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Case Report

γ-Hydroxybutyric acid-induced psychosis and seizures

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ABSTRACT

Disulfiram and γ-hydroxybutyric acid (GHB) are used to treat alcohol dependence and may both increase dopamine brain levels and modulate GABAergic transmission. We describe a patient affected by bipolar disorder (on valproate as mood-stabilizing treatment) and alcohol dependence who developed a disulfiram-induced hypomanic episode and in whom the switch from disulfiram to GHB induced recurrent convulsive seizures, not responsive to treatment with diazepam, and psychosis. Seizures and psychiatric symptoms ceased after GHB discontinuation. We outline the deregulation of the neurotransmitter systems (GABAergic and dopaminergic networks) that are involved in these drug–drug interactions and that might be responsible for both psychosis and generalized tonic–clonic seizures resistant to standard treatments.

1. Introduction

Concomitant administration of drugs with different pharmacological profiles may induce unpredictable interactions yielding side effects that are difficult to counteract. Disulfiram and γ-hydroxybutyric acid (GHB) are used to treat alcohol dependence and may both increase dopamine brain levels and modulate GABAergic transmission. Disulfiram may cause or exacerbate psychosis by inhibiting dopamine β-hydroxylase, an enzyme converting dopamine to norepinephrine [1]. GHB acts on GABAergic and dopaminergic systems [2].

Here we describe a patient affected by bipolar I disorder (taking valproate as mood-stabilizing treatment) and alcohol dependence who developed a disulfiram-induced hypomanic episode and in whom the switch from disulfiram to GHB induced psychosis and drug-resistant epileptic seizures, which ceased after GHB discontinuation. A scenario in which the deregulation of GABAergic and dopaminergic neurotransmitter systems caused by drug–drug interactions might be responsible for both psychiatric impairment and generalized tonic–clonic seizures is proposed.

2. Case report

A 62-year-old woman with a history of bipolar disorder, alcohol-related liver cirrhosis (Child–Pugh class A), and alcohol dependence was hospitalized in July 2009 for progressive cognitive impairment and confusion developing over 2 weeks. In the preceding month she had been taking disulfiram 400 mg/day to successfully treat alcohol addiction and valproate 500 mg twice daily as mood-stabilizing treatment. Her family and personal medical history was negative for epilepsy or provoked epileptic seizures. On admission she complained of severe memory deficits for recent events. On neuropsychological examination, long-term memory was normal and severe deficits of attention and logical thinking with confabulation were detected. Mood was dysphoric. Clinical symptoms were suggestive of a hypomanic episode. Neurological examination was normal. Routine blood tests were within the normal range, except for increased liver enzymes: aspartate transaminase 122 U/L (normal 10–35), alanine transaminase 218 U/L (normal 10–35), γ-glutamyl transferase 237 U/L (normal 3–45). Serum electrolyte concentrations were normal (Na 145 mmol/L, normal 136–145; K 4 mmol/L, normal 3.4–4.5), as were white blood cell count, renal function indexes, erythrocyte sedimentation rate (38 mm/h, normal. 2–39), and C-reactive protein (2.92 mg/L, normal 0–6) levels. Her alcohol blood level was 0.0 g/L, confirming that the patient had abstained from alcohol consumption. The arterial ammonia concentration was normal, and her EEG study was normal, similar to a previous EEG performed 1 year earlier as part of the screening for minimal hepatic encephalopathy, thus excluding hepatic encephalopathy. On the third day of admission, she was switched from disulfiram to GHB 46 mg/kg/day (3500 mg/day) in light of the possibility of disulfiram-induced toxicity of the central nervous system. Over the following days the patient grew more confused and developed

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psychotic behavior with religious delusions. Moreover, she had generalized tonic–clonic seizures daily that were resistant to benzodiazepine treatment (intravenous diazepam 10 mg twice daily) and ongoing valproate therapy (500 mg twice daily) with a drug level within the therapeutic range (467 μmol/L, range 347–693). Repeated EEG studies revealed bursts of spike–wave activity predominantly in the left

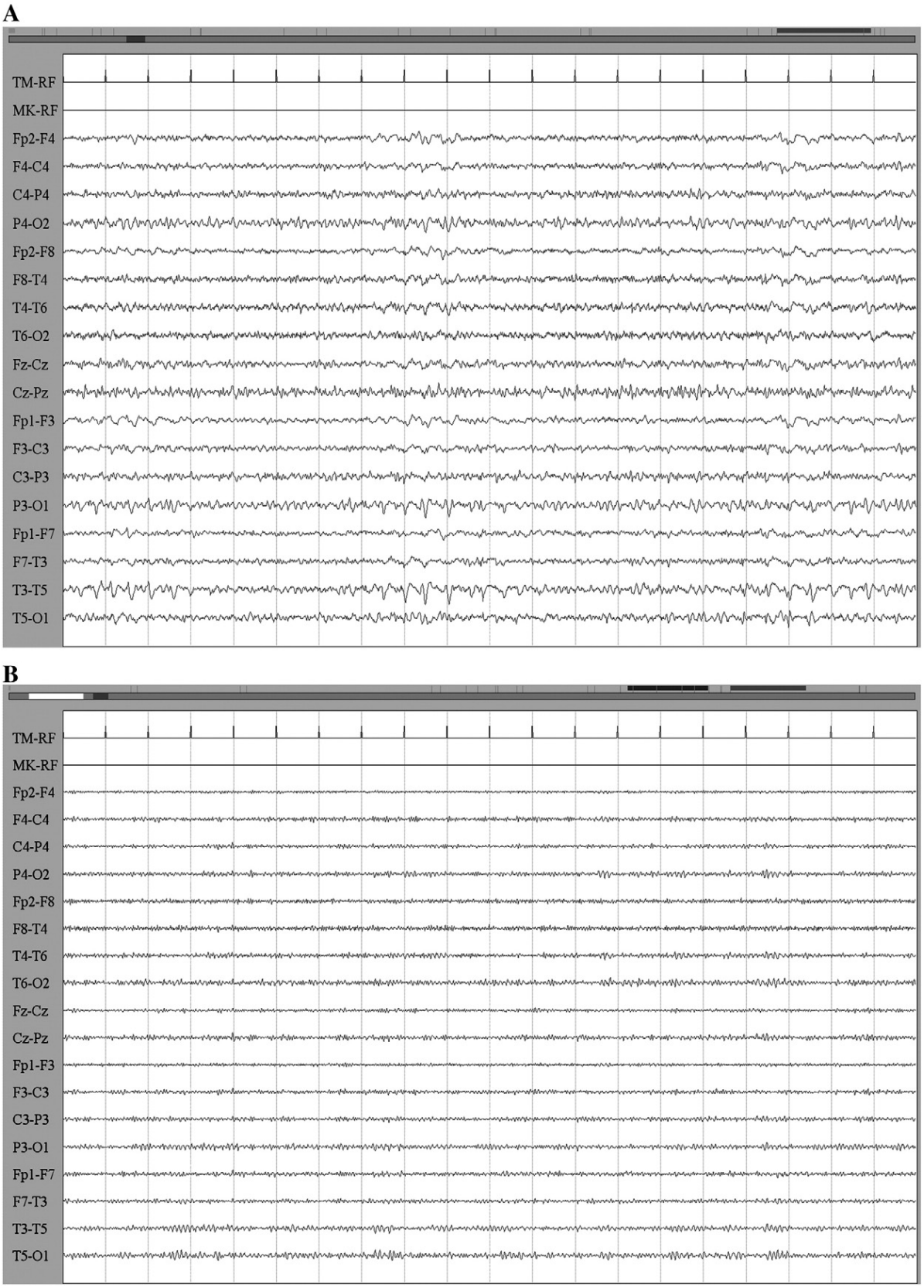

Fig. 1. (A) Interictal EEG during GHB treatment showing spike–wave bursts predominant in the left posterior temporal and occipital regions. (B) Normalization of EEG activity

posterior temporal and occipital lobes (Fig. 1A). Infusion of diazepam did not modify the EEG pattern. Brain MRI with T1/T2-weighted sequences and gadolinium enhancement did not show any significant signal alteration. Noteworthy, the focality observed on the EEG was not correlated with any finding on the MRI images, and no definite lesion was identified in the left posterior temporal and occipital lobes. Results of chemical and microbiological tests of the cerebrospinal fluid were normal. After 6 days GHB was discontinued with immediate remission of seizures. Olanzapine (5 mg/day) was initiated, and her psychotic symptoms improved within 1 week. A control EEG pattern (2 weeks later) was normal, even though it revealed a larger amount of bilateral beta activity (Fig. 1B). The antipsychotic treatment was discontinued 1 month later without recurrence of psychotic behavior.

3. Discussion

Psychosis and manic episodes induced by disulfiram in predisposed patients such as those with preexisting psychiatric comorbidities have been described [3,4]. Disulfiram and its metabolite may increase dopamine brain levels in the central nervous system secondary to the inhibition of dopamine β-hydroxylase [1]. After withdrawal of disulfiram, the increase in central dopamine levels may persist 1–2 weeks because of slow elimination of the active metabolite carbon disulfide. In addition, GHB-mediated disinhibition of the dopaminergic circuitry, which develops in a brain with increased levels of dopamine induced by the long-lasting effects of disulfiram, might have been responsible for the development of psychosis. In fact, increased activity of the dopaminergic mesocorticolimbic circuitry, possibly mediated by decreased GABAergic disinhibition of dopaminergic neurons, is the neurochemical substrate for the development of addiction in GHB abusers [2].

More intriguing is the interpretation of the development of recurrent and resistant generalized epileptic seizures, which occurred immediately after the switch from disulfiram to GHB, as seizures are a rare side effect of GHB treatment, have been described mainly in experimental models and are typically absence seizures [2,5]. We therefore suggest that an interaction between valproate and GHB might have induced an imbalance in GABAergic neurotransmission and triggered the seizures. It is well recognized that GABAergic and glutamatergic transmission may be implicated in the antiepileptic and mood-stabilizing actions of valproate [6]. On the other hand, it is less well known that valproate is a potent in vitro inhibitor of succinic semialdehyde dehydrogenase (SSADH), which catalyzes the production of succinate from succinic semialdehyde, an intermediate product in the metabolic pathway transforming GHB into GABA and vice versa [6]. An inherited deficiency of SSADH activity leads to accumulation of succinic semialdehyde and, consequently, a 30-fold increase in GHB level and a 2- to 4-fold increase in GABA in the brains of affected rats [7]. Clinical manifestations include tonic–clonic seizures and convulsive status epilepticus.

In our case the neurotoxicity resulting from overproduction of endogenous GHB was further increased by the simultaneous administration of GHB drug, thus supporting the hypothesis that a high GHB/GABA ratio may play a pivotal role in the onset of seizures. GHB is a high-affinity agonist to the recently characterized GHB receptors and a weak partial agonist of the postsynaptic $GABA_B$ binding sites [2]. GHB, which binds with high affinity to the presynaptic GHB receptors, decreases the release of GABA. When exogenous GHB was administered to this patient, the drug was delivered to a brain already prone to develop epileptic discharges given the high levels of endogenous GHB and the reduced availability of GABA. This impairment of GABA neurotransmission is also demonstrated by the inability of benzodiazepines and valproate to control seizures. Only GHB discontinuation restored the neurotransmitter balance and caused seizures to cease.

We cannot rule out the alternative hypothesis of GHB intoxication caused by slow drug metabolism in a patient with chronic liver disease. Although the blood level of GHB was not assessed, we believe GHB intoxication is unlikely the cause as the dose was adjusted in light of the patient's mild liver cirrhosis and tonic–clonic seizures are rarely reported in GHB abuse. Finally, the possibility of an individual idiosyncratic reaction to GHB also cannot be excluded.

In summary, we suggest that the combined effects of disulfiram and GHB on neurotransmission, with valproate increasing the endogenous GHB levels, may be responsible for the acute neurotoxicity. Disulfiram and GHB may both increase dopamine brain levels and reduce GABAergic transmission. High brain dopamine levels might have induced psychosis, and reduced GABAergic transmission and high levels of both endogenous and exogenous GHB might have contributed to drug-resistant seizures. This observation outlines the risk of drug–drug interactions, resulting in resistant seizures and psychosis, when multiple drug treatments are prescribed for alcohol dependence in patients with psychiatric comorbidities.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

Acknowledgments

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