CASE REPORT

Unintentional baclofen intoxication in the management of alcohol use disorder

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SUMMARY

In recent years, there has been a growing interest in using baclofen for the management of alcohol use disorder. This *off-label* indication usually involves high doses of the medication. We report a case of severe baclofen overdose in a 66-year-old man. The patient was found severely agitated, and he presented with delirium and auditory hallucinations. At hospital admission, his daily dose was 180 mg baclofen. He was admitted to the intensive care unit for sedation and supportive care. When sedation was withdrawn, the patient presented with a normal neurological status. In this clinical context, baclofen intoxication was suspected. This was confirmed by measuring blood baclofen levels. This intoxication was probably mediated by a combination of risk factors including a high daily dose of baclofen and acute renal failure, conducive to drug accumulation.

BACKGROUND

According to the WHO's 2004 report, more than 75 million people around the word suffer from alcohol abuse or dependence.[1] As a complement to psychological interventions, several different medications can be used in order to reduce heavy drinking and increase the number of days of abstinence.[2]

In recent years, there has been a growing interest in using baclofen to manage alcohol use disorders.[3–5] It appears to reduce the potential for alcohol abuse and dependence by modulating the activity of γ-aminobutyric acid (GABA)-B receptors.[3 5] The doses used in this *off-label* indication can be very different: low doses (30 mg/day) were evaluated in Italian clinical trials, with inconsistent results.[6] In France, however, high daily doses are used, mainly based on case reports or retrospective cohort studies.[6] High daily doses can range from more than 80 mg/day, up to a maximum daily dose of 400 mg in some cases.[4] Effective, safe doses currently remain subject to debate.

Baclofen is an analogue of GABA. Although its specific mechanism of action is not yet fully understood, baclofen interacts with GABA-B receptors. It is widely used to treat muscle spasticity in multiple sclerosis and spinal lesions. Adverse effects at usual dosages include weakness, drowsiness, headache, dizziness and arterial hypotension.

Baclofen is rapidly and completely absorbed after oral ingestion. The time to peak serum concentration is reached within 2 h, and 85% is excreted unchanged in urine and faeces.[7] The remaining fraction of baclofen is metabolised by the liver.[8] Its half-life is about 2–4 h, but this can be longer in cases of overdose or renal impairment.[9–11] In cases of overdose, baclofen acts as a strong central nervous system (CNS) depressant and can provoke symptoms such as muscular hypotonia, respiratory depression, seizure, coma and arrhythmia.[12 13] Clinical symptoms can differ between acute and chronic intoxications: impaired consciousness, autonomic disorders, neuromuscular and respiratory depression are mostly described for acute intoxications; hallucinations, impaired memory, catatonia and acute mania can be observed in cases of chronic intoxication.[14]

We report a case of severe baclofen overdose when used as an *off-label* indication for the management of alcohol use disorder.

CASE PRESENTATION

A 66-year-old man, already living in a nursing home because of chronic alcohol overuse, was discovered in a confused and severely agitated state: blood pressure 145/90 mm Hg, heart rate 60 bpm, respiratory rate 30 breaths/min, Glasgow Coma Scale 14/15, blood sugar level 8.2 mmol/L and normal body temperature. The patient presented with delirium and auditory hallucinations. No focal neurological abnormalities were observed. For sedation, 5 mg of intranasal midazolam was used, with a good response. The patient was transferred to our hospital's emergency unit.

In addition to his alcohol use disorder, the patient was known to have a metabolic syndrome involving hypertension, diabetes, hypercholesterolaemia and excess weight. His standard medical treatment consisted of low dose aspirin, carvedilol, valsartan and hydrochlorothiazide, amlodipine, simvastatin, ezetimibe, metformin, allopurinol, venlafaxine, calcium vitamin D_3 and baclofen. Baclofen had been used at increasing doses over the previous 5 months, reaching a daily dose of 180 mg at the time of admission.

The patient's medical record reported a history of multiple failed alcohol withdrawals. Prior to hospitalisation, he had maintained controlled but persistent alcohol consumption in the nursing home; however, his precise consumption over the last few days was unknown. A general decline in health, involving vertigo and balance disorders, was reported for a few days prior to hospitalisation. On questioning, the patient reported no suicidal thoughts or intentions, and confirmed taking the doses prescribed by his alcohol specialist.

INVESTIGATIONS

Blood investigations revealed anaemia (haemoglobin 116 g/L), hypernatraemia (sodium 150 mmol/L),

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impaired renal function (creatinine clearance 32 mL/min), normal liver tests and a negative alcohol test. A blood gas analysis showed normal pH and lactates. Urine drug screening was positive for cannabis. ECG showed sinus bradycardia at 55 bpm with normal QRS and QT interval. Chest X-ray, brain CT scan and cerebrospinal fluid were normal. An EEG performed under heavy sedation with propofol and midazolam showed a burst suppression pattern.

In the context of high-dose baclofen treatment, we performed a blood level measurement. Samples had to be sent to a specialised laboratory abroad, and the results were not available until 1 week after admission, by which time the patient had already recovered from his condition.

DIFFERENTIAL DIAGNOSIS

The diagnosis was difficult because of the range of possible differential diagnoses with very similar clinical presentations: alcohol withdrawal syndrome, alcohol intoxication, other substance abuse and even baclofen withdrawal syndrome.[15 16] Furthermore, the patient's detailed medical history was difficult to obtain. In the acute phase, the diagnosis of baclofen overdose was supported by the exclusion of other causes, following a head CT scan, lumbar puncture, toxicological screening and an EEG. Lactic acidosis due to metformin intoxication was excluded by normal blood gas analysis results. Venlafaxine intoxication was a possible differential diagnosis, but was less likely in the clinical context of agitation rather than CNS depression, the lack of mydriasis on clinical examination and an ECG that showed no signs of possible venlafaxine intoxication other than a sinus bradycardia.

Even though there is a high rate of suicide attempts in alcohol-dependent patients, we could find no signs of voluntary intoxication. Although our patient was being treated for depression, he denied any attempt of self-poisoning, and said that he had followed his prescription scheme. We could find no indications of a suicide attempt at the scene of his discovery, and the nursing staff had not noticed any unusual behaviour.

TREATMENT

In order to control his agitation, the patient was admitted to the intensive care unit (ICU) for sedation and supportive care. Endotracheal intubation was performed on the second day after admission. Sedation was managed by continuous and intermittent midazolam, propofol and fentanyl administration. Hypernatraemia and acute kidney injury were rapidly corrected using intravenous fluid therapy.

Given this evidence, baclofen intoxication, alcohol withdrawal or a combination of both was suspected; the patient therefore received a treatment of thiamine and benzodiazepines. In this context, baclofen treatment was suspended. In order to avoid a baclofen withdrawal syndrome, baclofen treatment was resumed at a lower dose (75 mg/daily) once renal function was again normal. The dose was progressively reduced by 12.5 mg every 48 h until discontinuation. After his stay in the ICU and taking into account the side effects from which he suffered before the intoxication, particularly drowsiness, the patient no longer wanted to take this medication. The general practitioner, alcohol specialist and ICU physicians agreed with this decision.

OUTCOME AND FOLLOW-UP

The results of the initial blood baclofen measurements were obtained 1 week after admission, confirming the intoxication: the baclofen blood level was 1510 μg/L, whereas the therapeutic range for spasticity treatment is 80–400 μg/L.[12] One week after admission, the baclofen blood level had returned to its normal range. After discontinuation of mechanical ventilation, the patient awoke with a normal neurological status and no recurrent confusion or agitation.

In accord with the patient's wishes, and with the agreement of his general practitioner and alcohol specialist, baclofen was discontinued at hospital discharge and not prescribed again. A specific follow-up was planned after hospital discharge, focusing on psychological support every 2 weeks. Nevertheless, 3 months after his hospital discharge, the patient was highlighting his persistent difficulties in controlling alcohol consumption since the discontinuation of baclofen.

DISCUSSION

Managing this case proved to be challenging. First, drug intoxication was probably the result of an accumulation of risk factors. An initial factor was treating the patient using a high daily dose of baclofen. This longstanding drug was introduced relatively recently for alcohol withdrawal and consumption control at significantly higher doses (80–400 mg/day) than for its original neurological indications (40–80 mg/day). A further factor was the acute renal failure that led to drug accumulation. Renal failure as a risk factor for intoxication has been emphasised by other authors;[11] in some specific cases, haemodialysis can be used to remove baclofen.[10] In the present case, renal failure was probably caused by dehydration and concomitant use of diuretics.

Second, clinical symptoms vary from case to case, following different patterns, dependent on whether the intoxication is acute or chronic. Patients may present with altered states of consciousness, autonomic disorder, hallucinations, impaired memory, respiratory depression, neuromuscular depression or seizure.[14] The main symptom, in this case, was impaired consciousness, which can appear in both acute and chronic settings.

The usual treatment is supportive and should consider a possible concomitant alcohol withdrawal syndrome. Thus, the prescription of thiamine, sedation with benzodiazepines or propofol, and mechanical ventilation are to be recommended, and were indeed used in this patient.

Most published cases of baclofen overdose include acute intentional overdose or intoxication in the context of spasmolytic treatment.[12 17] To the best of our knowledge, this is the first case report of unintentional overuse of baclofen in alcohol disorder management.

This case presents an unintentional baclofen overdose in a clinical context involving high-dose baclofen treatment for a chronic alcohol use disorder further complicated by renal impairment.

Similar cases may be observed in the future, given that an increasing number of patients could be using baclofen at substantially higher doses than those required for neurological indications. As observed in this patient, acute kidney injury can lead to rapid drug accumulation.

This emphasises the importance of thoroughly informing patients and families about baclofen's potential side effects and the symptoms of intoxication. Clinicians in primary and emergency care should be aware of the clinical presentation of baclofen intoxication and maintain it high on the index of suspicion, as the prevalence of this condition could increase over the coming years.

Learning points

- High daily doses of baclofen can be used to manage alcohol use disorders.
- A high daily dose therapy increases the risk of intoxication.
- In this context, acute kidney injury can lead to rapid drug accumulation and intoxication.
- Clinical symptoms can differ between acute and chronic intoxications.
- Comprehensively informing patients and families about baclofen's potential side effects and the symptoms of intoxication is important in order to avoid unintentional overdoses.

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