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Baclofen overdose: Defining the spectrum of toxicity

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Abstract

Objectives: To describe the spectrum of toxicity of baclofen in overdose, and investigate dose-related clinical effects.

Methods: Consecutive baclofen overdoses were identified from a prospective database of all poisoning admissions presenting to a regional toxicology service. Ingestion was corroborated on more than one occasion and from multiple sources. Demographic, clinical and outcome variables were extracted for each presentation for a retrospective review, and the data sets were divided into high dose (≥200 mg) and low dose (<200 mg) groups for comparison of clinical effects.

Results: There were 23 presentations, of which eight patients ingested baclofen alone. Seizures were reported in four cases, a decreased level of consciousness (GCS < 9) occurred in eight patients and delirium was recorded in eight patients. Five patients had miosis and seven patients had dilated pupils, 13 patients had absent or depressed reflexes. The only arrhythmias were sinus bradycardia in six patients and sinus tachycardia in five. Hypertension occurred in 13 patients and hypotension in one. The reported total ingested dose of baclofen was known in 19 patients (Mean 630 mg, SD 730 mg; 80–2500 mg). A higher ICU admission rate, rate of mechanical ventilation and prolonged length of stay occurred in those ingesting 200 mg or more. Coma, delirium and seizures occurred only with doses of 200 mg or more, and hypertension was more common with higher doses.

Conclusions: Baclofen overdose causes mainly neurological effects and excepting hypertension cardiovascular effects were uncommon. Doses greater than 200 mg were predictive of patients developing delirium, coma and seizures, requiring long hospital admissions and ICU admission.

Key words: *baclofen*, *overdose and $GABA_B$ receptor*, *poisoning*, *toxicity*.

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Introduction

Baclofen is a synthetic derivative of the naturally occurring inhibitory neurotransmitter γ-aminobutyric acid (GABA).[1] It is a lipophilic drug that readily penetrates the blood–brain barrier and although its precise mechanism of action has yet to be elucidated, it appears that baclofen acts principally on the $GABA_B$ receptor at the spinal level in therapeutic doses. Baclofen has been widely used in multiple sclerosis, and other spinal lesions that cause skeletal hypertonus and spasticity.

The pharmacokinetics of baclofen are well established. It is rapidly and completely absorbed from the gastrointestinal tract with peak serum concentrations achieved in 2 h.[2] About 15% of baclofen is metabolized by the liver and its mean plasma elimination half-life is 3.5 h.[1]

Respiratory depression, seizures, arrhythmias and coma have been commonly reported in overdose[3–5] and the literature suggests that baclofen overdose is potentially fatal. However, in two reported overdose fatalities, the cause of death was unclear and a direct link between the observed effects and the resultant death was questionable.[4,6] Chapple *et al.*[7] reported no paediatric or adolescent deaths in a review of the literature of 18 overdoses from 1966 to 1998. Some authors caution that most patients require ICU admission for ventilation or haemodynamic monitoring.[8]

Reports of oral baclofen overdoses are predominantly single case reports,[2,9–13] with just one report describing a group overdose by 14 adolescents at a single event.[14] The aim of our study was to describe the spectrum of clinical effects in baclofen overdoses and the implications these have for management practices and hospital resources. We propose that the toxic effects of baclofen overdose are broad and dose-related and examine the likelihood that patients will experience adverse events based on the total dose of baclofen ingested.

Methods

This study was a retrospective review of prospectively collected data on poisoning admissions. The database is a quality assurance tool that also facilitates research and its use for retrospective reviews has previously been assessed by the Institutional Ethics Committee as an audit and has been exempted.

The study was carried out at a regional toxicology unit that is a tertiary referral centre for a population of 500 000. All patients presenting with poisoning to emergency departments in the region are either admitted to the unit or notified to the unit. Detailed predefined data on all presentations are prospectively entered into a Microsoft Access database. A preformatted admission sheet is used by medical staff to collect data on all poisoning admissions. Clinical and demographic information is entered prospectively (within a week of admission) into the database by two trained data entry technicians blinded to any study hypotheses. A trained and blinded computer technician extracts specific data from the database using data fields predefined by the investigators. The emergency department information system is searched by the data entry technicians every 6 months to ensure no cases are missed which is further supported by weekly quality assurance meetings.

We reviewed all overdoses from the database that included baclofen between April 1992 and May 2003. All patients had the history of baclofen ingestion confirmed on at least two occasions and confirmation by history from ambulance officers, family, friends and empty drug containers. The following descriptive data were extracted from the database: patient demographics (age, sex), details of the overdose (estimated dose, coingestants) and clinical effects (GCS, seizures, delirium, BP, heart rate [HR], arrhythmias, pupillary reaction [sluggish/absent *vs* brisk], pupillary size [constricted/normal/dilated] and limb reflexes), treatment (decontamination, ventilation and ICU admission) and length of stay (LOS).

The data set was initially categorized into high (≥400 mg) and low (<400 mg) dose groups to assist in differentiating between high and low risk patients. The 400 mg dose was decided *a priori* and based on anecdotal evidence describing more severe toxicity at doses of 450 mg or more.[2,3,12,15,16] However, an initial inspection of the data demonstrated that more severe effects occurred with doses of 200 mg or more and this was used in the final analysis. The ordinal GCS scale was converted to a dichotomous variable using a GCS of 9 as the cut-off because it is the standard indicator used to determine the need for airway protection. For measures of GCS, HR and BP, the minimum (coma, bradycardia, hypotension) or maximum (tachycardia and hypertension) recorded on arrival and where available at regular intervals during the admission, were used for the analysis. Descriptive data were quoted as means and standard deviations (SD), or medians and interquartile ranges (IQR) for non-parametric data. Confidence intervals (95%) were calculated with StatMate (Version 1.01 July 1, 1996).

Results

There were 23 presentations with baclofen overdose between April 1992 and May 2003. The median age of patients was 35 years (IQR: 32–45 years; range 13–63 years) and 13 were women. Baclofen alone was ingested in eight cases, ethanol, benzodiazepines or both were coingested in 12 cases and other coingestants were reported in three cases (Table 1).

Seizures occurred in four cases, three of which were baclofen-only ingestions. Ten patients had a decreased level of consciousness (GCS < 9). Two further patients with no recorded GCS were intubated, so we assume they had a GCS < 9. Delirium was recorded in eight patients. Eight patients had depressed limb reflexes and five had absent reflexes (four had no reflexes recorded). Five patients had miosis and seven patients had dilated pupils. Pupillary reflexes were reported as sluggish in nine patients and absent in two patients.

Sixteen patients were admitted to ICU and 11 patients required intubation and ventilation for 2–105 h (Median 32 h). Decontamination is reported in Table 1. Benzodiazepines were used in three patients, two of whom had delirium post extubation, and one who had been documented as having had a seizure. There were no deaths.

The reported dose of baclofen was available in 19 cases, with doses ranging from 80 to 2500 mg (Mean 630 mg, SD 730 mg). The frequency of the major clinical effects and disposition determinants are summarized in Table 2 for the low (<200 mg) and high (≥200 mg) dose groups. Delirium, seizures or coma did not occur in patients with doses less than 200 mg and those ingesting 200 mg or more where far more likely to be admitted to ICU, require intubation and had longer LOS. Hypertension was considerably more common in the higher dose group. Tachycardia was slightly more common in larger doses, but bradycardia and hypotension were

Table 1. Description of the 23 baclofen overdoses including all coingestants, clinical effects, ICU admission (including ventilation or not) and decontamination

Sex/age (years)	Dose (mg)	Coingestants	Clinical effects	ICU	Decontamination
M/37	80	Paracetamol, codeine	GCS 10	Ventilated*	Lavage and charcoal
M/35	100	Temazepam, naproxen (5 g)	Tachycardia	No	Charcoal
F/28	100		Minor	No	Charcoal
F/31	100		Bradycardia	Admitted	Nil
F/32	100	Alcohol, amphetamines	Hypertension	No	Charcoal
F/38	150		Minor	No	Nil
F/41	200		Seizure, coma, hypertension, tachycardia	Ventilated	Nil
M/48	300	Diclofenac (1.5 g), felodipine (300 mg), paracetamol, cotrimoxazole	Hypertension, tachycardia, hypotension (Systolic = 83 mmHg)	Ventilated	Lavage and charcoal
M/42	350	Diazepam	Delirium, hypertension	No	Charcoal
M/42	375	Clonazepam, alcohol	Hypertension	No	Charcoal
M/33	375	Alcohol	Coma, hypertension, tachycardia	Admitted	Nil
M/33	375	Alcohol	Coma, delirium, hypertension, bradycardia	Admitted	Nil
F/52	750		Seizure, coma, delirium	Ventilated	Charcoal
F/50	800	Alcohol	Seizure, hypertension	Admitted	Nil
F/28	800	Temazepam	Delirium, coma, hypertension, bradycardia, tachycardia	Ventilated	Charcoal
F/28	1000		Seizure, coma, delirium, hypertension,	Ventilated	Lavage and charcoal
F/51	1000	Alcohol	Delirium,	Ventilated	Lavage and charcoal
M/35	2500		Delirium	Admitted	Lavage and charcoal
M/35	2500	Alcohol	Delirium, coma	Ventilated	Charcoal
F/15	?		Coma, bradycardia	Ventilated	Lavage and charcoal
F/50	?	Clonazepam, diazepam	Coma, hypertension, bradycardia	Ventilated	Nil
F/13	?	Metoclopramide (180 mg)	Coma, hypertension, bradycardia	Ventilated	Lavage and charcoal
M/63	?	Diazepam, temazepam, paracetamol/codeine	Hypertension	No	Nil

**Intubated for decontamination (ventilated for 7 h only). F, female; M, male.*

Table 2. Outcome differences between high and low dose groups

	Low dose (Dose < 200 mg [$n = 6$]) n (%)	High dose (Dose > 200 mg [$n = 13$]) n (%)
Minimum GCS < 9	0 (0)	7 (54)
ICU admission	2 (33)	11 (85)
Ventilated	1* (17)	7 (54)
Delirium	0 (0)	8 (62)
Seizures	0 (0)	4 (31)
Bradycardia	1 (17)	2 (15)
Tachycardia†	1 (17)	4 (31)
Hypertension	1 (17)	9 (69)
Hypotension	0 (0)	1 (8)
Abnormal reflexes	6 (100)	10/12 (83‡)
Hospital LOS	21 h (IQR 16–25)	43 h (IQR 30–93)

**One patient in the <200 mg intubated for decontamination (see Table 1); †One patient with bradycardia also developed tachycardia; ‡Limb reflexes not available in one case. Hypotension was defined as a systolic BP < 90 mmHg, hypertension as a systolic BP > 140 mmHg. Bradycardia was defined as an HR < 60 bpm and tachycardia as an HR > 100 bpm. IQR, interquartile range; LOS, length of stay.*

uncommon and did not differ between high and low dose groups. Pupillary size and limb reflexes were similar between dose groups.

Discussion

This study illustrates the spectrum of severity in baclofen overdose and supports previous literature that suggests that most patients with baclofen overdoses recover completely with adequate supportive care. In addition, it provides some information on the dose-related effects, and the likelihood that a patient will require ICU admission or be able to be discharged home from the emergency department. It suggests that baclofen overdoses of 200 mg or more have a significant impact on hospital resources because of a marked prolongation of hospital stay when compared to other overdoses (compared to a median LOS of 17 h and ICU admission in 16% of all overdose patients to the same unit).[17]

One previous study[2] provided a table of reported clinical effects in baclofen overdose: hyporeflexia 100%, coma 100%, respiratory depression 100%, hypotonia 100%, required ventilation 92%, bradycardia 50%, generalized seizures 42%, myoclonic jerking 42%, hypotension 33%, tachycardia 33%, hypertension 25%, cardiac conduction abnormalities 8%. However, these data were collated from eight separate case studies and only a total of 12 patients. These figures provide a skewed impression of the severity of baclofen overdose which differed to our study (Table 2). The majority of clinical effects previously reported were seen with large doses, and overdoses of 200 mg or less (which have not been represented in the literature) were not associated with coma, seizures and requirement for mechanical ventilation. Hyporeflexia, hypotension and bradycardia, were uncommon and did not govern the clinical picture in our series. Hypertension appeared to be more common in patients ingesting 200 mg or more.

Delirium has been rarely reported in baclofen toxicity. One patient developed auditory hallucinations which disappeared following cessation of high dose therapy,[18] and another patient developed prominent perseveration which recovered fully over a short period of time.[19] In our study, 35% of patients had delirium and the total dose ingested was a significant risk factor for this. The possible complication of delirium is important because staff can prioritize the need to provide a safe environment for observing and managing patients who are recovering from larger baclofen overdoses.

Although lavage and activated charcoal were used in a large proportion of patients in this study, it was hard to interpret the efficacy of decontamination. This is because of the variable time of use of decontamination, including the use of lavage and charcoal after patients were intubated for coma. Until there is evidence to suggest otherwise, it is reasonable to consider the early use of activated charcoal in patients with a protected airway,[20] particularly in patients who have ingested 200 mg or more.

In this study doses of baclofen less than 200 mg were not associated with severe effects and it might be possible to discharge these patients from the emergency department after a nominated period of observation. With doses of 200 mg or more patients are more liable to require close monitoring, intubation and ICU admission. The use of the 200 mg as a cut-off in this study was somewhat arbitrary but provides some help in determining patients that are likely to be more severely poisoned.

This study is limited by a relatively small sample size which reflects the potentially serious yet uncommon pattern of baclofen overdoses. As such, some results were limited by the small numbers. Another limitation of our study was that plasma concentrations of baclofen were not obtained and not corroborated with the history of total drug taken. However, all poisoned patients

admitted have the drug of ingestion confirmed by history taking on at least two occasions, and this is confirmed by history from ambulance officers, family and friends as well as evidence of empty drug containers.[21] Quantification of baclofen concentration in plasma would allow correlation between peak plasma concentration and clinical effect, although a more comprehensive analysis including an estimate of dose is required to do this.

Unfortunately, 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. A prospective study would improve the completeness of data collection including the time of onset of clinical features, which is important for determining the length of observation in the ED. Such a study would also improve the neurological examination which was only partially performed in some cases. Multicentre studies will need to be carried out to verify the significance of a number of trends noted in this study.

In summary, studies on baclofen overdoses have described cases of interest where seizures, coma or cardiac abnormalities have been the dominating features. This series challenges some and confirms other current beliefs regarding the effects of baclofen poisoning. There appears to be a dose-related effect whereby overdoses of 200 mg or more are more likely to cause CNS depression or delirium, and require ICU admission and longer hospital admissions.

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Author contributions

NYL had the idea for the study and GKI designed the study; IMW designed the database; Deb Whyte and Toni Nash entered the data into the database and Stuart Allen extracted the data; GKI and NYL were responsible for analysis and interpretation of t he data; GKI and NYL wrote the manuscript and IMW commented on it. GKI is the guarantor.

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Competing interests

Geoff Isbister is a Toxicology Section Editor of *Emergency Medicine Australasia*.

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References

1. Anderson P, Noher H, Swahn CG. Pharmacokinetics in baclofen overdose. *Clin. Toxicol.* 1984; **22**: 11–20.
2. Nugent S, Katz MD, Little TE. Baclofen overdose with cardiac conduction abnormalities: case report and review of the literature. *J. Toxicol. Clin. Toxicol.* 1986; **24**: 321–8.
3. Ghose K, Holmes KM, Matthewson K. Complications of baclofen overdose. *Postgrad. Med. J.* 1980; **56**: 865–7.
4. Haubenstock A, Hruby K, Jager U *et al.* Baclofen (Lioresal) intoxication report of four cases and review of the literature. *Clin. Toxicol.* 1983; **20**: 59–68.
5. Lee TH, Chen SS, Su SL *et al.* Baclofen intoxication: report of four cases and review of the literature. *Clin. Neuropharmacol.* 1992; **15**: 56–63.
6. Fraser AD, Wallace M, Isner AF. Toxicological analysis of a fatal baclofen overdose. *J. Forensic Sci.* 1991; **36**: 1596–602.
7. Chapple D, Johnson D, Connors R. Baclofen overdose in two siblings. *Pediatr. Emerg. Care* 2001; **17**: 110–12.
8. Ellenhorn MJ. *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. 2nd edn. Baltimore: Williams and Wilkins, 1997.
9. Ostermann ME, Young B, Sibbald WJ *et al.* Coma mimicking brain death following baclofen overdose. *Intensive Care Med.* 2000; **26**: 1144–6.
10. Paulson GW. Overdose of Lioresal. *Neurology* 1976; **26**: 1105–6.
11. VanDierendonk DR, Dire DJ. Baclofen and ethanol ingestion: a case report. *J. Emerg. Med.* 1999; **17**: 989–93.
12. McDonald NJ, Festa MS, Wilkins B. Teenage coma. *J. Paediatr. Child Health* 2001; **37**: 395–6.
13. Lipscomb DJ, Meredith TJ. Baclofen overdose. *Postgrad. Med. J.* 1980; **56**: 108–9.
14. Perry HE, Wright RO, Shannon MW *et al.* Baclofen overdose: drug experimentation in a group of adolescents. *Pediatrics* 1998; **101**: 1045–8.
15. Chern TL, Kwan A. Flumazenil-induced seizure accompanying benzodiazepine and baclofen intoxication (Letter). *Am. J. Emerg. Med.* 1996; **14**: 231–2.
16. Ferner RE. Atropine treatment for baclofen overdose. *Postgrad. Med. J.* 1981; **57**: 580–1.
17. Isbister GK, Balit CR, Whyte IM *et al.* Valproate overdose: a comparative cohort study of self poisonings. *Br. J. Clin. Pharmacol.* 2003; **55**: 398–404.
18. Roy CW, Wakefield IR. Baclofen pseudopsychosis: case report. *Paraplegia* 1986; **24**: 318–21.
19. Liu HC, Tsai SC, Liu TY *et al.* Baclofen–induced frontal lobe syndrome: case report. *Paraplegia* 1991; **29**: 554–6.

20. Chyka PA, Seger D. Position Statement: single-dose activated charcoal. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J. Toxicol. Clin. Toxicol.* 1997; **35**: 721–41.

21. Balit CR, Isbister GK, Whyte IM. Quetiapine poisoning: a case series. *Ann. Emerg. Med.* 2003; **42**: 751–8.