P2-377

Effects of Exenatide on Weight and Appetite in Overweight Adolescents and Young Adults with Prader-Willi Syndrome

Parisa Salehi, M.D.[1], Isabel Hsu, M.D., Ph.D.[2], Colleen G. Azen, M.S.[3], Steven D. Mittelman M.D., Ph.D.[2,4], Mitchell E. Geffner, M.D.[2,4], Debra Jeandron, M.D.[2]

[1]Division of Endocrinology, Seattle Children's Hospital, University of Washington, Seattle, WA, USA; [2]Center for Endocrinology, Diabetes, and Metabolism, Children's Hospital Los Angeles, Keck School of Medicine of University of Southern California, Los Angeles, CA, USA; [3]Clinical and Translational Science Institute (CTSI), The Saban Research Institute, Children's Hospital Los Angeles, Keck School of Medicine of University of Southern California, Los Angeles, CA, USA; [4]The Saban Research Institute, Children's Hospital of Los Angeles, Keck School of Medicine of University of Southern California, Los Angeles, CA, USA

Background

- Prader-Willi Syndrome (PWS) is a genetic disorder associated with hyperphagia and hyperghrelinemia with major morbidity due to obesity.
- There is no effective medical therapy for the hyperphagia.
- A therapy targeting appetite could potentially be an effective treatment in PWS.
- Exenatide [Byetta (synthetic exendin-4); AstraZeneca, Wilmington DE] is a GLP-1 receptor agonist that causes reduced appetite and weight loss, actions which are believed to be, in part, centrally mediated.
- Animal studies have shown that exendin-4 decreases levels of ghrelin, an orexigenic hormone.
- Thus, exenatide could improve the hyperphagia and obesity in patients with PWS.

Objective

- To determine the effect of a 6-mo trial of exenatide on appetite, weight, and gut hormones in youth with PWS.

Methods

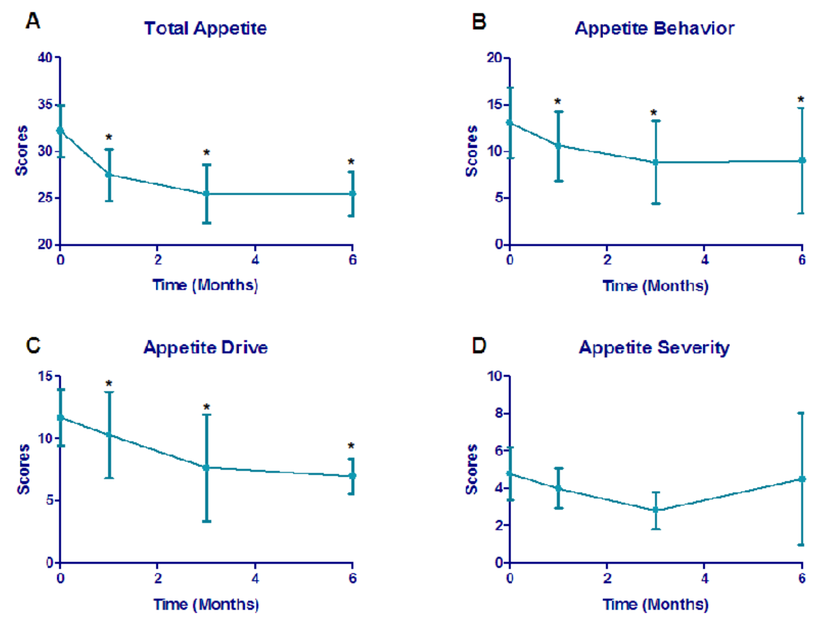
- Ten overweight or obese subjects with PWS (13-25 yr old) were recruited for an open-label, non-randomized, 6-month longitudinal exenatide trial.
- Exenatide was given using standard dosing.
- No dietary modifications were made during the study.
- Primary outcomes were weight, BMI, truncal fat, appetite, and basal acylated (active) ghrelin at 0,1, 3, and 6 mo and during mixed meal tolerance tests (MMTT) at 0 and 6 mo.
- Subjects underwent serial appetite questionnaires, MMTTs, DEXA scans, anthropometrics, and assays of metabolic markers (insulin, acylated ghrelin, leptin, and pancreatic polypeptide (PP)).
- A PWS-validated appetite questionnaire was used at each visit with questions based on appetite behavior, drive, and severity (Dykens et al. Obesity 2007;15:1816-1826).
- Consistent caregivers completed questionnaires with possible total appetite scores between 11-55 (higher values = higher appetites) with scores subdivided into behavior, drive and severity sub-categories.
- Data are presented as mean ± SD unless not normally distributed, in which case they are presented as median with intra-quartile ranges (25th and 75th percentiles).
- Within-subject changes between visits were analyzed by mixed model repeated measures.
- Area-under-the-curve (AUC) was used to analyze MMTT data.

Results

- The medication was well-tolerated without serious adverse side effects.
- Appetite scores significantly decreased from baseline (32.2 ± 8.7) after 1, 3, and 6 mo of treatment (27.5 ± 8.8, 25.4 ± 9.3, 25.4 ± 7.2, respectively; p=0.004) due mainly to significant decrease in appetite behavior and drive scores (p=0.003 and 0.03, respectively) (Figure 1).
- There were no significant changes in weight, BMI z-score, or truncal fat (Figure 2).
- There was a significant decrease in mean HbA1c from baseline after 1, 3, and 6 mo of treatment (Table 1).
- There was no significant change in fasting insulin, leptin, PP, or acylated ghrelin from baseline at any visit point during treatment (Table 1).
- There was no difference in excursion of acylated ghrelin or pancreatic polypeptide (PP) during the MMTT based on AUC data with p-values of 0.5 and 0.7, respectively (Figure 3).

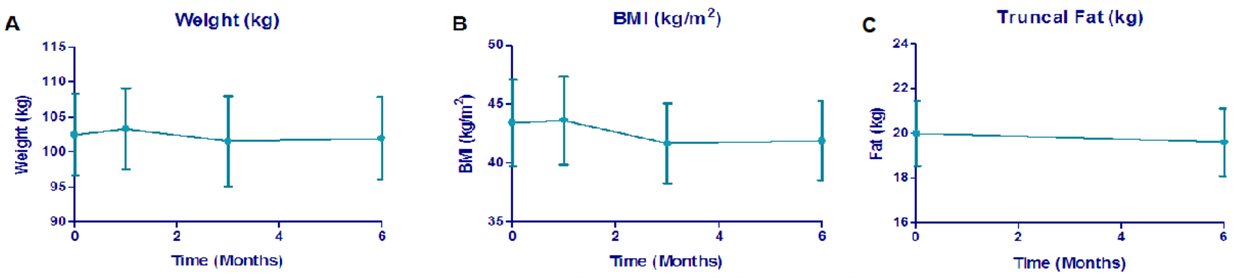
Figures and Tables

Figure 1. Appetite Scores Before and After Treatment with Exenatide



Shown as mean ± SD. (A) Total appetite scores, (B) Appetite behavior scores, (C) Appetite drive scores, and (D) Appetite severity scores. * denotes scores that were significantly different from Time 0.

Figure 2. Weight, Body Mass Index (BMI), and Truncal Fat Before and After Treatment with Exenatide



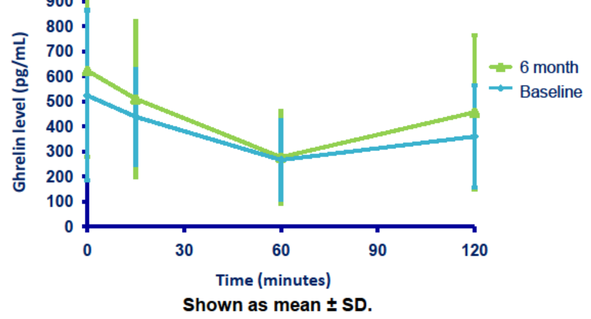
Shown as mean ± SD. (A) Weight, (B) BMI, and (C) Truncal fat

Table 1. Insulin, Leptin, and Acylated Ghrelin (Acy Ghr), and Pancreatic Polypeptide (PP) over Time †

	Baseline	1 mo	3 mo	6 mo	P-Value across Visits
HbA1c (%)	5.9 (5.6, 7.9)	5.8 (5.1, 5.9)	5.8 (5.3, 6.0)	5.6 (5.4, 5.9)	0.04*
Insulin (uIU/mL)	10.5 (6.0, 21.0)	14.5 (5.0, 42.0)	12.5 (9.0, 15.0)	13.5 (6.5, 18.0)	0.8*
Leptin (ng/mL)	36.4 ± 18.3	30.0 ± 18	27.5 ± 13.3	29.0 ± 14.5	0.2
Acy Ghr (pg/mL)	362.3 (259.0, 740.7)	378.5 (273.9, 644.6)	503.9 (375.5, 828.3)	625.3 (358.5, 767.2)	0.2*
PP (pg/mL)	89 (31.0, 662.0)	104.0 (67.0, 468.0)	138.0 (58.0, 496.0)	104.0 (25.0, 423.0)	0.04*€

†Data expressed as mean ± SD or median (IQR) for non-normally distributed variables
*P-value from analysis of log-transformed values
€No significant differences from baseline; p-value most likely due to differences among subsequent time points, which were not included in *post hoc* pairwise comparisons

Figure 3. Acylated Ghrelin During MMTT



Shown as mean ± SD.

Conclusions

- This pilot study showed that exenatide was safe and effective in decreasing appetite in youth with PWS, without decreases in weight or BMI in the short term.
- Obesity in PWS has a multifactorial basis and requires a treatment strategy which may include the use of a therapeutic agent in conjunction with lifestyle modifications.
- Larger, controlled trials in PWS patients are needed to confirm the safety and efficacy of exenatide, and to evaluate whether its use might induce weight loss when used in conjunction with lifestyle modification.

ESPE 2015
377--P2
Fat Metabolism, Obesity
Parisa Salehi
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology