

TREATMENT

A Case of De novo Seizures Following a Probable Interaction of High-Dose Baclofen with Alcohol

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Abstract — Aims: Baclofen is a promising medication for the treatment of alcohol dependence, and the prescription of high-dose baclofen (HDB) is increasing within the medical community, especially for patients who are unresponsive to approved treatments. Although baclofen is considered to be quite safe at low doses, the possible interactions between HDB and alcohol have not been precisely studied. Methods: We report the case of a 46-year-old patient without any history of neurological disorders who experienced two episodes of seizures after a short relapse of alcohol misuse while undergoing treatment with up to 240 mg/day of baclofen. Results: Although both alcohol and baclofen may theoretically induce seizures individually, we discuss and largely rule out the likelihood that either of these two drugs was solely responsible for the patient’s seizures. We hypothesize that the seizures resulted from an interaction between alcohol and HDB, and determined that this hypothesis is ‘probable’ with Horn’s Drug Interaction Probability Scale. Conclusion: We encourage our colleagues who prescribe HDB to acquaint their patients with the possible enhanced risk of seizures, notably in persistence of alcohol abuse. Moreover, until data from a large study on the safety of HDB use by alcohol misusers are available, this treatment should be conducted under strict supervision and after having carefully evaluated the benefit–risk ratio.

INTRODUCTION

The gamma-aminobutyric acid B (GABA-B) agonist baclofen has been a long-time approved medication for spasticity. A few years ago, a major publication reported that a 30-mg/day dose of baclofen in subjects with alcoholic liver cirrhosis could significantly reduce the risk of relapse into alcohol dependence, with a very good safety level (Addolorato et al., 2007). However, a negative result was published soon thereafter (Garbutt et al., 2010). Consequently, the exact efficacy of low doses of baclofen on alcohol misuse is under debate, even if it appears that this molecule is quite safe at low doses (Leggio et al., 2010). In parallel, the off-label use of high-dose baclofen (HDB) to treat heavy drinking has recently increased in the medical community (Pastor et al., 2012; Rigal et al., 2012), and more specifically in France (Rolland et al., 2012). However, the precise safety level of this therapeutic practice is uncertain because it remains unclear whether there are harmful interactions between alcohol and HDB in some patients (Rolland et al., 2012). Baclofen overdose occurs with doses of 200 mg or more, and may induce confusion, coma, delirium and seizures (Leung et al., 2006). In addition, alcohol intoxication can also trigger rather similar complications (Vonghia et al., 2008). Therefore, because there is currently a lack of data on HDB, assessing the point at which the baclofen toxicity spectrum is reached in chronic use is difficult, notably in the persistence of alcohol abuse. It seems necessary that physicians who prescribe HDB carefully supervise their patients and report any adverse event they have encountered with the use of this treatment (Rolland et al., 2012). Our team has set up a system of off-label HDB prescriptions, which provides precise information and increased supervision to the patients (Rolland et al., 2010). We report here the case of a patient that was included in this protocol and experienced two consecutive episodes of seizures after a short relapse of alcohol use. This patient had no previous medical history of epilepsy or convulsions.

CASE REPORT

The patient was a 46-year-old Caucasian male with a medical history of obesity (body mass index = 37 kg/m²) and chronic obstructive pulmonary disease. He was seen for the treatment of alcohol abuse that had started 10 years previously and was determined to be consuming ~150 g/day of alcohol at that time. Despite numerous detoxification attempts, the patient was not able to maintain abstinence for >3 weeks over the 10-year period. He was treated several times with acamprosate and naltrexone, but neither of these medications helped him maintain abstinence or reduce the amount of alcohol consumed. The patient also smoked tobacco (40 cigarettes per day, 35 pack-years). He experienced a major depressive episode in 2005, which was treated with 20 mg/day mirtazapine. The patient’s other medications included 20 mg/day lorazepam that had been prescribed for anxious symptoms and 7.5 mg/day zopiclone for insomnia. The general psychiatric state was stabilized when the patient was met. He had no history of neurological disorders and had never experienced seizures.

To care for the patient’s treatment-resistant alcohol dependence, he was included in a system that provides a protocolized HDB prescription and reinforced supervision (Rolland et al., 2010). As planned by this protocol, the patient was informed that HDB would be delivered off-label, and despite the fact that it is a care protocol and not a research trial, we ask patients to provide a written consent before receiving this off-label medication. Moreover, the dose of baclofen was increased by 15 mg/day each week, i.e. 15 mg/day during the first week, 30 mg/day during the second week, and so on. Meanwhile, lorazepam and zopiclone were stopped. Ten weeks after the beginning of the treatment (see Fig. 1), the patient was receiving 120 mg/day of baclofen and reported a reduction in alcohol drinking from 150 to 50 g/day. This reduction was confirmed by his family and prompted an increase in the dose of baclofen. At
underlie the occurrence of seizures (Rathlev et al., 2006). Several reports have linked baclofen to seizures in cases of withdrawal (Kofler and Arturo Leis, 1992) but also in cases of overdose, in particular, after intrathecal bolus of baclofen (Kofler et al., 1994; D’Aleo et al., 2011). The incidence of seizure activity is ~7% among patients with multiple sclerosis who have been treated with intrathecal baclofen (Schuele et al., 2005). The exact mechanisms through which baclofen induces seizure are poorly understood. However, seizures might result from the exertion of a complex regulation by GABA-B on both the GABAergic and glutamatergic systems (Bowery, 2010). Moreover, experimental data suggest that activating the GABA-B receptors could accentuate neural excitation contrast in some parts of the brain (Fujita et al., 2011). This might explain why baclofen mixes both pro- and anti-convulsive properties.

Because the patient had no other potential cause of the seizures except for alcohol and baclofen, the relative likelihood of each of these two substances being involved in the occurrence of convulsions must be addressed. We believe that it is improbable that alcohol was the only cause of the seizures. The period during which the patient relapsed and consumed large amounts of alcohol was short, and despite drinking level being high, it is hard to believe that alcohol by itself could have induced the level of cerebral vulnerability necessary to cause seizures so quickly. Furthermore, the patient did not have a history of any epileptic events despite self-reported severe alcohol abuse that lasted for many years. Moreover, the hypothesis that the seizures resulted from alcohol withdrawal syndrome does not fit the medical history reported by the patient and his family. Regarding baclofen, although this drug can also be involved in the occurrence of seizures, the patient was treated with HDB for several months and did not present any important adverse effects. The patient denied any interruption in his treatment, even during the period of alcohol relapse, which makes a baclofen withdrawal episode unlikely. Consequently, neither alcohol nor baclofen seems to be a sufficient sole cause of the two seizure episodes.

We assume that the seizures experienced by the patient resulted from the interaction between alcohol and baclofen. To assess the likelihood of a baclofen–alcohol interaction, we used the Horn’s Drug Interaction Probability Scale (DIPS) (Horn et al., 2007). Although the DIPS was initially developed to assess interactions between two different medications, it is now considered a valuable tool for the evaluation of interactions between treatment drugs and drugs of abuse (Lindsey et al., 2012). The results of the DIPS are presented in Fig. 2. To the best of our knowledge, this case is the first reported case of such an interaction (−1). As we have observed, this interaction is consistent with the known interactive properties of both ethanol (+1) and baclofen (+1), both of which are proepileptic drugs. The two episodes of seizures are compatible with the time course of the interaction that has been described in the case report (+1). No seizure was observed during the first hospitalization of the patient, during which alcohol consumption was stopped and baclofen was present (+1). In contrast, a second episode of seizures occurred in the presence of baclofen when the patient experienced a relapse in alcohol abuse after the first hospitalization (+2). As discussed earlier, we do not believe that there was any other credible cause of seizures for the case of the patient (+1). The

Week 16, the patient reached the dose of 200 mg/day of baclofen, but his drinking level remained stable at ~50 g/day. The patient requested a further increase in the baclofen dose, and this increase was approved by a medical team, with the requirement that the patient’s state be monitored every 2 weeks. Slightly >2 weeks later, while taking a dose of 240 mg/day, the patient experienced a period in which his drinking level dramatically increased; he later reported a period of 5 days during which he drank ~160 g/day. During this period, he experienced the first episode of tonic–clonic seizures, after which he was hospitalized. An electroencephalogram and a computed tomography scan of the brain were performed, but neither found any anomaly. The patient left the emergency department the next day, and before we were able to see him, he consumed alcohol again and subsequently experienced a new episode of seizures. The patient was hospitalized a second time. When we met the patient, he did not agree to be hospitalized immediately. First, we checked whether the patient had any other risk factors for developing seizures (i.e. stress, infection or the introduction of another treatment). Second, we slowly began to reduce the baclofen dose to limit the risk of causing further seizures. The patient agreed to be hospitalized 10 days later. The baclofen dose was slowly reduced to 100 mg/day, and the patient received only 40 mg/day of diazepam and vitamins for 1 week. During this time, the patient did not experience any alcohol withdrawal symptoms. Since then, he has not experienced additional seizure episodes. The patient currently remains abstinent from alcohol but he is in an aftercare centre. The patient has not been put back on baclofen.

DISCUSSION

Both ethanol and baclofen might be involved in triggering the convulsions that the patient experienced. Alcohol can induce seizures in individuals experiencing withdrawal (Eyer et al., 2011) and under certain conditions of chronic abuse (Hattener et al., 2008). In both cases, seizures result from an imbalance between the excitatory glutamatergic system and the inhibitory GABAergic system (Hillbom et al., 2003). In these situations, however, alcohol is rarely the only cause of seizures, and other risk factors, such as pre-existing epilepsy, structural brain lesions or the abuse of other drugs, often
level of baclofen in the patient’s blood was not determined (0), and no other objective evidence for a possible interaction is available (0). Last, because it is difficult to compare the intensities of different tonic–clonic seizures, we chose to score question 10 as NA (0). Consequently, the final score for the evaluation of a baclofen–alcohol interaction with the DIPS was 6 out of 10, which indicates that this interaction is ‘probable’ (see Fig. 2).

To date, the possibility of the occurrence of acute interactions between baclofen and intoxicating doses of alcohol has been addressed only by a single study, which showed that baclofen appeared to be safe in combination with high doses of alcohol (Evans and Bisaga, 2009). However, in that study, the dose of baclofen did not exceed 80 mg/day, and there are no data that indicate that harmful interactions could not occur at higher doses. Moreover, only 18 participants were included in this research, and this small sample size might be insufficient to detect rare effects of the baclofen–alcohol interaction, including seizures.

### CONCLUSION

Baclofen is a promising medication for alcohol dependence, and the prescription of this drug at high doses is increasing, notably for patients for whom approved medications have failed. However, unpredicted interactions with alcohol could occur in some cases, and the seizures presented by the patient could be illustrative of this risk. Until data from a large study on the safety of high-dose baclofen use by alcohol misusers are available, treatment with HDB should be conducted under strict supervision and after having carefully evaluated the benefit–risk ratio.

### REFERENCES


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**Fig. 2.** Assessment of the interaction between alcohol and baclofen with Horn’s Drug Interaction Probability Scale (DIPS). NA, not applicable.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answer</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous credible reports of this interaction in humans?</td>
<td>No</td>
<td>-1</td>
</tr>
<tr>
<td>2. Is the observed interaction consistent with the known interactive properties of precipitant drug?</td>
<td>Yes</td>
<td>+1</td>
</tr>
<tr>
<td>3. Is the observed interaction consistent with the known interactive properties of object drug?</td>
<td>Yes</td>
<td>+1</td>
</tr>
<tr>
<td>4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?</td>
<td>Yes</td>
<td>+1</td>
</tr>
<tr>
<td>5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (if no dechallenge, use Unknown or NA and skip Question 6)</td>
<td>Yes</td>
<td>+1</td>
</tr>
<tr>
<td>6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?</td>
<td>Yes</td>
<td>+2</td>
</tr>
<tr>
<td>7. Are there reasonable alternative causes for the event?</td>
<td>No</td>
<td>+1</td>
</tr>
<tr>
<td>8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?</td>
<td>NA</td>
<td>0</td>
</tr>
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**Total** = 6

| Highly Probable: | 8+ |
| Probable: | 6–8 |
| Possible: | 2–4 |
| Doubtful: | <2 |

A consider clinical conditions, other interacting drugs, lack of adherence, risk factors (eg, age, inappropriate doses of object drug). A NO answer pre-supposes that enough information was presentation so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.


