An Increase of Heart Rate and Electrocardiographic Changes after Subcutaneous Liraglutide

Wei-Wei Zhou, Bo Huang, Mei-Lin Liu

Department of Geriatrics, Peking University First Hospital, Beijing 100034, China

To the Editor: Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome results (LEADER) trial illustrated that among patients with type 2 diabetes mellitus, those in the liraglutide group had lower rates of cardiovascular events and death from any cause than did those in the placebo group.[1] Herein, we reported a case of an increase of heart rate (HR) and electrocardiographic changes after subcutaneous liraglutide.

The patient, a 59-year-old man with type 2 diabetes mellitus, had poorly controlled blood glucose was admitted to Peking University First Hospital on November 14, 2015. He had a history of postpercutaneous coronary intervention for exertional chest pain on July 8, 2013. He underwent catheter ablation for paroxysmal atrial fibrillation on March 19, 2014, and he suffered one episode of documented paroxysmal atrial fibrillation within the 20 months after the ablation, so he took dabigatran (a direct thrombin inhibitor) as an anticoagulation treatment. He denied any history of fever, cough, shortness of breath, abdominal pain, paroxysmal nocturnal dyspnea, and weight loss. His exercise tolerance was normal. For the past 2 years, he has been on oral aspirin, metoprolol succinate, isosorbide mononitrate, rosuvastatin calcium, and losartan potassium for coronary heart disease. He had taken metformin hydrochloride, acarbose, and insulin glargine for the control of blood glucose.

On admission, physical examination did not reveal any significant abnormality except obesity (body mass index 31.9; height, 168 cm; and weight, 90 kg). Electrocardiography (ECG) showed normal sinus rhythm [Figure 1a]. Laboratory tests only showed markedly increased serum glucose, a high glycated hemoglobin value of 9.1%, a high fasting blood glucose level of 8–15 mmol/L, and a high postprandial blood glucose level of 13–20 mmol/L. Therefore, a glucagon-like peptide 1 (GLP-1) receptor agonist (liraglutide) was initiated at the dose of 0.6 mg/d on November 17, 2015, with the dose raised to 1.2 mg/d 3 days thereafter.

On November 24, 2015, he complained of palpitation at rest. We found an increase in mean HR (from 65 beats/min to 85 beats/min) and ECG changes in the form of ST segment depression and T-wave inversion in leads II, III, aVF, V4–V6 [Figure 1b]. His serum troponin I level of 0.01 ng/ml (normal range 0–0.04 ng/ml) and a creatine kinase-myocardial band isoenzyme level of 0.6 ng/ml (normal range <5 ng/ml) were within normal limits. Other than starting liraglutide therapy 1 week prior, he had no changes in medications, supplements or lifestyle. The patient's liraglutide therapy was withheld. A 12-lead ECG was done daily for a week with the same machine, which revealed mean HR and ST segment gradually normalized.

The patient underwent coronary angiography (CAG) to establish a confirmative diagnosis without any complications on December 10, 2015. Angiogram shows the coronary dominance pattern was right coronary artery (RCA). CAG findings [Figure 1c–1e] showed a 30% stenosis in the proximal left anterior descending artery, a 30–40% stenosis in the proximal left circumflex artery, and one patent stent in mid-RCA with mild in-stent neointimal hyperplasia.

A mean HR acceleration of 3 beats/min was observed in type 2 diabetes patients with liraglutide treatment,[1] but can be as high as 10 beats/min.[2] In this case, the patient showed a significant increase of HR and obvious electrocardiographic changes after subcutaneous liraglutide. The HR and ECG changes got reverted 3 days after liraglutide was withheld. CAG revealed only mild stenosis of coronary artery. Liraglutide injection resulted in 3 mmol/L reduction of blood glucose, but no symptomatic hypoglycemia. Nevertheless, elevated HR and ECG changes occurred after meal when the glucose level was higher, which highly indicated that liraglutide induced those changes were not associated with blood glucose level. The potential mechanisms include GLP-1-induced vasodilation leading to reflex tachycardia;[3] direct stimulation of the GLP-1 receptor on sinoatrial cells[4] and involvement of sympathetic nervous system activity.[5] This case represents, to the best of our knowledge, a very rare report of liraglutide-induced ECG change. The mechanism behind the effect of liraglutide on HR and ECG is yet to be determined.

Although elevated HR and ECG changes do not seem to prevent overall beneficial results in terms of clinical endpoints in the LEADER trial,[1] this case raises prescriber awareness about the

Address for correspondence: Dr. Mei-Lin Liu,
Department of Geriatrics, Peking University First Hospital,
Beijing 100034, China
E-Mail: meilinliu@yahoo.com

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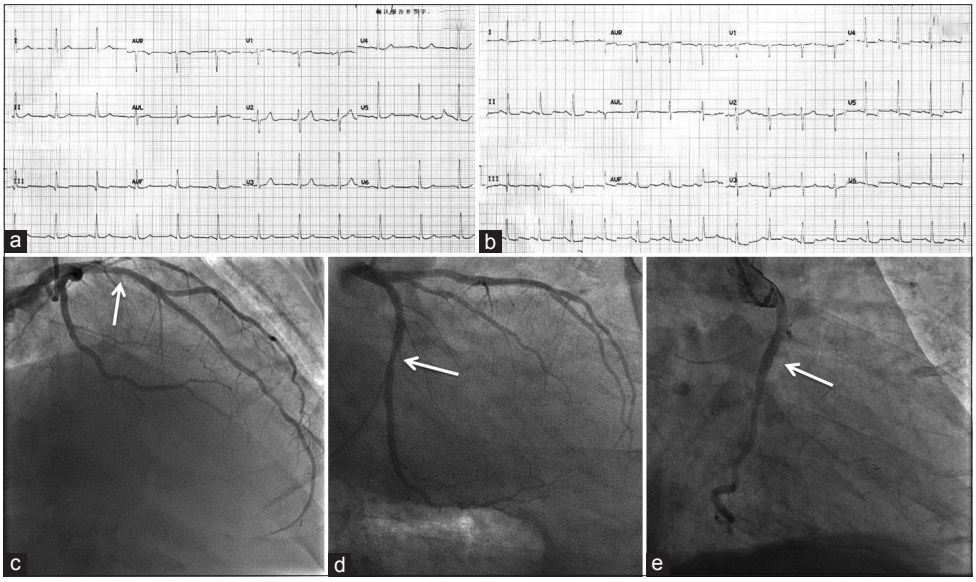

Figure 1: Representative images of the patient. (a) Normal electrocardiogram on admission (on November 14, 2015); (b) electrocardiogram showed ST depression and T-wave inversion in leads II, III aVF, V4–V6 on November 24, 2015 (7 days after subcutaneous liraglutide). (c) Coronary angiography findings showed a 30% stenosis in the proximal left anterior descending artery (arrow); (d) a 30–40% stenosis in the proximal left circumflex artery (arrow); (e) one patent stent in mid-right coronary artery with mild in-stent neointimal hyperplasia (arrow).

potential adverse effects of GLP-1 receptor agonists on HR and ECG in diabetes mellitus patients with coronary heart disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s)/patient's guardians has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients/patient's guardians understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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