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**BACLOFEN OVERDOSE FOLLOWING RECREATIONAL USE IN ADOLESCENTS AND YOUNG ADULTS: A  
CASE REPORT AND REVIEW OF THE LITERATURE**

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Running title: recreational baclofen overdose in young adults

## **Abstract**

Over the past twenty years, psychotropic drug abuse by young people, especially by teenagers, has received special attention. Here, we present the case of baclofen overdose in a 16-year-old male who recreationally, and probably recurrently, self-administered baclofen. In addition, a review of other cases was conducted. The 16-year-old boy presented to emergency department with digestive signs followed by agitated confusion. Detection and determination of baclofen concentration were achieved using liquid chromatography tandem mass spectrometry. Baclofen was detected in plasma and urine, at 420 ng/mL and 64 900 ng/mL respectively. Further, an English exhaustive literature search was performed using several different scientific databases without any limiting period in order to identify scientific articles dealing with baclofen overdose following a recreational use among adolescent and young adults. Five publications describing baclofen overdoses following a recreational use among adolescents and young adults have been published reporting 19 cases, all involving a non-fatal overdose, with baclofen concentrations ranging from less than 20 to 1322 ng/mL. Baclofen is a psychotropic drug and its recreational use among adolescents and young adults represent a serious problem and should be considered by healthcare professionals. Among young people, baclofen poisoning remains relatively infrequent or most likely underestimated and these observations highlight the importance of constructive communication and joining efforts of clinicians and analytical toxicologists.

Keywords: baclofen, overdose, drug abuse, adolescent

## **Introduction**

Adolescence is a preparation period for adulthood, during which key stages of development take place both physically and psychologically or even emotionally. It is a period, where peer influence, social and family contexts are likely to have a decisive influence on the adult-to-be, and where the tendency to explore one's limits and abilities is heightened. In fact, during this period, many teenagers adopt risky behaviors: unprotected sexual activity, use of alcohol, tobacco, cannabis or even hard drugs such as cocaine or ecstasy [1].

A gradual increase in psychotropic drug abuse by young adults has been documented worldwide [2]. These drugs include several categories of products whose mechanism of action mainly influences brain activity. In most cases, the use of these drugs is therapeutic, sometimes even in a context of self-medication. However, due to their pharmacological properties, these drugs can also be subject to intentional or unintentional harmful usage leading to complications [3-5]. These substances range from psychostimulant drugs such as methylphenidate, mainly used for cognitive doping purposes, to codeine cough syrups, often used for recreational purposes [5;6].

In this study, a case of a teenager admitted with medical signs of no specific etiology and with no known history of drug abuse or misuse albeit a suspicion of baclofen intake is described. Further, other cases of baclofen overdose following recreational use among adolescent and young adults were reviewed.

## **Methods**

### ***Materials and reagents***

Baclofen drug standard and prazepam internal standard were purchased from LGC (Molsheim, France). N-propanol was bought from Fischer Scientific SA (Illkirch-Graffenstaden, France) and baclofen-d4 from Cerilliant Corporation (Round Rock, TX, USA) whereas methylmilnacipran (a non-marketed molecule) was obtained as a gift from the pharmaceutical laboratory Pierre Fabre (Labège, France). All solvents and reagents were of HPLC grade or analytical grade. Milli-Q water (Millipak® Express 40 filter, Merck Millipore [Molsheim, France]) was used throughout the analysis. Drug-free human plasma was obtained from the hospital blood bank (Angers Hospital, France).

### ***Analytical procedures***

Ethanol (EtOH) concentration in blood and urine samples was determined using gas chromatography with flame ionization detection (GC-FID) (6850, Agilent Technologies, Santa Clara, CA, USA) after precipitation using sodium tungstate and sulfuric acid 1N. The injection technique was direct injection and the internal standard was n-propanol. Routine screening for the identification and quantification of drugs of abuse (DOA), prescription drugs and other toxicants was performed using several methods: urinary immunochemical analyses for DOA (several opioids, benzoylecgonine, amphetamine and 11-nor-9-carboxy- $\Delta^9$ -tetrahydrocannabinol) using Enzyme Multiplied Immunoassay Technique (EMIT) (ADVIA chemistry XPT, Siemens Healthineers, Erlangen, Germany), blood and urine analyses using

liquid chromatography with diode array detection (LC-DAD) and urine analyses by gas chromatography with mass spectrometry detection (GC-MS).

For LC-DAD analysis, sample preparation was performed using two methods. The first liquid/liquid extraction was conducted by adding 25  $\mu\text{L}$  of internal standard (prazepam, 20 mg/L in methanol; final concentration, 1 mg/L) to 500  $\mu\text{L}$  of sample. Then 30  $\mu\text{L}$  of sodium hydroxide (1 M) and 5 mL of dichloromethane were added. After mixing the preparation for 1 min and centrifuging briefly, the non-aqueous (organic) supernatant was evaporated to dryness at 50° C under nitrogen gas. The residue was dissolved in 50  $\mu\text{L}$  of methanol then completed to a total volume of 70  $\mu\text{L}$  with water. In the second liquid/liquid method, 25  $\mu\text{L}$  of internal standard (methylnilnacipran, 20 mg/L in methanol; final concentration, 1 mg/L) was added to 500  $\mu\text{L}$  of sample and 100  $\mu\text{L}$  of sodium hydroxide (4 M). Then an extraction using 4 mL of hexane/isoamyl alcohol (80/20, v/v) was performed. After mixing and centrifugation, the organic layer was isolated and mixed with 100  $\mu\text{L}$  of hydrochloric acid (0.02 M). Following vortex mixing and centrifugation, the aqueous layer was kept for injection into the chromatographic system (1100 HPLC system, Agilent Technologies, Les Ulis, France). For both preparation procedures, the injection volume was 10  $\mu\text{L}$ . The chromatographic separation was achieved over 20 minutes run time on an Uptisphere C18 ODB column (5 $\mu\text{m}$ , 100x 2.1 mm (Agilent Technologies, Les Ulis, France)). Data acquisition was performed at three wavelengths (210 nm, 230 nm and 254 nm). Products were identified by comparing UV spectra and retention times to a homemade spectrum library (established using authentic standards).

For GC-MS, 50  $\mu\text{L}$  of internal standard (3-(5, 11-dihydro-10, 10-dioxo-11-methyl-dibenzo[c,f]-thiazepinyloxy) tropane maleate or RN927, a non-commercialized antihistaminic molecule, 1 mg/mL; final concentration, 50 mg/L) was added to 1 mL of urine sample then extracted using 5 mL of dichloromethane under alkaline conditions (500  $\mu\text{L}$  of carbonate 1 M

buffer pH 9.2 and 50  $\mu$ L of sodium hydroxide 1 M). The organic phase was evaporated at 50°C under nitrogen gas and the residue dissolved in 100  $\mu$ L of hexane/isopropanol mixture (85/15, v/v). Finally, 2  $\mu$ L of the dissolved sample was injected (splitless mode) in the GC-MS system (Agilent GC system model *HP 6890N*, Agilent Technologies, Santa Clara, CA) with a HP5 MS 5% phenylmethyl column (30 m, internal diameter 0.25 mm, 0.25  $\mu$ m film) (Agilent Technologies, Les Ulis, France). The injector temperature was set to 275°C. The initial column temperature (70°C) was increased to 210°C at a rate of 30°C/min, and held at 210°C, then ramped up to 300°C at a rate of 20°C/min and finally held at 300°C for 15 min. Helium was used as a carrier gas and delivered at a flow rate of 1.6 mL/min. The mass spectrometer source and quad temperature were set at 230°C, and 150°C, respectively. Acquisition was carried out in a positive scan mode, for m/z ranging from 35 to 500. Peaks spectrum research was realized in comparison with different spectrum libraries (home-made library, Cayman spectral library, Nist 98 library) and peak identification was confirmed after authentic standard analysis.

For baclofen determination and quantitation, 50  $\mu$ L of biological samples (including plasma and urine) were added to 450  $\mu$ L of IS dilution (baclofen d4 at a concentration of 100 ng/mL, prepared in acetonitrile; final concentration, 900 ng/mL) and mixed for 10 min. After centrifugation (1060 g, 5min), the aqueous supernatant was injected into the liquid chromatography-tandem mass spectrometry (LC-MS/MS) system. Chromatographic analysis was carried out using a Shimadzu LC-20AD pump (Shimadzu Corporation, Marne-la-Vallée, France). Separation was achieved using a Kinetex C18 core-shell column (2.1 x 50 mm); 2.6  $\mu$ m (Phenomenex SAS, Le Pecq, France). Mobile phase A was composed of ammonium formate buffer (2 mM in 0.2 % formic acid) and deionized water while mobile phase B included ammonium formate buffer (2 mM in 0.2 % formic acid) and acetonitrile.

Chromatographic separation was performed at a column temperature of 50°C and a flow rate of 0.40 mL/min. The injection volume was 10 µL and the run time was 5 minutes. Compounds were detected and quantified by an API 4000 QTRAP mass spectrometer (ABSciex, Les Ulis, France) equipped with an electrospray ionization (ESI) source. Data were collected in multiple-reaction monitoring mode (MRM). Protonated molecular ions [M + H]<sup>+</sup> of baclofen (m/z 214.1) and baclofen-d4 (m/z 218.1) were used and fragmented with different collision energies (**Table 1**). Retention time of baclofen was 1.4 min. Mass spectrometer parameters were as follows: curtain gas: 25 psig, collision gas: 6 psig (medium), ion spray temperature: 500°C; ion spray voltage: 5500 V, ion source gas 1 and ion source 2: 40 and 60 psig, respectively. Hardware control and data acquisition were realized using Analyst Software™ (version 1.6.2).

### ***Validation protocol***

Validation of the baclofen quantification method was based on the Food and Drug Administration (FDA) guidelines for bioanalytical method validation [7]. Briefly, stock solution of baclofen (1,000 ng/mL) and the internal standard baclofen-d4 (100 ng/mL) were prepared in deionized water. Standards and internal quality controls (QC) were prepared by diluting the stock solution in drug-free plasma. For the validation purpose, three QC levels were evaluated: low (20 ng/mL), medium (400 ng/mL), and high (1500 ng/mL). Validation consisted of the evaluation of: limit of detection (LOD), lower limit of quantification (LLOQ), linearity, between run and within run reproducibility, matrix effect, and stability of samples.

## ***Review of the literature***

An English exhaustive literature search was performed using several different electronic databases: PubMed, Scopus, Web of Science and Google Scholar, without any limiting period. The search was carried out using the terms: “baclofen”, “overdose”, “poisoning”, “abuse”, “misuse”, “adolescent”, “young adults”, combining them in an appropriate manner. The goal was to identify all available scientific articles dealing with baclofen overdose following a recreational use among adolescent and young adults.

## **Results**

The method was linear between 10 and 2,000 ng/mL, with determination coefficients  $r^2 \geq 0.99$ . The calibration curve was linear. The best calibration curve fitting was obtained using a weighting factor of  $1/[\text{concentration}]^2$ . LOD was 3 ng/mL. LLOQ was 10 ng/mL, with an accuracy at 93.8 % and a coefficient of variation (CV) at 4.59 %. The overall precision of the back-calculated standard concentrations was lower than 5%. Based on QC samples, the within-run and between-run precision was lower than 10%. Within-run and between-run accuracies ranged from 93.8 to 99.8%. The assessment of the matrix effect on three QC levels showed a recovery ranging from 96.4 to 105.4 with CV below 10 %. Plasma samples were stable for either three freeze-thaw cycles, up to 6 hours at room temperature storage, or for after a 3 month-storage at  $-20^\circ\text{C}$ . Extracted samples were stable up to 24 hours on the autosampler.

A previously fit and healthy 16-year old boy was admitted to the emergency department with symptoms of confusion and marked agitation. He presented a 48-hour history of vomiting,

headaches, and a diffuse abdominal pain, followed by agitated confusion. Several empty baclofen blisters were found in his room. No one in his family was being treated with this drug. The patient had no history of drug abuse. However, the patient's medical record reported a coma episode, several months earlier, with no identified etiology despite a substantial number of paraclinical investigations. Previous exams included brain computed tomography (CT) scan, brain magnetic resonance imaging (MRI) electroencephalogram, microbiological, metabolic and toxicological investigations, with no specific research for baclofen. Upon arrival, the patient presented with an acute confusional state characterized by inconsistent speech and motor restlessness. The Glasgow Coma Scale was 10/15. He was eupneic. The patient's heart rate was 40 bpm and the blood pressure value 159/85 mmHg. His pupils were of regular width and normally reacting to light. He was normothermic with no skin rashes. The rest of the clinical examination was without any particularities. Laboratory investigations including full blood count, coagulation profile, renal and liver tests, blood glucose level, and blood ammonia level, were all within normal ranges. In addition, plasma and urine were collected in order to perform toxicological analyses, including baclofen detection and quantification.

The initial screening (using LC-DAD and GC-MS) of plasma and urine yielded negative results. Blood and urine alcohol concentrations were < 0.10 g/L. Baclofen was detected in plasma and urine, at 420 ng/mL and 64 900 ng/mL respectively.

The review of literature showed that five publications describing baclofen overdoses following a recreational use among adolescents and young adults have been published between 1983 and 2010 [8-12]. These articles reported an overall of 19 cases, all involving a

non-fatal overdose. The patients' characteristics and circumstances are summarized in **Table 2** [8-12].

## **Discussion**

Despite an increase in psychotropic drug abuse, witnessed in the past decades, the real number of cases might even be higher, especially for baclofen. The unspecificity of abuse-related symptoms and physical signs, but above all, the fact that baclofen is not systematically investigated in most of toxicological laboratories can render the establishment of a diagnosis difficult. In that sense, this case study perfectly illustrates such difficulties because, without any contextual information, baclofen research would not have been conducted and the baclofen overdose would not have been identified. In fact, although the measured plasma concentration - 420 ng/mL - was close to the therapeutic range reported for spasticity treatment (80-400 ng/mL) [13], it appeared in agreement with other overdose cases reported in the literature [9;11]. Furthermore, taking into account pharmacokinetic parameters of this substance, it can be reasonably hypothesized that the baclofen concentration was higher in the hours preceding sampling. Indeed, peak plasma concentrations occur less than 2 hours after oral administration with a plasma half-life ranging from 2 to 4 hours. In overdose cases, though, the drug half-life can reach 34.6 hours because of renal elimination saturation [14-15]. Moreover, the young patient was not chronically treated with baclofen and was thus likely more sensitive to its effects, especially toxic effects. After symptomatic management, the patient considerably improved and was finally discharged to an adolescent psychiatric unit for more appropriate care. Psychiatric assessment reported that the adolescent recreationally used baclofen. It was not the first episode and so, the coma reported in the medical chart was most likely related to one of these baclofen abuse sessions. In this context, segmental hair

analysis could have provided a map of baclofen exposure over time and so, achieved evidence of a baclofen abuse/misuse in the past. Unfortunately, no hair specimen had been collected due to patient refusal. At usual therapeutic doses, baclofen ( $\beta$ -(4-chlorophenyl)- $\gamma$ -aminobutyric acid) is a specific agonist of central (and peripheral) gamma-amino-butyric acid (GABA) type B receptors, which has been used for many years in the treatment of muscle spasticity associated with multiple sclerosis and other diseases of medullary or central origin. Following Ameisen's works on the high-dose baclofen use in the treatment of alcohol dependence, baclofen prescriptions have increased in France with this indication [16-19]. In this context, the action of baclofen would rely on the combination of several complementary effects, including an anti-craving effect and an anxiolytic effect.

Side effects associated with baclofen use are numerous and nonspecific. They are characterized by a huge variability both in their frequency of occurrence and in their clinical presentation (ranging from metabolic disorders to central nervous system troubles). They most often occur at the beginning of the treatment because of a too rapid increase in the dosage or the use of very high doses. These effects remain transient and can be partially or totally suppressed by reducing the dosage. They only rarely lead to a termination of the treatment [20]. The widespread and increasing use of baclofen in France has entailed reports on baclofen overdose. However, signs of toxicity resulting from the administration of various doses remain poorly documented. In fact, few studies have succeeded to highlight a correlation between levels of exposure and clinical manifestations [21;22]. The clinical features appear various and unspecific, ranging from coma to manic or hypomanic symptoms [21;22]. Some authors propose to classify clinical presentations of baclofen overdose into two states: one associated with signs of CNS depression (convulsion, coma or respiratory depression), which occurs preferentially during acute intoxication, and another presentation,

conversely associated with signs of CNS excitation (like hallucinogenic and euphoriant effects or manic symptoms), which occurs rather during chronic intoxication. However, in clinical practice, these two presentations are often entangled. In fact, depending on the presynaptic or postsynaptic location of the GABA receptor, baclofen-induced hyperpolarization may induce either an excitatory effect or an inhibitory effect. This duality, explains, at high doses, the coexistence of signs of CNS excitation and CNS depression. In all cases, the severity of baclofen poisoning is increased when it is associated with other substances which exhibit CNS activity (such as benzodiazepines or alcohol) [22].

Baclofen poisoning cases are not only observed in patients under treatment. Baclofen overdose can result from accidental ingestion and is also encountered in healthy individuals who may ingest baclofen for recreational purpose. In fact, baclofen is promoted as a “fun drug” through the Internet [8] and its abuse/misuse potential has been reported [23;24], especially among adolescents and young adults. As reviewed here, several baclofen overdoses following a recreational use have been described. The patients’ mean age was 17 year’s old (14 - 23 years) [8;10-12]. A male predominance emerged with a sex ratio of 2.5 [8;10-12]. Baclofen ingested doses ranged from 60 to 2,250 mg and, except for one case; there was no previous reported history of baclofen abuse and/or baclofen overdose. In one case, a 17-years-old girl had presented 5 episodes of severe alteration of consciousness, which were initially misdiagnosed as conversion disorder. This case was also the only one where baclofen was regularly prescribed, in order to treat a severe hemidystonia of unknown origin, [12]. In other cases, the substance appeared to be diverted. At the emergency department, the reported clinical manifestations were unspecific and included both cardiovascular and neurological signs including bradycardia, hypertension, hypothermia, hyporeflexia, and coma [8-12]. Furthermore, digestive symptoms, including nausea and vomiting, were also reported, in 3 cases, in the hours or even days preceding the admission [10-12]. Of the 19 cases, 15 have

been hospitalized for monitoring and symptomatic management and the duration of hospital stay ranged from 2 days to 14 days [8-12]. Invasive supportive cares with intubation and mechanical ventilation was required in 11 cases [8-12]. Baclofen plasma concentrations were reported in 10 cases [9;11;12]. These concentrations were variable, ranging from less than 20 ng/mL to 1322 ng/mL [9;11;12]. In all cases, the evolution was favorable and the patients were finally discharged without any complications. To the author's knowledge, a baclofen fatal poisoning in a recreational context among adolescents and young adults has never been reported.

Effects of high dose intake are described to be similar to those observed with other GABA agonists such as gabapentin, pregabalin or *gamma*-hydroxybutyric acid (GHB) [10;25], and thus raise concerns not only in clinical toxicology but also in forensic toxicology, where such properties could be diverted for criminal purposes such as drug facilitated sexual assault.

In agreement with previously reported cases, the case study highlights the heterogeneity and unspecificity of baclofen overdose symptoms and physical signs that can appear among adolescent and young adults. As a consequence, baclofen abuse diagnosis may be particularly complicated in this population. It is essential to emphasize the importance of the discussion between physicians and toxicologists in the diagnosis of baclofen overdose, especially among young patients, in a recreational context. In fact, since baclofen is a highly polar amphoteric compound, it is relatively difficult to extract it efficiently from biological specimen without specific optimized extraction procedures, which are time consuming and/or expensive [26]. Consequently, baclofen detection can hardly be optimized during routine screening methods development and implementation in hospital toxicology laboratories. In the case reported here, at the first admission, only routine toxicological analyzes had been carried out, and baclofen was not specifically researched, probably leading the physician to misdiagnose a

baclofen overdose. Facing such issues, it appears of great importance that toxicological laboratories adapt their routine toxicological screening methods in order to routinely detect the widest range of substance, including psychotropic drugs with potential of abuse.

## **Conclusion**

The widespread abuse of psychotropic drugs by teenagers and young adults is a significant issue that should be considered by healthcare professionals. Baclofen intoxication remains fairly uncommon among such drugs, most likely due to confounding factors such as the non-specificity of symptoms and the lack of systematic identification in routine toxicology screening. From the author's point of view, baclofen testing in clinical situations of CNS excitation or CNS depression should be more systematic for young adults, even more today, at a time where the availability of psychotropic substances is being facilitated, especially through the internet, contributing to their widespread.

## **Compliance with ethical standards**

***Conflict of interest*** There are no financial, or other, relations that could lead to a conflict of interest.

***Ethical approval*** This article does not contain any studies with human participants or animals that were performed by any of the authors.

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**Table captions:**

Table.1: MRM transitions used for baclofen and baclofen-d4

Table.2: Baclofen overdose following recreational use in adolescents and young adults

Table 1 MRM transitions used for baclofen and baclofen-d4

| Compound           | Parent | Products | Declustering Potential (DP) | Entrance Potential (EP) | Collision Energy (CE) | Collision Cell Exit Potential (CXP) |
|--------------------|--------|----------|-----------------------------|-------------------------|-----------------------|-------------------------------------|
| <b>Baclofen</b>    | 214.1  | 116.1    | 46                          | 10                      | 47                    | 20                                  |
|                    |        | 151.0    | 46                          | 10                      | 23                    | 26                                  |
| <b>Baclofen-d4</b> | 218.1  | 154.0    | 46                          | 10                      | 25                    | 12                                  |

Table 2 Baclofen poisoning following recreational misuse in adolescents and young adults

|                               | Number of patients | Patient's age (year)     | Gender               | Baclofen ingested dose (mg) | Baclofen plasma concentrations (ng/mL) |
|-------------------------------|--------------------|--------------------------|----------------------|-----------------------------|--|
| <b>May et al. (1983)</b>      | 4                  | 23 and <i>n/a</i>        | 1 female and 3 males | 900-1,250                   |  |
| <b>Perry et al. (1998)</b>    | 12                 | <i>n/a</i> (adolescents) | <i>n/a</i>           | 60-600                      | <20 - 850                              |
| <b>McDonald et al. (2001)</b> | 1                  | 14                       | male                 | 500                         |  |
| <b>Weißharr et al. (2012)</b> | 1                  | 15                       | male                 | 2,250                       | 320                                    |
| <b>Masi et al. (2013)</b>     | 1                  | 17                       | female               | 625                         | 1322                                   |
| <b>Case study</b>             | 1                  | 16                       | male                 | unknown                     | 420                                    |

*n/a* information not available in publication