

oral hydrocortisone 10 mg/m²/day and fludrocortisone 0.1 mg/day, with subsequent normalization of electrolytes. Insulin therapy dosage had to be doubled (1.4 IU/kg/day), which decreased hypoglycemia episodes.

Severe hyponatremia may cause rhabdomyolysis, which has mainly been reported in cases of water intoxication.^{6,8} Association of rhabdomyolysis with primary adrenal insufficiency is extremely uncommon. Concomitant hyponatremia exists in almost all cases, except in one reported in 2003.⁹ The lowest sodium level seen was 97 mmol/L.⁷ Potassium levels were increased in more than half the cases (highest value reported, 5.8 mmol/L⁷). Our patient showed hyponatremia of 120 mmol/L and hyperkalemia of 6.8 mmol/L. Children with severe hyperkalemia (>7 mmol/L) may experience ascending muscle weakness, with occasional progression to flaccid paralysis. These findings are similar to those of patients with Guillain-Barré.

In adrenal insufficiency, cortisol deficiency stimulates CRH release, with increased ADH secretion and decreased sodium levels. On the other hand, aldosterone deficiency promotes renal sodium excretion, causing hypovolemia and ADH release mediated by baroreceptors.⁶

The mechanism by which rhabdomyolysis occurs in the setting of hyponatremia is not clear, and various hypotheses have been proposed: rupture of the myocyte cell membrane caused by fluctuation in intracellular and extracellular osmolality by an increase in intracellular calcium through the sodium-calcium exchanger^{6,8,10}; on the other hand, correction of severe hyponatremia may also cause rhabdomyolysis because CPK increase has occasionally been seen some days after correction of electrolyte imbalance.⁶

Measurement of CPK levels in patients with adrenal insufficiency complicated with hyponatremia appears to be necessary because association with rhabdomyolysis may occur more frequently than previously recognized.^{6,7}

Our patient is probably the first clinical case reported in children of an association of hyponatremic rhabdomyolysis and adrenal insufficiency in the setting of a Carpenter syndrome.

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Lixisenatide clinical experience on patients with type 2 diabetes and obesity in endocrinology offices in Malaga[☆]



Experiencia clínica con lixisenatida en pacientes con diabetes tipo 2 y obesidad en consultas de atención especializada en Málaga

Glucagon-like peptide 1 (GLP-1) agonists decrease glucose levels with a very low risk of hypoglycemia, limit weight

increase associated to insulin therapy and have favorable effects on dyslipidemia, high blood pressure, endothelial function, cardiac contractility, intestinal lipoproteins, inflammation, and indirect kidney function markers.¹⁻³

A prospective study with within-subject measures of change was conducted on 43 patients (62.8% females) with type 2 diabetes mellitus and obesity who started treatment with lixisenatide (Lyxumia[®], Sanofi Aventis S.A.) to assess drug tolerability and impact on weight and metabolic control. Subgroups without and with prior antihypertensive treatment (23.3% and 76.7% respectively) and lipid-lowering treatment (41.9% and 58.1% respectively) and occurrence of side effects were analyzed. Mean age was 58 ± 13.4 years, and mean time since diabetes onset 11.9 ± 7.3 years. A family history of cardiovascular disease (CVD) and diabetes was found in 41.4% and 62.9% of patients respectively. At the baseline visit, treatment consisted of oral agents (86% of patients), GLP-1 analogues (18.6%), and insulin (79.1%; basal 37.2%, premixes 25.6%, and basal-bolus 16.3%). Mean

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Table 1 Change in clinical and laboratory variables before and after lixisenatide treatment.

Variable	Baseline	With lixisenatide	<i>p</i>
Weight (kg)	97.5 ± 17.9	94.3 ± 18.1	<0.001
BMI (kg/m ²)	37.7 ± 6.3	36.2 ± 6.1	<0.001
WC (cm)	99 ± 12.9	94.4 ± 11.8	0.058
SBP (mmHg)	153.2 ± 21.6	136.1 ± 25.0	0.001
DBP (mmHg)	86.2 ± 12.6	81.5 ± 12.3	0.088
HR (bpm)	79.9 ± 11.0	79.4 ± 11.0	0.907
Blood glucose (mmol/L)	10.7 ± 3.9	9.2 ± 2.7	0.076
HbA1c (mmol/mol)	58.6 ± 8	53.9 ± 8	<0.001
TC (mmol/L)	4.5 ± 0.9	4.1 ± 0.9	0.031
LDL-C (mmol/L)	2.4 ± 0.9	2.2 ± 1.1	0.342
HDL-C (mmol/L)	1.2 ± 0.4	1.2 ± 0.3	0.899
TG (mmol/L)	2.1 ± 1.1	2.2 ± 1.3	0.754
GGT (IU/L)	21.8 ± 11.2	21.1 ± 9.6	0.673
GGT (IU/L)	30.3 ± 16.5	30.7 ± 14.9	0.818
GGT (IU/L)	52.1 ± 56.5	53.8 ± 50.4	0.763
Microalb/Cr (mg/L)	28.1 ± 24.1	61.2 ± 64.7	0.487
Microalb/Cr (mg/g)	32.5 ± 42.9	29.0 ± 46.2	0.774
IU of insulin	55.4 ± 38.7	47.9 ± 35.0	0.003
Anti-HTs (%)	76.7	81.1	<0.001
Lipid-lowering drugs (%)	58.1	73	<0.001

Data are given as mean ± standard deviation.

WC: waist circumference; TC: total cholesterol; HR: heart rate; GGT: gamma glutamyltranspeptidase; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; HbA1c: glycosylated hemoglobin; HDL-C: HDL cholesterol; HBP: high blood pressure; BMI: body mass index; LDL-C: LDL cholesterol; Microalb/Cr: microalbumin/creatinine ratio; DBP: diastolic blood pressure; SBP: systolic blood pressure; TG: triglycerides; IU: insulin units.

follow-up time from start of lixisenatide was 3.9 ± 1.5 months. Table 1 shows change over time in clinical and laboratory variables. Improvement in systolic blood pressure (SBP) and total cholesterol (TC) was significant in the subgroups without and with antihypertensives before and after treatment with lixisenatide (SBP before 147 ± 26.5 mmHg vs SBP after 113.6 ± 7.9 mmHg, $p=0.023$; and SBP before 153.6 ± 21 mmHg vs SBP after 140.0 ± 25.4 mmHg, $p=0.020$, respectively), while TC decrease only remained significant in the subgroup taking lipid-lowering drugs before lixisenatide was started (TC before 178.5 ± 36 mg/dL vs TC after 152.6 ± 25.6 mg/dL; $p=0.007$), in which a significant decrease was also seen in LDL cholesterol (LDL-C) (LDL-C before 93.3 ± 37.2 mg/dL vs LDL-C after 73.1 ± 25.9 mg/dL; $p=0.023$). No change was seen in amylase levels (mean amylase level 40.6 ± 6.7 IU/L). As regards digestive tolerability, 20% did not tolerate the drug, 5% tolerated 10 mcg/day, and 75% tolerated 20 mcg/day.

No significant improvement in fasting blood glucose was seen in our study. GLP-1 analogues have been shown to achieve similar improvements in basal blood glucose, but lixisenatide 20 mcg achieves greater reductions in the area under the curve as compared to postprandial blood glucose and greater slowing of gastric emptying.⁴ A significant decrease in HbA1c was seen in our patients. GLP-1 analogues have shown to be non inferior to other hypoglycemic agents⁵ and to achieve greater and similar HbA1c reductions in a meta-analysis as compared to oral agents and basal and biphasic insulin respectively.⁶

Significant weight and BMI decreases were seen, consistent with reports by other authors,⁷ with a mean weight

loss of 3.2 kg. These results are similar to those previously reported of decreases by 1.4 kg and 4.8 kg versus placebo and insulin respectively,⁵ as well as reductions by 3.31 kg versus diabetic controls on other treatments and by 1.22 kg versus placebo in a meta-analysis.⁸

Despite similar HbA1c decrease, 35% less hypoglycemic episodes were reported with GLP-1 as compared to insulin.⁷ Meier et al. found greater risk of hypoglycemia with lixisenatide as compared to liraglutide,⁴ while Rosenstock et al. reported less episodes of symptomatic hypoglycemia in the lixisenatide group (2.5% vs 7.9%, $p<0.05$).⁹ In agreement with this last study, our patients had no symptomatic hypoglycemia.

Lixisenatide has been reported to have a more favorable profile of digestive tolerability than exenatide twice daily⁹ and liraglutide.⁴ Most patients in our study tolerated well lixisenatide treatment.

As regards lipid profile, improvement was seen in TC levels and remained significant in the subgroup already taking lipid-lowering drugs. A significant LDL-C decrease was also found. In agreement with our results, other authors have reported lipid improvement in patients treated with GLP-1 analogues.¹⁻³

Treatment with lixisenatide decreased SBP values, with no statistical significance achieved as compared to DBP levels. These results agree with reports by other authors.^{7,8}

No significant changes were found in heart rate (HR). However, a meta-analysis concluded that GLP-1 analogues increase HR by 1.86 beats per minute versus placebo and by 1.90 beats per minute as compared to other antidiabetics,

an effect which was more evident with liraglutide as compared to exenatide twice daily.⁸ Lixisenatide causes a lower increase⁵ and even a decrease in HR¹⁰ as compared to liraglutide.

Limitations of our study include the small number of studies reported in standard clinical practice with which our results could be compared, the small sample size, the short follow-up time, and lack of assessment of postprandial blood glucose.

Our analysis shows that treatment with lixisenatide significantly improves anthropometric parameters, and blood glucose control in terms of HbA1c with less insulin requirements, and causes significant SBP and TC decreases. Tolerability was good in most patients. A significant intensification of antihypertensive and lipid-lowering treatment, not only hypoglycemic therapy, was also seen in our clinical practice, with an overall metabolic approach to patients. Longer studies with larger sample sizes are needed to assess the long-term efficacy and safety of therapies with GLP-1 analogues.

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Conflict of interest

The authors state that they have no conflicts of interest.

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