

Increase of baclofen intoxications: risks involved and management

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ABSTRACT

Baclofen has been increasingly used in the treatment of alcohol withdrawal syndrome (AWS). We present a patient with AWS and psychiatric comorbidity who ingested 700 mg of baclofen. ICU admission was necessary for ventilatory support and symptomatic treatment. The patient was dismissed without sequelae.

KEYWORDS

Alcohol withdrawal syndrome, baclofen, intoxication, overdose, poisoning

INTRODUCTION

Baclofen is a centrally acting lipophilic derivative of gamma-aminobutyric acid (GABA) and acts as an agonist on the GABA_B receptor.¹ Baclofen is used in the treatment of muscle spasticity in patients suffering from spinal or cerebral disorders or from multiple sclerosis,² and off-label it is used in the treatment of chronic hiccups.³

In recent years, baclofen is increasingly used in the treatment of alcohol withdrawal syndrome (AWS).⁴ AWS is a cluster of symptoms that may occur after cessation or reduction in alcohol use in heavily or prolonged alcohol users.⁵ Some data suggest that baclofen has comparable efficacy to the benzodiazepine diazepam and that it potentially reduces the need for benzodiazepines.^{6,7}

We present a patient with AWS and psychiatric comorbidity, who self-ingested a massive amount of baclofen.

What was known on this topic?

Baclofen is a centrally acting GABA_B receptor agonist and is used in the treatment of muscle spasticity in patients suffering from spinal or cerebral disorders or from multiple sclerosis.

What does this add?

We have noticed an increased risk of baclofen intoxications, e.g. amongst users treated for substance withdrawal syndromes. Although baclofen intoxications are in most cases not fatal, respiratory support is crucial in severe intoxications. We encourage healthcare professionals to prepare themselves on the difficulties involved to diagnose a baclofen intoxication and the management of these intoxications.

CASE REPORT

A 46-year-old female with a history of at least eight years of alcohol abuse was treated for panic disorders and alcohol abuse with baclofen 10 mg three times a day, oxazepam 10 mg daily and clomipramine 75 mg daily. The baclofen was prescribed to prevent AWS and to treat the craving for alcohol.

She was admitted to the hospital emergency ward after having ingested 700 mg of baclofen (70 tablets of 10 mg) as reported by her spouse. At admission, three hours after

ingestion, she was restless and sweating with nausea and vomiting. She found it difficult to attain her attention and she could barely answer questions. However, she indicated that she had not consumed alcohol during the last three days. Her Glasgow Coma Scale was E4M6V4 on admission, but consciousness decreased rapidly thereafter. She had wide pupils reactive to light, hypothermia (35.4 °C) and hypertension 220/114 mmHg with a pulse of 80 beats/min. The ECG showed no abnormalities.

She was admitted to the ICU, where she was intubated and mechanically ventilated because of respiratory failure, to protect the airways for aspiration, and to perform adequate bronchial toilet. Thereafter, she was sedated with propofol via continuous infusion to facilitate the mechanical ventilation and mitigate AWS symptoms. Following intubation active charcoal and a laxative were administered through a nasogastral tube.

Besides a slight hyponatraemia and hypokalaemia, the laboratory values were normal. Serum ethanol levels were undetectable. The serum carbohydrate-deficient transferrin (N-Latex) level was in the normal range suggesting no recent excessive alcohol ingestion. The serum clomipramine level was low. Serum baclofen levels were sampled at several time points (*figure 1*). The serum baclofen level at admission was 8221 µg/l, therapeutic levels are 80-400 µg/l.¹ The level dropped to 171 µg/l 23 hours after ingestion.

During the night the restlessness persisted. Therefore propofol was only discontinued on day 2, after which she regained consciousness, and was weaned from the mechanical ventilation. She recalled that she had heard voices, after which she had ingested the baclofen. She had

not taken an overdose before, and did not have an active death wish. The patient was discharged to a psychiatric hospital without sequelae from the baclofen intoxication.

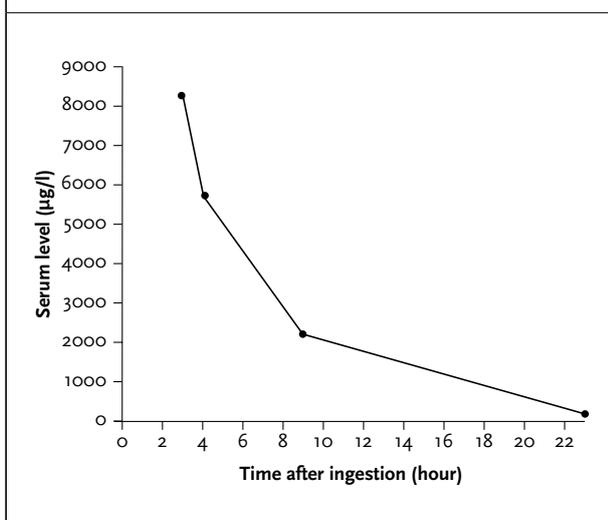
DISCUSSION

Generally, following an overdose with baclofen, effects on the central nervous system (CNS) can be observed within 2-6 hours after ingestion. Patients may become lethargic and flaccid, and experience loss of muscle strength, followed by respiratory depression, bradycardia and depressed consciousness to coma. Generalised convulsions and heart conduction disorders can also occur. Other symptoms are confusion, areflexia, hypothermia, miosis or mydriasis, sialorrhoea, hypotension, nausea, vomiting, diarrhoea, hypotonia and myoclonia.^{8,9} Also transient elevations of lactic dehydrogenase, aspartate transaminase, alkaline phosphatase, white blood cell count, and glucose have been reported.¹ With an intoxication of unknown cause, it may be difficult to distinguish the symptoms caused by baclofen from many other drugs acting on the CNS. Consequently, it is important to consider the possibility of a baclofen intoxication and a specific laboratory analysis should be performed because baclofen cannot be determined with standard toxicological screening methods.

There are literature reports of prolonged baclofen intoxications that have lasted for five days in which patients were mistakenly diagnosed with brain death.¹⁰ This prolonged effect was probably due to baclofen accumulation in the brain. First, toxic doses of baclofen may occasionally result in prolonged serum elimination half-life,¹⁰ up to 34.5 hours,¹¹ compared with 3-4 hours after therapeutic doses in adults. In the present case the serum elimination half-life was within the normal range (3.6 hours). Furthermore, baclofen clearance from the brain, probably mediated by organic anion transporters, may be limited.^{8,10} Therefore, one should be aware that serum concentrations may not correlate with the extent of CNS depression.

The management of baclofen intoxications is mainly symptomatic. Baclofen intoxications are not fatal in most cases, although respiratory support is crucial in severe intoxications.^{2,8} There were no lethal cases reported to the Dutch National Poisons Information Centre amongst 149 baclofen intoxications in the period 2009-2011.¹² Generally, it is recommended to administer active charcoal only within one hour after baclofen ingestion.¹³ Theoretically the benzodiazepine-antagonist flumazenil could counteract the binding of baclofen. However, clinical data of the efficacy of flumazenil in baclofen intoxications, and possible risks of flumazenil-induced seizures are limited.⁸

Figure 1. Serum baclofen levels after ingestion of 700 mg baclofen



Patients with renal insufficiency have a higher risk of baclofen accumulation and toxicity, because 69-85% is eliminated unchanged by the kidney.¹⁴ Haemodialysis can enhance baclofen elimination in cases with baclofen overdose with prolonged elimination half-life, for example due to renal failure, which is supported by its drug characteristics (e.g. low volume of distribution [0.83 l/kg in adults] and low protein binding [30%]).¹⁴ Although some authors have performed haemodialysis in a patient with an overdose and normal kidney function,¹⁵ generally, haemodialysis is not needed.

We have noticed an increase in published intoxications with baclofen.^{2,8,10} Moreover, the Dutch National Poisons Information Centre reported an increase of baclofen-intoxicated patients from 27 in 2009, to 49 in 2010, and 73 in 2011.¹² One reason for this increase of baclofen intoxication may be the shift to intrathecal administration to treat spasticity. The therapeutic window is much smaller compared with the oral route, because of administration directly into the CNS. Secondly, there are several case reports of adolescents that are intoxicated with baclofen after using it as a recreational drug.^{1,2} Although baclofen is a prescription drug, one can buy it on the internet without prescription. Finally, as described in the present case, we have noticed a rise in the use of baclofen in the treatment of AWS, and its use is also suggested for other substance withdrawal syndromes, such as with gammahydroxy butyric acid.¹⁶ The dose of baclofen for withdrawal syndromes varies from 30 mg per day used in trials up to 270 mg per day as described in case reports.¹⁷ There is evidence that alcohol-dependent patients frequently have comorbid psychiatric disorders.⁸ These patients have a higher risk of self-intoxication or suicide.⁸ Recently, a French report described a case series of 12 alcohol-dependent patients with co-existing psychiatric illness who committed a suicide attempt with baclofen, as in our case.⁸

CONCLUSION

We have noticed a rise in baclofen intoxications in recent years. The use of baclofen in substance-dependent syndromes, e.g. alcohol dependency, which is frequently accompanied by psychiatric disorders, may increase the risk of baclofen self-intoxication. Although most patients survive, ICU admission is often necessary for ventilatory support and symptomatic treatment. Healthcare professionals should be aware of the increased risks of baclofen intoxications and should prepare themselves on the management of these intoxications.

DISCLOSURES

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