Baclofen Intoxication

Baklofen aşırı dozu

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SUMMARY

Baclofen, a derivative of γ-aminobutyric acid, is used for symptomatic relief of skeletal muscle spasm and spasticity. Overdose of this drug can cause profound central nervous system depression, including coma, hypotonia, respiratory depression, seizures, and cardiovascular effects. In this paper, we reported a case of 19 year-old female with baclofen overdose presenting to the emergency department with coma. She recovered and discharged after supportive care including mechanical ventilation. An acutely confused or comatose patient is admitted to emergency department, baclofen intoxicitation should be kept in mind in the differential diagnosis.

Key words: Baclofen overdose; baclofen intoxication.

ÖZET

Baklofen bir gama-aminobütirik asit derivesidir; iskelet kas spazmında ve spastisitede semptomatik rahatlama için kullanılır. Bu ilacın aşırı dozları koma, hipotoni, solunum depresyonu, konvulsiyonu da içerecek şekilde santral sinir sistemi depresyonuna ve kardiyovasküler etkilere neden olabilir. Bu yazıda, acil servise özkıyım amaçlı baklofen aşırı alımı sonrası koma ile getirilen 19 yaşında kadın bir olgu sunuldu. Hasta mekanik vantilasyon dahil yapılan destek tedavi ile iyileşti ve taburcu oldu. Acil servise konfüzyon veya koma ile başvuran hastalarda, baklofen aşırı dozu ayırıcı tanıda akılda tutulmalıdır.

Anahtar sözcükler: *Baklofen aşırı dozu; baklofen zehirlenmesi.*

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Introduction

Baclofen, a derivative of γ-aminobutyric acid, is used for symptomatic relief of skeletal muscle spasm and spasticity, particularly in patients with multiple sclerosis. Although its exact mechanism is not fully understood, its main effects at the spinal end of upper motor neurons are thought to cause muscle relaxation.[1]

The recommended maximum dose is 80 mg per day in adults; 60 mg per day in children ≥8 years of age. Adverse effects of baclofen at usual doses include drowsiness, headache, dizziness, and occasionally, orthostatic hypotension. Intentional or accidental overdose of this drug can cause profound central nervous system depression, including coma, hypotonia, respiratory depression, seizures, and cardiovascular effects such as bradycardia.[2] We describe a patient with baclofen overdose presenting to the emergency department with coma.

Case Report

A 19-year-old female was brought to the emergency department after she was found unresponsive at home. On admission she was comatose, with a Glasgow Coma Score of 5. Her blood pressure was 130/90 mmHg, with a regular heart rate of 106 beats/min and a respiratory rate of 30 shallow breaths/min and oxygen saturation 88% in room air. She was afebrile (36.9°C) and had no external signs suggestive of head injury or tongue biting. Her pupils were fixed dilated with no response to light. Her extremities were flaccid, with no spontaneous movement. The deep tendon reflexes were absent. Cardiovascular, respiratory, and abdominal examinations were normal. Her past medical history was unremarkable.

In the emergency room she received dextrose (25 gr iv), naloxone (2 mg iv), thiamine (100 mg iv), with no improvement. She was intubated, ventilated and transferred to medical intensive care unit (ICU).

During the medical ICU course, the initial investigation revealed a sinus tachycardia without ST segment and T wave abnormality and normal chest radiogram. Her blood profile showed no abnormality except mild leukocytosis ($14.3x10^3$ cells/mm^3). Sodium, potassium, urea, creatinine, glucose, calcium, liver enzymes, creatinine phosphokinase and coagulation profile were normal. Arterial blood gases taken immediately after intubation showed a pH: 7.36, pCO_2: 37.3 mmHg, pO_2: 59.4 mmHg, HCO_3: 20.8 mmol/L. Toxicology screen was negative for salicylates, paracetamol, benzodiazepines, tricyclic antidepressants, cocaine, opiates, and alcohol. Computed tomography of the head was normal. Electroencephalography showed a burst suppression pattern without reactivity to stimulation.

Over the following 2 days, the patient had a dramatic improvement in consciousness. She became alert, awake with her eyes opened and able to follow commands. She was extubated about 12 hours after regaining consciousness. On interview she revealed that she had taken 20 baclofen tablets (10 mg) with suicidal intention. She also told that her mother was taking baclofen due to multiple sclerosis. She was dicharged with excellent neurological functions on day 6.

Discussion

Baclofen, a lipophilic analogue of the naturally occurring neurotransmitter gamma-aminobutyric acid (GABA), is the drug of choice for treatment of spasticity from spinal cord lesions and multiple sclerosis.[1]

The pharmacokinetics of baclofen at therapeutic doses has been well studied. It is readily absorbed from the gastrointestinal tract, with peak serum concentrations reached in 2 hours. It is 30% plasma protein-bound. Therapeutic serum concentrations range from 0.08 to 0.4 μg/mL. Elimination half-life after therapeutic use follows first-order kinetics, with half-life ranging from 2 to 6 hours (mean 3.5 hours). Eighty-five percent is excreted unchanged in the urine and the remaining 15% is deaminated to β-(ρ-chlorophenyl)-gamma-hydroxybutyric acid in the liver and excreted in the stool.[3] When taken as prescribed, baclofen has very few side effects, and serious adverse effects are rare. The most common side effects reported include transient drowsiness, dizziness, weakness, and mental confusion.[2]

Signs of toxicity have been reported after ingestion of as little as 100 mg of baclofen. Baclofen toxicity has been reported after intrathecal and oral administration including iatrogenic, suicidal, and recreational administration.[4] The clinical manifestations are a consequence of an exaggeration of its muscle relaxing effects and of direct central nervous system depression, possibly by stimulation of GABA B receptors in the spinal cord, brainstem and hippocampus. These effects are potentiated by other

CNS depressants, for example, alcohol.[5] Adverse effects of baclofen overdose are well defined in the literature, and include somnolence, coma, seizures, encephalopathy, respiratory depression, flaccidity, hyporeflexia, and cardiac conduction abnormalities.[2,6] Autonomic disturbances are also frequent but inconsistent; patients may have either bradycardia or tachycardia, hypotension or hypertension, and miosis or mydriasis. Seizures are generally brief, tonic-clonic, and respond rapidly to pharmacologic intervention. Reported cardiac effects have included prolonged QTc, first-degree heart block, premature atrial contractions, and supraventricular tachycardia.[7]

Baclofen toxicity is a clinical diagnosis; measuring plasma levels is not always possible, and results can be misleading. The half-life is 3.5 hours in therapeutic use but a serum half-life of up to 34 hours has been estimated after overdose. Animal experiments with radiolabeled baclofen indicate that concentrations in nerve tissue and brain are lower than in blood, but the apparent elimination rate of 24 hours from nerve tissue is much slower. This might explain why prolonged periods of unconsciousness have been reported, even when the plasma concentrations of baclofen were within therapeutic range.[8]

Treatment consists of symptomatic and supportive care, intravenous fluids, inotropes, and mechanical ventilation if necessary. In the event of seizures, diazepam or phenytoin was recommended. Physostigmine, which may antagonize the benzodiazepine-induced anticholinergic syndrome, has been suggested to reverse baclofen toxicity. However, reports suggest that this therapy is not always effective and may produce adverse effects, including bradycardia and increased airway secretions.

Physostigmine has been recommended by some authors after intrathecal overdose, although others have not demonstrated benefit from administration of physostigmine. It has also been reported that flumazenil, a specific benzodiazepine antagonist, may counteract the central neuronal inhibitory effects of baclofen without interfering with its muscle relaxant properties. Again, this has not been confirmed in other case reports. In another case presentation, it was reported that Ondansentron, which is known as a 5-HT3 receptor antagonist and used as an antiemetic, becomes effective when used in cases of baclofen overdose. Yet its mechanism is unclear and it has not been suggested for routine usage. In a few case reports, it was proved that hemodialysis becomes effective in eliminating baclofen from blood.[9-12] Most patients recover with supportive care alone. However, fatalities have been reported.[13]

In our case, the patient appeared to present in the classic manner associated with baclofen overdose. The amount of baclofen the patient had ingested was 200 mg. This amount is regarded in some studies as the limit value for serious toxic effects.[8] She recovered after supportive care including mechanical ventilation. Since coma may occur rapidly after baclofen overdose and the respiratory depression may be exacerbated, primary concern in the treatment of such ingestions should be placed on maintenance of an airway and respiratory support. Although our patient remained hemodinamically stable, the experience of others demonstrates that both conduction defects and rhythm disturbances can occur and warrant close observation in the acute baclofen overdose.

Conclusion

Emergency physcians should consider baclofen overdose in patiens presenting with acute loss of consciousness, flaccidity and hyporeflexia even in the absence of history about suicidal ingestion. Since routine toxicology screening does not include baclofen, diagnosis is made only by obtaining detailed history. The prognosis is good if full supportive care is administered properly.

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