Toxicology Clinics-Bench to Bedside Baclofen Overdose or Brain Death?

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Baclofen is a synthetic derivative of GABA, most commonly used in the management of painful muscle spasms such as spinal cord injury, cerebral palsy, and multiple sclerosis. It is closely related to the recreational drug, Gamma-Hydroxybutyrate (GHB).

What are the clinical features of baclofen overdose?

- In overdose, it causes a picture similar to barbiturate coma
- Profound CNS depression with loss of brainstem reflexes.
- Flaccid tone with absent deep tendon reflexes.
- Bradycardia.
- Respiratory depression.
- Hypothermia.

What are the other effects seen with baclofen overdose?

- Hypertension or hypotension (the former is more commonly reported).
- Paradoxical seizures.
- Pupil abnormalities — miosis or mydriasis.
- Agitated delirium.
- 1st degree AV block and QT prolongation are rarely reported.

How does the baclofen agent exert its toxic effects?

- Baclofen acts as an agonist at pre-and postsynaptic GABA-B receptors in the brain and spinal cord.
- Antispasmodic effects occur primarily at the spinal cord level; an overdose there is also increased GABA activity within the brain.
- At a therapeutic dose, it acts on spinal GABA-B receptors, but in overdose, this selectivity is lost, and the GABA receptors in the brain are targeted, resulting in sedation and coma.
- Activation of presynaptic GABA-B receptors causes inhibition of excitatory neurotransmitter release within the CNS.
- The mechanism is thought to involve hyperpolarisation of the presynaptic membrane and reduced calcium influx into the nerve terminal with resultant impairment of calcium-dependent exocytosis of excitatory neurotransmitters.
- The net result is a generalized CNS depression similar to that seen with barbiturates, propofol, and other general anesthetics.
- Paradoxical seizures occur due to presynaptic inhibition of inhibitory neurons (i.e., disinhibition).

What is the toxicokinetics of this agent?

- Rapidly and completely absorbed following oral administration.
- Peak serum levels occur at ~ 2 hours post-ingestion.
- Lipophilic so readily crosses the blood-brain barrier.
- Relatively small Vd (0.7 L/kg).
- Primarily excreted unchanged in the urine.
- 15% metabolized by the liver.
- The mean elimination half-life is 3.5 hours, although this may be prolonged in overdose (15-35 hours in some case reports).

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What is the toxic dose?

- Acute ingestion of more than 200 mg is expected to produce significant CNS toxicity, with delirium, coma, and paradoxical seizures.
- Smaller doses may cause mild drowsiness and delirium.
- One 25mg tablet can produce a coma in a 10 kg toddler

What is the half-life of baclofen?

- The half-life is 3.5 hours in therapeutic use, but a serum half-life of up to 34 hours has been estimated after an overdose.

What is the duration of the coma?

- Intoxication will develop within 2 hours; delirium is most evident just prior to the onset of coma.
- The duration of a coma is usually 24 to 48 hours but maybe prolonged (i.e., several days) with massive doses or in patients with renal failure.
- In massive overdoses, patients can appear brain dead with fixed dilated pupils, hypotonia, areflexia (including absent brainstem reflexes)

Why is the duration of the coma prolonged?

- 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 the therapeutic range.

What are the Differential Diagnoses?

- When diagnosing baclofen toxicities, it is important to rule out other possible causes of the clinical signs, including:
- An overdose of other skeletal muscle relaxants, amphetamines, barbiturates, benzodiazepines, opioids, propofol, tricyclic antidepressants, selective serotonin reuptake inhibitors, zolpidem, and botulinum toxin

Which are the toxicological agents that may mimic brain stem death in overdose?

Agents that may cause coma with transient loss of brainstem reflexes

- Barbiturates
- Baclofen
- Carbamazepine
- A clinical picture of coma, flaccidity, and absent reflexes that mimics brain death can persist for up to 5-7 days after the severe overdose. Continue to provide symptomatic and supportive care.

When to Measure plasma baclofen levels?

- Measuring plasma baclofen levels are less widely available. Hence this diagnosis is usually a clinical one (often made retrospectively once collateral history becomes available). Moreover, results can be misleading.

What are key elements to distinguish overdose from withdrawal?

- Baclofen overdose and withdrawal may present with overlapping symptoms
- Withdrawal symptoms have a more insidious onset than overdose and generally do not occur until 12-24 hours after the pump malfunction has occurred, while overdose tends to occur relatively quickly (minutes)
- Increased muscle rigidity and spasticity may be noted in withdrawal.
- Bradycardia and respiratory depression are seen with an overdose
- A spectrum of CNS depression depends on overdose severity.

How is baclofen overdose managed?

Resuscitation

- Early intubation and ventilation are indicated for patients with coma or respiratory depression.

- Paradoxical seizures are treated with benzodiazepines.
- Hypotension usually responds to fluid resuscitation.

Decontamination

- Nasogastric activated charcoal (60g) given following intubation may reduce the total dose of baclofen absorbed.
- It is given with the intention of reducing the duration of coma and length of ICU stay.
- Due to the rapid absorption kinetics of baclofen, charcoal is only likely to be useful if given within the first few hours.
- Conversely, activated charcoal is not recommended in the patient with an unprotected airway due to rapid onset of coma and seizures with the potential for charcoal pulmonary aspiration.

Antidote

- There is no antidote
- Managed with symptomatic and supportive care

Enhanced Elimination

- Enhanced elimination is not normally necessary as patients do well with supportive care alone.
- However, a recent case report has suggested that there may be some benefit from hemodialysis (HD) in reducing the duration of coma in large baclofen overdose — the authors reported an elimination half-life of 15.7 hours before and 3.1 hours after the instigation of HD in a 420 mg baclofen ingestion. Although this is a single case report, it appears that hemodialysis does not remove baclofen effectively.

Is there any role for lipid emulsion therapy?

- Lipid rescue should be considered in severe toxicity. While administration of lipid rescue infusions in baclofen overdose patients may help to enhance drug metabolism and reduce the serum levels, though this is not currently standard practice, but a lot of promising case reports are published.

Are there any other drugs used to counteract the baclofen overdose?

- Physostigmine has been recommended by some authors after an intrathecal overdose, although others have not demonstrated benefit from the 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 Ondansetron, 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.

Acknowledgments

We thank Prof. P. Thirumalaikolandusubramanian, M.D, for the critical review.

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