Role of Pramlintide in Diabetes Care

Matthew C. Riddle, MD
Professor of Medicine
Oregon Health & Science University

Practical Ways to Achieve Targets in Diabetes Care
Keystone, Colorado
17 July 2014
Duality of interest disclosure

I have received honoraria and/or research support from the following companies

Astra-Zeneca
Elcelyx
Eli Lilly
NovoNordisk
Sanofi
Valeritas
Outline of this talk

Brief history of amylin and pramlintide

Current clinical recommendations for pramlintide

Potential future uses of pramlintide

Alternative to rapid insulin for T2DM

Pram-insulin fixed ratio for T1DM
Brief history of amylin and pramlintide

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Amylin
A second beta-cell hormone

Patterns of hormones which regulate postprandial metabolism and satiety

- Amylin
- Insulin
- GLP-1
- Ghrelin

Hours after beginning a meal

Cummings DE et al. Diabetes 2001;50: 1714-1719
Amylin’s metabolic effects
Mediated by the CNS

Suppresses or prevents increase of glucagon, thereby reducing hepatic glucose production

Modulates gastric emptying

Promotes satiety, limits food intake
Pramlintide
An stable injectable analogue of amylin

Peak after sc injection at ~20 minutes, duration ~3 hours

CNS-mediated effects like those of amylin
  • Attenuates mealtime glucagon secretion
  • Slows gastric emptying
  • Enhances satiety and limits food intake

Effects vs PLBO in early trials:

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔA1c (%)</td>
<td>-0.33</td>
<td>-0.40</td>
</tr>
<tr>
<td>Δ Wt (kg)</td>
<td>-1.7</td>
<td>-1.7</td>
</tr>
</tbody>
</table>
Pramlintide added to basal-bolus therapy
6-month open-label clinical experience in T1 & T2DM

7-point self-monitored glucose profiles

Glucose
mg/dL
Mean±SE

Baseline
6 Months

A1c 8.3%
△ A1c -0.6%
△ Wt  -2.8 kg
△ Insulin -6.4%

*KP <0.05

Brief history of amylin and pramlintide

Current clinical recommendations for pramlintide

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Alternative to rapid insulin for T2DM

Pram-insulin fixed ratio for T1DM
Current clinical recommendations for use of pramlintide

FDA package insert
Complex, and advising strict professional supervision and frequent SMBG

ADA Clinical Practice Recommendations 2014
No mention

ADA/EASD Position Statement: Management of T2DM 2012
“. . . typically reserved for patients treated with intensive insulin therapy, usually in T1DM. . .”

AACE Consensus Panel on T2DM: Algorithm for glycemic control: Listed in text/table but not included in algorithm
Pramlintide (Symlin)
FDA-approved label for T2DM

- SYMLIN is given at mealtimes and is indicated for . . .
- Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin . . .

- Initiate SYMLIN at 60 mcg subcutaneously, immediately prior to major meals;
- Reduce preprandial, rapid-acting or short-acting insulin dosages, including fix-mix insulins (70/30) by 50%;
- Monitor blood glucose frequently, including pre- and post-meals and at bedtime;
- Increase the SYMLIN dose to 120 mcg when no clinically significant nausea has occurred for 3-7 days . . . SYMLIN dose adjustments should be made only as directed by the healthcare professional
- Adjust insulin doses to optimize glycemic control once the target dose of SYMLIN is achieved and nausea (if experienced) has subsided. Insulin dose adjustments should be made only as directed by the healthcare professional; . . .
So . . . is there a role for pramlintide in management of diabetes?

Probably there is – physiology is parsimonious, and prominent mechanisms are there for a purpose.

All patients with diabetes are deficient in amylin.
Brief history of amylin and pramlintide

Current clinical recommendations for pramlintide

Potential future uses of pramlintide

Alternative to rapid insulin for T2DM – INSTEAD study

Pram-insulin fixed ratio for T1DM – PICOS study
INSTEAD study
Head-to-head comparison of pramlintide vs rapid-acting insulin + basal insulin for T2DM

Design
6-month 1:1 randomized open-label

Population
T2DM requiring basal insulin + oral agents

Randomized treatments
Both groups received titrated glargine or detemir
Pramlintide group started 120 mcg with each meal
Rapid insulin group started 5 U with each meal, titrated 1-2 U once or twice weekly

Riddle M et al. Diabetes Care 2009;32:1577-1582
### INSTEAD study

#### Baseline characteristics of treated participants

<table>
<thead>
<tr>
<th></th>
<th>PRAM N=56</th>
<th>RAI N=56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male / Female; %)</td>
<td>61 / 39</td>
<td>66 / 34</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55 ± 11</td>
<td>54 ± 10</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td>10 ± 7</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>108 ± 22</td>
<td>103 ± 18</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>36 ± 6</td>
<td>36 ± 6</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.2 ± 0.8</td>
<td>8.3 ± 0.8</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>155.1 ± 39.6</td>
<td>164.3 ± 49.6</td>
</tr>
<tr>
<td>Prior OAD use (MET / SU / TZD; %)</td>
<td>79 / 70 / 38</td>
<td>77 / 61 / 39</td>
</tr>
<tr>
<td>Prior insulin use (Yes; %)</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>Baseline insulin use (U/day)</td>
<td>20 ± 10</td>
<td>24 ± 12</td>
</tr>
</tbody>
</table>

*Means ± SD*

Riddle M et al. Diabetes Care 2009;32:1577-1582
INSTEAD study
Fasting plasma glucose during treatment

Weeks of treatment

FPG (mg/dL)

-30 ± 7 mg/dL (PRAM)
-41 ± 7 mg/dL (RAI)

Δ from baseline (LOCF)

ITT Population; mean ±SE

Riddle M et al. Diabetes Care 2009;32:1577-1582
INSTEAD study
A1c during treatment

A1C (%)

Weeks of treatment

PRAM
RAI

Δ from baseline (LOCF)
-0.9 ± 0.2 % (PRAM)
-1.1 ± 0.2 % (RAI)

ITT Population; mean ±SE

Riddle M et al. Diabetes Care 2009;32:1577-1582
**INSTEAD study**

Change of body weight during treatment

Δ Body weight (kg)

Weeks of treatment

Δ from baseline (LOCF)
+4.2 ± 0.6 kg (RAI)

-0.3 ± 0.7 kg (PRAM)

ITT Population; mean ±SE
** = P<0.01 vs. RAI; *** = P<0.001 vs. RAI

Riddle M et al. Diabetes Care 2009;32:1577-1582
INSTEAD study
Insulin dosage during treatment

Weeks of treatment

Total insulin use (U/day)

Mealtime insulin use $37 \pm 3$ U

ITT Population; mean ±SE

Riddle M et al. Diabetes Care 2009;32:1577-1582
INSTEAD study
% of participants with nausea or hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>PRAM</th>
<th>RAI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nausea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild or moderate</td>
<td>18%</td>
<td>0%</td>
</tr>
<tr>
<td>Severe</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Causing withdrawal</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild or moderate</td>
<td>55%</td>
<td>82%</td>
</tr>
<tr>
<td>Severe</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Causing withdrawal</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Riddle M et al. Diabetes Care 2009;32:1577-1582
INSTEAD study
Primary composite endpoint
A1c ≤ 7.0%, no weight gain, no severe hypoglycemia

Patients achieving composite endpoint (%)

Treatment

PRAM: 30%
RAI: 11%

* = P<0.05

Riddle M et al. Diabetes Care 2009;32:1577-1582
For insulin-requiring, obese T2DM, with systematically titrated basal insulin, mealtime pramlintide:

1) Was as effective as titrated prandial insulin
2) Caused 4.5 kg less weight gain
3) Caused more nausea but less hypoglycemia
How can we improve the use of pramlintide in type 1 diabetes?

What does Mother Nature do?
PICOS
Pramlintide-Insulin COformulation Studies
PICOS rationale

Treatment with a fixed ratio of pramlintide to insulin

• Consistent with normal physiology

• Complimentary clinically relevant effects

• Could be titrated and adjusted together for:
  – Simplicity
  – Minimization of side effects

• Basal (as well as prandial) delivery by CSII might provide additional glycemic stabilization and weight-control
Pramlintide effects with meals in type 1 diabetes
Combination with rapid-acting analogue vs regular insulin

PICOS rationale

Plasma glucose mg/dl

Minutes after meal and injection

Lispro Insulin
Pramlintide 60 µg + Lispro Insulin

Regular Insulin
Pramlintide 60 µg + Regular Insulin

Evaluable population; Mean (SE)
Pramlintide + Lispro insulin (n = 20)
Pramlintide + Regular insulin (n = 18)
Fixed doses of pramlintide and variable doses of insulin by separate CSII in T1DM

N=11 T1DM
Mean age 39, BMI 29.7, A1c 8.2%

Basal pramlintide 9 mcg/hr
Prandial pramlintide 60 mcg
Mean basal insulin ~ 28 U/d
Mean prandial insulin ~33 U/d
Δ A1c -0.35%
Δ Weight -0.43 kg

PICOS study A
Seeking optimal ratio for fixed-ratio combination

Design
Single-day, 4 way crossover breakfast meal study

Population
T1DM requiring MDI or CSII therapy
Switched to MDI with glargine as basal for studies

Randomized treatments
Four ratios of prandial treatment, separately injected
Placebo + regular insulin (30% < usual rapid ins. dose)
6 mcg pramlintide per 1 unit insulin
9 mcg
12 mcg
PICOS study A
Participant characteristics

N = 19 T1DM on MDI or CSII
Mean age 46 yr
Mean BMI 26.4
Mean baseline A1c 7.75%
Breakfast dose ≤ 10 units
Exclusion criteria: hx gastroparesis, hypo unawareness, hypo requiring medical assistance
PICOS study A
Glucose response to meal

Figure 2. Postprandial glucose concentrations over time for each treatment group (N=19)

- Placebo
- Pramlintide 6 µg/U insulin
- Pramlintide 9 µg/U insulin
- Pramlintide 12 µg/U insulin

ITT, intent-to-treat; LS, least-squares; SE, standard error.
*Time point 0 represents predose, defined at each visit as the average of values collected within 30 minutes prior to dosing.
PICOS study A
Glucagon response to meal

Figure 3. Glucagon concentration over time for each treatment group (N=19)

ITT, intent-to-treat; LS, least-squares; SE, standard error.
*Time point 0 represents predose, defined at each visit as the average of values collected within 30 minutes prior to dosing.
PICOS study A
Pramlintide concentrations

Figure 4. Arithmetic mean (SD) pramlintide concentration over time for each pramlintide dose
PICOS study A
Summary of ratio-finding study

1) All ratios reduced glucose AUC$_{1-3h}$ vs placebo
   - 6 mcg/U by 60%
   - 9 mcg/U by 58%
   - 12 mcg/U by 72%

2) All ratios limited increase of glucagon

3) No hypoglycemia during studies

4) One participant reported mild nausea with all 3 ratios
So . . . is there a role for pramlintide in management of diabetes?

For both T2DM and T1DM, proof of concept studies support tactics for pramlintide use that have not been adequately studied.
Thanks for your attention!

Riddle brothers’ ranch
Little Blitzen River Valley
Harney County, Oregon