Use of GLP-1 Receptor Agonists in Prader-Willi Syndrome: Report of Six Cases

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A high incidence of glucose metabolism alterations (impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes) has been observed in Prader-Willi syndrome (PWS) (7–40%), particularly after pubertal age and in obese subjects (1). Glucagon-like peptide 1 (GLP-1) receptor agonist (exenatide) and analog (liraglutide) are the new drugs recently introduced for type 2 diabetes that simultaneously reduce appetite and body weight, and their beneficial effects have been reported only in few cases with PWS (2–5).

We report, for the first time, the effects of long-term liraglutide or exenatide treatment in six genetically confirmed (3 deletion and 3 uniparental disomy of chromosome 15) (UPD) adult PWS patients (3 males, aged 20.7–37.7 years; all but one obese, BMI 28–57.2 kg/m^2) never treated with growth hormone, affected by type 2 diabetes. All patients were treated at least 12 months with metformin (1,700–3,000 mg/day) and/or gliclazide (30 mg/day) before therapy with GLP-1 agonists/analogs. The range used for GLP-1 agonists was 1.2 to 1.8 mg/day for liraglutide (4 patients) and 20 μg/day for exenatide (2 patients) (Table 1).

At the time of the study, four patients suffered from hypertension and were treated with ACE inhibitors (patients 1 and 3), angiotensin receptor blockers (patient 3), and furosemide (patient 6). Four patients (patients 1, 3, 4, and 5) had hypertriglyceridemia and/or hypercholesterolemia and one was treated with statins (patient 5). Two individuals (patients 1 and 5) were undergoing sex steroid replacement. None of them experienced growth hormone therapy (Table 1).

Every 6 months, anthropometric (BMI and waist circumference) and metabolic parameters (glycemia, HbA_{1c}) were evaluated. Continuous glycemic monitoring (iPRO2 Professional, Medtronic, MiniMed, Inc., Sylmar, CA) was performed for 72 h at the beginning of therapy and after 12 months.

Statistical analyses were performed using SPSS 17.00 (SPSS, Inc., Chicago, IL) software. Written informed consent was obtained by the patients and their parents.

During the 24 months of treatment, we detected a tendency to decrease BMI, HbA_{1c}, and waist circumference and a significant decrease of mean glycemia during continuous glycemic monitoring at 12 months in respect to baseline (114.3 ± 10.7 mg/dL vs. 148.5 ± 20.5 mg/dL; $P < 0.05$).

Our data seem to support the previously reported efficacy of exenatide and liraglutide in these patients, with variability of response in single patient and a tendency to improvement during the period of observation—in particular the glycemic control, especially during the first 12 months. Probably an increasing dose of GLP-1 analogs should be considered, but we have to take into consideration that liraglutide can delay gastric emptying and there are several reports of binge eating–induced and idiopathic gastric necrosis and fatal rupture in PWS (6). Therefore, some caution in the use of GLP-1 agonists and monitoring of gastric emptying during therapy may be appropriate in these patients.

In conclusion, we found our six PWS patients treated with GLP-1 agonists/analogs had a tendency to an improvement/stabilization of altered glucose metabolism and clinical parameters, more evident during the first 12 months of therapy. Moreover, these drugs seem to be well tolerated in PWS patients. Their relevance, however, remains to be fully established in a larger number of patients as to counteract the wide distribution of individual changes.

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Table 1—Characteristics of the patients and variation of parameters and therapy during the period of therapy/observation of six PWS patients

				Basal		12 months		24 months		
Patient	Sex	Age (years)	Therapy	BMI	HbA_{1c} % (mmol/mol)	BMI	HbA_{1c} % (mmol/mol)	BMI	HbA_{1c} % (mmol/mol)	Therapy
1	M	37.3	Lrg 1.2 Met 1,700	36	7.6 (60)	33	6.3 (45)	32.4	6.9 (52)	Testosterone 250 mg Ramipril 5 mg Calcitriol 0.5 μg
2	M	20.7	Exn 20 Met 3,000	28	8.2 (66)	28	7 (53)	26.5	6.8 (51)	Topiramate 40 mg
3	M	27.7	Lrg 1.2 Met 1,700	44	7.5 (58)	44	6.9 (52)	44	7.4 (57)	Ramipril 5 mg Candesartan 8 mg
4	F	30.4	Lrg 1.2 Met 3,000	50	8.7 (72)	48	7.3 (56)	48.1	7.8 (62)	Allopurinol 150 mg
5	F	37.1	Lrg 1.8 Met 2,000 Glic 30	30	8.3 (67)	31	8.6 (70)	30.2	9.3 (78)	Simvastatin 20 mg EEPP
6	F	34.5	Exn 20 Met 3,000	57	9.5 (80)	59	9.5 (80)	58.5	10.1 (87)	Furosemide 25 mg

All therapies are intended daily except for testosterone (patient 1), which was administered monthly. EEPP, estroprogestin; Exn, exenatide (μg/day); F, female; Glic, gliclazide (mg/day); Lrg, liraglutide (mg/day); M, male; Met, metformin (mg/day).

the manuscript. A.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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