

[CASE REPORT]

Suppression Failure of Cortisol Secretion by Dexamethasone May Occur in Glucagon-like Peptide-1 Receptor Agonist-treated Patients with Diabetic Autonomic Neuropathy

Yasuki Nagai¹, Kosuke Mukai¹, Michio Otsuki¹, Takekazu Kimura¹, Junji Kozawa¹, Hitoshi Nishizawa¹, Norikazu Maeda², Taka-aki Matsuoka¹, Hiromi Iwahashi³, Akihisa Imagawa⁴ and Iichiro Shimomura¹

Abstract:

Two diabetic women (case 1, 75 years old; case 2, 49 years old) being treated with glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) showed no suppression of cortisol secretion on a dexamethasone suppression test (DST). However, its secretion was suppressed after switching from GLP-1 RAs to insulin. We also checked the cortisol secretion by a DST in five consecutive inpatients (case 3-7) being treated with GLP-1 RAs. The coefficients of R-R interval variation at rest and during deep breathing were lower in the two false-positive cases (case 1 and 2) than in the five true-negative cases (case 3-6). GLP-1 RAs can be switched to insulin in order to eliminate the slow absorption effect of dexamethasone by GLP-1 RAs if a DST is planned in diabetic patients receiving GLP-1 RAs.

Key words: GLP-1 receptor agonists, dexamethasone suppression test, autonomic diabetic neuropathy

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Introduction

Incretin hormones are secreted from gastrointestinal L cells predominantly located in the ileum and colon in response to nutrients and stimulate glucose-dependent insulin secretion from pancreatic β cells. The two main incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 receptor agonists (GLP-1 RAs) therapies are used as agents to promote insulin secretion and inhibit glucagon secretion in the treatment of type 2 diabetes mellitus (1). Furthermore, GLP-1 RAs are suggested to possess pleiotropic effects, such as appetite suppression via the central nervous system, cardioprotective effects (2), antiatherosclerotic effects (3) and delayed gastric emptying and small bowel transit (4-6).

It has been reported that the administration of GLP-1 RAs resulted in the slow absorption of oral drugs due to delayed gastric emptying (7-13). We previously reported that the GLP-1 RA exenatide delayed the absorption hydrocortisone and induced acute adrenal insufficiency in diabetic patients with panhypopituitarism (14). Our findings indicated that GLP-1 RAs affect the actions of short-half-life glucocorticoids.

We herein report two patients who presented with false-positive results on a dexamethasone suppression test (DST) due to the GLP-1 RAs induced-slow absorption of dexamethasone, a synthetic long-half-life glucocorticoid. Five consecutive diabetic patients using GLP-1 RAs also underwent a DST. Our findings suggest that autonomic diabetic neuropathy might be related to the false-positive results of DST induced by GLP-1 RA administration. This study was

¹Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Japan, ²Department of Metabolism and Atherosclerosis, Osaka University Graduate School of Medicine, Japan, ³Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, Japan and ⁴Department of Internal Medicine (I), Osaka Medical College, Japan

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Correspondence to Dr. Michio Otsuki, otsuki@endmet.med.osaka-u.ac.jp

Table 1. Laboratory Data on Admission in Case 1 and Case 2.

Variable	Case 1	Case 2	Variable	Case 1	Case 2		
WBC	8,380	6,870	/ μ L	T-Cho	137	147	mg/dL
RBC	410	496	$\times 10^4/\mu$ L	TG	112	140	mg/dL
Hb	12.9	13.3	g/dL	HDL-C	36	42	mg/dL
Ht	37.4	41.7	%	CRP	<0.04	0.07	mg/dL
Plt	23.6	27.1	$\times 10^4/\mu$ L	Na	144	142	mEq/L
AST	15	26	U/L	K	2.6	3.9	mEq/L
ALT	10	32	U/L	Cl	105	106	mEq/L
LDH	214	243	U/L	FPG	118	89	mg/dL
γ -GTP	18	13	U/L	HbA1c	10.5	8.3	%
T-Bil	0.8	0.6	mg/dL	TSH	2.02	0.93	μ IU/mL
TP	7.0	7.1	g/dL	FT4	1.0	1.2	ng/dL
ALB	3.6	4.0	g/dL	FT3	2.4	2.9	pg/mL
BUN	8	13	mg/dL	ACTH	60	89	pg/mL
Cr	0.62	0.61	mg/dL	cortisol	12.8	10.6	μ g/dL
UA	3.4	6	mg/dL	Urinary free cortisol	57.5	44.9	μ g/day

approved by the Ethics Committee of Osaka University and was conducted according to the requirements of the Declaration of Helsinki.

Case Reports

Case 1

A 75-year-old woman was admitted to our hospital for the treatment of diabetes mellitus in April 2016. She had been diagnosed with diabetes mellitus at 63 years of age and started insulin treatment at 73 years of age. She had also suffered from hypertension, dyslipidemia, constipation and depression. She had a history of abdominal surgery for uterine procidentia. She had no family history of diabetes mellitus.

Her clinical characteristics are shown in Table 1. On admission, her height was 141.5 cm, weight 50.9 kg and body mass index 25.4 kg/m². A physical examination did not show any obvious Cushing's symptoms, such as moon face, buffalo hump, central obesity, purple or red striae on the trunk, reddish stretch marks and thin skin. Laboratory data on admission showed that the fasting plasma glucose (FPG) level was 118 mg/dL, hemoglobin A1c (HbA1c) 10.5%, plasma adrenocorticotropic hormone (ACTH) level 60 pg/mL (normal range 0-60 pg/mL) and serum cortisol level 12.8 μ g/dL (normal range 4.3-20 μ g/dL) (Table 1). She had no diabetic retinopathy or nephropathy. With regard to diabetic neuropathy, she had diabetic polyneuropathy because the coefficient of R-R interval variation (CV_{R-R}) during deep breathing was not increased compared with the CV_{R-R} at rest (2.52% vs. 2.89%). Liraglutide was started after her admission, and the dosage was gradually increased from 0.3 mg/day to 0.9 mg/day. She had chronic constipation that was exacerbated by liraglutide treatment and was thus prescribed sennoside and magnesium oxide for palliation.

To rule out chronic glucocorticoid excess-induced obesity,

diabetes and hypertension, a low-dose overnight DST was performed during liraglutide treatment, and the cortisol secretion was not suppressed (serum cortisol level: 14.8 μ g/dL after DST). We suspected that the delayed gastric emptying and small bowel transit induced by liraglutide might be the cause. Therefore, a low-dose overnight DST was performed again 3 days after switching from liraglutide to insulin, and the cortisol secretion was suppressed (serum cortisol level: 0.8 μ g/dL after DST).

Case 2

A 49-year-old woman was admitted to our hospital for the treatment of diabetes mellitus in May 2016. She had been treated with exenatide and insulin since January 2013. She had been diagnosed with diabetes mellitus at 27 years of age. She also suffered from dyslipidemia, chronic constipation, spinal canal stenosis and bronchial asthma. She had a family history of diabetes on her mother's side (her mother and maternal grandmother). She had no history of abdominal surgery.

On admission, her height was 160.5 cm, weight 83.5 kg and body mass index 32.4 kg/m². A physical examination showed no obvious Cushing's symptoms, as described above. Laboratory data on admission showed that the FPG level was 89 mg/dL, HbA1c 8.3%, plasma ACTH level 89 pg/mL and serum cortisol level 10.6 μ g/dL (Table 1). She had proliferative diabetic retinopathy after panretinal photocoagulation and vitrectomy, diabetic polyneuropathy (diminished Achilles reflex and decline in vibration sense) and diabetic autonomic neuropathy (decline in CV_{R-R} at rest) but not nephropathy (Table 2).

As in Case 1, a low-dose overnight DST was performed during exenatide treatment in order to evaluate chronic glucocorticoid excess. Cortisol secretion was not suppressed (serum cortisol level: 4.2 μ g/dL after DST). We suspected that the delayed gastric emptying and small bowel transit induced by exenatide might be the cause. Therefore, a low-

Table 2. Clinical Characteristics of 7 Diabetic Patients Treated with GLP-1 RAs.

	0.5 mg DST: positive			0.5 mg DST: negative			
	Case1	Case2	Case3	Case4	Case5	Case6	Case7
Age (years)	75	49	66	57	74	66	46
Sex (male/female)	F	F	M	M	F	F	F
Body mass index (kg/m ²)	25.4	32.4	32.0	29.8	22.0	28.5	34.4
Duration (years)	11	22	11	11	20	19	12
HbA1c (%)	10.5	8.3	7.7	8.1	9.2	8.3	9.3
Retinopathy (NDR/SDR/PrePDR/PDR) †	NDR	PDR	NDR	NDR	NDR	NDR	SDR
Nephropathy (Stage1-5) ‡	Stage 1	Stage 1	Stage 3	Stage 1	Stage 1	Stage 1	Stage 1
Neuropathy							
Peripheral sensorimotor neuropathy							
Sensory disturbance (+/-)	-	-	-	-	+	+	-
Achilles reflex (+/±, R/L)	+/+	-/-	+/+	+/+	±/±	±/±	±/±
Vibration perception with diapason C128 (seconds, R/L)	10/8	8/8	9/10	15/14	12/12	4/5	13/12
Autonomic neuropathy							
Coefficient of R-R interval variation (CV _{R-R}) (%) at rest	2.89	2.11	NR	3.09	4.54	3.19	NR
CV _{R-R} With deep breathing (%)	2.52	2.00	3.97	3.68	4.85	3.92	NR
Orthostatic hypotension (+/-) ‡	-	-	-	-	-	-	-
Abdominal surgical history (+/-)	+	-	+	-	+	+	-
Constipation (+/-)	+	+	-	+	+	+	+
Plasma ACTH (pg/mL)	60	89	19	54	18	13	32
Serum cortisol (µg/dL)	12.8	10.6	10.9	14.3	8.5	6.0	9.5
Serum cortisol levels after 0.5mg DST (µg/dL)	14.8	4.2	1.9	1.0	1.7	1.6	0.7
Other diabetic medications	-	Biguanide	-	Biguanide	Biguanide Insulin	Biguanide SGLT2i	Biguanide Insulin
GLP-1 RAs	Liraglutide 0.9 mg	Exenatide 10 µg daily	Liraglutide 0.9 mg	Liraglutide 0.9 mg	Liraglutide 0.6 mg	Liraglutide 0.3 mg	Exenatide 20 µg daily
Administration period of GLP-1 RAs	9 days	5 years	16 days	13 days	1 year	6 months	4 years

†Retinopathy was classified according to the Davis classification: NDR: no diabetic retinopathy, SDR: simple diabetic retinopathy, PrePDR: preproliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy including panretinal photocoagulation

‡Nephropathy was classified according to the Classification of Diabetic Nephropathy 2014: Stage 1, normoalbuminuria [urinary albumin excretion (UAE) of <30 mg/day]; Stage 2, microalbuminuria [UAE of 30-299 mg/day]; Stage 3, overt albuminuria [UAE of >300 mg/day]; Stage 4, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², regardless of albuminuria; and Stage 5, dialysis therapy.

‡Orthostatic hypotension was diagnosed fall in blood pressure, at least 20 mmHg for systolic or 10 mmHg for diastolic blood pressure, after the patient changes posture from supine to standing.

NR: not reported

dose overnight DST was done again 4 days after switching from exenatide to insulin, and the cortisol secretion was suppressed (serum cortisol level: 0.6 µg/dL after DST). We also measured the plasma ACTH and serum cortisol levels for 2 days (from Day 1 to Day 2 and from Day 8 to Day 9) after the DST to investigate the effect of the absorption delay induced by exenatide on the DST (Figure). Although there was no marked difference between the plasma ACTH and serum cortisol levels in the evening on Day 1 (exenatide treatment) and in the evening on Day 8 (insulin treatment), these levels with exenatide treatment in the morning on Day 2 were lower than with insulin treatment in the morning on Day 9 (Figure).

Clinical characteristics of seven diabetic patients treated with GLP-1 RAs (including Case 1, 2)

Given the findings in the two cases described above, we also checked the cortisol secretions using a low-dose overnight DST in five consecutive inpatients being treated with GLP-1 RAs. Table 2 shows the clinical characteristics of Cases 1-7. The cortisol secretion in Cases 3-7 was suppressed by a low-dose overnight DST. With regard to the age, sex, body mass index, diabetes duration, initial glycaemic control, diabetic retinopathy, nephropathy, concomitant medications, GLP-1 RAs type and dose, abdominal surgical history and constipation, there was no obvious trend compared with the two false-positive cases (Case 1 and 2). The CV_{R-R} values at rest and during deep breathing were lower in the two false-positive cases (Case 1 and 2) than in four of

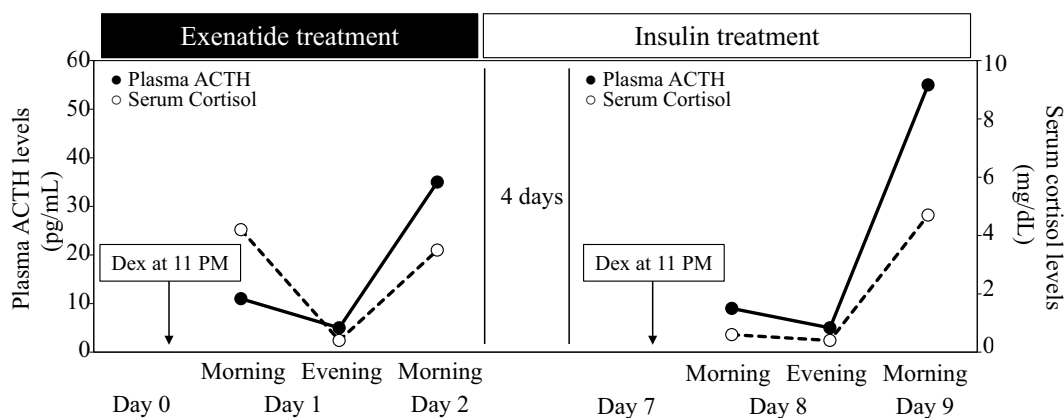


Figure. The change in the plasma ACTH and serum cortisol levels for two days after a low-dose overnight DST during exenatide and insulin treatment in Case 2 (plasma ACTH levels: filled circles, serum cortisol levels: open circles, Dex: Dexamethasone).

the true-negative cases (Case 3-6). The results of the Schellong test were negative in all cases. Four and six patients had a history of abdominal surgical and constipation, respectively.

Discussion

We encountered two patients who presented with false-positive results of the DST caused by the GLP-1 RA-induced slow absorption of dexamethasone, a synthetic long-half-life glucocorticoid. We also checked the results of a DST in five consecutive inpatients with diabetes mellitus who were being treated with using GLP-1 RAs. Our findings suggest that autonomic diabetic neuropathy might be related to the false-positive results of the DST induced by GLP-1 RA administration.

In order to investigate whether or not delayed gastric emptying and small bowel transit induced by exenatide affect dexamethasone absorption, we measured the plasma ACTH and serum cortisol levels for two days after the DST in patients receiving exenatide treatment and insulin treatment (Figure). Although there was no marked difference between the plasma ACTH and serum cortisol levels in the evening on Day 1 (exenatide treatment) and in the evening on Day 8 (insulin treatment), these levels with exenatide treatment in the morning on Day 2 were lower than with insulin treatment in the morning on Day 9 (Figure). These results suggested that the delayed absorption of dexamethasone by GLP-1 RAs might affect the hypothalamic-pituitary-adrenal (HPA) axis for two days after the DST. Previous studies have reported that the administration of GLP-1 RAs resulted in the slow absorption of concomitant, orally administered medications due to delayed gastric emptying (7-13). We also reported that exenatide delayed the absorption of hydrocortisone and induced acute adrenal insufficiency in a diabetic patient with panhypopituitarism (14). The mechanism underlying the acute adrenal insufficiency in this patient was that the serum concentration of cortisol was not elevated until 240 minutes after hydrocortisone admini-

stration in exenatide treatment (14). The present findings suggest that the delayed absorption of dexamethasone induced by GLP-1 RAs might cause false-positive results on the DST.

We compared the clinical characteristics of Cases 1 and 2, who showed false-positive results on the DST performed during GLP-1 RAs treatment, with those of Cases 3 to 7, who showed negative results on the DST. No marked differences in the age, sex, body mass index, diabetes duration, initial glycemic control, diabetic retinopathy, nephropathy, concomitant medications, GLP-1 RAs type and dose, abdominal surgical history, constipation or psychiatric disorders were noted between the two group. The CV_{R-R} values at rest and during deep breathing were lower in Cases 1 and 2 than in Cases 3-7. This result suggests that diabetic autonomic neuropathy might be related to the false-positive results on the DST. Asakawa et al. suggested that the CV_{R-R} during deep breathing might be a good indicator of diabetic gastropathy (15). Furthermore, two cases of transient paralytic ileus caused by the administration of liraglutide showed common clinical features, such as constipation, the long-term duration of type 2 diabetes mellitus, diabetic polyneuropathy and autonomic neuropathy, as we previously reported (16). Therefore, the gastrointestinal motility in Cases 1 and 2 may have been reduced by impaired autonomic neurons.

Certain conditions and drugs may interfere with the performance of the DST. First, depression and other psychiatric disorders, alcoholism, morbid obesity, and diabetes mellitus, which induce the activation of the HPA axis or physiological hypercortisolism, can cause false-positive low-dose DST results (17). Second, drugs such as phenobarbitone, carbamazepine (18), rifampicin (19) and phenytoin accelerate the dexamethasone metabolism via the induction of CYP3A4, thereby leading to false-positive DST results. Third, estrogen increases the hepatic production of cortisol-binding globulin (CBG), resulting in false-positive rates for the DST in 50% of women taking oral contraceptives because of increased serum CBG and total cortisol levels (20).

However, neither Case 1 nor 2 had a history of these concomitant drugs, so these conditions can be excluded.

Although further studies are needed to confirm our findings because of the small number of cases in the present report, our present findings suggest that diabetic autonomic neuropathy might reinforce the slow absorption effect of dexamethasone induced by GLP-1 RA administration. GLP-1 RAs can be switched to insulin in order to eliminate the slow absorption effect of dexamethasone by GLP-1 RAs if a DST is planned in diabetic patients receiving GLP-1 RAs.

The authors state that they have no Conflict of Interest (COI).

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