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CCC: 0377-8282/2001

Pramlintide Acetate

Antidiabetic

Prop INNM; USAN

AC-0137
Normylin™
Symlin™

L-Lysyl-L-cysteinyl-L-asparaginyl-L-threonyl-L-alanyl-L-threonyl-L-cysteinyl-L-alanyl-L-threonyl-L-glutaminyl-L-arginyl-L-leucyl-L-alanyl-L-asparaginyl-L-phenylalanyl-L-leucyl-L-valyl-L-histidyl-L-seryl-L-seryl-L-asparaginyl-L-asparaginyl-L-phenylalanylglycyl-L-prolyl-L-isoleucyl-L-leucyl-L-prolyl-L-prolyl-L-threonyl-L-asparaginyl-L-valylglycyl-L-seryl-L-asparaginyl-l-threonyl-L-tyrosinamide cyclic (2→7)-disulfide acetate hydrate

25-L-Proline-28-L-proline-29-L-prolineamylin (human) acetate salt hydrate

$C_{171}H_{267}N_{51}O_{53}S_2.C_2H_4O_2.H_2O$ Mol wt: 4027.4930

CAS: 196078-30-5
CAS: 187887-46-3 (as anhydrous)
CAS: 151126-32-8 (as anhydrous free base)

EN: 201519

Synthesis

Pramlintide was prepared by solid-phase synthesis (1). Proline residues replaced the 25-Ala, 28-Ser and 29-Ser residues of the 37-amino acid peptide amylin. The presence of these proline residues reduced the propensity of the natural peptide to aggregate and precipitate, while enhancing stability and retaining biological activity (2).

Introduction

Diabetes is an increasingly common disease, currently affecting over 5 million people in North America and Europe. Many of these both type 1 and type 2 diabetic patients require daily treatment with insulin to compensate for the reduced secretion of, and/or sensitivity to, insulin of pancreatic β cells. Amylin is a hormone that is cosecreted by β cells and is now believed to play a role in the development of insulin resistance.

Amylin has a number of physiological effects and exerts most, if not all, of these by activation of specific amylin receptors. Amylin modifies the action of insulin, and can decrease insulin-induced glucose uptake in skeletal muscle, inhibit glycogen synthesis and activate glycogen phosphorylase. It can suppress insulin secretion *in vivo* and is a potent inhibitor of gastric emptying. These animal data suggested that administration of amylin might prove effective in helping to control diabetes in humans.

Natural amylin is a 37-amino acid peptide that is labile to proteolysis and is also prone to aggregate in solution, rendering it unsuitable for potential therapeutic use. Amylin Pharmaceuticals initiated a program to identify stable amylin mimetics suitable for therapeutic evaluation in the treatment of diabetes that led to the identification of pramlintide and its selection for clinical development.

Pharmacological Actions

In vitro *activity*

Binding studies using amylin, CGRP and calcitonin receptors indicated that pramlintide binds to all three with comparable affinities to both human and rat amylin. Pramlintide inhibited the binding of [^{125}I]-rat amylin to rat nucleus accumbens membranes with a K_i value of 23 pM, of [^{125}I]-human α-CGRP to SK-NMC cell membranes with a K_i value of 3.8 nM and [^{125}I]-salmon calcitonin to T47D cell membranes with a K_i value of 5.1 nM.

Amylin inhibits the insulin-stimulated incorporation of [^{14}C]-glucose into [^{14}C]-glycogen. Using a rat soleus muscle preparation, pramlintide inhibited this conversion with an IC_{50} value of 3.0 nM. In this assay pramlintide was significantly (2.5-fold) more potent than human amylin but was not significantly more potent than rat amylin (3).

In vivo *activity*

When administered to the rat as an intravenous bolus of 0.1 mg, pramlintide produced a 2-fold increase in

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Table I: Pharmacokinetics of pramlintide in animals (mean ± SEM).

Species	Dose	C_{max} (nM)	C_{ss} (pM)	$t_{1/2}$ (min)	V_d (ml)	Cl (ml/min)	Ref.
Anesthetized rat	1-1000 μg i.v.	-	-	11.5-13.8	105 ± 10	-	3
Anesthetized rat	0.1-1000 μg/h i.v. infusion	-	-	13.2-21.4	-	-	3
Sham-operated rat (n = 5)	1 μg/h i.v. infusion	-	202 ± 15	-	-	21.5 ± 1.6	5
Nephrectomized rat (n = 6)	1 μg/h i.v. infusion	-	639 ± 20	-	-	6.6 ± 0.2	5
Rabbit (n = 6)	0.03 mg/kg s.c.	6.2 ± 1.2		15.8 ± 0.6			
	0.1 mg/kg s.c.	14.8 ± 3.0	-	21.3 ± 2.4	-	-	4
	0.3 mg/kg s.c.	45.8 ± 10.3		24.7 ± 1.0			
Dog (n = 8)	0.1 mg/kg s.c. o.d. 52 wk	7.3		46.1			
	0.3 mg/kg s.c. o.d. 52 wk	221	-	69.3	-	-	4
	0.6 mg/kg s.c. o.d. 52 wk	18.0		54.3			

plasma glucose concentrations over a 2-h period accompanied by a 3-fold increase in plasma lactate and a slow decline (by about 20%) of plasma calcium concentrations. Both human and rat amylin produced qualitatively and quantitatively similar changes and all three agents produced superimposable dose-response curves. Administered in this fashion, pramlintide induced a dose-dependent inhibition of gastric emptying with an ED_{50} value of 0.13 μg. When administered subcutaneously, the ED_{50} was found to be at an approximate plasma concentration of 15 pM (3).

Infusions of pramlintide at doses of 0.1-1000 μg/h showed dose-related effects at >1 μg/h in the rat. This produced up to a 3-fold increase in plasma glucose and lactate accompanied by a 35% decrease in plasma calcium, although the latter was barely dose-related. Infusions of 100 and 1000 μg/h also produced dose-related decreases in arterial pressure. From these data EC_{50} values were extrapolated of 130 pM for hypocalcemic effects and 167 nM for hypotensive effects. The latter effects were attributed to activation of CGRP receptors (3).

Toxicology

No data have been reported on the toxicological properties of pramlintide, but no serious toxic effects have been reported in human trials.

Metabolism and Pharmacokinetics

Pramlintide is primarily metabolized by proteolysis, although the site(s) at which proteolysis occurs have not been reported. It is considerably more stable in human plasma than in plasma of other species. *In vitro* incubation of pramlintide with human plasma only produced 3% degradation after 1 h at 37 °C, compared with 65% degradation in rabbit serum (4).

After subcutaneous administration of doses of 1 or 3 μg/kg to the rat, the bioavailability of pramlintide was found to be 39.2%, decreasing at higher doses. Pramlintide has a short terminal $t_{1/2}$ in both rats and rabbits, but a somewhat higher $t_{1/2}$ in dogs. In nephrectomized rats, the clearance of pramlintide is reduced and concentrations are elevated after i.v. infusion. These results suggest that at least in rats clearance is mainly via renal excretion (3-5) (Table I).

In man, the pharmacokinetics of pramlintide were compared when administered to diabetic patients by bolus injection or intravenous infusion in a crossover study. Both routes of administration produced linear pharmacokinetics over the dose range tested. Both the clearance and $t_{1/2}$ of pramlintide were dose-independent. The initial volume of distribution or volume in the central compartment [V_{dc}] was comparable to that of the extracellular water space (6) (Table II).

Table II: Pharmacokinetics of pramlintide in man administered as a 2-min bolus or a 2-h infusion to groups of 8 diabetic men (mean ± SD) (6).*

Dose (μg)	C_{max} (nM)	t_{max} (min)	$AUC_{0-\infty}$ (ng·min/ml)	V_{dc} (l)	$t_{1/2}$ (min)	Cl (l/min)
30*	1.20 ± 0.56	4 ± 3	2.13 ± 8.0	27.1 ± 20.9	21 ± 3	1.9 ± 1.6
100*	5.14 ± 1.27	6 ± 2	110 ± 19	15.2 ± 3.1	47 ± 19	0.9 ± 0.2
300*	14.60 ± 2.40	7 ± 0	311 ± 56	15.4 ± 3.2	44 ± 12	1.0 ± 0.1
30	0.27 ± 0.03	90 ± 27	27.8 ± 7.2	19.7 ± 11.9	20 ± 2	1.2 ± 0.3
100	0.87 ± 0.14	110 ± 24	99.3 ± 25.1	26.7 ± 12.0	36 ± 10	1.1 ± 0.3
300	3.26 ± 0.39	90 ± 27	371 ± 48	21.5 ± 10.2	46 ± 10	0.8 ± 0.1

Box 1: Effects of pramlintide on gastric emptying in patients with IDDM (7) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, crossover clinical study
Population	Healthy nonobese patients with uncomplicated insulin-dependent diabetes mellitus (n = 8)
Treatments	Glucose i.v. infusion + Insulin i.v. infusion + Pramlintide, 25 μg/h i.v. infusion x 5 h Glucose i.v. infusion + Insulin i.v. infusion + Placebo
Adverse Events	Pr: 4/8 (50.0%) [nausea 4/8 (50.0%), vomiting 2/8 (25.0%)]
Results	AUC of 3-ortho-methylglucose level after meal (mmol/min·l): Pl (31.7) > Pr (8.4) [$p = 0.002$] AUC of blood glucose (mmol/l) @ 0 min: Pl (7.3) ≥ Pr (5.8) Peak blood glucose level (mmol/l) @ 0 min: Pl (10.4) > Pr (7.9) [$p = 0.023$] Peak serum insulin level (pmol/l) @ 0 min: Pl (527.5) > Pr (195.4) [$p = 0.021$] Gastric solid emptying lag phase (min), after meal: Pr (150) > Pl (44.5) [$p = 0.016$] Gastric liquid emptying lag phase (min), after meal: Pr (69) > Pl (7.5) [$p = 0.008$]
Conclusions	Pramlintide delayed gastric emptying and may improve glycemic control in insulin-dependent diabetes mellitus

Box 2: Effects of single-dose pramlintide on gastric emptying in patients with IDDM (9) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, dose-finding, crossover clinical study
Population	Healthy nonobese patients with uncomplicated insulin-dependent diabetes mellitus (n = 11)
Treatments	Pramlintide, 30 μg s.c. Pramlintide, 60 μg s.c. Pramlintide, 90 μg s.c. Placebo
Results	AUC of 3-ortho-methylglucose level after first meal (mmol/min·l): Pl (40.5) ≥ Pr30 (29.5) ≥ Pr90 (27.7) ≥ Pr60(25.6) [$p < 0.02$]; after second meal: Pl ≥ Pr30 ≥ Pr90 ≥ Pr60 [$p > 0.05$] Time to peak plasma 3-ortho-methylglucose level after first meal (mmol/min·l): Pr90 (213.3) ≥ Pr60 (192.5) ≥ Pr30 (175.5) ≥ Pl (65.0) [$p < 0.0001$]; after second meal: Pr60 (330.0) ≥ Pr30 (318.0) ≥ Pl (312.5) ≥ Pr30 (310.0) AUC of blood glucose @ 0-120 min: Pl ≥ Pr30 ≥ Pr90* ≥ Pr60** [*$p = 0.0215$ *vs.* Pl; **$p = 0.0101$ *vs.* Pl] Gastric emptying lag phase (min), after first meal: Pr90 (70.3) ≥ Pr60 (56.4) ≥ Pr30 (54.4) ≥ Pl (32.5); after second meal: Pr90 (48.2) ≥ Pr30 (46.5) ≥ Pr60 (40.0) ≥ Pl (34.2)
Conclusions	Pramlintide delayed gastric emptying and prolonged the time to peak plasma 3-ortho-methylglucose level after a first meal but not after a second meal

Box 3: Effects of pramlintide on gastric emptying in healthy volunteers (10) [Prous Science CSline database].

Design	Randomized, placebo-controlled clinical study
Population	Healthy volunteers (n = 19)
Treatments	Pramlintide, 30 μg t.i.d. x 5 d (n = 6) Pramlintide, 60 μg t.i.d. x 5 d (n = 7) Placebo (n = 5)
Withdrawals	Pl: 1/6 (16.7%)
Results	Meal retained in stomach (%) @ 120 min: Pr30 (72) > Pl (47) [$p = 0.033$] Small bowel transit time (min): Pl (185) ≥ Pr30 (179) ≥ Pr60 (178) Gastric emptying (Kx100): Pl > Pr60 ≥ Pr30 [$p = 0.025$] Gastric emptying lag phase (min): Pr60 ≥ Pr30 ≥ Pl Gastric emptying $t_{1/2}$ (min): Pr60 ≥ Pr30 > Pl [$p = 0.03$] Pancreatic polypeptide concentration (pg/ml) @ 1 h after meal: P > Pr30 ≥ Pr60 [$p < 0.01$] Pancreatic polypeptide concentration (pg/ml) @ 15-30 min after meal: Pl ≥ Pr30 ≥ Pr60* [*$p < 0.025$ *vs.* Pl]; @ 30-60 min after meal: Pl ≥ Pr30 ≥ Pr60* [*$p < 0.025$ vs. Pl] Colonic geometric center @ 8 h: Pr30 ≥ Pr60 ≥ Pl
Conclusions	Pramlintide delayed gastric emptying in healthy volunteers

Box 4: Effects of pramlintide on glycemic control in patients with IDDM (11) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Patients with insulin-dependent diabetes mellitus (n = 215)
Treatments	Insulin + Pramlintide, 30 mg s.c. q.i.d. x 4 wks (n = 45) Insulin + Pramlintide, 30 mg s.c. t.i.d. [breakfast, lunch, dinner] x 4 wks (n = 41) Insulin + Pramlintide, 30 mg s.c. t.i.d. [breakfast, dinner, snack] x 4 wks (n = 44) Insulin + Pramlintide, 60 mg s.c. b.i.d. x 4 wks (n = 43) Insulin + Placebo (n = 42)
Withdrawals	Adverse events 6/173 (3.5%)
Adverse Events	Pr: nausea 16-37%, anorexia 2-9%, vomiting 2% Pr30q: hypoglycemia 22.2% Pr30bld: hypoglycemia 12.2% Pr30bds: hypoglycemia 25.0% Pr60: hypoglycemia 20.9% Pl: hypoglycemia 26.2%, nausea 5%, anorexia 0%, vomiting 2%
Results	24-h plasma glucose levels (mmol/l), change @ 4 wks: Pr30q* (–1.4) ≥ Pr60 (–0.9) ≥ Pr30bds (–0.1) ≥ Pr30bld (–0.03) ≥ Pl (0.3) 24-h glucose AUC (mmol/min·l), change @ 4 wks: Pr30q* (–2080) ≥ Pr60 (–1261) ≥ Pr30bds* (–209.6) ≥ Pr30bld (–45.2) ≥ Pl (358.8) Glucose C_{max} (mmol/l), change @ 4 wks: Pr60 (–1.9) ≥ Pr30q (–1.2) ≥ Pr30bld (–0.3) ≥ Pr30bds (–0.03) ≥ Pl (0.4) Glucose C_{min} (mmol/l), change @ 4 wks: Pr60 (–1.5) ≥ Pr30q (–0.5) ≥ Pl (–0.5) ≥ Pr30bds (–0.2) ≥ Pr30bld (0.2) Serum fructosamine levels (µmol/l), change @ 4 wks: Pl (369.4) ≥ Pr30bld (362.3) ≥ Pr30bds (355.1) ≥ Pr60 (348.5) ≥ Pr30q* (339.4) Insulin levels (µU/ml), change @ 4 wks: Pr30q* (–4.4) ≥ Pr30bld* (–3.9) ≥ Pr30bds* (–2.7) ≥ Pr60* (–0.5) > Pl (8.5)
Conclusions	Pramlintide improved blood glucose control in insulin-dependent diabetes mellitus

*p <0.05

Box 5: Effects of pramlintide on glycemic control in type 2 diabetic patients (12) [Prous Science CSline database].

Design	Randomized, single-blind, placebo-controlled, crossover clinical study
Population	Patients with type 2 diabetes mellitus treated with insulin (n = 12) or managed with diet and/or oral hypoglycemics (n = 12)
Treatments	Insulin + Pramlintide i.v. infusion over 5 h Insulin + Placebo i.v. infusion over 5 h Diet + Hypoglicemic agent p.o. + Pramlintide i.v. infusion over 4.5 h Diet + Hypoglycemic agent p.o. + Placebo i.v. infusion over 4.5 h
Adverse Events	Pr: nausea 14/24 (58.3%), vomiting 5/24 (20.8%) Pl: nausea 6/24 (25.0%), vomiting 1/24 (4.2%)
Results	Plasma glucose levels (mmol/l) @ 4 h: Pl (12.0) > Pr (9.8) [p = 0.0012]; I+Pl (13.7) > I+Pr (10.2) [p = 0.0031]; D+HA+Pl (10.2) ≥ D+HA+Pr (9.5) Incremental plasma glucose AUC (mmol·h/l) @ 4 h: Pl (11.3) > Pr (2.9) [p = 0.0004]; I+Pl (15.8) > I+Pr (2.8) [p = 0.0012]; D+HA+Pl (6.9) = D+HA+Pr (3.0) Incremental plasma glucose C_{max} (mmol/l) @ 4 h: I+Pl (6.6) > I+Pr (2.3) [p = 0.0007]; D+HA+Pl (3.7) > D+HA+Pr (2.2) [p = 0.038] Serum insulin levels (pmol/l) @ 4 h: Pl (467.4) > Pr (266.7) [p = 0.0001]; I+Pl (531.3) > I+Pr (343.1) [p = 0.022] ; D+HA+Pl (375.0) > D+HA+Pr (189.6) [p = 0.0001] C-peptide levels (nmol/l) @ 4 h: Pl (0.74) > Pr (0.37) [p = 0.0001]; I+Pl (0.50) > I+Pr (0.20) [p = 0.005]; D+HA+Pl (0.98) > D+HA+Pr (0.54) [p = 0.0001]
Conclusions	Pramlintide may improve glycemic control in patients with diabetes who require insulin treatment or who are poorly controlled on diet and/or hypoglycemic agents

Box 6: Effects of pramlintide on plasma glucose profiles in patients with IDDM (13) [Prous Science CSline database].

Design	Multicenter, dose-finding, placebo-controlled clinical study
Population	Patients with insulin-dependent diabetes mellitus (n = 168)
Treatments	Pramlintide, 10 μg q.i.d. x 14 d (n = 43) Pramlintide, 30 μg q.i.d. x 14 d (n = 41) Pramlintide, 100 μg q.i.d. x 14 d (n = 42) Placebo (n = 42)
Adverse Events	Pr10: nausea 2.3%, hypoglycemia 34/43 (79.1%) Pr30: nausea 19.5%, anorexia 2.4%, hypoglycemia 35/41 (85.4%) Pr100: nausea 42.9%, anorexia 9.5%, hypoglycemia 34/42 (81.0%) Pl: nausea 2.4%, hypoglycemia 34/42 (81.0%)
Results	Correlation between baseline HbA1c and baseline 24 h plasma glucose concentration (r): Pr30 (0.46) ≥ Pl (0.36) ≥ Pr10 (0.33) ≥ Pr100 (–0.02) Glucose AUC (mmol/min·l) @ 2 wks: Pr100 (303.1) ≥ Pr30 (247.7) Glucose AUC reduction (%) @ 2 wks: Pr100 > Pr10 [p = 0.0034]; Pr30 > Pr10 [p = 0.0035] Glucose AUC reduction (mmol/min·l), change @ 2 wks: Pl (–172.8) ≥ Pr10 (–149) Glucose (mmol/l), change @ 2 wks: Pr30 (–1.9) > Pl (–0.03)
Conclusions	Pramlintide reduced plasma glucose concentrations in patients with insulin-dependent diabetes mellitus

Box 7: Effects of pramlintide on hepatic glucagon responses in patients with IDDM (14) [Prous Science CSline database].

Design	Randomized, placebo-controlled, double-blind, crossover clinical study
Population	C-peptide negative patients with insulin-dependent diabetes mellitus (n = 13)
Treatments	Insulin, 0.25-1 mU/kg·min i.v. infusion over 420 min q.i.d. x 4 wks + Pramlintide, 30 mg s.c. q.i.d. x 4 wks Insulin, 0.25 mU/kg·min i.v. infusion over 420 min q.i.d. x 4 wks + Placebo
Results	Serum fructosamine levels (μmol/l) @ 4 wks: Pl (350.1) > Pr (314.3) [p = 0.008 *vs.* Pl] Maximum endogenous glucose production rate (mg/kg·min) @ 225-270 min: Pr (2.27) ≥ Pl (2.08) Plateau endogenous glucose production rate (mg/kg·min) @ 345-360 min: Pl (1.60) ≥ Pr (1.27) Glucose disposal: Pr (2.40) ≥ Pl (2.33) Glucose oxidation: Pr (2.28) ≥ Pl (1.80) Glucose nonoxidation: Pl (0.63) > Pr (0.28) [p <0.01] Lipid oxidation rate: Pl (0.54) ≥ Pr (0.43) Respiratory quotient: Pr (0.89) ≥ Pl (0.86)
Conclusions	Pramlintide did not change insulin-mediated glucose disposition rate or plasma glucose response to a glucagon challenge

Clinical Studies

Extensive clinical studies with pramlintide have generally shown it to be well tolerated and devoid of toxic effects. However, the majority of these studies have also noted a propensity for pramlintide treatment to induce nausea and, in some cases, emesis (7). Examination of the effects of pramlintide on bone metabolism, as part of a 12-month study in 223 type 1 diabetic patients, found that it produced no significant change in bone density or markers of bone metabolism (8).

Administration of pramlintide has been shown to delay gastric emptying, which helps to achieve glycemic control. These effects have been shown in diabetic patients and healthy subjects. Short-term efficacy studies with pramlintide were focused on assessing glycemic control by measuring the regulation of plasma glucose and fructosamine levels, rather than by measuring the reduction in HbA1c. These studies, using a variety of doses and generally t.i.d. or q.i.d. dosing, did show some signs of improved glycemic control even after only 4 weeks of treatment with pramlintide (7, 9, 10) (Boxes 1-3).

One 4-week study in 219 IDDM patients suggested that q.i.d. administration of subcutaneous pramlintide provided superior glycemic control to t.i.d. pramlintide but, like a number of studies, failed to demonstrate a dose-related effect (11) (Box 4). Similar efficacy was demonstrated in a study with infused pramlintide in type 2 diabetic patients. This study indicated that coadministration of insulin, not unexpectedly, provided superior glycemic control and also highlighted the lower sensitivity of type 2 diabetic patients to pramlintide (12) (Box 5).

Box 8: Effects of pramlintide on glycemic control and postprandial glucagon concentrations in patients with IDDM (15) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, crossover clinical study
Population	Male patients with type 1 diabetes mellitus (n = 14)
Treatments	Pramlintide, 30 μg q.i.d. x 4 wks Placebo
Adverse Events	Pr: hypoglycemia 11/14 (78.6%), abdominal discomfort 1/14 (7.1%), anorexia 3/14 (21.4%), vomiting 1/14 (7.1%), constipation 1/14 (7.1%) Pl: hypoglycemia 7/14 (50.0%), diarrhea 2/14 (14.2%)
Results	Daily insulin requirements @ 1 wk: Pl (48.2) ≥ Pr (46.3); @ 2 wks: Pl (46.6) ≥ Pr (45.6); @ 3 wks: Pl (50.2) > Pr (46.3) [$p = 0.02$]; @ 4 wks: Pl (49.5) > Pr (46.1) [$p = 0.02$] Postprandial plasma glucose (mmol/l), change @ 0-120 after breakfast: Pl (134) > Pr (125) [$p = 0.001$] Postprandial plasma glucose (mmol/l), change @ 0-120 after lunch: Pl (117) > Pr (54) [$p = 0.01$] AUC for plasma glucagon (ng/l) @ 0-120 after breakfast: Pl (7538) > Pr (5707) [$p = 0.02$] Blood glucose home measurements (mmol/l) @ 1 wk: Pl (8.5) = Pr (8.5); @ 2 wks: Pr (7.8) ≥ Pl (7.7); @ 3 wks: Pl (8.2) ≥ Pr (7.9); @ 4 wks: Pl (8.5) = Pr (8.5) Blood glucose levels: Pl (0.04) > Pr (0.029) [$p = 0.01$]
Conclusions	Pramlintide may improve metabolic control in type 1 diabetes

Box 9: Effects of pramlintide as an adjunct to insulin therapy in patients with IDDM (16) [Prous Science CSline database].

Design	Randomized, multicenter, double-blind, placebo-controlled, dose-finding clinical study
Population	Patients with type 1 diabetes mellitus (n = 586)
Treatments	Insulin s.c. + Pramlintide, 60 μg t.i.d. x 26 wks Insulin s.c. + Pramlintide, 90 μg b.i.d. x 26 wks Insulin s.c. + Pramlintide, 90 μg t.i.d. x 26 wks Insulin s.c. + Placebo
Adverse Events	Nausea, hypoglycemia
Results	HbA1c levels (%), change @ 26 wks: Pl (0.1) = Pr90tid (0.1) > Pr90bid* (–0.1) > Pr60** (–0.2) [*p <0.05 *vs.* Pl; **p = 0.007 *vs.*+Pl] HbA1c > 0.5% reduction rate (%) @ 4 wks: Pr (41-45) > Pl (24.8) [p <0.005] Body weight (kg), change @ 26 wks: Pr90tid (1.6) = Pr60 (1.6) > Pl (0.3) > Pr90bid (–0.7)
Conclusions	The addition of pramlintide to an insulin-based regimen improved glucose control in patients with type 1 diabetes mellitus

Another study in IDDM patients confirmed that pramlintide treatment improved postprandial glycemic control but failed to demonstrate any dose response (13) (Box 6).

Two short-term studies examined the interrelationship between amylin receptor activation and glucagons in patients with type 1 diabetes. Pramlintide did not affect the response to exogenous glucagon stimulation nor did it reduce plasma glucagon, but it did slowly reduce the required daily dosage of insulin for maintenance of glycemic control (14, 15) (Boxes 7 and 8).

In patients with type 1 diabetes, the effects of long-term treatment with pramlintide have been reported for periods of between 6 months and 2 years, while only 6- and 12-month studies in type 2 diabetic patients have been reported. In type 1 diabetic patients, t.i.d. administration of either 60 or 90 μg or b.i.d. administration of 90 μg pramlintide were all found to produce significant improvements in glycemic control after 6 months of treatment. This study showed no significant differences between active treatment groups and only marginally significant effects were produced with the 90 μg t.i.d. dose which was intended as the primary dosage group for regulatory submission (16) (Box 9).

A 12-month study in patients with type 1 diabetes also failed to show any differences between t.i.d. and q.i.d. administration of 60 μg pramlintide, although both treatment regimens produced a highly significant decrease in HbA1c (17) (Box 10). A third study employed q.i.d. administration of 30 μg pramlintide and was a 1-year placebo-controlled study followed by an open continuation for the active treatment arm. This lower dose was reported to produce clinically relevant improvements in HbA1c,

Box 10: Effects of pramlintide on long-term metabolic control in patients with IDDM (17) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with type 1 diabetes mellitus (n = 479)
Treatments	Pramlintide, 60 μg s.c. t.i.d. + Insulin x 1 y Pramlintide, 60 μg s.c. q.i.d. + Insulin x 1 y Placebo + Insulin x 1 y
Adverse Events	Mild nausea
Results	HbA1c levels, % change @ 26 wks: Pr60t* (–0.4%) ≥ Pr60q* (–0.3) [*p <0.001 *vs.* Pl]; % change @ 52 wks: Pr60t (–0.7%) ≥ Pr60q (–0.7%) [*p <0.002 *vs.* Pl] HbA1c reduction > 1% rate (%) @ 52 wks: Pr60q (30) ≥ Pr60t (25) > Pl (7) Body weight (kg), change @ 52 wks: Pr60q* (–1.7) ≥ Pr60t* (–1.4) [*p <0.005 *vs.* Pl]
Conclusions	Pramlintide plus insulin combined regimen improved long-term metabolic control in type 1 diabetes mellitus

Box 11: Effects of pramlintide as an adjunct to insulin therapy on glycemic control in patients with IDDM (18) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with insulin-dependent diabetes mellitus (n = 480)
Treatments	Insulin + Pramlintide, 30 μg q.i.d. x 104 wks Insulin + Placebo x 52 wks → Insulin + Pramlintide, 30 μg q.i.d. x 52 wks
Adverse Events	Nausea
Results	HbA1c levels (%), change @ 52 wks: Pr (–0.4) > Pl (-0.15) [p = 0.0118]; @ 104 wks: Pr (–0.35) HbA1c > 0.5% reduction rate @ 4 wks: Pr (44)
Conclusions	The addition of pramlintide to insulin improved glucose control in type 1 diabetes mellitus

Box 12: Effects of pramlintide as an adjunct to insulin therapy on metabolic control in patients with NIDDM (19) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Patients with noninsulin-dependent diabetes mellitus (n = 499)
Treatments	Insulin s.c. + Pramlintide, 120 μg b.i.d. x 26 wks Insulin s.c. + Pramlintide, 90 μg b.i.d. x 26 wks Insulin s.c. + Pramlintide, 90 μg t.i.d. x 26 wks Insulin s.c. + Placebo
Adverse Events	Mild nausea
Results	HbA1c levels (%), change @ 26 wks: Pr120* (–0.4) = Pr90tid* (–0.4) ≥ Pr90bid (–0.3) ≥ Pl (–0.1) [*p <0.05 *vs.* Pl] HbA1c > 0.5% reduction rate (%) @ 4 wks: Pr (47-50) > Pl (25.2) [p <0.001] Body weight (kg), change @ 26 wks: Pr120 (–1.4) ≥ Pr90tid (–1.3) ≥ Pr90bid (–0.8) > Pl (0.1)
Conclusions	The addition of pramlintide to an insulin-based treatment improved metabolic control in type 2 diabetes mellitus

although these were only marginally significant, which were sustained over a second year (18) (Box 11).

A 6-month study in type 2 diabetic patients compared the effects of 90 and 120 μg t.i.d. dosing to 90 μg b.i.d. dosing. All these doses produced similar, significant decreases in body weight and HbA1c and produced no significant difference from each other (19) (Box 12).

Two 12 month studies have been reported that respectively examined the effects of q.i.d. or t.i.d. dosing of 60 μg and t.i.d. dosing of 30, 75 or 150 μg pramlintide.

Box 13: Effects of pramlintide in insulin-requiring type 2 diabetic patients (29) [Prous Science CSline database].

Design	Placebo-controlled, dose-finding clinical study
Population	Patients with type 2 diabetes mellitus with a mean BMI of 30.7 (n = 539)
Treatments	Pramlintide, 30 μg t.i.d. + Insulin, 60 [mean] U/d x 1 y (n = 116) Pramlintide, 75 μg t.i.d. + Insulin, 60 [mean] U/d x 1 y (n = 133) Pramlintide, 150 μg t.i.d. + Insulin, 60 [mean] U/d x 1 y (n = 126) Placebo + Insulin, 60 [mean] U/d x 1 y (n = 132)
Adverse Events	Pr: mild transient nausea, tachyphylaxis
Results	HbA1c levels, % change @ 13 wks: Pr150 (–10.1) ≥ Pr75 (–9.3) ≥ Pr30 (–7.3) ≥ Pl (–5.4); @ 26 wks: Pr150 (–8.2) ≥ Pr75 (–8.0) ≥ Pr30 (–5.6) ≥ Pl (–3.9); @ 52 wks: Pr150 (–6.3) ≥ Pr75 (–5.0) ≥ Pr30 (–3.7) ≥ Pl (–2.1) Body weight (kg), change vs. P @ 1 y: Pr150 (–2.7) ≥ Pr75 (–1.6)
Conclusions	Pramlintide combined with insulin was more effective than insulin alone in the control of HbA1c and weight in type 2 diabetes mellitus

Box 14: Effects of pramlintide as an adjunct to insulin on metabolic control in patients with NIDDM (21) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with type 2 diabetes mellitus (n = 498)
Treatments	Pramlintide, 90 μg b.i.d. + Insulin x 1 y Pramlintide, 120 μg b.i.d. + Insulin x 1 y Placebo + Insulin x 1 y
Adverse Events	Pr120: severe nausea 4.1% Pr90: severe nausea 1.2% Pl: severe nausea 2.4%
Results	HbA1c levels, % change @ 26 wks: Pr120 (–0.4 ≥ Pr90 (–0.3); @ 52 wks: Pr120* (–0.6) ≥ Pr90 (–0.3) [*p <0.003 *vs.* Pl] HbA1c reduction > 1% rate (%) @ 52 wks: Pr120 (42) ≥ Pr90 (30) ≥ Pl (22) Body weight (kg), change @ 52 wks: Pr120 (–1.2) ≥ Pr90 (–0.5) > Pl (0.7)
Conclusions	Pramlintide plus insulin combined regimen improved long-term metabolic control in type 2 diabetes mellitus

One of the studies showed no difference between q.i.d. and t.i.d. dosing and suggested that a 60 μg dose was efficacious in reducing body weight and HbA1c. While the second study, in obese patients, suggested that a 30 μg dose was only marginally effective in patients with type 2 diabetes, it clearly indicated that higher doses were effective and suggested a dose-response with respect to the observed weight loss. However, in this study there did appear to be a decline in the reduction of HbA1c over the course of the study (20, 21) (Boxes 13 and 14).

Six phase III studies have examined the effects of pramlintide in over 3500 patients, with 3 studies performed in type 1 and three in type 2 diabetic patients. All these studies are sufficiently large so as to be amenable to analysis of subgroups within them. Little of this detailed analysis has yet been reported and no peer reviewed papers detailing the phase III trials have yet been published.

Pramlintide acetate is scheduled for review by the FDA's Endocrinologic and Metabolic Drugs Advisory Committee on July 26, 2001. The NDA was submitted to the FDA in December 2000 seeking approval for its use as an adjunctive therapy to insulin for the treatment of type 1 or insulin-using type 2 diabetes. The regulatory submission process for Europe is also under way.

Manufacturer

Amylin Pharmaceuticals, Inc. (US).

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