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Bicalutamide

Updated: March 15, 2023.

OVERVIEW

Introduction

Bicalutamide is a second generation, oral nonsteroidal antiandrogen similar in structure to flutamide that has been used widely in the therapy of prostate cancer. Bicalutamide is associated with a low rate of serum enzyme elevations during therapy and has been linked to rare instances of liver injury.

Background

Bicalutamide (bye" ka loo' ta mide) is an orally available nonsteroidal antiandrogen that is similar in structure to flutamide and nilutamide used in the treatment of prostate cancer. Bicalutamide acts by binding to intracellular androgen receptors and competitively inhibiting the action of endogenous androgens on sensitive tissue, including testes, prostate, breast, skin and hypothalamus. Bicalutamide was approved for use in the United States in 1995. Current indications are for the therapy of metastatic prostate cancer in combination with luteinizing hormone releasing hormone (LHRH) analogs such as leuprolide or goserelin. Bicalutamide is available in tablets of 50 mg generically and under the trade name of Casodex. The recommended dose is 50 mg once daily. Common side effects of bicalutamide include fatigue, drowsiness, anxiety, gynecomastia and loss of libido. Rare but potentially severe adverse events include acute liver injury, Stevens Johnson syndrome, and severe hemorrhage when used with warfarin for anticoagulation.

Hepatotoxicity

Bicalutamide therapy is associated with mild, asymptomatic and transient elevations in serum aminotransferase levels in approximately 6% of patients. The frequency and height of the ALT elevations appears to be less with bicalutamide than flutamide. Similarly, there have been rare case reports of clinically apparent liver injury due to bicalutamide, but less frequently than with flutamide. In the Spanish pharmacovigilance study, there were 11 reports of hepatotoxicity from bicalutamide, none of which were fatal. On the other hand, the product label for bicalutamide mentions that a few cases of fatal hepatic failure have been reported. The clinical pattern of liver injury with bicalutamide appears to resemble that of flutamide. The latency to onset is usually 2 to 3 months, but can be shorter with reexposure and occasionally arises 4 to 6 months after starting. The typical pattern of serum enzyme elevations is hepatocellular and severe, fulminant cases have been described. Rash, fever and eosinophilia are not common and autoantibody formation is not described.

Likelihood score: B (likely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of bicalutamide hepatotoxicity is unknown. It is metabolized by the liver via the cytochrome P450 system, largely via CYP 3A4 which it can inhibit and thus cause drug-drug interactions. Thus, liver injury from bicalutamide may be caused by toxic or immunogenic metabolites of the agent. The lower frequency of hepatotoxicity from bicalutamide compared to flutamide may be due to its lower dose or its lower rate of hepatic metabolism.

Outcome and Management

The mild ALT elevations during bicalutamide therapy are usually self-limiting even with continuation of the medication. The rare instances of clinically apparent liver injury have ranged in severity from mild self-limiting cases to fatal acute liver failure. Monitoring of liver tests during therapy is recommended. There is no information on cross sensitivity to hepatic injury among the various antiandrogens. Rechallenge should be avoided and switching therapy to flutamide or nilutamide cannot be recommended.

Drug Class: Antineoplastic Agents, Antiandrogens

CASE REPORTS

Case 1. Acute liver failure arising after two doses of bicalutamide.(1)

A 60 year old man with prostate cancer developed acute liver failure following two doses of bicalutamide and a few days after stopping a 3 month course of flutamide. Liver test results were reported to be normal at the time of diagnosis of prostate cancer. Following an initial month of therapy with cyproterone acetate, flutamide and monthly subcutaneous goserelin acetate was started. Although flutamide was well tolerated, it was discontinued after 3 months and bicalutamide was substituted. After the second dose of bicalutamide, the patient developed jaundice and confusion. All medications were stopped and he was admitted for evaluation and therapy. He had no previous history of liver disease, no risk factors for viral hepatitis and no recent use of alcohol or acetaminophen. Serum bilirubin was 19.5 mg/dL, and serum ALT was markedly elevated with minimal increase in alkaline phosphatase levels (Table). The INR was 2.2. Tests for hepatitis A, B, C and for EBV infection were negative as were autoantibodies. An abdominal ultrasound revealed no evidence of biliary disease or liver metastasis. The patient developed mental obtundation and required intensive care support, vitamin K, and lactulose. After an initial period of worsening, he improved slowly. Eight weeks later, serum enzymes and bilirubin levels were normal.

Key Points

Medication:	Bicalutamide, 50 mg, 2 doses, and flutamide, 750 mg daily for 3 months
Pattern:	Hepatocellular
Severity:	4+ (jaundice, hospitalization, coagulopathy and encephalopathy)
Latency:	2 days for bicalutamide, 3 months for flutamide
Recovery:	2 months
Other medications:	Flutamide, cyproterone acetate, goserelin acetate

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Bicalutamide 50 mg daily for two days					

Table continued from previous page.

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
2	0	2690	181	19.5	INR=2.2
8 weeks	8 weeks	Normal	Normal	Normal	Asymptomatic
Normal Values		**<35**	**<130**	**<1.2**	

Comment

Although widely cited as an example of bicalutamide hepatotoxicity, this case can only be said to be "possibly" related to bicalutamide and is much more likely due to flutamide hepatotoxicity with the typical abrupt hepatocellular pattern of injury arising after 3 months of therapy. Indeed, even with the most severe hepatic injury (in the absence of hemolysis), it would take more than 2 days for serum bilirubin to rise from normal to 19 mg/dL. Cyproterone has also be linked to similar cases of hepatocellular injury, but the appearance of jaundice several months after stopping this agent, makes it unlikely as the cause.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Bicalutamide – Generic, Casodex®

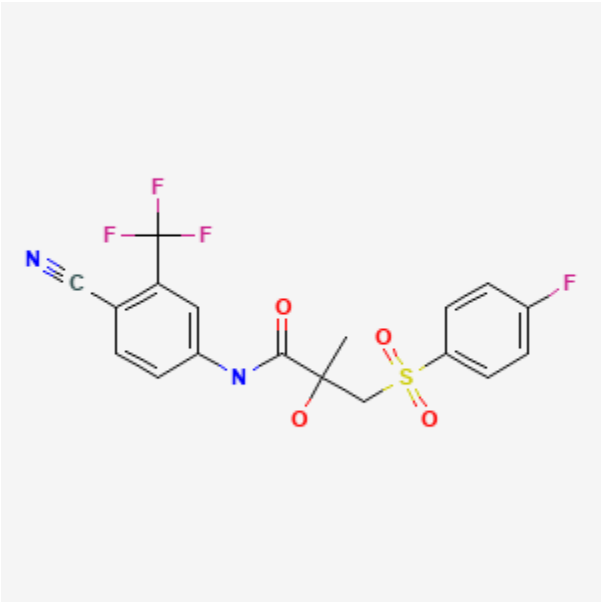
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Bicalutamide	90357-06-5	C18-H14-F4-N2-O4-S	

CITED REFERENCE

1. Dawson LA, Chow E, Morton G. Fulminant hepatic failure associated with bicalutamide. Urology. 1997;49:283–4. PubMed PMID: 9037299.

ANNOTATED BIBLIOGRAPHY

References updated: 15 March 2023

Abbreviations: LHRH, luteinizing hormone releasing hormone; PSA, prostate specific-antigen.

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, p. 699.

(Expert review of hepatotoxicity published in 1999, mentions that flutamide has led to instances of severe hepatic necrosis and fulminant hepatic failure).

DeLeve LD. Flutamide. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd Edition. Amsterdam: Elsevier, 2013. pp. 559.

(Textbook on drug induced liver injury mentions that flutamide has been implicated in 46 cases of severe liver injury with 20 fatalities; bicalutamide is not discussed).

Moy B, Lee RJ, Smith M. Hormone therapy in prostate cancer. Natural products in cancer chemotherapy: hormones and related agents. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1763-9.

(Textbook of pharmacology and therapeutics; discusses the role of androgen receptor blockers in prostate cancer including bicalutamide, flutamide and nilutamide).

Kennealey GT, Furr BJ. Use of the nonsteroidal anti-androgen Casodex in advanced prostatic carcinoma. Urol Clin North Am. 1991;18:99–110. PubMed PMID: 1992575.

(Review of pharmacokinetics and early phase studies of bicalutamide for prostate cancer; no mention of hepatotoxicity).

Schellhammer P, Sharifi R, Block N, Soloway M, Venner P, Patternson AL, Sarosdy M, et al. A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer. Casodex Combination Study Group. Urology. 1995;45:745–52. PubMed PMID: 7538237.

(Analysis of trial of bicalutamide vs flutamide in 813 men with prostate cancer at 60 sites; abnormal liver function reported in ~12% of flutamide vs ~8% of bicalutamide treated patients, but few details given as to nature, severity or reversibility).

Kotake T, Usami M, Isaka S, Shimazaki J, Oishi K, Yoshida O, Ozono S, et al. Hinyokika Kiyo. 1996;42:143–53. [Phase I study of bicalutamide (Casodex), a nonsteroidal antiandrogen in patients with prostatic cancer]. Japanese. PubMed PMID: 8712091.

(Trial of escalating doses of bicalutamide for 12 weeks in 16 patients; 3 developed abnormal liver tests, but all reversed with stopping therapy [abstract only]).

Dawson LA, Chow E, Morton G. Fulminant hepatic failure associated with bicalutamide. Urology. 1997;49:283–4. PubMed PMID: 9037299.

(60 year old man with prostate cancer was given cyproterone and flutamide for 3 months and then switched to bicalutamide developing jaundice after 2 doses [bilirubin 19.5 mg/dL, ALT 2690 U/L, Alk P 181 U/L, INR 2.2 and encephalopathy], improving within 2 months: Case 1).

Chodak GW. Bicalutamide-associated fulminant hepatic failure. Urology. 1997;50:1027.

(Letter disputing the role of bicalutamide in case described by Dawson [1997] because flutamide had been stopped a few days before and was the more likely culprit).

Schellhammer PF. Fulminant hepatic failure associated with bicalutamide. Urology. 1997;50:827.

(Letter regarding case report by Dawson [1997] expressing doubt that the injury was due to bicalutamide [given for 2 days only] rather than flutamide [given for 3 months] or cyproterone [given for 1 month]).

McLeod DG. Tolerability of nonsteroidal antiandrogens in the treatment of advanced prostate cancer. Oncologist. 1997;2:18–27. PubMed PMID: 10388026.

(Overview of the safety and side effects of the nonsteroidal antiandrogens; ALT elevations in 6% receiving bicalutamide vs 10% with flutamide; clinically apparent hepatitis can occur but is rare).

Palmberg C, Kylmala T, Tammela T. Reduction of flutamide-induced alanine aminotransferase elevation after replacement by bicalutamide in a patient with N+ disease treated with maximal androgen blockade as a primary treatment. Br J Urol. 1997;79:808–9. PubMed PMID: 9158528.

(46 year old man with prostate cancer developed ALT elevations [106 U/L] without jaundice after 21 months of flutamide [750 mg/day], which improved on stopping [to 73 U/L] and increased again [108 U/L] with restarting [500 mg/day]. Switching to bicalutamide [50 mg/day] was followed by decrease of ALT but not to normal [53 U/L]).

Tyrrell CJ, Kaisary AV, Iversen P, Anderson JB, Baert L, Tammela T, Chamberlain M, et al. A randomised comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol. 1998;33:447–56. PubMed PMID: 9643663.

(European trial of bicalutamide vs orchiectomy in 1453 men with prostate cancer, found bicalutamide monotherapy less effective; no mention of serious adverse events or hepatotoxicity).

Schellhammer PF, Davis JW. An evaluation of bicalutamide in the treatment of prostate cancer. Clin Prostate Cancer. 2004;2:213–9. PubMed PMID: 15072604.

(Review of randomized trials of bicalutamide for prostate cancer with no new information on hepatotoxicity).

Thole Z, Manso G, Salgueiro E, Revuelta P, Hidalgo A. Hepatotoxicity induced by antiandrogens: a review of the literature. Urol Int. 2004;73:289–95. PubMed PMID: 15604569.

(Systematic review of the literature from the Spanish pharmacovigilance group; 21 reports on hepatotoxicity of cyproterone, 46 flutamide, 4 nilutamide and only 1 bicalutamide; 6 cases of hepatocellular carcinoma linked to cyproterone therapy).

Manso G, Thole Z, Salgueiro E, Revuelta P, Hidalgo A. Spontaneous reporting of hepatotoxicity associated with antiandrogens: data from the Spanish pharmacovigilance system. Pharmacoepidemiol Drug Saf. 2006;15:253–9. PubMed PMID: 16294367.

(Analysis of spontaneous reporting to Spanish Pharmacovigilance system found 88 cases of flutamide, 11 bicalutamide and 15 cyproterone hepatotoxicity, latency 3-6 months; 2 fatalities, both from flutamide).

Castro Beza I, Sánchez Ruiz J, Peracaula Espino FJ, Villanego Beltrán MI. Drug-related hepatotoxicity and hepatic failure following combined androgen blockade. Clin Transl Oncol. 2008;10:591–2. PubMed PMID: 18796378.

(61 year old man with prostate cancer developed jaundice 3 months after starting bicalutamide [bilirubin 11.5 mg/dL, ALT 1923 U/L, Alk P 169 U/L], and subsequently developed progressive liver failure and died).

O'Bryant CL, Flaig TW, Utz KJ. Bicalutamide-associated fulminant hepatotoxicity. Pharmacotherapy. 2008;28:1071–5. PubMed PMID: 18657023.

(59 year old man with prostate cancer developed abdominal pain 4 days after restarting bicalutamide [bilirubin not given, ALT 111 rising to 2050 U/L, INR 3.4], which was followed by multiorgan failure and death in 4 days).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to an antiandrogen).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to antiandrogen therapies).

Hussain S, Haidar A, Bloom RE, Zayouna N, Piper MH, Jafri SM. Bicalutamide-induced hepatotoxicity: A rare adverse effect. Am J Case Rep. 2014;15:266–70. PubMed PMID: 24967002.

(81 year old man with prostate cancer developed jaundice 3 weeks after starting bicalutamide [bilirubin 3.7 mg/dL, ALT 576 U/L, Alk P 223 U/L, INR 1.5], which improved rapidly after stopping).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 1 case [0.1%] was attributed to bicalutamide: 50 year old man with prostate cancer developed jaundice 4 months after starting bicalutamide [bilirubin 3.4 mg/dL, ALT 2412 U/L, Alk P 147 U/L, INR 1.2] with slow but complete resolution upon stopping).

Yun GY, Kim SH, Kim SW, Joo JS, Kim JS, Lee ES, Lee BS, et al. Atypical onset of bicalutamide-induced liver injury. World J Gastroenterol. 2016;22:4062–5. PubMed PMID: 27099451.

(62 year old man with prostate cancer developed jaundice 19 weeks after starting bicalutamide [bilirubin 1.6 mg/dL, ALT 677 U/L, Alk P 87 U/L, INR 1.17], resolving completely within 3 months of stopping).

Crawford ED, Schellhammer PF, McLeod DG, Moul JW, Higano CS, Shore N, Denis L, et al. Androgen receptor targeted treatments of prostate cancer: 35 years of progress with antiandrogens. J Urol. 2018;200:956–966. PubMed PMID: 29730201.

(Review of the development of antiandrogen therapies of prostate cancer starting with discovery of the androgen sensitive nature of prostate cancer, the effects of orchiectomy, followed by the development of androgen receptor antagonists, first generation agents flutamide and nilutamide, second generation agent bicalutamide and third generation agents enzalutamide, apalutamide and darolutamide that have more potent androgen receptor inhibition).

Liu J, Agyapong G, Misra D, Taylor CD, Hirsh DA. A rare case of idiopathic cholestasis: Clinical conundrums complicating enzalutamide therapy in metastatic prostate cancer. Clin Case Rep. 2019;7:2068–2073. PubMed PMID: 31788253.

(88 year old man with metastatic prostate cancer developed jaundice one week after stopping a 5 month course of bicalutamide and starting enzalutamide while continuing on leuprolide [bilirubin 3.8 mg/dL, ALT 45 U/L, Alk P 654 U/L, GGT 988 U/L, INR 1.2], with little improvement after stopping all therapy and death from suspected progressive disease 2 weeks later).

Saito S. Successful recovery from multiple organ failure associated with bicalutamide and leuprorelin acetate for prostate cancer. Urol Case Rep. 2019;29:101108. PubMed PMID: 31934548.

(79 year old man with metastatic prostate cancer developed renal failure, proteinuria, hypertension, pulmonary dysfunction and liver test abnormalities shortly after starting bicalutamide and leuprorelin [ALT 147 U/L, AST 89 U/L, creatinine 5.6 mg/dL, bilirubin and Alk P not provided], resolving with supportive care).

Vaishampayan UN, Heilbrun LK, Monk P 3rd, Tejwani S, Sonpavde G, Hwang C, Smith D, et al. Clinical efficacy of enzalutamide vs bicalutamide combined with androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a randomized clinical trial. JAMA Netw Open. 2021;4:e2034633. PubMed PMID: 33496795.

(Among 71 men with advanced prostate cancer treated with either enzalutamide [160 mg] or bicalutamide [50 mg] daily with androgen-depletion therapy using a LHRH analog, the biochemical and overall survival outcomes were greater with enzalutamide than bicalutamide, particularly in Black subjects; no mention of hepatic adverse events).

Yanagisawa T, Kimura T, Mori K, Suzuki H, Sano T, Otsuka T, Iwamoto Y, et al. Abiraterone acetate versus nonsteroidal antiandrogen with androgen deprivation therapy for high-risk metastatic hormone-sensitive prostate cancer. Prostate. 2022;82(1):3–12. PubMed PMID: 34559410.

(Among 312 men with prostate cancer treated with abiraterone [1000 mg] or bicalutamide [80 mg] daily, overall and cancer specific survival were similar in the two groups, but adverse events were more common with abiraterone [27% vs 21%] as was "impaired liver function" [16% vs 2%], and there were no deaths or severe adverse events attributed to liver injury).