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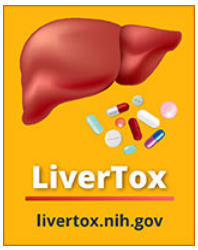


Histrelin

Updated: March 22, 2018.

OVERVIEW

Introduction

Histrelin is a gonadotropin releasing hormone (GnRH) agonist that is a potent inhibitor of production of testosterone (in men) and estrogen (in women) and is used predominantly to treat advanced prostate cancer. Histrelin is associated with a low rate of transient serum enzyme elevations during therapy, but has not been linked convincingly to cases of clinically apparent acute liver injury.

Background

Histrelin (his trel' in) is a nonapeptide analogue of gonadotropin releasing hormone that acts on the pituitary to cause the synthesis and release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), two gonadotropins that act on the male testes to stimulate the production of testosterone and on the female ovaries to induce synthesis of estrogen. Histrelin and other GnRH agonists cause an initial surge of gonadotropin release, but then lead to down-regulation of their synthesis and secretion which results in a decline in testosterone and estrogen production. Histrelin, alone or in combination with other antiandrogens, has been found to be palliative in advanced prostate cancer and as effective as surgical castration. Histrelin was approved for use in the United States in 1991 and as a once-yearly implant formulation in 2004. The major indications for histrelin are advanced prostate cancer and precocious puberty. Histrelin is available generically and under the brand names Supprelin (for precocious puberty) and Vantas (for prostate cancer) in solution as implants of 50 mg, which are inserted subcutaneously in the inner aspect of the upper arm at 12 month intervals. Histrelin and the other GnRH analogues cause a profound hypogonadism ("chemical castration") and its common side effects are typical of androgen deprivation, including hot flashes, loss of libido, erectile dysfunction, depression, nausea, diarrhea, weight gain and fluid retention. Rare, but potentially severe adverse events include hypersensitivity reactions and transient tumor flare with the first injection.

Hepatotoxicity

Histrelin has been associated with serum enzyme elevations during therapy in rates similar to those of other GnRH analogues. The serum enzyme elevations are generally mild, asymptomatic and resolve even without dose adjustment or drug discontinuation. ALT elevations above 3 times the upper limit of normal occur in less than 1% of recipients. Histrelin has been linked to a single case of acute liver injury, but it was unclear from the report whether the episode was associated with jaundice or symptoms and other diagnoses remained possible. Thus, clinically apparent liver injury from histrelin may occur, but it is extremely rare and usually self-limited in course. There have been no episodes of acute liver failure, chronic hepatitis or vanishing bile duct syndrome associated with histrelin or other GnRH analogue therapy.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the minor serum enzyme elevations that can occur during histrelin therapy is unknown. Histrelin is a short peptide similar to GnRH and is metabolized locally in tissue and not by the hepatic cytochrome P450 system. Some serum enzyme elevations may be caused by nonalcoholic fatty liver arising because of weight gain or metabolic changes caused by the androgen deprivation state induced by the GnRH agonist.

Outcome and Management

The serum enzyme elevations during histrelin therapy rarely require dose modification or drug discontinuation and should instead lead to investigation of other possible causes of liver injury. There is no evidence for cross sensitivity to liver injury among the various GnRH analogues, despite their similarity in chemical structure.

Drug Class: Antineoplastic Agents, GnRH Analogues

Other Drugs in the Subclass, GnRH Analogues: Degarelix, Goserelin, Leuprolide, Triptorelin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Histrelin – Supprelin®

Histrelin – Vantas®

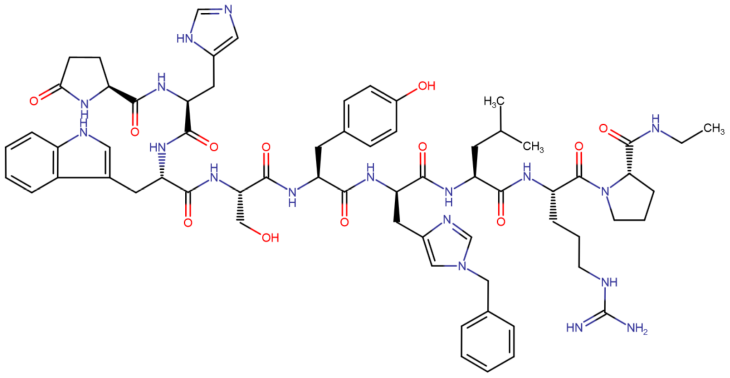
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Histrelin	76712-82-8	C66-H86-N18-O12	

ANNOTATED BIBLIOGRAPHY

References updated: 22 March 2018

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, pp. 699.

(Expert review of hepatotoxicity published in 1999; GnRH analogues such as histrelin are not discussed).

Chitturi S, Farrell GC. Estrogen receptor antagonists. Adverse effects of hormones and hormone antagonists on the liver. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 610-2.

(Review of hepatotoxicity of hormonal products; does not discuss the GnRH agonists such as histrelin).

Moy B, Lee RJ, Smith M. Gonadotrophin-releasing hormone agonists and antagonists. 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. 1764.

(Textbook of pharmacology and therapeutics).

Chertin B, Spitz IM, Lindenberg T, Algur N, Zer T, Kuzma P, Young AJ, et al. An implant releasing the gonadotropin hormone-releasing hormone agonist histrelin maintains medical castration for up to 30 months in metastatic prostate cancer. J Urol 2000; 163: 838-44. PubMed PMID: 10687989.

(Among 21 men with advanced prostate cancer who were treated with a long acting implant of histrelin, LH and testosterone levels were suppressed long term, while adverse events included loss of libido; ALT elevations were not mentioned).

Schlegel PN, Kuzma P, Frick J, Farkas A, Gomahr A, Spitz I, Chertin B, et al. Effective long-term androgen suppression in men with prostate cancer using a hydrogel implant with the GnRH agonist histrelin. Urology 2001; 58: 578-82. PubMed PMID: 11597543.

(Among 42 men with advanced prostate cancer who were treated with 1 to 4 hydrogel implants of histrelin, testosterone suppression lasted for at least 12 months and adverse events included implant site pain or irritation and 50% had hot flashes; there were no serious adverse events attributable to the histrelin and no mention of ALT elevations or hepatotoxicity).

Lewis KA, Eugster EA. Experience with the once-yearly histrelin (GnRHa) subcutaneous implant in the treatment of central precocious puberty. Drug Des Devel Ther 2009; 3: 1-5. PubMed PMID: 19920916.

(Review of the use of histrelin implants in management of precocious puberty including results from 3 studies in a total of 78 children mentions that the most common adverse reactions are complications at the implant site, and that there have been "no reported significant abnormalities in...clinical laboratory evaluations").

Deeks ED. Histrelin: in advanced prostate cancer. Drugs 2010; 70: 623-30. PubMed PMID: 20329807.

(Review of the pharmacology, clinical efficacy and safety of histrelin implants which can result in testosterone suppression to castrate levels for up to a year; major side effects are those of androgen deprivation; no mention of ALT elevations or hepatotoxicity).

Ricker JM, Foody WF, Shumway NM, Shaw JC. Drug-induced liver injury caused by the histrelin (Vantus) subcutaneous implant. South Med J 2010; 103: 84-6. PubMed PMID: 19996852.

(69 year old man with prostate cancer developed liver test abnormalities while on ketoconazole and marked worsening one month after placement of a histrelin implant [bilirubin not given, ALT ~1000 U/L, Alk P ~300 U/L], resolving within a month of removal of the implant).

Shore N, Cookson MS, Gittelman MC. Long-term efficacy and tolerability of once-yearly histrelin acetate subcutaneous implant in patients with advanced prostate cancer. BJU Int 2012; 109: 226-32. PubMed PMID: 21851539.

(Review of efficacy and safety of histrelin implant therapy of advanced prostate cancer; mentions side effects of hot flashes, fatigue, testicular atrophy, gynecomastia, decrease in libido and erectile dysfunction, but does not mention ALT elevations or hepatotoxicity).

Van Poppel H, Klotz L. Gonadotropin-releasing hormone: an update review of the antagonists versus agonists. Int J Urol 2012; 19: 594-601. PubMed PMID: 22416801.

(Review of androgen deprivation therapy for prostate cancer using GnRH agonists and antagonists stressing the more rapid onset of action and similar if not better safety profile of GnRH antagonists).

Walker LM, Tran S, Robinson JW. Luteinizing hormone--releasing hormone agonists: a quick reference for prevalence rates of potential adverse effects. Clin Genitourin Cancer 2013; 11: 375-84. PubMed PMID: 23891497.

(Systematic review of adverse event profile of long term use of GnRH agonists which mostly relate to the hormonal changes that occur: hot flashes, gynecomastia, genital shrinkage, hair loss, osteoporosis, mild anemia, hyperglycemia, increased weight, loss of skeletal muscle mass, emotional lability, depression, loss of sexual desire and erectile dysfunction; no mention of ALT elevations or hepatotoxicity).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none of the 96 were attributed to histrelin or any of the GnRH analogues).

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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to histrelin or any of the GnRH analogues).

Bolton EM, Lynch TH. Are all gonadotropin-releasing hormone agonists equivalent for the treatment of prostate cancer? A systematic review. BJU Int 2018;122 (3): 371-83. PubMed PMID: 29438592.

(Systematic review of literature on relative efficacy and safety of different GnRH agonists, indicates that there is little evidence of superiority of any of the four, largely because of lack of adequately powered, controlled studies comparing them).