Massive Baclofen Overdose

D. J. COOPER, J. BERGMAN
Department of Intensive Care and Hyperbaric Medicine, The Alfred Hospital, Melbourne, VICTORIA

ABSTRACT

A case is presented of a massive baclofen overdose with the highest blood baclofen concentrations currently reported. Interesting clinical features included profound hypotension, distributive shock and absent brainstem reflexes. Cerebral recovery was surprisingly slow but complete, and was then unexpectedly terminated by a sudden major splenic arterial haemorrhage followed by a severe haemorrhage of the aorta which proved to be due to cystic medial necrosis. This arterial anatomic abnormality and cause of death may have been coincidental, or may instead be a previously unreported complication of massive baclofen toxicity. (**Critical Care and Resuscitation 2000; 2: 195-197**)

Key words: Baclofen, overdose, distributive shock, cystic medial necrosis

Baclofen is a presynaptic gamma-aminobutyric acid (GABA) agonist used to treat muscle spasticity.[1] In usual therapeutic doses of 15 - 60 mg per day, baclofen acts at the spinal level by reducing the tonic activity of spinal gamma motor neurones.[2] Side effects include sedation, confusion, diarrhoea and convulsions.[1] Overdose has been associated with tachycardia, bradycardia, hypothermia, impaired consciousness, muscle weakness, hypotonia, areflexia, myoclonus, miotic or mydriatic pupils and respiratory failure lasting up to 72 hr.[2] Arterial medial necrosis has not been previously described.

CASE REPORT

A 47 year old woman with a histrionic personality disorder, reactive depression, and a past history of long standing back pain leading to an unsuccessful spinal fusion, was found unconscious along side three recently prescribed, empty bottles of baclofen (300 x 10 mg tablets) and an empty wine bottle. Daily medications included baclofen 20 mg, 8-hourly and amitriptyline 20 mg at night. Emergency management during transport to hospital included endotracheal intubation for respiratory arrest, intravenous Haemaccel (500 mL) for hypotension (systolic blood pressure 85 mm Hg) and sodium bicarbonate 50 mmol intravenously for presumed tricyclic antidepressant overdose.

In the emergency department she was hypothermic (33°C), flaccid, hyporeflexic, unconscious with fixed dilated pupils, absent brain stem reflexes, and had a Glasgow coma score of 3. There were no clinical features to suggest Marfan's syndrome or any other connective tissue diseases. While she was clinically well perfused, her systolic blood pressure was 50 mm Hg and intravenous adrenaline was commenced (3 x 1mg followed by an infusion which increased rapidly to 20 μg/min). This was accompanied by ventricular tachycardia requiring direct current cardioversion and an intravenous infusion of lignocaine (2 μg/minute). The patient was then transferred to the intensive care unit (ICU).

She remained hypotensive with a systolic blood pressure of 75 mmHg and peripherally dilated despite the high dose of adrenaline and a central venous pressure of 10 mm Hg. Haemaccel (1000 ml over 1 hr) was infused, the adrenaline was replaced with intravenous noradrenaline (15 μg/min), and a pulmonary artery catheter was inserted. With the change in vasopressor therapy the systolic arterial blood pressure increased to 120 mm Hg. The cardiac output was 9 L/min, pulmonary artery occlusion pressure was 16 mm Hg and the urine output was 250 mL/hr. She developed a lactic acidosis with an arterial pH of 7.29, bicarbonate 13 mmol/L, and lactate of 8.4 mmol/L. The high urine output with urine osmolality 183 mmol/L and serum osmolality 316 mmol/L suggested diabetes insipidus and

Correspondence to: Dr. D. J (Jamie) Cooper, Department of Intensive Care, The Alfred Hospital, Prahran, Melbourne Victoria 3181 (e-mail: djamiec@ozemail.com.au)

was controlled with two doses of intravenous desmopressin (2 μg). Blood tested on admission revealed an alcohol concentration of 0.16 g/100mL, amitriptyline of 1.8 mg/L (therapeutic range 0.04 -0.16 mg/L), and baclofen of 20.0 mg/L (therapeutic range 0.08 - 0.4 mg/L). A computed tomography head scan revealed mild cerebral atrophy and an old, small, middle cerebral artery cortical infarct. On the second day an EEG was performed which was abnormal but could not discriminate between drug overdose and hypoxic brain injury. The blood baclofen concentration was also repeated on the second day revealing a level of 3 mg/L.

The patient's neurologic status remained unchanged for the following four days. Her pupils remained fixed and dilated, brainstem reflexes were absent, and she had facial twitching for which she received intravenous phenytoin 200 mg and intravenous clonazepam 23 mg (during the first day only). Between the fourth and the fifth days her pupils became smaller and reactive, she began to move spontaneously and on day 5 she began to obey commands and open her eyes to voice.

Intravenous noradrenaline was continued until the third day and was then ceased. Her haemodynamic state remained stable until the fifth day when a progressive uneventful recovery was interrupted by acute hypotension, a rapidly distending abdomen and hypovolemic cardiac arrest. Immediate laparotomy revealed a completely unexpected ruptured splenic artery aneurysm. This was ligated, splenectomy was performed, and resuscitation completed. A small hepatic artery aneurysm was also noted but left untouched. Recovery in ICU was progressive over the next 48 hr with extubation on the seventh day at which time she was noted to be restless, but normotensive, communicating well and obeying commands. At this point she was thought to have recovered from the overdose.

However, early on the eighth day she again experienced acute hypotension and abdominal distension. A second laparotomy revealed an extensive new retroperitoneal and extraperitoneal haematoma with no identifiable source. An abdominal cross clamp was placed but massive bleeding from the upper aorta could not be controlled and was followed by the patient's demise.

An autopsy revealed multiple longitudinal tears of the aorta and transection of the descending aorta at the level of the diaphragm. Histological examination revealed cystic medial necrosis and dissection of the descending aorta, iliac and renal arteries. The extent of the arterial degeneration was in excess of that seen in normal ageing. Also the features were not characteristic of Marfan's syndrome as there was no evidence of dissection of the proximal aorta or aortic arch and all other arteries were histologically normal. Furthermore, there were no other clinical features of Marfan's syndrome identifiable by the pathologist.

DISCUSSION

Baclofen is a pre-synaptic GABA agonist which, in therapeutic concentrations decreases excitatory neurotransmitter output from the spinal cord and reduces muscle tone, thereby improving spacticity.[2] In overdose, central nervous system (CNS) depression is well described.[3] This patient's baclofen overdose is currently the largest reported.

Therapeutic doses of baclofen are rapidly absorbed, maximum blood levels are reached in 1 - 2 hr, and the usual elimination half life is 2 - 4 hr.[4] Conventional doses are therefore eliminated within 24 hr. Large overdoses are less rapidly absorbed, but once absorbed, baclofen in overdose has been reported to exhibit first order elimination kinetics. In large overdose, a constant half life of about 8.6 hr has been previously reported.[2] Baclofen in overdose is therefore eliminated from the blood within about 48 hr and is cleared from the urine within 72 hr. Previous case reports have, however, described a more prolonged action of baclofen which has been thought to be due to delayed clearance from the CNS.[2] Consistent with these reports, the two blood baclofen concentrations measured in our patient suggested elimination should have been complete by 24 - 48 hr, although signs of brain stem function did not begin to return until over 100 hr in the ICU.

On admission, in addition to extremely high blood concentrations of baclofen, this patient had high blood concentrations of alcohol and amitriptyline which also influenced her depressed neurological state during the first 24 - 48 hr. An amitriptyline elimination half life of 20 hr predicted therapeutic concentrations within about 3 days. Clonazepam was also infused (23 mg in total soon after admission), and would have also influenced her neurological status during the first few days. The 200 mg phenytoin intravenously on day 2 is unlikely to have had any significant effect on neurological status.

The signs of acute baclofen intoxication present in this patient, have been previously reported. These include encephalopathy, seizures, respiratory depression, muscle hypotonia and hyporeflexia, and non-reactive pupils.[5] There is no clinically available antidote for baclofen intoxication although a weakly potent antagonist "Phaclofen" has been developed for experimental use.[6] Patient management is supportive and consists of intravenous fluids, enteral charcoal and respiratory support. Seizures may be controlled with benzodiazepines.

There are several interesting features in this patient's presentation, management and complications which may

be highlighted. First, to our knowledge, this overdose (likely to be about 3000 mg) is the largest currently reported and was associated with the highest blood baclofen concentration (20 mg/L) yet reported in patients. Second, this patient presented with clinical features consistent with distributive shock including a high cardiac output, and adrenaline was largely ineffective in providing adequate perfusion pressures. Adrenaline therapy was further complicated by life threatening arrhythmias and lactic acidosis. In contrast, haemodynamic stability was rapidly obtained using intravascular volume expansion and intravenous noradrenaline. Third, this patient had an extremely prolonged period with absent brain stem reflexes (four days), and despite this, neurologic recovery was essentially complete, in keeping with the known tendency of baclofen in overdose to have delayed clearance from the central nervous system. This potential for complete cerebral recovery despite clinical features which might be confused with brain death, is extremely important when assessing such patients for withdrawal of therapy or as possible candidates for organ donation. Finally, in this patient the cause of unexpected death was haemorrhage due to dissection and rupture of multiple major internal arteries. There was no history of hypertension or coagulopathy. It is highly likely that the patient's first haemorrhage from the splenic artery (from which she was successfully resuscitated) was also due to cystic medial necrosis and arterial dissection, but tissue samples from this procedure were not retained. At autopsy, microscopic examination of the aorta revealed extensive medial necrosis atypical for Marfan's syndrome, as the ascending aorta and arch were not involved and the associated clinical features were not present. The causes of cystic medial necrosis in general are unknown. In this patient the baclofen overdose and the cystic medial necrosis may have been completely unrelated. Alternatively, it is possible that the two were causally related and that cystic medial necrosis is a previously unreported toxic effect of massive baclofen overdose.

Received 21 June 2000
Accepted 26 June 2000

REFERENCES

1. Ghose K, Holmes K. Complications of baclofen overdosage. Postgrad Med J 1980;56:865-867.
2. Gerkin R, Curry S, Vance M, Sankowski P, Meinhart I. First-order elimination kinetics following baclofen overdose. Annals Emerg Med 1986;15:843-846.
3. Roberge R, Martin T, Hodgman M, Benitez J, Brunswick J. Suprventricular tachyarrythmia associated with baclofen overdose. Clin Toxicol 1994;32:291-297.
4. Ferner R. Atropine treatment for baclofen overdose. Postgrad Med J 1981;57:580-581.
5. Lee T, Chen S, Su S, Yang S. Baclofen intoxication: Report of 4 cases and review of the literature. Clin Neuropharmacol 1992;15:56-62.
6. Kerr D, Ong J, Prager R, Gynther B, Curtis D. Phaclofen: a peripheral and central baclofen antagonist. Brain Research 1987;405:150-154.