Review

A Review of Baclofen Overdoses in Australia: Calls to a Poisons Information Centre and a Case Series

Nazila Jamshidi1,*, Kirsten C. Morley2, Rose Cairns3, Andrew Dawson1,3,4, and Paul S. Haber1,2,4

1Drug Health Services, Royal Prince Alfred Hospital, NSW 2050, Australia, 2School of Medicine, NHMRC Centre of Research Excellence in Mental Health and Substance Use, Central Clinical School, Sydney Medical School, University of Sydney, NSW 2050, Australia, 3NSW Poisons Information Centre, The Children's Hospital at Westmead, Sydney 2145, Australia, and 4Central Clinical School, Royal Prince Alfred Hospital, University of Sydney, Sydney

*Corresponding author: Dr Nazila Jamshidi. Tel: +02 9515 7754; Fax: +02 9515 5779; E-mail: Nazila.jamshidi@health.nsw.gov.au

Received 3 April 2018; Revised 22 October 2018; Editorial Decision 28 October 2018; Accepted 29 October 2018

Abstract

Aim: to describe trends in baclofen reports to Australia’s largest Poisons Information Centre (PIC) and present a case series detailing severity of overdoses.

Short summary: PBS data demonstrates baclofen use is increasing in Australia, while calls to NSWPIC illustrate an increase in number of exposures associated with toxicity. Baclofen toxicity may require prolonged intensive care admission. To minimize harms associated, especially with off-label baclofen prescribing for AUD, prescribers should pay careful attention to psychiatric comorbidities, and closely monitor treatment and dispensing.

Methods: this is a retrospective observational study of baclofen overdoses reported to New South Wales PIC (NSWPIC) from January 1 2004 to 31 December 2016. In addition, referrals to a metropolitan toxicology service relating to baclofen toxicity from 2014 to 2017 were analysed. The number of Pharmaceutical Beneﬁt Scheme (PBS) claims for baclofen were also reviewed.

Results: during the 13-year study period, 403 cases of baclofen toxicity were reported to NSWPIC. There was a 230% increase in annual exposures over this period, 71% of patients were symptomatric, with 77% requiring hospitalization. Coingestants were reported in 53%, with 57% being psychoactive medications (including alcohol). An increase in number of baclofen dispensing episodes was also noted. From the five cases of deliberate self-harm reported to the metropolitan toxicology service, three obtained baclofen for management of alcohol use disorder (AUD) and required prolonged treatment in the intensive care unit (ICU).

Conclusions: NSWPIC data shows an increase in number of calls regarding intentional baclofen exposures in parallel with increase the number of baclofen PBS claims. These closely parallel the increase in dispensing of baclofen since 2008. Case studies presented reinforce the severity of baclofen toxicity. Together, they demonstrate the potential risk of harm of baclofen prescribing, and the greater need for caution. Baclofen should be considered carefully in patients high risk of overdose or be used only in specialist services with close monitoring.
INTRODUCTION

The gamma-aminobutyric acid (GABA)-B receptor agonist, baclofen, is a muscle relaxant introduced in the 1960s for the treatment of muscle spasticity due to multiple sclerosis, spinal cord and cerebral injury (Dario and Tomei, 2004). For these indications typical doses can range from 5 to 70 mg/day, and may be titrated up to 150 mg/day (Boels et al., 2017). There has been a recent widespread increase in the use of baclofen in the treatment of alcohol disorder (AUD; Chaignot et al., 2015; Agabio et al., 2018). The efficacy of baclofen in reducing alcohol consumption appears to relate to its agonist effect at the GABA-B receptor which is located within several brain regions including the mesolimbic reward system (Colombo et al., 2004).

While results of randomized controlled trials (RTCs) have been mixed (e.g. Addolorato et al., 2007; Morley et al., 2014; Morley et al., 2018) a recent meta-analysis reported evidence of efficacy at low doses (30–60 mg) for achieving abstinence especially amongst heavy drinkers (Pierce et al., 2018). There has been a growing rate of off-label baclofen prescriptions in Europe, particularly in France (Rolland et al., 2012; Chaignot et al., 2015). High dose baclofen prescribing is supported by a German RCT (Müller et al., 2015), and has been both widely promoted and conditionally approved for the treatment of AUD in France (Rolland et al., 2016). Most clinical trials report a high tolerability of baclofen (Pierce et al., 2018).

Despite this, a number of serious adverse events have been reported in patients treated with baclofen using doses less than 270 mg (Leung et al., 2006; Auffret et al., 2017). Doses greater than 270 mg have been associated with harm and can result in severe toxicity including neurotoxicity (coma, seizures, respiratory depression, and delirium) and cardiovascular complications (lengthening of QT interval and autonomic instability). Baclofen intoxication may require intensive care support and prolonged mechanical ventilation (Leung et al., 2006). To date only a few cases of death caused by baclofen alone (Haujenstock et al., 1983; Fraser et al., 1991) or with coingestants (De Giovanni and d’Aloja, 2001) have been published. However, the latest (2016) poisons centre data from North America reports baclofen as the primary cause of death in six cases and a contributing factor in at least 10 others (Gammill et al., 2017).

In the light of potential toxicity of high dose baclofen, the French government has modified the dose of baclofen approved for AUD in the ‘Temporary Recommendations for Use’ (TRU) to a maximum dose to 80 mg/day (ANSM: Agence nationale de sécurité du médicament et des produits de santé, 2018). Although baclofen is not approved for treatment of AUD in Australia, there is increasing off-label use globally for this indication, which raises concern about potential harms (Thompson et al., 2017). In this study we provide the first report of Australian trends in intentional exposures to baclofen reported to the New South Wales Poisons Information Centre (NSWPIC) over a 13-year period, 2004–2016. These calls are compared with trends into baclofen prescribing based on Pharmaceutical Benefits Scheme (PBS) data. In Australia baclofen is available in 10 mg and 25 mg dosage forms in bottles of 100 tablets. We also describe five cases of baclofen overdose presented to a central toxicology service from 2014 to 2017.

METHOD

Data source

PIC data

The NSWPIC is Australia’s largest Poisons Information Centre (PIC), taking calls from New South Wales (NSW), Tasmania and the Australian Capital Territory (ACT) between 6 am and midnight each day, and, as part of a national after-hours roster, from all Australian states between midnight and 6 am on seven nights each fortnight. The structure of the NSWPIC and its operational hours are further detailed in Cairns et al. (2016). The NSWPIC services a population of 7.92 million. This PIC receives approximately 100,000 calls from the public and health care professionals each year, and accounts for around half of all Australian PIC calls.

This is a retrospective observational study of calls about intentional overdoses with baclofen reported to the NSWPIC from 1 January 2004 to 31 December 2016. The NSWPIC database was searched for ‘intentional’ exposures to baclofen during the study period. Re-calls (where the PIC receives multiple calls about the one patient) were excluded from the exposure count to provide an accurate number of cases. Continuous data were summarized as median and interquartile range (IQR). Since our focus was capturing intentional exposures associated with AUD, paediatric ingestions of accidental or intentional nature were excluded (cases <18 years of age).

Search strategy and inclusion criteria:

The NSWPIC database was searched for the exposures coded as ‘baclofen’ and only cases coded as ‘intentional’ (including deliberate self-poisoning, intentional: other and recreational codes) were included. Characteristics including age, sex, coingestants, symptom disposition and treatment recommendation were extracted. The presence of symptoms (at the time of the call) was coded in real-time as ‘related’ or ‘unrelated’ by the poisons information specialist who took the call. Coingestants were re-coded retrospectively into individual groups of psychotropic medications (i.e. antidepressants, benzodiazepines and antipsychotics), opioids (prescription and illicit) and alcohol. All non-psychoactive medications, except antiepileptics were classified as ‘other’ (see Supplementary data 1 for full list and grouping) such as antihypertensives medications and simple analgesics. Management recommendations by the PIC (such as remain in hospital was re-coded to remain in medical care, and attend a hospital or family physician as refer to medical care) were re-coded by the authors based on ongoing management into three groups: referred to medical care, remain in medical care or no further action. Where no treatment was recorded in PIC database, this was re-coded as unknown.

Those exposures classified as having related-symptoms where the further analysed by each record being manually reviewed for syndromic clinical features associated with baclofen toxicity as per previous publications (Leung et al., 2006).

Hospital cases

Cases referred to a metropolitan toxicology service from 2014 to 2017 were collected by the hospital toxicology registrar and reviewed by an Addiction/Toxicology specialist. Cases of baclofen overdose were identified. The personal data of patients were anonymized. Patient files or computer records were further reviewed to confirm the diagnosis, length of stay (LOS) and the dose of baclofen ingested. Baclofen blood levels were not available for any of the cases reported here.

PBS data

The Pharmaceutical Benefits Scheme data system contains records of all medicine dispensing that are subsidized by the Government under the Pharmaceutical Benefits Scheme (PBS) and is available on the public domain (http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp). Data on item numbers pertaining to baclofen
(Codes 2730Q and 2729P) from January 2004 to December 2016 was extracted by year and as the national total.

Ethics
Ethics approval was obtained from the Human Research Ethics Committee of the Sydney Children’s Hospitals Network (approval number LNR/-16/SCHN/44) and Royal Prince Alfred Hospital (approval number X-17–0445).

Results
NSWPIC handled 403 cases of intentional baclofen poisoning, 2004–2016.

Calls stratified by year
Trends in baclofen overdose with time (Fig. 1: Dotted line) show a 3.5-fold increase in exposures from 2008 (14 calls) to 2010 (50 calls). The number baclofen exposures reported to PIC continue to rise steadily after 2011.

PBS data
There was a 32% increase in the total number of PBS dispensings for baclofen from 2004 to 2016 (Fig. 1: solid line).

Demographic data
Patient demographic data is displayed in Table 1. Exact age was known for 189 patients and ranged from 18 to 88 years, median of 35 years. The majority were female (47%), and no gender was recorded for 6% of the calls.

Symptoms
Patients were symptomatic in the majority (71%) of calls, with only 5% having unrelated symptoms. 19% of calls were associated with asymptomatic patients and 5% were unknown.

From the symptomatic cases, drowsiness (43%) and reduced GCS < 9 (35%), were the most common clinical features. A further 19% of total symptomatic cases required ventilation at the time of call to PIC (Table 2).

Management paradigms
About 77% of the calls received were with regards to individuals in medical care, i.e. either with a general practitioner or were inpatients in a hospital setting. About 20% of all calls where referred to medical care, which was either primary care or hospital setting. Only 2% of individuals required no further medical intervention.

Coingested substances
Of the 403 calls, 189 individuals had no recorded coingestants (47%), and 214 individuals had 1 or more coingestants (53%). ‘Other’ or non-psychoactive medications made up 32% of coingestants. Of the psychoactive medications benzodiazapines were the most commonly coingested (19%), followed by antidepressants (17%) and alcohol and opioids at 12% and 13%, respectively.

Case studies
Review of cases admitted from January 2014 to December 2017 to a metropolitan hospital with intentional baclofen overdose revealed five presentations (Table 3). Of the five patients, three patients were using baclofen for AUD and two for spasticity. Blood alcohol levels were preformed on all these patients and were zero in all cases. Four of five patients required intubation, but all required prolonged ICU admission and supportive care. One case (Case 2) developed baclofen withdrawal syndrome after 3 days and was restarted on low dose baclofen. None of the cases required renal replacement therapy.

DISCUSSION
The NSWPIC in Australia has seen a 3.5-fold increase in the number of calls regarding baclofen overdose in the past 13 years. The majority of the calls to PIC (77%) were associated with symptomatic individuals requiring medical care (71%). Of the exposures that had baclofen related-symptoms, drowsiness and a reduced conscious state (GCS < 9) where the most common initial presentations. Further, 63% of these had taken at least one coingestant, in keeping with previous studies (Leung et al., 2006; Léger et al., 2017). The increase in number of calls and the frequency of presenting symptoms suggests an increase in the rate of harm associated with baclofen use. These findings are in keeping with the trends noted by Pelisseri et al. (2017) and Leung et al. (2006) and others (Franchitto et al., 2014; Kiel et al., 2015) who reported patients with baclofen overdose may require close monitoring and the involvement of intensive care units with ventilator support.

The breakdown of coingestants associated with baclofen overdoses based on drug class demonstrated a high prevalence of coingestion of antidepressants (17%) and alcohol (12%). Further, psychoactive medications made up 58% of all coingestants. In addition, the PBS prescription data shows an increased trend in baclofen prescribing over the past 13 years, despite an unlikely rise in the annual incidence of spasticity (most common indication for prescribed baclofen (Froestl and Enna, 2007)) or a change in prevalence of AUD in Australia (3.9%) (Teesson et al., 2010). Although this study does not have information on indication of baclofen prescribing for PIC calls, together, the increase in number of calls and increase in prescribing trends are suggestive a potential new indication for this medication, such as AUD. The rate of increase in calls cannot simply be attributed to the relative increase population size or an incidence of AUD in Australia. This is evident from the constant rate of prescribing of other AUD pharmacotherapies including naltrexone and acamprosate over this time period (Morley et al., 2016).
Kiel demonstrated that baclofen hypertension as a systolic BP number of patients with hypotension 13 (5%) hypertensive 17 (7%) tachycardia 26 (10%) delirium 19 (8%) ventilation 47 (19%) ICU admission 23 (9%) GCS ≥ GCS 9 87 (35%) GCS 10–13 38 (15%) GCS ≥ 14 (Drowsy) 109 (43%) ICU admission 23 (9%) ventilation 47 (19%) seizures 8 (3%) delirium 19 (8%) bradycardia 16 (6%) tachycardia 26 (10%) hypertension 17 (7%) hypotension 13 (5%) abnormal reflexes 5 (2%) number of patients with >1 coingestants 159 (63%) number of patients with alcohol as a coingestant 39 (15%).

Hypotension was defined as a systolic blood pressure (BP) < 90 mmHg, hypertension as a systolic BP > 140 mmHg. Bradycardia was defined as a heart rate (HR) < 60 bpm and tachycardia as a HR > 100 bpm.

AUD is often associated with intoxication, psychiatric disorders, with increased impulsivity (Léger et al., 2017) and greater rates of depressive episodes (Regier et al., 1990). Further, suicidal attempts are also more prevalent in people with substance use disorders than in the general population (Grant et al., 2004). Additionally, given that it has been suggested that baclofen increases impulsivity (Lee et al., 2011), in patients with poor impulse control such as those with borderline personality disorder, the use of baclofen for alcohol dependence needs specialist input. This is further supported by the study by Rolland et al. who demonstrated a higher rate of self-poisoning in those with comorbid borderline personality disorder and AUD (Rolland et al., 2015). Therefore, particular care should be taken when selecting patients for treatment of AUD with baclofen. This includes taking an extensive psychiatric history and ensuring that baclofen is used in a limited, safe and in an evidence-based manner.

There are some limitations to this study worth noting. Firstly the numbers of calls identified from PIC data do not represent all baclofen overdose cases, as not all exposure results in a call to PIC, and hospitals with local toxicology services are unlikely to call PIC for advice. Therefore, these call numbers are expected to underestimate the true frequency of baclofen overdose/misuse. PIC calls are biased towards more severe cases of overdose. This is correspondingly reflected in the high number of patients in medical care reported here. Further we only investigated intentional overdoses, not adverse reactions or therapeutic errors, and thus we do not report on complications associated with baclofen at lower or therapeutic doses. Additionally, the PIC data does not delineate calls associated with baclofen overdose prescribed for AUD specifically. Although symptoms are recorded in the PIC database, they reflect cross-sectional information. Recorded exposure cases may have progressed to require intubation, but follow-up data is not available. Further, given 63% of symptomatic patients had a coingestant on board; recorded symptoms may not all necessarily have been attributable to baclofen. The PBS data obtained also has major limitations, despite showing an increase of 32% in the number of baclofen prescriptions from 2004 to 2016. The data may not reflect the true baclofen prescribing patterns, given that PBS data does not capture private prescribing of baclofen. In both PIC and PBS datasets the exact number of patients treated for AUD with baclofen and those with psychiatric comorbidities cannot be obtained.

Baclofen dependence, tolerance and a withdrawal have been reported in the literature (Dore et al., 2011). Tolerance can complicate response to baclofen and make dose-response predictions unreliable. As a consequence, toxicity can be observed across a wide dose range (Table 3). Kiel et al. (2015) demonstrated that baclofen in the presence of coingestants such as alcohol and other CNS depressants demonstrate a greater level of CNS depression, making a dose-response relationship difficult to interpret. Abrupt cessation can present as a withdrawal delirium that responds to reinstatement or gradual tapering over several weeks (Dore et al., 2011). The authors also have experience in the management of a number of cases of baclofen withdrawal (e.g. Case 2, Table 2).

Further, we here, and others (Franchitto et al., 2014; Kiel et al., 2015) have demonstrated that ingestion of large amounts of baclofen in an attempt to self-harm can be associated with increased morbidity (see Table 2). In overdose baclofen can cause seizures including non-convulsive status, prolonged coma requiring intubation and intensive care admission, and can mimic brain death (Dore et al., 2011). These have all been increasingly reported in the literature as a consequence of unsupervised treatment in high risk patients with alcohol dependence (Léger et al., 2017).

**CONCLUSIONS**

Reports of toxicity relating to baclofen are increasing in Australia and include severe poisonings, requiring prolonged intensive care. In
order to minimize these harms, off-label prescribing of baclofen for AUD requires appropriately skilled practitioners (i.e. Addiction medicine and Psychiatry or equivalently expert General Practitioner) with close follow-up of patients started on treatment. Additionally, baclofen should be avoided in those at high risk of overdose such as that of borderline personality disorders or history of self-harm. Rapid dose escalation and sudden discontinuation should be avoided. Prescribers should consider staged/limited supply of medication (given available large pack sizes in Australia). Ongoing pharmacovigilance at the population level will be required to identify toxicity not seen thus far in small clinical trials.

### SUPPLEMENTARY MATERIAL

Supplementary data are available at *Alcohol and Alcoholism* online.

### ACKNOWLEDGEMENTS

The authors would like to thanks Janet Gaon for her assistance in collation of PBS data.

### CONFLICT OF INTEREST STATEMENT

RC is an associate investigator on an untied educational grant from Seqirus Pty Ltd to study tapentadol misuse.

Table 3. Cases of baclofen overdose presented to local hospital from 2014 to 2017

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age (years) and Sex</th>
<th>History and presentation</th>
<th>Coingestants</th>
<th>Indication/Dose</th>
<th>Management</th>
<th>Length of Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40 Female</td>
<td>History of Alcohol dependence, Depression, anxiety, Borderline Personality disorder. Found unconscious by partner with suicide note and Bottle of baclofen. GCS8, unconscious. Myoclonic Jerks. BP 103/56, HR 56.</td>
<td>None</td>
<td>AUD/ unknown</td>
<td>Supportive care: intubation/ ICU admission. Psychiatry review</td>
<td>4 days</td>
</tr>
<tr>
<td>2</td>
<td>43 Male</td>
<td>History of Alcohol dependence, polysubstance abuse. Brought by ambulance after being found with reduced GCS 11 at accommodation. Reflexes were absent.</td>
<td>Cannabis</td>
<td>AUD/ 325 mg</td>
<td>Required ICU admission and initial intubation. Woke after 3 days, but was delirious for ~ 24 hrs. Delirium responded to low dose baclofen. When recovered reported that he had taken 13 × 25 mg baclofen as a suicide attempt. Care was transferred to psychiatry after recovery</td>
<td>10 days</td>
</tr>
<tr>
<td>3</td>
<td>34 Male</td>
<td>History of IVDU, polysubstance abuse, alcohol dependence and psychiatric illness. Recurrent baclofen overdoses (three in 2017). Found unconscious on kitchen floor and brought to ED. Intentional baclofen overdose. Became drowsy, hypotensive and bradycardic.</td>
<td>None</td>
<td>Orolingual dystonia (failed previous treatments)/360 mg</td>
<td>Required ICU admission, Required Fluid resuscitation and continuous ECG monitoring with supportive care in the ICU.</td>
<td>6 days</td>
</tr>
<tr>
<td>4</td>
<td>44 Female</td>
<td>History of alcohol dependence. Witnessed overdose of 800 mg baclofen. Had out of hospital seizure. On presentation to hospital had GCS 3, requiring intubation</td>
<td>None</td>
<td>AUD/800 mg</td>
<td>Required ICU admission and supportive care. When extubated had an agitated delirium which responded to diazepam</td>
<td>7 days</td>
</tr>
<tr>
<td>5</td>
<td>59 Male</td>
<td>History of MVA with C4–C6 incomplete quadriplegia. Found with reduced GCS, slumped over on chair. Fluctuating GCS 3, pin-point pupils. Bradycardic with paroxysmal atrial flutter and first degree heart block. Given 1.2 mg naloxone with no improvement</td>
<td>Urine Drug Screen positive for opiates (unspecified)</td>
<td>Spasticity secondary to traumatic spinal cord injury/125 mg</td>
<td>Intubated and admitted to ICU. Hypokalaemia corrected with oral and IV replacement. Glycopyrronium for bradycardia. Discharge home with ongoing community support services as pre-existing. When recovered reported that he had taken 5 × 25 mg baclofen to self-manage pain</td>
<td>4 days</td>
</tr>
</tbody>
</table>

AUD, Alcohol use disorder; GCS, Glasgow Coma Scale; ICU, intensive care unit; IVDU, Intravenous drug use; ECG, Electrocardiogram; Bp, blood pressure; HR, heart rate; MVA, motor vehicle accident.
REFERENCES


