Drug Update

Pramlintide

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ABSTRACT

Amylin is a second beta-cell hormone that is co-secreted with insulin, in response to nutrient stimuli. Diabetes represents a state of bihormonal beta cell deficiency and that lack of amylin action may contribute to abnormal glucose homeostasis. Amylin has glucose-lowering effects in both animals and humans.The effects of Pramlintide (amylin analogue)can be summarized as follows : (1) suppression of endogenous glucagon production, especially in the postprandial state; (2) consequent reduction of postprandial hepatic glucose production; (3) reduction in gastric emptying time; (4) centrally mediated induction of satiety; and (5) reduction in postprandial glucose levels. Pramlintide has been approved as an adjunct to insulin in both type 1 and type 2 DM. Though it has not yet found place in any of the standard guidelines.

History of Amylin :

In year 1900, Opie had identified a hyaline material in islets of Langerhans, which was later found out to be amyloid[1]. In 1987, a sequence of a 37 amino acid peptide was extracted from amyloid containing pancreatic material in patients with Type 2 diabetes mellitus. This was initially called IAP or "islet amyloid polypeptide, DAP" or "diabetes associated peptide". This was changed in 1988 to amylin to indicate the origin of the peptide and the fact that its presence was not restricted to individuals with type 2 diabetes mellitus[2,3,4,5]. Following the discovery of amylin, a second beta-cell hormone that is co-secreted with insulin in response to nutrient stimuli, it was realized that diabetes represents a state of bihormonal beta cell deficiency and that lack of amylin action may contribute to abnormal glucose homeostasis. Experimental studies show that amylin acts as a neuroendocrine hormone that complements the effects of insulin in postprandial glucose regulation through several centrally mediated effects[6]. The analog of human amylin was given the name pramlintide and proprietary name Symlin[2].

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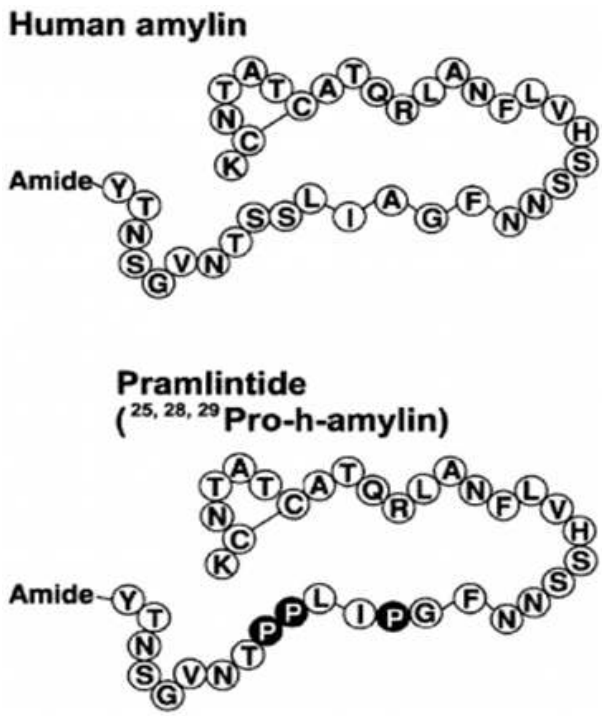
Chemical Structure :



Human amylin and Pramlitide[7]

Pramlintide is a water-soluble salt with a pH of 4.0. This leads to an issue with combination with other injectible anti-hyperglycemic agents[7]. Native amylin was characterized as "glue like," somewhat unstable as a compound in solution, modifying amylin to a compound with more manageable physical properties resulted in the development of pramlintide. Pramlintide has similar physiologic effects as native amylin, but could be produced as

the stable inject able product now available for clinical use as Symlin™[8]

Mechanism of Action -

An amylin analog, pramlintide, is used to treat insulin-requiring diabetes. Its anorexigenic actions give it potential as an obesity treatment. There are 3 amylin receptors (AMY1, AMY2, AMY3), comprising the calcitonin receptor and receptor activity-modifying proteins 1, 2 and 3, respectively[9].

SYMLIN does not extensively bind to red blood cells or albumin (approximately 40% of the drug is unbound in plasma).

Metabolism and Elimination

Absorption

The absolute bioavailability of pramlintide following a single subcutaneous dose of SYMLIN is approximately 30% to 40%. In healthy individuals, the half-life of pramlintide is approximately 48 minutes. The primary metabolite, Des-lys1 pramlintide (2-37 pramlintide), is biologically active in vitro. Overall exposure (AUC) to pramlintide is relatively constant with repeat dosing of SYMLIN, indicating no bioaccumulation[6].

Renal Impairment

No studies have been conducted in patients with end-stage renal disease. In a single-dose pharmacokinetic study in patients with type 1 diabetes, 60 mcg of SYMLIN was administered to 4 patients with normal renal function (ClCr > 90 mL/min), 9 patients with mild renal impairment (ClCr 60-89 mL/min), 5 patients with moderate renal impairment (ClCr 30-59 mL/min) and 3 patients with severe renal impairment (ClCr 15-29 mL/min). No statistically significant differences were noted in total (AUC0-8) and peak (Cmax) exposure of pramlintide for mild, moderate, and severe renal impairment categories in comparison to patients with normal renal function; although, inter-patient variability in pharmacokinetic parameters was high[6].

Hepatic Impairment

Pharmacokinetic studies have not been conducted in patients with hepatic impairment[6].

Geriatric

Pharmacokinetic studies have not been conducted in the geriatric population[6].

Pediatric

The efficacy and safety of SYMLIN have not been established in the pediatric population. The use of SYMLIN is not recommended in pediatric patients due to the risk of severe hypoglycemia[6]

Gender

No study has been conducted to evaluate the effect of gender on pramlintide pharmacokinetics[6].

Race/Ethnicity

No study has been conducted to evaluate the effect of ethnicity on pramlintide pharmacokinetics[6].

Drug Interactions

Effect of Pre-Mixing SYMLIN with Insulin

Pharmacokinetic profiles of pramlintide and insulins after coadministration of 30 mcg SYMLIN with different insulins (regular, NPH, and 70/30 premixed formulations of recombinant human insulin) as one subcutaneous injection, premixed in one syringe, were compared to those observed after the co-administration of SYMLIN and different insulins given as separate subcutaneous injections. The effects of premixing on pramlintide pharmacokinetics varied across the different insulin products with a maximum decrease of 40% in pramlintideCmax and a maximum increase of 36% in pramlintide AUC0-8. Similarly, effects of premixing on insulin pharmacokinetics varied across different insulin products with a maximum increase of 15% in insulin Cmax and up to a 20% increase in insulin AUC0-600min. Always administer SYMLIN and insulin as separate injections and never mix.

Acetaminophen : SYMLIN did not affect acetaminophen AUC regardless of the time of acetaminophen administration in relation to SYMLIN injection.

Oral Contraceptives : When a single dose of a combination oral contraceptive product, containing 30 mcg ethinyl estradiol and 300 mcg norgestrel, was administered 15 minutes after SYMLIN

injection (90 mcg dose) in healthy female subjects, there was no statistically significant change in the Cmax and AUC of ethinyl estradiol. However, the norgestrel Cmax was reduced by about 30% and Tmax was delayed by 45 minutes; there was no effect on norgestrel AUC. The clinical relevance of this change is unknown.

Ampicillin : The Tmax for ampicillin was delayed by approximately 60 minutes[6].

Actions of Pramlintide / Amylin :

Amylin has glucose-lowering effects in both animals and humans[10]. The effects of Pramlintide and amylin can be summarized as follows : (1) suppression of endogenous glucagon production, especially in the postprandial state; (2) consequent reduction of postprandial hepatic glucose production; (3) reduction in gastric emptying time; (4) centrally mediated induction of satiety; and (5) reduction in postprandial glucose levels.

Pramlintide and Type-1 Diabetes :

In a multicenter study of 480 patients with type 1 DM, White house and colleagues showed that treatment with pramlintide led to a mean reduction in HbA1c of 0.67% from baseline to week 13 that was significantly ($p<0.0001$) greater than the placebo reduction (0.16%); a significant placebo-corrected treatment difference was sustained through week 52 ($p=0.007$). This was not accompanied by an increased overall event rate of severe hypoglycemia. Ratner and colleagues showed that the addition of pramlintide 60 ìg 3 times daily (tid) or 4 times daily (qid) to insulin led to significant reductions in HbA1c of 0.29% ($p<0.011$) and 0.34% ($p<0.001$) respectively, compared with a 0.04% reduction in placebo group, over 52 weeks. In this study, the proportion of pramlintidevs placebo-treated patients who achieved an HbA1c of <7% was 3-fold higher. This was achieved without an increase in concomitant insulin use in the pramlintide-treated group. In a subset of these patients combined with patients from other studies in whom HbA1c values were <8.0% at entry, favorable effects on glycemic control were also demonstrated[10,11,12,13]

Pramlintide and Type 2 Diabetes :

In type 2 DM pramlintide has been approved for use as an adjunct to preprandial insulin with or without concurrent metformin or sulfonylurea therapy in patients with sub-optimal glucose control. This approval was based on the ability of pramlintide to improve glucose control when added to insulin therapy and has been supported by both short and long term studies[14,15].

Pramlintide and Food Intake :

Pramlintide administration led to sustained weight loss when given for up to one year to type 1 and type 2 diabetic patients at doses resulting in plasma concentrations close to those in non-diabetic humans[16,17,18]. The weight change in type 1 was 0.5 kg for the 30/60 µg pramlintide four-times daily and in type 2, -1.5kg for the 150 µg pramlintide three-times daily, as compared with+1.0 kg for the placebo group. Meal termination, satiety and anorexia induced by amylin and its analogue pralamintideis supposed to be muli-factoral. The various mechanisms leading to this effect are : 1). Via gastrointestinal hormones. 2). Direct action on area post-rema outside blood brain barrier by amylin 3). Amylin may induce anorexia through its effect on brain serotonin by increasing the transport of the precursor tryptophan into the brain to inhibit feeding by serotonin action in the paraventricular nucleus. 4). Inhibition of stimulation of feeding by the potent hypothalamic neuropeptide Y (NPY)[19].

Pramlintide and Gastric Emptying :

A subcutaneous injection of amylin produced a dose-related slowing of gastric emptying in both diabetic and control rats, in greater magnitude than other gut peptides. The major brain sites regulating gastric motility are the dorsal vagal complex of the brainstem, composed of the nucleus tractussolitarius, dorsal motor nucleus of the vagus, and area postrema. Amylin receptors are identified in these locations and also in stomach fundus[19].

Pramlintide and CAD :

Pramlintide use has also been associated with a significant reduction in postprandial markers of

oxidative stress including significantly reduced postprandial excursions of glucose, nitrotyrosine, and oxidized LDL8. Pramlintide has no significant effect on blood pressure.

Dose, Administration and Side Effects :

Pramlintide is presently available only in a pen system. There are 2 different pens available: 60 mcg pen generally utilized for Type 1 DM individuals and 120 mcg pen utilized for Type 2 DM individuals. Both pens have various increments with the 60 mcg pen allowing for an initial starting dose of 15 mcg and increasing in 15 mcg increments to 60 mcg. The 120 mcg pen allows for 60 mcg and 120 mcg doses.

It is generally administered in divided doses prior to each meal subcutaneously. It is approved in the US to be used with individuals, both Type 1 and Type 2 DM who are utilizing insulin therapy. It is not approved at the present time to be utilized with other agents such as GLP-1 agonists and other oral agents.

The most common side effect of pramlintidehas been nausea, vomiting, anorexia or decrease in appetite. Hypoglycemia can be an issue also, particularly if intake is diminished[16]. Weight loss was noted in individuals and several studies indicated that nausea was not responsible[17].

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