The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis

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CRD summary
The review found that pramlintide was associated with a small reduction in HbA1c and a modest reduction in weight in patients with type 2 diabetes or non-diabetic obesity. Incidence of nausea increased during therapy. The authors' conclusions reflect the limited evidence base, but risks of bias in the included studies and the analyses make the reliability of the conclusions uncertain.

Authors' objectives
To assess the effect of pramlintide acetate on glycaemic control, weight and incidence of nausea and hypoglycaemia in patients with type 2 diabetes mellitus and in obese patients without diabetes.

Searching
MEDLINE, EMBASE, The Cochrane Library, DARE, Biomedical Reference Collection, CINAHL, Nursing and Allied Health Collection and Ageline were searched up to July 2010 for relevant studies in adults. There were no language restrictions. Limited search terms were reported. Reference lists, relevant journals and personal files were searched.

Study selection
Eligible studies were randomised controlled trials (RCTs) of either parallel group or crossover design that included adults with type 2 diabetes mellitus or non-diabetic obesity where doses of at least 120mcg of pramlintide before two to three meals per day were compared with placebo. Primary outcomes included glycaemic control, weight and tolerability (nausea, hypoglycaemia) in patients with type 2 diabetes mellitus. Secondary outcomes included weight and nausea in obese patients without diabetes. Study duration was required to be 12 weeks or more. Abstracts and non-original research studies were excluded.

In the included studies, 58% of participants were female and 73% were Caucasian. Age ranged from 31 to 67 years. In type 2 diabetes mellitus patients, mean baseline glycated haemoglobin (HbA1c) ranged from 8.2% to 9.2% and mean duration of diabetes ranged from nine to 13 years. All patients were obese and mean BMI ranged from 30 to 38kg/m². Some of the non-diabetic obese patients participated in an individualised lifestyle intervention program. Doses of pramlintide ranged from 120 to 360mcg two or three times per day before major meals, delivered subcutaneously. Pramlintide was mostly compared with placebo but, in one trial, the comparator was rapid-acting insulins. Type 2 diabetes mellitus participants took concomitant insulin in both treatment arms.

Two reviewers independently performed study selection. Discrepancies were resolved by consensus.

Assessment of study quality
Studies were evaluated for risk of bias using Cochrane risk of bias tool criteria; these included random allocation sequence, allocation concealment, blinding, incomplete data, selective outcome reporting and other bias.

Two reviewers independently assessed the studies for risk of bias. Disagreements were resolved by consensus.

Data extraction
Continuous data on HbA1c and weight were extracted from several time points. Change from baseline to the time point and mean differences and their 95% confidence intervals (CIs) were calculated. Dichotomous data on tolerability were extracted and risk ratios (RRs) and their 95% CIs were calculated. Authors of studies were contacted where data were not in a usable format, but all requests were declined.
Two reviewers independently extracted data.

Methods of synthesis
Studies were pooled in meta-analyses and summary effect measures were calculated using a random-effects model. Separate analyses were mostly performed for different types of participants, type 2 diabetes mellitus and non-diabetic obese patients; tolerability was assessed overall for both types of patients combined. Heterogeneity was assessed with $X^2$ (cutoff for significant heterogeneity p<0.1) and $I^2$ was used to quantify the extent of heterogeneity. Sources of heterogeneity were evaluated by use of subgroup analyses and sensitivity analyses, where possible. Publication bias was assessed by generating funnel plots.

Results of the review
Eight RCTs (n=1,616 participants) were included in the review. Four RCTs (n=930) included participants with type 2 diabetes mellitus and four RCTs (n=686) included obese participants without diabetes. All or most studies had an unclear description of randomisation method, allocation concealment and blinding. Intention-to-treat analysis was reported in all studies, but the individual study definitions did not meet the strict criteria of the Cochrane Collaboration definition. Three studies had high risk of bias as a result of drop-out rate above 15% and most studies imputed missing data. Two studies had selective under reporting of outcomes and five had imbalances in groups at baseline. All the RCTs were sponsored by a pharmaceutical company and most authors were employed by the company. Treatment duration mostly ranged from 16 to 24 weeks; two studies had a duration of 52 weeks.

Patients with type 2 diabetes mellitus: Pramlintide significantly reduced HbA1c (WMD -0.33%, 95% CI -0.51 to -0.14; four studies) and weight (WMD -2.57kg, 95% CI -3.44 to -1.70; four studies) versus the control group. There was evidence of significant heterogeneity in the analysis of weight; when the single study where the control group received rapid-acting insulins rather than placebo was removed, results remained significant with no evidence of heterogeneity. There was no evidence of a significant difference between groups in the other measures of glycaemic control or in the incidence of hypoglycaemia. Incidence of nausea was significantly higher in pramlintide-treated patients compared to control (RR 1.97, 95% CI 1.29 to 2.99; three studies).

Obese patients without diabetes: Pramlintide significantly reduced weight (WMD -2.27kg, 95% CI -2.88 to -1.66; four studies, one with multiple arms with different doses of pramlintide) and waist circumference (WMD -2.02cm, 95% CI -2.98 to -1.07; two studies, one with multiple arms with different doses of pramlintide). There was no evidence of a difference between treatments in the incidence of nausea; significant heterogeneity was identified in this analysis.

Both groups combined: Pramlintide was associated with a greater incidence of nausea than control (RR 1.88, 95% CI 1.32 to 2.67; six studies) in type 2 diabetes mellitus patients and obese patients without diabetes, although there was evidence of substantial heterogeneity. Subgroup analysis confirmed that pramlintide increased nausea regardless of short- or long-term therapy and dose, except in obese non-diabetic patients separately.

There were insufficient trials to adequately assess publication bias.

Authors' conclusions
Pramlintide was associated with a small reduction in HbA1c and a modest reduction in weight in patients with type 2 diabetes mellitus or non-diabetic obesity. There was increased incidence of nausea but not hypoglycaemia at any time during therapy.

CRD commentary
The review addressed a clear research question. Inclusion criteria appeared mostly appropriate. Although inclusion criteria specified that studies were to be placebo-controlled, one included study had a different comparator (rapid acting insulins). A wide range of sources were searched for relevant studies. There were no language restrictions. No explicit attempts were made to identify grey literature. Appropriate methods were used to select studies, extract data and assess studies for risk of bias.

Risk of bias was unclear in most of the included studies, mostly because of lack of reporting. Studies were synthesised
in meta-analyses and subgroup analyses were undertaken to assess differential effects at different time points and with different doses of pramlintide. In some of the forest plots (figures 4 and 5) the single control group of one study (Smith 2008) was counted multiple times in comparisons of different doses of pramlintide and this made the reliability of the summary effect estimates uncertain. Sensitivity analyses were performed (removal of the study where rapid-acting insulins were used for control) to assess the effects of pramlintide when compared to placebo. The authors acknowledged that concomitant medications during the trial may have caused confounding. There were insufficient studies to fully assess publication bias.

The authors' conclusions reflect the limited evidence base, but risks of bias in the included studies and the analyses make the reliability of the conclusions uncertain.

Implications of the review for practice and research

Practice: The authors stated that patients who required a small reduction in HbA1c without further weight gain may benefit from the addition of pramlintide to short- and long-lasting insulin regimens.

Research: The authors stated that larger studies were required to assess efficacy, tolerability and cost effectiveness in patients newly diagnosed with type 2 diabetes mellitus and who were not on additional insulin; studies should compare monotherapy with pramlintide and combination therapy with pramlintide together with other agents.

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