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A case of bradycardia in an elderly patient in treatment with levetiracetam at the therapeutic dose

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Abstract

Objective: To describe a side cardiovascular effect induced by levetiracetam in an old female patient.

Case report: An 81-year-old woman was admitted to our Emergency Department (ED) for right upper limb hyposthenia and comitial crisis lasting about 5 minutes. After the execution of Cerebral Computerized Tomography (CT), electroencephalogram (EEG), and neurological visit a therapy with levetiracetam (3000 mg per day intravenous) was started. After this, the patient was admitted for clinical observation and execution of diagnostic exams to the geriatric ward for acute patients "Cognitivo-Funzionale Unit". During the hospital stay, the patient had bradycardia, which was not present in ED, before and immediately after the introduction of the therapy with levetiracetam. The review of the ongoing therapy did not find drugs with known or potential bradycardia effect, therefore a potential side effect of the only new drug started before the detection of bradycardia, levetiracetam, was suspected. An echocardiogram was performed to investigate cardiac reasons for bradycardia, but it did not demonstrate significant and clinically relevant findings. After the reduction of the levetiracetam dose, we observed a gradual recovery of heart frequency. Moreover, we found a serum concentration of 40.7 mg/L (therapeutic range: 10-40 mcg/ml) after 4 days of levetiracetam reduction.

Discussion: High dose levetiracetam appears to cause bradycardia. Based on a substantially normal echocardiogram, the mechanism that could explain this has to be identified in levetiracetam action at the level of heart muscarinic M2 receptors for high drug blood concentration.

Keywords

Levetiracetam overdose; Bradycardia; Elderly patient; Cardiovascular toxicity.

Introduction

Levetiracetam is approved as anticonvulsant therapy in children and in adults. It is considered a well-tolerated anticonvulsant, but it has been associated with some adverse effects. Its mechanism of action is still not well known but seems unrelated to the actions of other anticonvulsants since it does not affect voltage-dependent sodium channels, gamma-aminobutyric acid (GABA) transmission, or affinity for GABA and glutamate receptors. Its pharmacokinetics therapeutically are well described with rapid absorption, and complete bioavailability with 66% of the ingested dose renal excreted unchanged with a half-life of 6–8 h [1-3]. Most reports describe its toxicity as mild central nervous system (CNS) depression, both in children and adults. There are no reports of cardiovascular toxicity at therapeutic doses. In this paper, we report a case of bradycardia associated with a high serum concentration of levetiracetam prescribed according to the registered dose.

Case Report

A 65 kg, 81-year-old woman, with cognitive impairment, chronic cerebral vasculopathy, schizophrenia, arterial hypertension, atherosclerotic vasculopathy, and coxarthrosis, without a past medical history of epilepsy and heart rhythm disorders, such as bradycardia in treatment with pantoprazole, furosemide, haloperidol, valproic acid, clonazepam, enoxaparin sodium, macrogol, clotiapine, vitamin D, zolpidem, atorvastatin, was admitted at the Emergency Department of our Polyclinic, for the appearance of right upper limb's weakness and seizure. At the arrival at the ED, the patient had a Glasgow Coma Scale (GCS) of 8, heart rate (HR) of 86 beats per minute (bpm), blood pressure of 147/116 mmHg, normal respiratory rate, oxygen saturation, at rest, in ambient air, of 95%, serum glucose level of 116 mg/dl and creatinine clearance of 70 ml/minute. The electrocardiogram made in ED showed sinus tachycardia with extrasystoles at 115 bpm. After the execution of brain CT that did not detect hemorrhage and/or acute ischemic injury, of EEG that relieved focuses of left slow activity and of a neurological visit, intravenous antiepileptic therapy with levetiracetam (3000 mg per day) was started. After the start of levetiracetam treatment, the patient's HR gradually decreased to the minimum value of 48 bpm, but despite the bradycardia, the patient remained well perfused with normal capillary return and with normal venous blood gas levels. The review of the ongoing therapy did not find drugs with known or potential bradycardia effects, therefore a potential side effect of levetiracetam, which was the only new drug started before the detection of bradycardia, was suspected and a reduction of levetiracetam dose was carried out. After the reduction of levetiracetam to 2000 mg bis in die, we observed a gradual recovery of heart frequency (Annex 1), moreover, we found a levetiracetam serum concentration of 40.7 mg/L (therapeutic range: 10-40 mcg/ml) after 4 days of dose reduction, and after about 6 hours from the levetiracetam morning administration. During the hospital stay, also, an echocardiogram was performed to investigate possible cardiac reasons for bradycardia, but it did not demonstrate significant and clinically relevant findings.

Discussion

We report a clinical case of bradycardia caused by the serum "overdose effect" of levetiracetam

prescribed at therapeutic dose, without significant organ impacts or hypoperfusion. In fact, the serum analysis found that the concentration of levetiracetam was still high after 4 days of drug reduction. To our best knowledge, only two single cases of levetiracetam cardiovascular toxicity have previously been described in a 43 years-old woman and, most recently, in a 22-year-old man, but in both that case, the toxicity was secondary to overdose ingestion in a suicide attempt (60–80 1000 mg levetiracetam tablet and 75.000 mg of levetiracetam, respectively), and only a few cases of levetiracetam overdose were reported in the literature [4-6]. A case is represented by a 49-year-old man who ingested, in a suicide attempt, over 22 500 mg levetiracetam tablets, and developed significant respiratory distress that required intubation and ventilator support [5]. One possible explanation for the described overdose effect can be represented by increased muscarinic activity or sensitivity of M2 receptors in our old patient. In fact, it is well known that stimulation of M2 muscarinic receptors leads to bradycardia, and in an animal model of pilocarpine-induced seizures, levetiracetam has been shown to have agonist-like activity at the M2 receptor [7]. Based on the review of literature there is no established significant association between serum levels of levetiracetam and seizure control efficacy [8]. A review of four major double-blind, placebo-controlled studies, shows that the most common side effects associated with levetiracetam in combination with other antiepileptic medications were infection, asthenia, dizziness, and somnolence, but bradycardia is not reported [9]. Moreover, there is scientific evidence that patients with a personal or family history of a psychiatric disorder, as it is in the case of our patient, present an increased risk of developing a psychiatric adverse effect with levetiracetam, but an association with adverse cardiac effects is still to be demonstrated [10]. It is interesting to note that in the analyzed trials the ingested dose of levetiracetam was very high, ranging from 3 to 10X the recommended dose, and levetiracetam blood levels, when the values were available, were 400 mcg/mL (6 h post-ingestion (PI), 72 mcg/mL (18 h PI) and 60 mcg/ml (20-5 h PI). Therefore, the value registered in our patient after over 6 hours from the levetiracetam morning administration is to be considered atypical considering the kinetic curve of levetiracetam, the reduction of dose occurred 4 days before, and finally, yet importantly, the absence of kidney impairment. Consequently, we can suppose that bradycardia is secondary to peculiar biological characteristics of our old patient that could explain modification in M2 receptors sensitivity but also in absorption and excretion of levetiracetam.

Conclusion

This is the 1st case of bradycardia described in an old person assuming levetiracetam to a therapeutic dosage. Based on the existing case reports, the majority of adverse events secondary to an overdose of levetiracetam are mild and transient and usually did not include bradycardia. Therefore, it is important to maintain surveillance of levetiracetam side effects to best understand the mechanism of action and the biological characteristics that can facilitate the onset of this “overdose effect” also at a therapeutic dose, and in particular the elderly population.

Declarations: The authors declare that there is no conflict of interest. This study was supported by the Italian Ministry of Health in the program: “Ricerca Corrente 2022”

Annex 1: Electrocardiograms (EKGs) performed during the hospital stay

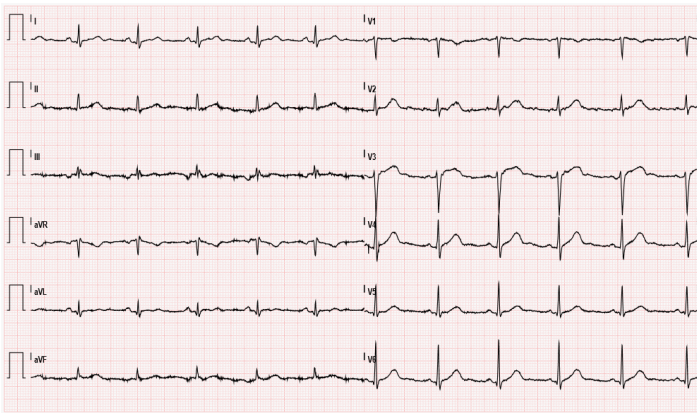

Figure 1: EKG performed on 06 September 2021 Time: 10.55.34 AM.
Ventricular rate: 66 BPM PR interval: 155 ms QRS duration: 98 ms QT/QTc: 431 418/ ms P-R-T axes: -22 45 41.

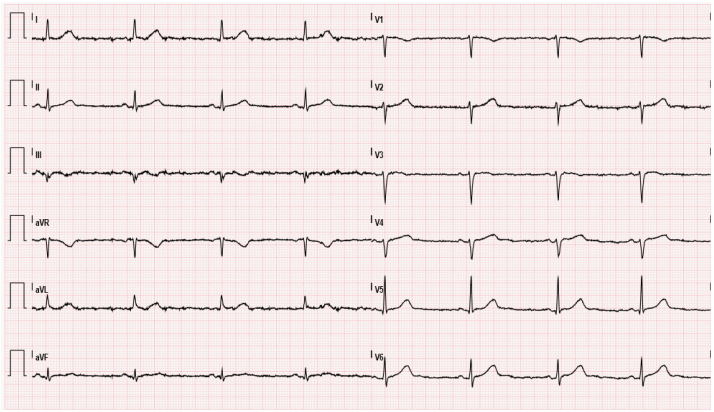

Figure 2: EKG performed on 08 September 2021 Time: 04.31.11 PM.
Ventricular rate: 48 BPM PR interval: 158 ms QRS duration: 93 ms QT/QTc: 437 472/ ms P-R-T axes: 81 12 26.

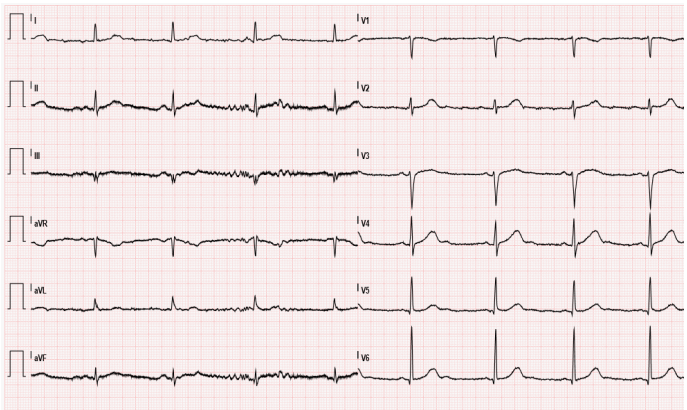

Figure 3: EKG performed on 09 September 2021 Time: 11.15.56 AM.
Ventricular rate: 49 BPM PR interval: 161 ms QRS duration: 96 ms QT/QTc: 460 490/ ms P-R-T axes: 77 18 49.

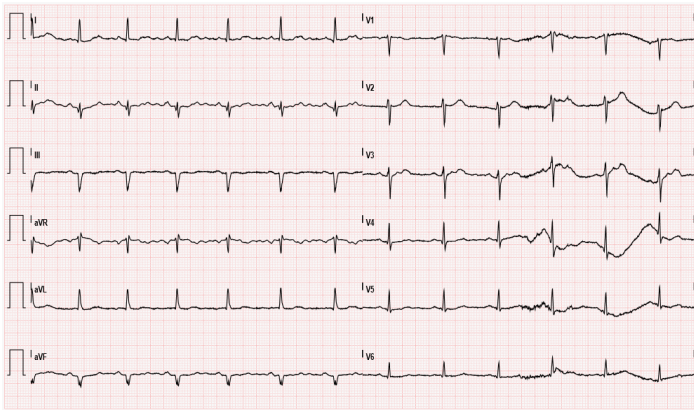

Figure 4: EKG performed on 15 September 2021 Time: 07.57.02 PM.
Ventricular rate: 75 BPM PR interval: 165 ms QRS duration: 90 ms QT/QTc: 299 270/ ms P-R-T axes: 55 -35 28.

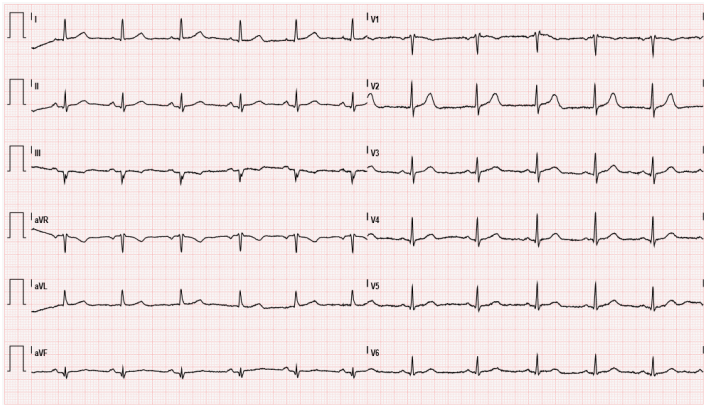

Figure 5: EKG performed on 16 September 2021 Time: 07.21.42 PM.
Ventricular rate: 68 BPM PR interval: 156 ms QRS duration: 104 ms QT/QTc: 447 429/ ms P-R-T axes: 66 -4 25.

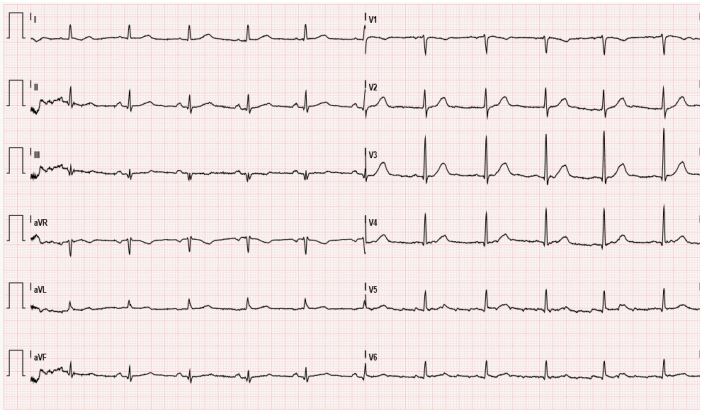

Figure 6: EKG performed on 20 September 2021 Time 9.58.23 PM.
Ventricular rate: 67 BPM PR interval: 160 ms QRS duration: 88 ms QT/QTc: 426 410/ ms P-R-T axes: 72 15 43.

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