Case Report

Focal nonconvulsive seizures during detoxification for benzodiazepine abuse

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Abstract

Chronic benzodiazepine (BDZ) abuse is currently treated with detoxification consisting of low-dose flumazenil infusion [1–3], a relatively recent and promising procedure. Given the possibility reported in the literature of the occurrence of generalized seizures during therapeutic BDZ detoxification, we usually administer preventive antiepileptic drug (AED) therapy. We describe two patients with no previous history of seizures or evidence of intracerebral lesions who, during detoxification for benzodiazepine abuse, developed repetitive focal nonconvulsive seizures instead of generalized seizures, even with appropriate doses of preventive AED therapy. There are no previous reported cases of focal nonconvulsive seizures occurring during this procedure or, more generally, during abrupt BDZ discontinuation. The cases we describe suggest that during detoxification for BDZ abuse, not only generalized, but also focal nonconvulsive seizures may occur. In this context, the focal seizures probably result from a diffuse decrease in the seizure threshold (caused by a generalized excitatory rebound), which may trigger focal seizures arising from cortical regions with higher intrinsic epileptogenicity. Detoxification for benzodiazepine abuse, even if performed with adequate-dosage AED treatment, may not be as safe a procedure as previously considered, because not only convulsive, but also nonconvulsive seizures may occur and go unnoticed. It is therefore strongly advisable to perform this detoxification under close medical supervision and to maintain a low threshold for EEG monitoring in the event of sudden onset of behavioral changes.

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1. Introduction

Chronic benzodiazepine (BDZ) abuse is currently treated with detoxification consisting of low-dose flumazenil infusion [1–3], a relatively recent and promising procedure. Given the possibility reported in the literature of the occurrence of generalized seizures during therapeutic BDZ detoxification, we usually administer preventive antiepileptic drug (AED) therapy. In fact, there are several clinical observations of seizures [4–6], although definite epidemiological data are still lacking. One retrospective study reported seizures in 1.8% of patients with BDZ withdrawal [7]. Conversely, a possible epileptogenic role for flumazenil has been reported only in patients pretreated with BDZs [8]. We describe two patients with no previous history of seizures who, during detoxification for benzodiazepine abuse, developed repetitive focal nonconvulsive seizures (not generalized seizures, as reported previously [4–7,9]), even with appropriate doses of preventive AED therapy. No previous cases of focal nonconvulsive seizures occurring during this procedure or, more generally, during abrupt BDZ discontinuation have been reported, to our knowledge.

2. Case 1

A 44-year-old woman (46 kg) had been addicted to lorazepam for 10 years. Her medical history was notable for Crohn's disease. There was no history of alcohol addiction. She took no drugs other than lorazepam. Four years earlier she underwent her first BDZ detoxification, but 6 months after this procedure, she relapsed with lorazepam addiction because of a depressive syndrome caused by a recurrence of Crohn’s disease. On admission she was taking 50 mg of lorazepam and 2 mg of lorazepam daily and no drugs for Crohn’s disease. Ten days before detoxification, slow-release valproic acid 500 mg twice daily (1000 mg/day) was prescribed for seizure prevention. Detoxification for benzodiazepine abuse consisted of low-dose flumazenil infusion (0.5 mg/day) for 14 hours daily over 10 days, with discontinuation during the night. On the same day of admission, the abused BDZ was replaced with clonazepam, which was progressively tapered over the next 3 days, so that on 4th day the patient was no longer receiving BDZs. On the 8th day she suddenly developed
behavioral changes characterized by impairment of consciousness (the patient was able to perform simple tasks such as open her eyes), sometimes with upper limb automatisms, lasting several minutes and alternating with long periods of normal behavior. No posturing, rotation, or clonic movements occurred. There were no secondarily generalized tonic–clonic seizures. Apart from these episodes, neurological examination was normal. At the time of the first seizure the patient was receiving 1000 mg/day valproic acid and no BDZ. Valproic acid serum levels were within the therapeutic range (54 mg/L, range: 50–100 mg/L). On the 11th day, after episodes such as those described above had occurred several times a day, resolving either spontaneously or after diazepam administration, an EEG recording was obtained. The EEG was recorded when the patient was still confused and disoriented. It showed, at the very beginning, continuous high-amplitude delta activity admixed with sharp components over left derivations, prevalent over temporal regions and lasting around 6 minutes (Fig. 1). Brain MRI results were normal (see Appendix). Additional EEG recordings obtained the day after and a prolonged video/EEG recording showed a normal alpha posterior dominant rhythm with fast activity over anterior regions due to a pharmacological effect. One month after the first seizure the EEG was completely normal. The patient was discharged on carbamazepine (400 mg three times daily; such a dose was well tolerated), escitalopram (10 mg daily), and clonazepam (1 mg three times daily). Two months later, under medical supervision, she discontinued clonazepam and carbamazepine. Since then (18 months of follow-up) she has had no more seizures.

3. Case 2

A 56-year-old woman (55 kg) without a history of alcohol abuse had been addicted to BDZs for 30 years. Previous medical history was unremarkable. On admission she was taking lorazepam 12.5 mg/day, clonazepam 12.5 mg/day, temazepam 20 mg/day, and zolpidem 10 mg/day. She did not take other drugs. She started preventive AED therapy with oxcarbazepine 300 mg/day, rapidly increased to 600 mg/day. The same detoxification procedure with the same dose of flumazenil described for case 1 was performed. On the 9th day she suddenly developed behavioral changes characterized by clusters of episodes with confusion, disorientation, fear, and partial impairment of consciousness (the patient was able to perform only simple tasks), lasting several minutes and alternating with periods of normal behavior. No limb or oromandibular automatisms, posturing, rotation, or clonic movements were observed. There were no secondarily generalized tonic–clonic seizures. At the time of the first seizure the patient was receiving 600 mg/day oxcarbazepine and no BDZ. Several episodes with the same clinical features occurred on the 12th, 13th, and 14th days, and resolved after diazepam or clonazepam administration. Apart from these episodes, neurological examination was normal. An EEG recording obtained on the 15th day revealed the sudden onset of rhythmic, irregular alpha–theta activity over right frontotemporal regions, evolving into high-voltage delta sequences admixed with sharp components, with minimal diffusion over homologous contralateral regions. Clinically the patient manifested the same features of the episodes described above. Such activity progressively attenuated, and after 2 minutes, the patient was able to follow simple commands (opening and closing eyes), although eye opening did not significantly modify the focal EEG discharges. This ictal activity gradually attenuated and ceased within 6 minutes. The oxcarbazepine dose was therefore increased to 900 mg/day. A subsequent standard EEG recording (16th day) and a prolonged sleep video/EEG recording were normal. Brain MRI results were normal (see Appendix). Two months later, under medical supervision, she

![Fig. 1](https://example.com/fig1.png)

(A) At the beginning of the recording, there is continuous high-amplitude delta activity over the left hemisphere, prevalent over the temporo-occipital electrodes. (B) At 5 minutes, there is marked attenuation of delta activity. (C) At 6 minutes, the patient performs simple tasks (eye opening, eye closing). The alpha posterior dominant rhythm is better represented over the right region. (D) At 8 minutes, low-amplitude delta waves persist over the temporo-occipital electrodes. The patient is oriented and the neurological examination unremarkable. Sensitivity: 7 μV/mm; time constant: 0.3 second; high filter: 50.0 Hz; each vertical bar: 1 second. Montage is the same for each EEG sample (A–D).
discontinued oxcarbazepine. Since then (5 years of follow-up) she has had no more seizures.

4. Discussion

Detoxification for BDZ abuse is a recently developed procedure performed in patients with chronic BDZ addiction and is usually safe, with rare abstinence physical or psychic complaints. In the literature most information concerns the occurrence of seizures after abrupt BDZ withdrawal, whereas to date seizures during detoxification for BDZ abuse have not been systematically evaluated and studied. Over 7 years, our group has performed detoxification with flumazenil in 286 patients, with generalized convulsive seizures occurring in 8 of them (2.8%) and focal nonconvulsive seizures in the 2 patients described here. A similar finding (1.8%) was previously reported in a study evaluating the proportion of drug-related seizures conducted retrospectively in 279 patients [7].

Our patients presented with nonconvulsive seizures in which the EEG and the clinical features pointed to a focal involvement of cerebral cortex, without evidence of intracerebral lesions. Neither patient was addicted to alcohol or taking drugs that lower seizure threshold, neither patient had a history of brain injuries or seizures, and their MRI scans were normal. There were therefore no other reasons, other than BDZ discontinuation, for the seizures these patients experienced.

In humans, the effects of flumazenil on epileptic activity remain controversial. Although induction and worsening of seizures have been reported in some studies [10,11], suppression of interictal discharges [12,13] and reduction in seizure frequency with flumazenil treatment [12,14] have been described in other studies. However, in the case of seizures possibly related to flumazenil administration, pretreatment of patients with BDZs seems to be a prerequisite for the proconvulsive effect of this drug [8].

Although a latent seizure disorder can be unmasked by sudden discontinuation of BDZs [15], we consider our patients as having acute situational seizures related to BDZ discontinuation, which by itself does not entail a diagnosis of epilepsy. The fact that our patients developed focal instead of generalized seizures is surprising. BDZs are drugs with diffuse action on GABA receptors, thus enhancing GABAergic activity (such as valproic acid) might be recommended. Decrease in seizure threshold (due to a generalized excitatory rebound), which may trigger focal seizures arising from the cortical regions with higher intrinsic epileptogenicity levels. Detoxification for BDZ abuse, even if performed with adequate-dosage AED treatment, may not be as safe a procedure as previously considered, because seizures may occur and go unnoticed. It is advisable to perform this procedure under close medical supervision and to maintain a low threshold for EEG monitoring in the event of sudden onset of behavioral changes. Further studies are required to evaluate the role of AEDs as preventive therapy during detoxification for BDZ abuse and, if their efficacy is confirmed, to establish the most appropriate AED.

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Conflict of interest statement

The authors have no conflicts of interest.

References