

## Self-Intoxication with Baclofen in Alcohol-Dependent Patients with Co-existing Psychiatric Illness: An Emergency Department Case Series

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**Abstract** — **Aims:** The aim of the study was to describe the characteristics and management of alcohol-dependent patients with co-existing psychiatric illness seen after self-intoxication with oral baclofen in an emergency department (ED). **Methods:** A retrospective review of medical records of such patients over a 12-month period from January 2012. **Results:** Twelve such patients were identified, median age 39.5 years. The median supposed ingested dose of baclofen was 340 mg (range 140–800 mg). Three patients who had co-ingested benzodiazepines had a decreased level of consciousness (Glasgow Coma Scale <8) and flumazenil had been given to reverse coma. Blood alcohol concentration, requested for all patients, was positive in three (ranging from 153 to 495 mg/100 ml). Gastric lavage was performed in two cases. All patients made a full recovery. They were discharged from the ED or intensive care unit after psychiatric assessment. **Conclusion:** Baclofen overdose affects the autonomic and central nervous system. Supportive care is symptom based. Care should be taken when prescribing baclofen with other central nervous system depressants and to patients with past attempted suicide.

### INTRODUCTION

Complications related to alcohol intoxication and specific drugs place significant demand on healthcare resources (Pirmohamed *et al.*, 2000; French *et al.*, 2008). Emergency physicians (EPs) are daily confronted with alcoholism in patients brought to the emergency departments (EDs) and are well placed to routinely offer detoxification (Whiteman *et al.*, 2000). About 40% of alcohol-dependent patients attempt suicide in the course of their life (Roy, 2003; Roy and Janal, 2007). These alcohol-dependent patients frequently have comorbid psychiatric disorders (Regier *et al.*, 1990; Jones *et al.*, 2011; Prisciandaro *et al.*, 2011), which lead to a higher risk of self-poisoning and a poorer outcome (Cornelius *et al.*, 2003; Dore *et al.*, 2011). Depressed alcohol-dependent patients are more likely to attempt suicide than non-depressed alcohol-dependent individuals (Boenisch *et al.*, 2010). Alcohol-use disorder (abuse and dependence), a well-known risk factor for attempted suicide, ranges from 7 to 37% in the general population (Lejoyeux *et al.*, 2008), necessitating emergency admission, and co-occurs with a lifetime prevalence of roughly 50% in people with bipolar disorder (Manwani *et al.*, 2007). Lifetime co-occurrence of an alcohol-use disorder and an anxiety disorder ranges from 6 to 20% depending on the specific type of anxiety disorder (e.g., social anxiety disorder, generalized anxiety disorder, obsessive compulsive disorder or posttraumatic stress disorder) (Kessler *et al.*, 1997). Many different drugs with very different targets have been tested as possible treatments for alcoholism, and among them baclofen, a gamma-aminobutyric acid B receptor agonist, seems to be a promising agent. This drug has been used for many years as a skeletal muscle relaxant for alleviation of symptoms of spasticity (Dario and Tomei, 2004). Doses of 10 mg three times daily are effective and well-tolerated (Addolorato *et al.*, 2002; Garbutt *et al.*, 2010; Leggio *et al.*, 2012). Moreover, some case reports have suggested that some patients could be treated with high doses of baclofen (>90 mg/day), up to 270 mg daily

(Ameisen, 2005; Bucknam, 2007). Off-label use of high-dose baclofen has also recently increased in France (Rolland *et al.*, 2012a). Baclofen has been proved to act on anxiety disorders (Breslow *et al.*, 1989; Drake *et al.*, 2003) and on anxiety associated with affective disorders (Addolorato *et al.*, 2002), which increases its interest for alcohol-dependent patients.

### MATERIALS AND METHODS

#### Study design

This observational single-centre study involved retrospective medical record review of all alcohol-dependent patients with co-existing psychiatric illness seen at a French ED over a 12-month period from January 2012 to January 2013 after self-poisoning with baclofen. Self-poisoning with suicidal intent was assessed in the ED after questioning of the patient and relatives. All such cases are reported to the poison control centre, which ensures toxicological surveillance from ED admission to discharge from hospital. The antipoison centre information system (SICAP<sup>®</sup> version 5.4.0) summarizes the reason for ED admission, medical evaluation, the patient's history, toxicology and laboratory test results, psychiatric report and diagnosis, and discharge to hospital or out-patient care. Medical records were retrospectively searched using the terms baclofen (INN), Baclofène<sup>®</sup> or Lioresal<sup>®</sup> (the French trade names), plus either intoxication or poisoning or toxic. A primary physician diagnosis coded F10.2 (WHO International Classification of Diseases, 10th revision) was considered to indicate alcohol dependence. All patients admitted after a suicide attempt are referred to an ED psychiatrist for assessment of psychiatric comorbidity. Any past history of suicide attempts is entered in the patient's record and this is completed by extracting data from the antipoison centre information system if patients have a previous admission to the ED for self-poisoning. Patients who were considered by the ED or the

psychiatrist to have an accidental overdose or drug mistake were not included.

The study was approved by the hospital ethics committee.

#### Data collection and outcome measures

Data collected included date of occurrence, patient demographics (age and sex), details of the overdose (estimated dose and co-ingestants) and clinical effects (Glasgow Coma Scale (GCS), seizures, delirium, blood pressure, heart rate, pupillary size (constricted/normal/dilated, limb reflexes), treatment (decontamination, ventilation and ICU admission), length of stay and past psychiatric history including suicide attempts. Prehospital management focused on GCS using 9 as the cut-off, because it is the standard indicator determining the need for airway protection. Blood alcohol concentration (BAC) levels and toxicological screenings (quantitative dosage of tricyclic antidepressants, paracetamol, carbamate and barbiturates, and qualitative dosage of benzodiazepines) were routinely obtained. More specific toxicological tests based on questioning of the patient or relatives were done if requested by the physician.

## RESULTS

Clinical characteristics are summarized in Table 1. Ten patients had a previous suicide attempt recorded by the psychiatrist. Patients' median age was 39.5 years (range 23–56 years), and seven were women. The median supposed ingested dose of baclofen was 340 mg (range 140–800 mg). All patients were transported to the ED by ambulance, and five were escorted by a mobile emergency team (an EP and a nurse with availability of advanced life support), because of coma (GCS < 6) (Patients 3, 6, 8 and 11) and seizures (Patient 9). Three patients who had co-ingested benzodiazepines with baclofen had a decreased level of consciousness (Patients 3, 8, 11) with a GCS < 8. They were given intravenous infusion of flumazenil to reverse the comatose state. No seizure was noted after flumazenil administration. Depressed limb reflexes were observed in 10 patients. Systolic blood pressure was within the normal range in eight patients. Hypertension (arterial blood pressure > 140/90 mmHg) was noted in four patients, in particular in Patient 2 who had taken cocaine and in Patient 9 who experienced seizures before admission. Hypertension resolved spontaneously, except in Patient 2 who received diazepam intravenously to reduce agitation and improve hemodynamic state.

All patients received an electrocardiogram. No patient had cardiac conduction abnormalities in spite of co-ingested psychotropic drugs. Chest X-rays were obtained in intubated patients. A brain CT scan was performed in Patient 9 because of seizures and was normal. A blood sample was obtained in all cases for tests including liver and kidney function, electrolytes, and blood glucose. A complete blood count was done only in patients who were admitted to the ICU.

BAC was requested for all patients and was positive in three (range 153–495 mg/100 ml). When BAC was < 10 mg/100 ml, the time of last alcohol consumption was not recorded and it was not known whether the patients had stopped consuming alcohol since starting baclofen or whether consumption was still regular. Benzodiazepines were the most frequent co-ingestant,

being positive in five patients (Patients 1, 2, 3, 8 and 11). Data concerning the daily dose of baclofen were lacking for three patients and no information on the prescriber of baclofen was noted in the medical record. Gastric lavage was performed in two cases. No death occurred.

## DISCUSSION

Publications on suicide attempts with oral baclofen are predominantly case reports or case series (Perry *et al.*, 1998; VanDierendonk and Dire, 1999; De Giovanni and d'Aloja, 2001; Leung *et al.*, 2006; Wall *et al.*, 2006; Macaigne *et al.*, 2011; Sullivan *et al.*, 2012; Weibhaar *et al.*, 2012), whatever the comorbid associations. Self-poisoning with baclofen seems likely to increase in France, as growing interest has made it a 'French craze' (Rolland *et al.*, 2012a).

The classic clinical presentation of baclofen overdose is associated with the neurotransmitter inhibitory effects of the drug, which usually occur quite rapidly after ingestion. These effects include impaired consciousness or coma, generalized muscular hypotonia with absent limb reflexes, respiratory depression, seizures, hemodynamic changes and cardiac abnormalities such as supraventricular tachycardias, premature atrial contractions and first-degree heart block.

Autonomic nervous system effects, hypertension and central nervous system depression are more likely to be linked with higher doses of baclofen. Bradycardia after baclofen overdose (Cohen *et al.*, 1986) may be successfully treated with atropine bolus. Atropine, a nonspecific muscarinic antagonist to all postganglionic parasympathetic fibres, reverses central vagal stimulation induced by baclofen.

Pupillary responses are reported to be inconsistent, as both miosis and mydriasis have been observed whatever the dose taken (Leung *et al.*, 2006).

The EP dispatched to the intoxicated patient may perform prehospital decontamination. Gastric lavage and activated charcoal, used in only two patients in this study, may not be effective if performed > 1 h after ingestion (Bond, 2002). Data on baclofen intoxication are not sufficient to make a definitive recommendation. However, EPs should consider early prehospital or hospital decontamination in patients with a protected airway because baclofen has prolonged sedative effects, especially, when co-ingested with sedative drugs (Leung *et al.*, 2006). No controlled study has supported the utility of forced diuresis. Leung *et al.* (2006) found that in adults severe complications occur only with a baclofen overdose of 200 mg or more, but this dose was arbitrarily chosen.

Four patients in our study were in coma before admission and required intubation and respiratory support. Coma after baclofen overdose is related to depression of neuronal activity in the central nervous system and may persist for several days. In baclofen overdose alone, profound sedation is observed as its toxicokinetic properties differ between therapeutic dose and overdose. At therapeutic doses, peak serum concentrations of baclofen are reached in 2 h after being rapidly and almost completely absorbed by the gastrointestinal tract. In contrast, higher doses (up to 200 mg) taken in voluntary intoxication result in prolonged elimination half-lives (Sullivan *et al.*, 2012). In our university hospital, baclofen concentration in plasma is not routinely measured, which limits correlation between the supposed ingested dose, clinical effects and peak

Table 1. Characteristics of alcohol-dependent patients with psychiatric comorbidity and baclofen self-intoxication

	Age (years)/sex	Daily baclofen dose (mg)	Supposed baclofen dose ingested (mg)	Time to onset of clinical signs (h)	Comorbid psychiatric disorder	Previous history of suicide attempt	Co-ingestants (toxicology screening)	BAC (mg/100 ml)	Length of stay (days)	Clinical signs	Decontamination	ICU
1	23/M	30	800	2	Anxiety disorder	No	Oxazepam (+)	<10	2	Confusion Drowsiness	–	No
2	25/F	Missing data	400	2	Opioid dependence Depression	Yes	Diazepam (+) Zopiclone (ND) Cocaine (ND)	153	4	Coma GCS 10	Gastric lavage Activated charcoal	No
3	56/F	120	200	4	Anxiety disorder	Yes	Oxazepam (+) Ketoprofen (–)	<10	3	Hypertension Confusion Hyperthermia GCS 6	Flumazenil	Yes
4	51/F	45	200	Missing data	Bipolar disorder	Yes	Venlafaxine (351 µg/l)	<10	1	GCS 13	–	No
5	40/F	30	200	Missing data	Depression	Yes	None (–)	243	0.5	Drowsiness	–	No
6	44/F	90	600	4	Depression	Yes	Naproxen (–) Amitriptyline (769 µg/l) Paracetamol (<2 mg/l) Tramadol (4461 µg/l)	<10	>30	GCS 3 Hypertension Tachycardia	Gastric lavage	Yes
7	25/M	45	340	1	Anxiety disorder	None	None	<10	1	Hypertension Mydriasis	–	No
8	46/F	Missing data	250	2	Bipolar disorder	Yes	BZP (+)	<10	1	Drowsiness GCS 6 Miosis	Flumazenil	No
9	30/M	45	600	1	Depression	Yes	None (–)	<10	1	Seizures Hypertension GCS 3	–	Yes
10	39/M	30	140	Missing data	Anxiety disorder	Yes	None (–)	<10	0.5	–	–	No
11	45/M	Missing data	Missing data	Missing data	Anxiety disorder	Yes	Diazepam (+)	<10	10	GCS 6 Miosis	Flumazenil	Yes
12	28/F	30	560	Missing data	Depression	Yes	Alcohol	495	1	Drowsiness	–	No

ND, not done; BAC, blood alcohol level; BZP, benzodiazepines; GCS, Glasgow Coma Scale.

plasma concentration. Whatever the plasma concentration, coma induced by baclofen overdose may range from hours to several days due to its lipophilic properties. Baclofen penetrates the blood–brain barrier and although its concentration in the brain is lower than in serum, it is eliminated more slowly from the central nervous system than from serum. CNS depression therefore persists even after plasma baclofen levels return to normal (Haubenstock *et al.*, 1983; Gerkin *et al.*, 1986). This latter observation underlines that there is no relation between the amount of drug ingested and coma duration (Van Dierendonk and Dire, 1999) and that controlled ventilation is preferable to a potentially risky and ineffective injection of flumazenil, even in co-intoxication with benzodiazepines. This is clinically relevant because three patients with a decreased level of consciousness before admission were given a titrated dose of flumazenil to reverse coma by the EP. Flumazenil may be of benefit in comatose patients by avoiding intubation and mechanical ventilation, as these procedures are risky in the prehospital setting. Flumazenil was used to decrease central nervous system depression in two patients, who were accidentally intoxicated with an intrathecal bolus of baclofen given to treat tetanus (Saissy *et al.*, 1992). The authors hypothesized that flumazenil, empirically given, counteracted baclofen overdosage by acting as a specific antagonist of the binding of benzodiazepines to the GABA complex. Nonetheless, flumazenil infusion when patients are intoxicated with both benzodiazepines and a proconvulsant drug is still debated, especially if patients are at risk of developing seizures. Flumazenil is not indicated in patients with a past medical history of seizure, or in patients who chronically use benzodiazepines (Kreshak *et al.*, 2012). Conversely, some authors pointed out the low incidence of flumazenil-induced seizure in combined intoxication with both benzodiazepines and a proconvulsant drug (Kreshak *et al.*, 2012; Veiraiiah *et al.*, 2012), and with use of slow flumazenil dose titration (Weinbroum *et al.*, 1997). To date, there has been only one case report of flumazenil-induced seizures accompanying benzodiazepine and baclofen intoxication (Chern and Kwan, 1996). The exact mechanisms through which baclofen induces seizure are poorly understood (Rolland *et al.*, 2012a,b). Only one patient in our series, who had never previously suffered from epilepsy, experienced seizures after a supposed ingested dose of 600 mg of baclofen. This patient did not co-ingest benzodiazepines or alcohol. Baclofen is considered as a proconvulsant drug, resulting from complex regulation by GABA-B of both the GABAergic and glutamatergic systems (Bowery, 2010), thus promoting epileptogenesis. Seizures may result from the exertion of a complex regulatory action by GABA-B on both the GABAergic and glutamatergic systems (Bowery, 2010), and experimental data suggest that activating the GABA-B receptors could accentuate neural excitation contrast in some parts of the brain (Fujita *et al.*, 2011).

Our findings support previous reports suggesting that most patients with baclofen overdose had a good outcome with adequate supportive care (Leung *et al.*, 2006). Notable in this series of alcohol-dependent patients is that baclofen self-poisoning was rarely associated with acute alcohol intoxication (Table 1). Baclofen administration inhibits voluntary ethanol intake (Addolorato *et al.*, 2000) with a concomitant anxiolytic effect reflecting GABA-B receptor stimulation within the amygdala (Gorsane *et al.*, 2012). The doses of baclofen tolerated by patients and reported to be helpful in

reducing alcohol craving are usually much higher, from 15 to 300 mg/day. Such doses have been experimentally given in alcohol dependence (Ameisen, 2005; Bucknam, 2007), heavy social drinkers (Evans and Bisaga, 2009; Rigal *et al.*, 2012) and comorbid psychiatric disorder (Bucknam, 2007). Dore *et al.* (2011) found that some patients may rapidly escalate the daily dose prescribed without medical consultation, thus leading to overdose. Our small sample size limits this observation, but we assume it is clinically relevant.

Our observational study has limitations: it was retrospective and performed in only one French university hospital, with a relatively small sample and the intrinsic limitations of a retrospective chart review, including incomplete recording of data in the charts; case selection may have been incomplete, since it depended on the accuracy of the EP discharge diagnosis codes.

Another limitation is that plasma concentrations of baclofen are not routinely obtained in our university hospital, and we cannot correlate baclofen intoxication with a supposed ingested dose. There was limited information on the time between ingestion and onset of clinical features because the database only recorded timed information on clinical effects for the latter part of the study period. Furthermore, both comorbid psychiatric illness and past history of suicide attempts were evaluated by the ED psychiatrist. We had no detailed information on history of alcohol dependence, psychiatric follow-up after discharge, patient outcome or subsequent management for their psychiatric disorder.

## CONCLUSION

The clinical course of acute baclofen overdose includes a wide range of symptoms, among them deep coma with flaccidity, absent tendon reflexes, lack of response to painful stimuli, severe respiratory depression and bradycardia. Management of oral baclofen intoxication is primarily symptomatic.

*Conflict of interest statement.* None declared.

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