to the drug, and previous report in medical literature.⁶

In the present case, the main causes that could lead to similar laboratory alterations were ruled out (acute viral hepatitis, auto-immune hepatitis); a temporal relationship was observed (use during seven months, discontinuation for one month, and use for two more consecutive months); withdrawal was followed by reduction and normalization of aminotransferase levels.

During the fifth month of flutamide, sibutramine was concurrently used (a serotonin and norepinephrine reuptake inhibitor, metabolized in the liver via CYP 3A4), therefore, a drug interaction could be questioned. However, a study in obese patients with non-alcoholic steatohepatitis showed that the use of sibutramine for six months was associated, in addition to weight loss, with a significant reduction in serum ALT, AST and GGT, which were previously increased, although with an unexplainable increase in alkaline phosphatase (AP) levels.⁸ Since AP levels were practically unchanged in the present case, sibutramine could be not related to the alterations found.

The literature shows that in several cases reported of flutamine-induced hepatotoxicity the dose used was 750mg/day, the indication was malignant prostate cancer, and patients were aged over 70 years.² In this age range, the use of concomitant medications, usually for chronic diseases, is more frequent and a higher potential of drug interaction occurs, leading to a higher probability of hepatotoxicity. A study on the treatment of acne with flutamine 250mg/day in 38 women at childbearing age for up to 18 months did not show significant clinical or laboratory alterations.⁹ Another study showed severe reactions following a three to six month period of flutamide use, ranging from 4 to 443 days, mean of 151 days, in patients with prostate cancer.² In the present case, no changes occurred other than the biochemical alterations, which were detected after a seven-month use, although the onset of these alterations could not be determined, given the absence of previous test results.

The most frequent clinical manifestations of drug-induced acute hepatitis are known to be systemic symptoms (asthenia, nausea and vomiting), jaundice, increased aminotransferase levels - especially of ALT, and AP, approximately five times the upper normal limit. In more severe cases, coagulation disorders

and encephalopathy, indicative of acute liver failure, may occur.⁷ In this case, both the increase in AST and ALT levels were 30 times higher than the upper normal limit. In the majority of cases described, the liver disease was characterized by jaundice and general manifestations, in a range including cholestatic hepatitis and hepatocellular or mixed hepatitis,^{2,4,5,10} some with good outcomes after drug discontinuation, but several progressing to severe liver failure and even death.^{2,5}

A study in patients with prostate cancer showed a significant reduction of flutamide-induced liver toxicity when associated to ursodeoxycholic acid, which is used in the treatment of drug-induced liver diseases, among other indications.¹¹ Another study demonstrated that the caffeine test may be used to predict a possible occurrence of liver toxicity in individuals with prostate cancer.³ This test measures the activity of cytochrome P450 (CYP1A2), which is the major enzyme involved in the activation of flutamide, by measuring urine metabolites four to five hours following coffee intake.³

The diagnosis of drug-induced hepatitis is difficult because this manifestation is sometimes similar to viral hepatitis. Asymptomatic viral hepatitis A cannot be ruled out, because, although IgM antibodies may be detected for six months and, rarely, for two years, in some patients these antibodies are detected for only 30 days or less, and seroconversion may occur in up to one week.¹² In the present case, anti-HAV IgG (positive) and anti-HAV IgM (negative) tests were performed only 10 days after confirmation of increased aminotransferases. However, the use of a potentially hepatotoxic drug for seven months, plus biochemical alterations, and improvement after drug discontinuation suggest that the presence of anti-HAV IgG is due to a prior infection not related to the current event.

After flutamide started to be marketed in the United States for the treatment of metastatic prostate carcinoma, the Food and Drug Administration (FDA) received, from February 1989 to December 1994, reports of 20 patients who died of and 26 who were hospitalized for flutamide-related hepatotoxicity.¹³

Although the mechanisms of hepatotoxicity are not completely known, the literature reinforces the hypothesis that this drug may induce severe acute hepatitis, since many cases have been reported in several countries (Chile, China, Denmark, Spain, USA, Italy, and Japan) of a probable association of hepatotoxicity with the use of flutamide.^{4,13,14} This geographic diversity suggests that race is unlikely to contribute to hepatotoxicity.

Also, it seems that the dose and the period of use do not interfere as predisposing factors for the

onset of adverse reactions. Case reports showed a wide-ranging variation of time for the onset of signs of toxicity after introduction of the drug.² Hepatotoxicity is described at 250mg/day,⁵ 375mg/day and 750mg/day doses.¹⁰ However, the incidence was higher among female patients when flutamide was indicated for conditions other than prostate cancer and benign prostatic hypertrophy.^{2,5}

A higher risk of developing antiandrogenic therapy-related hepatotoxicity in patients with chronic viral hepatitis B or C is suggested.¹⁴ These data, however, do not support the recommendation of previous serologic testing for chronic hepatitis B or C when flutamide is used. Further studies are necessary.

In Brazil, the National Agency of Health Surveillance (Anvisa)¹⁵ determined the updating of the package insert of the product marketed, emphasizing flutamide-related hepatotoxicity, and disseminated a technical alert on the cases reported of fulminant hepatitis associated with this drug. Anvisa also conducted a study on flutamide use, by means of a questionnaire applied to doctors regarding the prescription of this drug for patients with dermatologic conditions, in addition to issuing a drug surveillance alert

on the risks of flutamide use in women with conditions for which the drug is not approved.¹⁵

Considering the possibility of developing severe liver dysfunction, patients on flutamide should be observed for the detection of signs and symptoms such as nausea, vomiting, fatigue, and jaundice, in addition to undergoing liver function tests prior to treatment, and at the second, fourth, sixth and eighth weeks. The drug should be discontinued immediately if abnormalities are detected.¹³

Based on the data presented, we conclude that, in the present case, flutamide at a 250mg/day dose used during seven months for the treatment of acne may have been responsible for hepatotoxicity with hepatocytic predominance. It is necessary to follow the recommendations established for the use of this drug, by monitoring liver biochemistry, including asymptomatic patients, to detect occasional alterations requiring discontinuation. Since the most likely mechanism of induction of flutamide-related hepatotoxicity is idiosyncratic, the risk/benefit ratio for the use of flutamide should be considered in conditions for which regulatory agencies have not approved the drug. □

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