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Pramlintide

Updated: June 6, 2016.

OVERVIEW

Introduction

Pramlintide is a recombinant DNA produced polypeptide analogue of human amylin that is used in combination with insulin in the therapy of diabetes. Pramlintide has not been associated with serum enzyme elevations during therapy or with instances of clinically apparent liver injury.

Background

Pramlintide (pram' lin tide) is a synthetic analogue of human amylin that is used in combination with insulin in the treatment of diabetes. Amylin is a human pancreatic hormone which, like insulin, is produced in pancreatic beta cells and aids in the control of blood sugar after meals by delaying gastric emptying, decreasing glucagon secretion and suppressing appetite. The loss of beta cell function that occurs early in type 1 diabetes and late in type 2 diabetes leads to deficiency in amylin secretion. Pramlintide differs from human amylin in 3 of its 37 amino acids, modifications which allow for a longer half-life of the hormone. Pramlintide was approved for use in diabetes as an adjunct to insulin therapy in the United States in 2005. Pramlintide is available in solution in vials and pens for injection under the brand name Symlin. The typical starting dose in type 1 diabetes is 15 μg subcutaneously before each meal, with subsequent titration to a target dose of 60 μg before each meal. The recommended starting dose in type 2 diabetes is 60 μg, with a target maintenance dose of 120 μg subcutaneously before each meal. Common side effects of pramlintide include nausea, vomiting, anorexia, fatigue, headache, dizziness and hypoglycemia. Severe adverse reactions include severe hypoglycemia, particularly in type 1 diabetes.

Hepatotoxicity

In large clinical trials, serum enzyme elevations were rare (<1%) during pramlintide/insulin therapy and no more common than with placebo and there were no reports of clinically apparent liver injury among treated patients. Since licensure, there have been no published case reports of hepatotoxicity due to pramlintide and the product label does not list liver injury as an adverse event. Thus, liver injury due to pramlintide must be rare, if it occurs at all.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Pramlintide is a polypeptide and is metabolized to amino acids by serum and tissue proteases, and is unlikely to have any direct hepatotoxic potential.

Drug Class: Antidiabetic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pramlintide – Symlin®

DRUG CLASS

Antidiabetic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Pramlintide	151126-32-8	Protein	Complex Polypeptide

ANNOTATED BIBLIOGRAPHY

References updated: 06 June 2016

Zimmerman HJ. Oral hypoglycemic agents and other diabetes therapy. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 575-9.

(Textbook of hepatotoxicity published in 1999, before the availability of pramlintide).

De Marzio DH, Navarro VJ. Antidiabetic drugs. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 528-32.

(Review of hepatotoxicity of drugs for diabetes; mentions that there have been no reports of hepatotoxicity attributable to pramlintide).

Powers AC, D'Alessio D. Therapy of diabetes. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1248-67.

(Textbook of pharmacology and therapeutics).

Thompson RG, Peterson J, Gottlieb A, Mullane J. Effects of pramlintide, an analog of human amylin, on plasma glucose profiles in patients with IDDM: results of a multicenter trial. Diabetes 1997; 46: 632-6. PubMed PMID: 9075803.

(Among 168 patients with diabetes on insulin therapy treated with 1 of 3 doses of pramlintide or placebo 4 times daily for a 2 week period, side effects included nausea, anorexia and dyspepsia; no mention of ALT elevations or hepatotoxicity).

Hollander PA, Levy P, Fineman MS, Maggs DG, Shen LZ, Strobel SA, Weyer C, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. Diabetes Care 2003; 26: 784-90. PubMed PMID: 12610038.

(Among 636 patients with diabetes on insulin who were treated with one of 3 doses of pramlintide or placebo for 52 weeks, there was greater decline in HbA1c and weight loss with pramlintide and there was "no evidence of … hepatic … toxicity or drug-related idiosyncratic side effects").

Ratner RE, Dickey R, Fineman M, Maggs DG, Shen L, Strobel SA, Weyer C, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabet Med 2004; 21: 1204-12. PubMed PMID: 15498087.

(Among 651 patients with type 1 diabetes on insulin treated with mealtime injections of 3 doses of pramlintide or placebo for up to 52 weeks, therapy led to a decrease in HbA1c levels, and side effects were mainly nausea, vomiting and anoxia, with a 40% drop out rate).

Pramlintide(symlin) for diabetes. Med Lett Drugs Ther 2005; 47 (1209): 43-4. PubMed PMID: 15912124.

(Concise summary of mechanism of action, clinical efficacy, side effects and costs of pramlintide shortly after its approval for use in the US, mentions side effects of anorexia, nausea and vomiting, headache and hypoglycemia).

Edelman S, Garg S, Frias J, Maggs D, Wang Y, Zhang B, Strobel S, et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care 2006; 29: 2189-95. PubMed PMID: 17003291.

(Among 296 patients with type 1 diabetes on mealtime insulin treated with pramlintide or placebo for 29 weeks, HbA1c levels decreased to a similar extent; side effects of pramlintide included nausea [63% vs 36%], anorexia [2% vs 9%] and vomiting [6% vs 13.5%]; no mention of ALT elevations or hepatotoxicity).

Aronne L, Fujioka K, Aroda V, Chen K, Halseth A, Kesty NC, Burns C, et al. Progressive reduction in body weight after treatment with the amylin analog pramlintide in obese subjects: a phase 2, randomized, placebo-controlled, dose-escalation study. J Clin Endocrinol Metab 2007; 92: 2977-83. PubMed PMID: 17504894.

(Among 204 obese subjects [not on insulin] treated with mealtime pramlintide vs placebo for 16 weeks, weight loss was greater with pramlintide [-3.6 kg] and side effects included nausea and hypoglycemia [8% vs 1%], and "no unexpected safety signals were observed as assessed by…clinical laboratory measures").

Smith SR, Aronne LJ, Burns CM, Kesty NC, Halseth AE, Weyer C. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. Diabetes Care 2008; 31: 1816-23. PubMed PMID: 18753666.

(Among 411 obese subjects given a life-style intervention with or without pramlintide (6 dose regimens) for 4 months, weight loss was greater with pramlintide [3.8 to 6.1 vs 2.8 kg] and the most common side effect was nausea [9% to 29% vs 2%]; no mention of ALT elevations or hepatotoxicity).

Riddle M, Pencek R, Charenkavanich S, Lutz K, Wilhelm K, Porter L. Randomized comparison of pramlintide or mealtime insulin added to basal insulin treatment for patients with type 2 diabetes. Diabetes Care 2009; 32: 1577-82. PubMed PMID: 19502544.

(Among 113 patients with type 2 diabetes treated with mealtime pramlintide or insulin for 24 weeks, there were similar decreases in HbA1c and fasting glucose, while adverse events included nausea [21% vs 0%] and hypoglycemia [55% vs 80%]).

Pencek R, Roddy T, Peters Y, De Young MB, Herrmann K, Meller L, Nguyen H, et al. Safety of pramlintide added to mealtime insulin in patients with type 1 or type 2 diabetes: a large observational study. Diabetes Obes Metab 2010; 12: 548-51. PubMed PMID: 20518811.

(Among 1297 patients with diabetes on insulin who started mealtime pramlintide therapy, severe hypoglycemia episodes occurred in 4.8% with type 1 and 2.8% with type 2 during the first 3 months, and declined to 1.8% and 0.3% during the second 3 months; no mention of ALT elevations or hepatotoxicity).

Younk LM, Mikeladze M, Davis SN. Pramlintide and the treatment of diabetes: a review of the data since its introduction. Expert Opin Pharmacother 2011; 12: 1439-51. PubMed PMID: 21564002.

(Review of the safety and efficacy of pramlintide in treatment of diabetes discusses adverse events of nausea, vomiting, anorexia and severe hypoglycemia; 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 was attributed to drugs for diabetes including pramlintide).

Drugs for type 2 diabetes. Treat Guidel Med Lett 2014; 12 (139): 17-24. PubMed PMID: 24566424.

(Concise overview and recommendations on the use of medications in diabetes mentions that pramlintide, an amylinomimetic agent that is injected subcutaneously before meals, reduces postprandial glucose excursions and promotes weight loss, but reduces HbA1c by only 0.5%; no mention of adverse events).

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 in the US collected between 2004 and 2012, 4 cases were attributed to drugs used for diabetes [metformin, glyburide, sitagliptin], but no cases were attributed to pramlintide).