Letter to the Editor

Serial electroencephalography changes in low-dose baclofen intoxication

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Introduction

Baclofen is a chemical derivative of the neurotransmitter γ-aminobutyric acid (GABA), which acts as a central nervous system depressant, GABA agonist, and muscle relaxant. It is a lipophilic drug that easily crosses the blood-brain barrier and acts as a presynaptic inhibitor by activating the GABA-B receptor (1). Baclofen is usually used to relieve spastic movement disorders, cramping, or tightness caused by cerebral palsy, spinal cord injury, motor neuron disease, or multiple sclerosis (2). Although many patients have no adverse drug reactions, some may have general weakness, dizziness, delirium, bradycardia, sedation, and even a comatose mentality, with loss of brainstem reflex (1). Serious side effects such as generalized tonic-clonic seizures (GTCS) and nonconvulsive status epilepticus can also occur, especially when ingested with a high overdose within a short period (1). Several patients showed comatose mentality, and GTCS reached beyond the therapeutic level by baclofen uptake in a short time (3-5). We report two cases of patients with abruptly altered mentality accompanied by specific electroencephalography (EEG) changes who received low-dose baclofen for several months.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patients for publication of these two case reports and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Case 1

A 77-year-old woman presented to the emergency room with loss of consciousness. She was a farmer and harvested water parsley at work. After working for 5 h, she suddenly fell and was reported to have an altered mental status in addition to nausea, vomiting, and dizziness. The patient had been receiving antihypertensive and diabetic medications for approximately 15 years, as well as baclofen 20 mg (10 mg twice a day), eperisone 100 mg (50 mg twice a day), pregabalin 25 mg, acetaminophen 162.5 mg, tramadol hydrochloride 18.75 mg, and aceclofenac 100 mg to relieve muscle pain for 3 months before the visit. Her vital signs were as follows: blood pressure, 200/90 mmHg; heart rate, 70 beats/min; respiratory rate, 20 breaths/min; and body temperature, 36.8 ℃. Neurological evaluation indicated that the patient was in stupor and showed a withdrawal pattern under pain. Pupil light, corneal, and oculocephalic reflexes revealed normal responses and absence of pathological reflexes presenting Glascow Coma Scale (GCS) of 6. Blood

Table 1 Drug toxicity analysis results for Case 1

Drugs	Analysis equipment	Analysis result, mcg/mL
Glimepiride	LC/MS	0.007
Metformin	LC/MS	0.440
Methylephedrine	LC/MS	0.011
Nicardipine	LC/MS	0.009
Baclofen	LC/MS	3.500
Pseudoephedrine or ephedrine	LC/MS	0.022
Chlorpheniramine	LC/MS	0.015
Pregabalin	LC/MS	0.583

LC/MS, liquid chromatography/mass spectrometry.

sodium concentration was 134 mmol/L, blood glucose level was 245 mg/dL, and glycated hemoglobin level was 5.6%. Blood creatinine level was 1.53 mg/dL and the glomerular filtration rate was 32.8 mL/min. The results of other electrolyte and blood tests were normal, and there were no specific findings in the urinary tests. The only abnormalities observed on computed tomography angiography and perfusion were stenoses of the left vertebral and left posterior cerebral arteries. An additional magnetic resonance imaging (MRI), including diffusion-weighted imaging, did not reveal any changes or signs of contrast medium enhancement.

In a cerebrospinal fluid study, there was an increase only in the protein level (49.4 mg/dL), and no other inflammatory findings were observed. Drug screening tests for 230 drugs, 260 pesticides, and other natural poisons were performed, and a positive toxic level of baclofen (3.5 mcg/mL, normal range, 0.08–0.60 mcg/mL) was found (*Table 1*). EEG performed 3 h after admission showed a high amplitude of 3–4 Hz epileptiform burst and suppression (B-S) patterns. On day 2 of hospitalization, the consciousness level deteriorated further to a semi-comatose state, and the patient did not show any eye response to pain stimulation. Neither of the upper extremities responded to external stimuli, and only the lower extremities showed mild flexion responses (GCS 5). EEG revealed a B-S pattern throughout the background (*Figure 1A*). All medications were discontinued and the patient's progress was monitored under hydration and supportive management. On the seventh day after discontinuing baclofen, the patient's consciousness improved to an alert state, and the patient showed proper orientation toward people and places. The muscle strength of both the upper and lower extremities was Medical Research Council (MRC) grade 4. Follow-up EEG revealed that the B-S found in the previous EEG had disappeared, and the patient's condition improved, with increased background activity and an overall alpha rhythm of 8–9 Hz (*Figure 1B*). The patient was intubated on the first day of hospitalization, and only the endotracheal tube was maintained without a mechanical ventilator. The patient was extubated due to improvement, and the patient was not sedated.

Case 2

A 40-year-old woman presented to the emergency room with GTCS and mental deterioration. She had a chronic headache and was receiving baclofen 10 mg, afloqualone 10 mg, and dexibuprofen 400 mg twice a day and amitriptyline 5 mg once a day for 2.5 months, without any specific medical history. The patient talked to her husband over the phone 15 h before admission and complained of a severe headache. However, she was still able to engage in normal conversations with others. When her caregiver arrived at home (10 h before hospitalization), the caregiver saw her lying in bed, assumed that she was sleeping, and did not wake her up. Three hours before admission, the caregiver discovered that the patient had sudden onset of seizures and dyspnea, and then took her to the emergency room. Upon admission, blood pressure was 105/55 mmHg, pulse rate was 80 beats/min, respiration rate was 20 breaths/min, and body temperature was 37.1 ℃. Two GTCS occurred immediately after admission and each seizure lasted for approximately 10 s. The patient was given intravenous (IV) lorazepam 4 mg and had no further seizures. Upon neurological examination, the patient was in a coma and did not respond to light, corneal, or oculocephalic reflexes. In addition, she did not show eye, verbal, or motor responses to external pain stimuli and did not have pathological reflexes such as the Babinski sign or ankle clonus (GCS 3). Basic blood test, chemistry examination, and blood gas examination showed elevated creatine kinase and lactate levels, which increased to 549 U/L and 5.4 mmol/L, respectively. At the same time, glomerular filtration rate, including electrolyte (91.1 mL/min) and creatinine (0.81 mg/dL), was normal. The patient's blood glucose level was 127 mg/dL. Computed tomography, angiography, and perfusion results were normal, and MRI did not reveal any abnormalities.

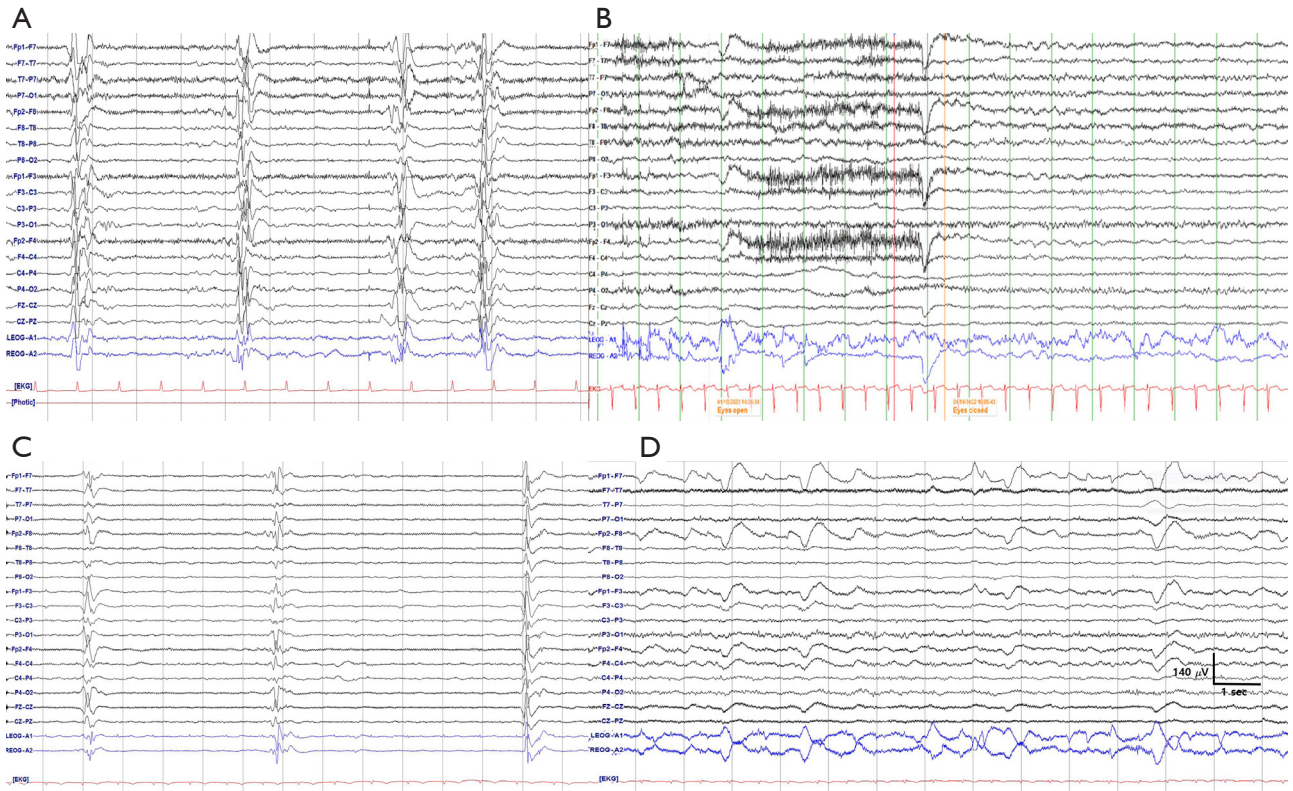

Figure 1 Serial EEG changes of both patients with baclofen intoxication (Cases 1 and 2). A 21-channel EEG was used according to the international modified 10–20 system. It was recorded for 30 minutes and Natus Neuroworks 9.2 was used. The filter was set to LFF: 0.5 Hz, and HFF: 70 Hz, while the montage was set to longitudinal bipolar montage. (A) EEG of the first patient shows a background activity of nearly continuous 3–4 Hz epileptiform B-S on both hemispheres. (B) The EEG was normalized on the seventh day after discontinuing baclofen. (C) EEG of the second patient shows a background activity of a nearly continuous 1–2 Hz epileptiform B-S on both hemispheres. (D) The EEG was normalized on the fourth day after discontinuing baclofen. LEOG, left electrooculogram; REOG, right electrooculogram; EKG, electrocardiogram; EEG, electroencephalography; LFF, low frequency filter; HFF, high frequency filter; B-S, burst and suppression.

Table 2 Poisoning analysis results for Case 2

Drugs	Analysis equipment	Analysis result, mcg/mL
Baclofen	LC/MS	5.747
Flumazenil	LC/MS	0.159
Lorazepam	LC/MS	0.046
Phenytoin	LC/MS	0.5829

LC/MS, liquid chromatography/mass spectrometry.

Cerebrospinal fluid analysis revealed elevated intracranial pressure (256 mmH_2O), no white or red blood cells, and protein (43.7 mg/dL) and glucose (64 mg/dL) levels within the normal range. Toxicity tests were conducted on 230 drugs, 260 pesticides, and other natural poisons to determine the possibility of drug intoxication by request from the poisoning analysis laboratory. The blood drug concentration test results showed that baclofen was 5.747 mcg/mL (normal range, 0.08–0.6 mcg/mL) (*Table 2*). Hydration and supportive management were administered to the patient as initial treatment, and progress was monitored. On the first day of admission, the patient was comatose with no response to light, corneal, oculocephalic, or noxious stimuli (GCS 3). An EEG was performed to check the patient's brain function, and a 1–2 Hz B-S pattern was confirmed (*Figure 1C*). On the fourth day of admission, the level of consciousness was restored to a drowsy state, the patient showed a normal response to the brainstem reflex, and the muscle strength recovered to MRC grade 4. The patient responded appropriately to questions related to

time, place, and person (GCS 14). As the patient's level of consciousness improved, a follow-up EEG was performed on the fourth day of admission to confirm that the patient showed a normal response, with an overall beta rhythm of 14–15 Hz (*Figure 1D*). The patient was intubated on the first day of hospitalization and mechanically ventilated with the pressure support ventilation (PSV) mode. After switching to continuous positive airway pressure (CPAP), the patient improved and was extubated, but the patient was not sedated. The patient's condition improved and she was discharged on the 8th day of admission.

Discussion

Orally administered baclofen is rapidly absorbed in the gastrointestinal tract, and its serum concentration reaches its highest level between 45 min and 2.5 h, with a half-life of 3.5 h. Baclofen relieves spastic movement disorders, cramping, or tightness caused by cerebral palsy, spinal cord injury, motor neuron disease, or multiple sclerosis (2). Although many patients have no adverse reactions, some may experience general weakness, dizziness, delirium, bradycardia, sedation, and even a comatose mental status with loss of brainstem reflex (1). Serious side effects, such as GTCS and nonconvulsive status epilepticus, may occur, especially when ingested with a high overdose within a short period (1). Several patients showed comatose mental status, and GTCS reached beyond the therapeutic level by baclofen uptake in a short time (3-5). As approximately 15% of drugs are metabolized by the liver and 85% are excreted through the kidneys, patients with renal dysfunction may experience more toxic adverse effects. Previous case studies on baclofen intoxication reported that intake a large dose of baclofen over a short period could cause acute intoxication symptoms, such as mental deterioration and seizures, and patients on dialysis showed acute intoxication even with a low dose of baclofen intake (3-7). Three cases of low-dose baclofen intoxication have been previously reported; the patients were receiving the drug at doses ranging from 10 to 40 mg and experienced acute altered mental status within 7 days. All patients had kidney problems, including one patient diagnosed with chronic kidney disease (CKD) after a left nephrectomy for cancer and two patients with end-stage renal disease receiving hemodialysis three times a week (6-8). Unlike the three previous cases, our patients experienced altered mental status with low-dose baclofen (20 mg) after 2.5 months. It is unclear what mechanism caused the patients' prolonged altered mental state, even with low-dose baclofen. In the first case, baclofen was estimated to be above the toxic level, and old age combined with newly diagnosed CKD may have contributed to mental health deterioration. The second patient was receiving afloqualone in addition to baclofen, both of which are known as GABA receptor agonists. There was a case of seizure in a 3-year-old girl who received an overdose of afloqualone (9). Although the second patient was younger than the first and had no specific underlying diseases, the two medications used over a long period might have led to seizures and confusion. The first patient took three more days to recover alert mentality than the second patient, possibly due to advanced age and newly diagnosed kidney disease. Based on blood test results on admission, the first patient was diagnosed with CKD stage 3b.

In this case study, both patients showed a B-S EEG pattern during 30 min of routine EEG (*Figure 1A,1B*). B-S was defined according to the 2021 American Clinical Neurophysiology Society (ACNS) guideline. The first patient underwent EEG three times (*Figure 2*). The EEG on the first and second days showed a B-S pattern when the patient was in a stuporous state (*Figure 1A*). On the seventh day of admission, the background rhythm recovered without a B-S pattern, and the patient's neurological symptoms improved with an alert mentality (*Figure 2*). The second patient showed a B-S EEG pattern on the day of admission, which was normal after 3 days with clinical improvement (*Figure 1D*). Known causes of a B-S pattern in EEG include space-occupying lesions, toxic metabolic factors, infection, brain trauma, stroke, coma due to hypoxic brain damage, general anesthesia, halogenated ethers, barbiturates, propofol, etomidate, N-methyl-D-aspartate receptor antagonists during GABAergic anesthesia, Ohtahara syndrome, and epilepsy syndromes, such as early myoclonus encephalopathy and hypothermia (10). A suggested mechanism of a B-S pattern in EEG is that baclofen binds to both postsynaptic and presynaptic inhibitory interneurons to inactivate them, which could excite the neuronal balance and cause a seizure (11). Patients with a B-S pattern show different prognoses depending on the cause. It is known that when it is medically induced in patients, the prognosis of a B-S pattern is good, whereas when it is due to a critical illness or hypoxic brain damage, the prognosis is poor (10). The favorable outcomes in our patients can be explained by the results of previous studies. When the first EEG was performed in two patients, we correlated the B-S EEG pattern with their stuporous mental status. After discontinuing baclofen, the B-S pattern disappeared, and the

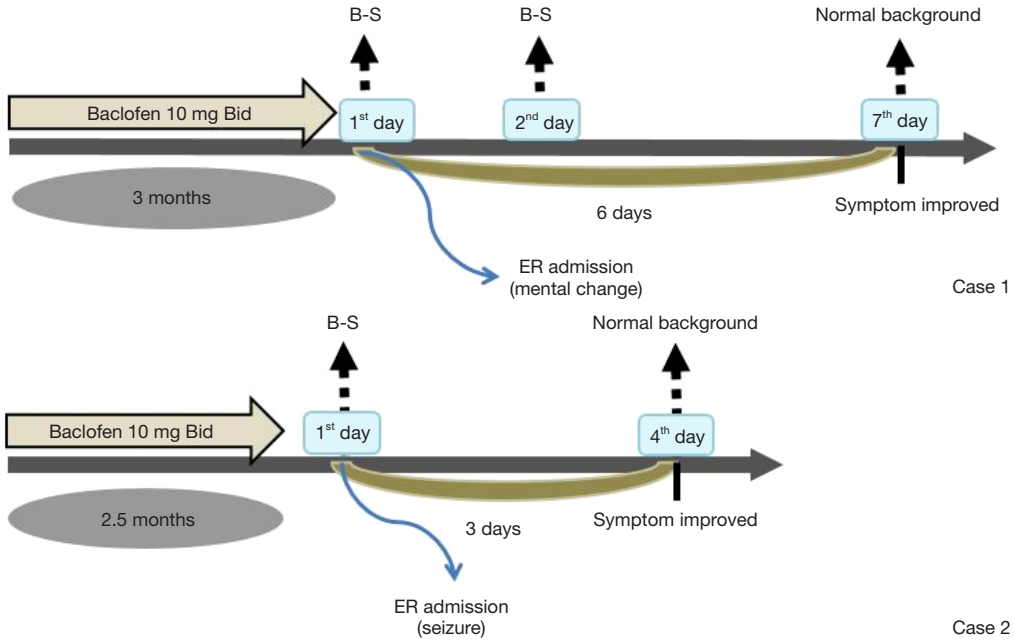

Figure 2 Timeline and clinical course of the patients (Cases 1 and 2). B-S, burst and suppression; ER, emergency room.

background was restored in the EEG over time. Although a low dose of baclofen was administered for several months, we confirmed the possibility of acute intoxication with a low dose of baclofen and a clear correlation between EEG findings and patients' clinical conditions.

Conclusions

This case study highlights the diagnosis of critical illnesses caused by baclofen by examining detailed neurological symptoms and medical history. When baclofen was administered for a long time, even at a low dose, the patient reached an acute comatose state and showed a B-S pattern on EEG. Comatose patients with a B-S pattern on EEG without a clear medical history should be considered not only for critical medical conditions, such as cardiac arrest or hypoxic brain damage, but also for drug intoxication.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-630/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patients for publication of these two case reports and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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