Baclofen

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Erin Stewart and Laura M. Tormoehlen

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E. Stewart (✉)
Kerlan-Jobe Orthopaedic Clinic, Los Angeles, CA, USA
e-mail: erin.stewart@kerlanjobe.com

L.M. Tormoehlen (✉)
Clinical Emergency Medicine and Neurology, Indiana University School of Medicine, Indianapolis, IN, USA
e-mail: laumjone@iupui.edu

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In the central nervous system, γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter. Three major GABA receptors – $GABA_A$, $GABA_B$, and $GABA_C$ – have been identified. Baclofen (β-(4-chlorophenyl)-γ-aminobutyric acid) is a GABA agonist, specific to $GABA_B$ at therapeutic doses, that has been used to treat spasticity of various etiologies (e.g., multiple sclerosis, paraplegia, quadriplegia, cerebral palsy). It has also been used off-label for dystonia, jerking, restless legs, chorea, stiff-person syndrome, torticollis, tetanus, hiccups, trigeminal neuralgia, cluster headaches, and musculoskeletal pain; with more recent investigations for the management of rumination, supragastric belching, and gastroesophageal reflux; alcohol, opioid, and cocaine abuse disorders; bladder spasm; and in combined use with antimuscarinic agents for overactive bladder [1–28].

Recently, elevated doses of baclofen (up to 300 mg/day) were prescribed to treat craving in alcoholic patients, following the self-experience reported by a French physician [29]. This protocol is based on animal studies showing that, in contrast to other therapies, increasing doses of baclofen are able not only to reduce but also to suppress craving in animals chronically intoxicated with ethanol. Several RCTs are ongoing to demonstrate whether these elevated doses are efficient or not. This experience led to the development of severe poisonings due to the huge presumed ingested doses [30–32].

Biochemistry, Pharmacology, and Pathophysiology

Baclofen is a structural analogue of GABA (Fig. 1) [33].

Pharmacokinetics

Baclofen is absorbed rapidly after oral administration, with a bioavailability of 70–85%. However, its central nervous system penetration is more limited, sometimes requiring relatively large oral doses to achieve therapeutic effects. Oral baclofen has a low therapeutic index, primarily because it is distributed evenly between spinal and supraspinal levels after oral administration. Peak blood concentrations occur 1–3.5 h after therapeutic ingestion; however, after overdose, absorption is prolonged and incomplete. Although signs and symptoms of toxicity can begin shortly after overdose, resolution can be protracted. After intrathecal or oral overdose, it may take days for the patient to become fully alert. Elimination of this moderately lipophilic GABA agonist from nerve and brain tissue is much slower than from serum, explaining the persistence of effects despite undetectable serum baclofen concentrations. Baclofen is excreted primarily by glomerular filtration, and its clearance is proportional to creatinine clearance. Generally, 50–85% of an ingested dose is eliminated unchanged in urine within 72 h. The remaining 15% is deaminated to β-(*p*-chlorophenyl)-γ-hydroxybutyric acid. However, large inter-individual variability has been observed in both elimination and oral absorption processes [5, 15, 27, 33–50]. In addition, in large ingestions, there may be a delayed rebound in plasma concentration, and this can be associated with recurrence of effect [51–53].

Pharmacokinetics of Baclofen Poisoning
Protein binding: 30–35%
Volume of distribution: 0.8–2.6 L/kg
Serum half-life: 2–8 h (longer after overdose and renal insufficiency)
Mechanism of clearance: primarily renal

$GABA_B$ Receptors and the Pathophysiology of Toxic Effects

$GABA_B$ receptors are expressed widely in the brain and the spinal cord, including the cerebral hemispheres, diencephalon, brainstem, and dorsal horn of the spinal cord. The $GABA_B$ receptor comprises two subunits and is coupled to G proteins. Activation of these receptors promotes a decline in calcium conductance and intracellular cyclic adenosine monophosphate production.

Baclofen binds to presynaptic and postsynaptic $GABA_B$ receptors (Fig. 2). Presynaptic receptor binding of GABA or baclofen hyperpolarizes presynaptic terminals by closing calcium channels and decreases neurotransmitter (e.g., catecholamines, glutamate, substance P) vesicle release from excitatory spinal pathways Fig. 2b), producing an inhibitory effect. Presynaptic binding also occurs at GABAergic autoreceptors, hyperpolarizing presynaptic terminals and decreasing

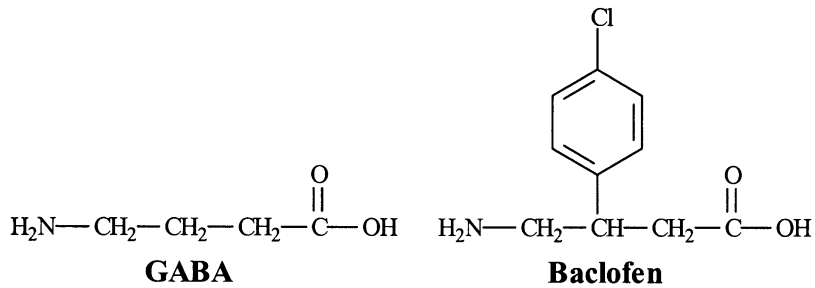

Fig. 1 Chemical structures of γ-aminobutyric acid (GABA) and baclofen. Baclofen is a GABA analogue containing a *para*-chlorphenyl moiety in the β position relative to the carboxylate

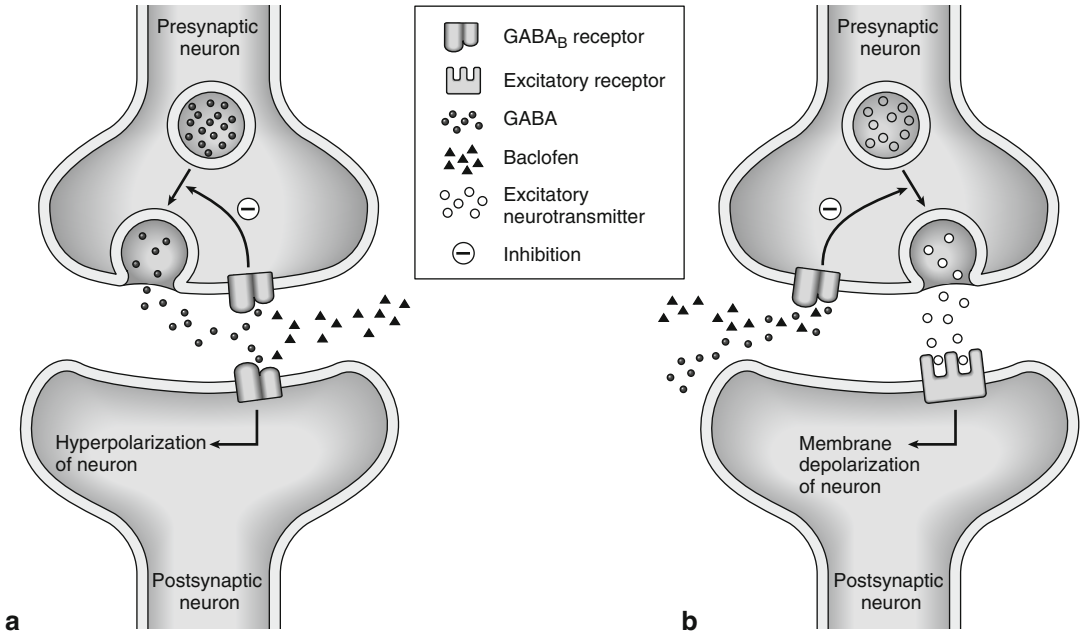

Fig. 2 Binding of γ-aminobutyric acid (GABA) and baclofen to $GABA_B$ receptors. (**a**) GABA is released from presynaptic GABAergic neurons and may bind to $GABA_B$ receptors on postsynaptic neurons, resulting in hyperpolarization of postsynaptic neurons. This has an inhibitory effect on the nervous system. GABA released from presynaptic GABAergic neurons also acts at $GABA_B$ receptors on the presynaptic neurons, resulting in decreased release of GABA from the neuron or autoregulation. This has an excitatory effect. (**b**) $GABA_B$ receptors also are located on presynaptic neurons that release excitatory neurotransmitters. When GABA binds to these receptors, the release of excitatory neurotransmitters is diminished. This has an inhibitory effect. Baclofen can bind at all of these $GABA_B$ receptors and produces an effect similar to that of GABA binding

GABA release (Fig. 2a), producing an excitatory effect. Postsynaptic binding to the $GABA_B$ receptor hyperpolarizes the neuron via two separate actions, opening slow potassium channels and inhibiting dendritic calcium influx channels, and results in inhibition by creating a net negative membrane potential (see Fig. 2a). Inhibitory and excitatory effects may occur with the binding of baclofen to $GABA_B$ receptors. Generally, when used therapeutically, the inhibitory effects prevail. The dual inhibitory and excitatory actions provide an explanation for the significant overlap of clinical manifestations (e.g., seizures) seen with overdose and withdrawal from baclofen.

Baclofen depresses γ and α motor neurons and inhibits monosynaptic extensor and polysynaptic flexor spinal reflexes. This activity accounts for the decreased muscle tone and the efficacy of baclofen in treating spasticity. Baclofen affects afferent depolarization in the dorsal horn of the spinal cord and modulates nociceptive input from primary afferent fibers to neurons of the spinothalamic tract. This effect, along with the inhibition of substance P release, accounts for the efficacy of baclofen in the treatment of pain. Central and peripheral GABA receptors also are known to play a role in regulation of body temperature; this may account for the hypothermia generally seen after overdose and the hyperthermia generally seen in withdrawal from baclofen. Central nervous system depression secondary to baclofen may be attributed to stimulation of $GABA_B$ receptors in the hippocampus, whereas respiratory and cardiovascular depression may result from stimulation of $GABA_B$ receptors in the brainstem [6, 28, 33, 47, 54–62].

Clinical Presentation

Routes of Exposure

Oral

Acute ingestions of 300–970 mg in adults can be expected to produce serious intoxications, and doses of 1250–2500 mg have been fatal in adults [27]. Additionally, a retrospective database review of 23 cases of baclofen poisoning demonstrated baclofen ingestions of 200 mg or greater were predictive of more severe clinical manifestations and prolonged hospital stay than ingestions less than 200 mg [63]. Baclofen abuse has been reported in persons with a history of substance abuse and in adolescents seeking intoxication [64–66].

Intrathecal

Intrathecal administration is accomplished by a pump with a reservoir that is implanted surgically in the subcutaneous tissue of the abdominal wall. A catheter is threaded into the intrathecal space, allowing direct delivery into the cerebrospinal fluid. Complications include mechanical problems (dislodgement, disconnection, kinking, blockage), pump failure, and infection [33, 67–85]. In an 8-year study of 30 patients, the overall incidence of pump complications was 62%. The most frequent complication was catheter disconnection, followed by retraction of the intrathecal catheter [81]. Borrini and colleagues [70] attempted to assess the frequency and characterize complications related to intrathecal baclofen pump therapy in a cohort of 158 adult patients who were implanted before and during 2010. During 1 year of follow-up, the rate of adverse events was 0.023 per month, with 29% of cases related to the device and predominantly involving catheter dysfunctions [70]. Also, in a multicenter Japanese study of 400 patients with intrathecal baclofen pumps, catheter problems (migration, obstruction, kinking, and dislodgement) were observed in 8.5% of patients, pump malfunction in 1.8% of patients, and device-related and surgical wound infections in 3% of patients [86]. A study of 100 children and young adults demonstrated more frequent device-related complications in those implanted with pumps with catheter access ports [78]. Separate from mechanical complications, intrathecal overdose has been reported in continuous infusion and after bolus injection [46, 56, 61, 87, 88].

Other Routes

Baclofen has also been used in topical formulations for the treatment of neuropathic pain; trialed in intravesical administration for bladder spasm; and proposed for subcutaneous, intravenous, and intraventricular delivery [17, 25, 35, 89, 90].

Clinical Manifestations of Baclofen Poisoning

Lee and colleagues [58] attempted to differentiate between acute and chronic baclofen poisonings, suggesting that acutely poisoned patients are more likely to present with encephalopathy (disturbances of consciousness or seizure or both), respiratory depression, muscular hypotonia, and generalized hyporeflexia. Chronically poisoned patients are more likely to present with hallucinosis, impaired memory, catatonia, or acute mania [58]. The same authors also noted that the acute intoxication syndrome has a faster onset, a shorter duration, more severe clinical manifestations, and a higher incidence of seizures compared with the chronic intoxication syndrome [58]. However, there is significant overlap in the clinical presentations of acute and chronic toxicity, as well as with the presentation of withdrawal, as discussed later.

Acute and Life Threatening Presentations

Neurologic. Headache, dizziness, incoordination, ataxia, myoclonus, fatigue, weakness, areflexia, flaccid extremities, encephalopathy, coma, and seizures, including status epilepticus, may occur [5, 27, 46, 47, 50, 56, 58, 61–66, 75, 88, 91–99]. The clinician needs to be aware of the risk of nonconvulsive (akinetic) status epilepticus [64, 97, 100]. Although baclofen has antiepileptic properties at low concentrations, it is proepileptic at high concentrations [56, 61, 96, 101]. Delayed psychosis and confusion with hallucinations have

been reported during the recovery phase [56, 63, 65, 95].

Pulmonary. Respiratory depression and failure may occur [5, 27, 46, 50, 56, 65, 75, 87, 91, 92, 95, 98, 102–105].

Cardiovascular. Hypertension or hypotension and tachycardia or bradycardia may occur. Tachycardia may alternate abruptly with bradycardia. Conduction abnormalities (including prolonged QT_c and first-degree heart block), premature atrial and ventricular contractions, supraventricular tachycardia, atrial flutter, and atrial fibrillation have been reported [5, 27, 46, 50, 56, 63, 65, 66, 75, 88, 95, 97–99, 103, 104].

Gastrointestinal. Nausea and vomiting may occur [5, 66, 91, 99, 103].

Ocular. Blurred vision, horizontal or vertical nystagmus, unreactive pupils, absent corneal reflexes, and absent doll's eye reflexes may occur. Pupils may be small or large [27, 50, 56, 58, 61, 63, 66, 92, 95–97, 103, 104].

Other. Hypothermia and hypersalivation may occur [27, 58, 66, 88, 97, 103]. Hyperthermia is reported rarely [58, 99] and is more likely to occur in baclofen withdrawal.

Chronic Intoxication

Toxicity can occur gradually after long-term intrathecal or oral dosing, especially in patients with concomitant renal insufficiency. Chronic intoxication may present with impaired memory, acute mania or catatonia, and hallucinosis; this has been called *chronic baclofen intoxication syndrome* [27, 58, 97]. Respiratory depression, apnea, bradycardia, tachycardia, hypotension, hypertension, tremor, weakness, hypotonia, areflexia, urinary retention, sedation, coma, seizures, orofacial dyskinesia, and hypothermia also have been reported as manifestations of chronic baclofen toxicity [15, 43, 48, 58].

Side Effects with Long-Term Use

Nausea, lightheadedness, vertigo, fatigue, drowsiness, confusion, and lethargy may occur as side effects of oral baclofen, owing to the narrow therapeutic margin [5, 48, 58, 61]. Occasionally, hypotension also is seen [48]. Other pharmacological complications of chronic baclofen use, particularly intrathecal use, have also been reported and include: hypotonia, sexual dysfunction in males, constipation, and drug tolerance [106, 107].

Coma and the Diagnosis of Brain Death

Deep coma and brainstem dysfunction may mimic brain death in patients with severe baclofen poisoning. Despite these findings, patients with baclofen poisoning may survive neurologically intact if aggressive supportive care is provided. The diagnosis of brain death should be made extremely cautiously in patients with suspected baclofen toxicity. The American Academy of Neurology practice standards require the documentation of a proximate and irreversible neurologic injury prior to initiation of the brain death examination [108]. Several days of intensive care, serial neurologic examinations, and imaging studies to demonstrate irreversible brain injury should be pursued before pronouncing brain death in these patients [95]. Recovery has been reported after 5–7 days of coma [109]. A more detailed discussion of brain death determinations in this setting can be found in ▶ Chap. 13, "Poisoning Fatalities".

Clinical Manifestations of Baclofen Withdrawal

Baclofen withdrawal may occur after diminished or discontinued oral administration or more commonly after intrathecal pump malfunction [5, 68, 76, 79, 82, 83, 110–113]. Withdrawal may occur shortly after recovery from baclofen toxicity when baclofen treatment is not reinitiated promptly in the long-term use [50, 104]. The withdrawal syndrome occurs within 12–96 h after cessation of use, and symptoms generally resolve within 24–72 h of resumption of treatment, although some improvement may be seen sooner [50, 72, 114].

Respiratory distress, tachypnea, hypotension or hypertension, bradycardia or tachycardia, dysrhythmias, heart block, sleeplessness, agitation, shaking, coma, areflexia, diplopia, dyskinesia, visual disturbances, loss of pupillary light and oculocephalic reflexes, hyperthermia, diaphoresis, and hypersalivation have been reported [5, 50, 57, 61, 67, 68, 71, 79, 83, 104, 110–112,

114–119]. Rhabdomyolysis, disseminated intravascular coagulation, renal failure, hepatic failure, cerebral ischemia, and brain death may ensue [57, 82, 115, 117, 119]. Elevations in liver transaminase, creatinine, creatine phosphokinase, white blood cell count, and prothrombin time levels have been reported [57, 113, 115]. Acidosis may occur [115]. Cases of reversible cardiomyopathies in the setting of baclofen withdrawal have also been reported [120, 121]. There is significant overlap in the clinical presentation of overdose and withdrawal (e.g., autonomic instability, coma, seizures, laboratory abnormalities), and differentiating between the two entities may be difficult [50]. One helpful clue is that spasticity and muscle spasms (likely to some degree an unmasking of an underlying condition) and hyperthermia are seen more commonly with withdrawal, whereas hypothermia and hypotonia is seen more commonly with overdose.

Baclofen withdrawal syndrome may appear clinically similar to benzodiazepine or ethanol withdrawal, serotonin syndrome, sympathomimetic syndrome, neuroleptic malignant syndrome, infection, other febrile illnesses, or multiorgan system dysfunction of other etiology [21, 57, 72, 113, 117, 119, 122, 123]. Infection of the pump pocket, meningitis, and sepsis must be considered in patients receiving intrathecal baclofen [57, 81, 83, 122]. Modern pumps have bacterial filters that generally prevent overwhelming intrathecal infection; however, infection still may occur [77, 81, 85]. Pump function can be assessed using computer program systems and by aspirating and measuring the amount of drug remaining in the system [57, 81, 119]. These maneuvers may help differentiate among withdrawal, toxicity, and infection [119].

Diagnosis

Laboratory Studies

Baclofen can be detected by gas chromatography–mass spectrometry and high-performance liquid chromatography [43, 45, 48, 64, 66, 93]. Plasma, rather than cerebrospinal fluid, concentrations generally are assessed [43]. In nonfatal overdose, plasma or serum concentrations of 0.5–15 mg/L have been reported [124]. In a single fatal overdose, the serum concentration was 17 mg/L [41]. Other laboratory abnormalities in poisoning may include elevated creatine phosphokinase, lactate dehydrogenase, glutamic oxaloacetic transaminase, alkaline phosphatase, amylase, blood glucose, and white blood cell count [45, 58, 97]. Analysis of cerebrospinal fluid should be considered to rule out other disease processes (e.g., meningoencephalitis).

Imaging Studies

Intrathecal pump systems are radiopaque. Radiographs may show loss of catheter integrity [76, 117, 119]. Imaging of the brain and spinal cord should be considered to rule out other disease processes (e.g., hemorrhage or infarction). Brain imaging is of particular importance when seizure occurs with focal-onset features.

Special Studies

Electroencephalography often reveals reversible abnormalities. Typical electroencephalography findings are diffuse slowing of background activity and burst suppression [56, 58, 61, 66, 94]. In more severe cases, periodic delta and triphasic waves and generalized epileptiform discharges suggestive of seizures are seen [47, 56, 58, 73, 94, 96]. Although some patients with severe baclofen toxicity may appear severely neurologically impaired by clinical and electroencephalography findings, these patients frequently recover fully with adequate supportive care.

Treatment

Generally, patients do well with aggressive supportive care. Fatalities have occurred, however, despite medical care [9, 45, 65]. Respiratory failure and deep coma should be managed promptly

and aggressively with intubation and mechanical ventilation.

Gastrointestinal Decontamination

Because of the rapid onset of coma, induction of emesis is not recommended. It is reasonable to administer oral activated charcoal without gastric lavage to patients with suspected ingestion of baclofen if an intact airway can be ensured [65]. The administration of activated charcoal has not been shown to alter the outcome of baclofen-poisoned patients, however. Administration of oral activated charcoal to patients who may develop a decrease in their level of consciousness should always be done cautiously. It is likely that any potential benefit of activated charcoal decreases as the time from ingestion increases, although delayed administration may be beneficial in the presence of documented persistent absorption [51] [Level III].

Cerebrospinal Fluid Removal

If a large bolus of baclofen accidentally is injected intrathecally, some cerebrospinal fluid may be removed immediately in an attempt to limit toxicity [56, 96, 98, 99, 125, 126] [Level III].

Extracorporeal Removal

Case series data indicate that duration of toxicity in patients with severe renal impairment may be shortened by hemodialysis [36, 127, 128] [Level III]. In contrast, in patients with normal renal function, hemodialysis seems not to modify the elimination half-life [51].

Specific Nonantidotal Treatments

Cardiovascular

Severe hypertension should be treated with short-acting agents because hypertension can deteriorate rapidly to hypotension. If hypotension is unresponsive to intravenous fluid administration, vasopressor (e.g., norepinephrine) administration may be necessary [50, 56, 117]. Symptomatic bradycardia may respond to atropine [50, 65, 103, 105, 129] [Level III].

Indications for ICU Admission in Baclofen Poisoning

Evidence of toxicity after acute ingestion

Evidence of toxicity after recent pump adjustment or filling of reservoir

Evidence of significant toxicity after chronic exposure

Evidence of withdrawal symptoms after cessation of baclofen

Evidence of withdrawal symptoms with suspected pump failure

Neurologic

Seizures occur with baclofen toxicity and withdrawal. These seizures generally are brief and respond readily to treatment [65, 88]. Benzodiazepines have been used to control seizures and other symptoms of toxicity and withdrawal (e.g., unmasked spasticity of withdrawal) [63, 97, 114, 115, 119, 126]. Paralytic agents may be used to limit spasticity and convulsions, but there is a risk of status epilepticus going unrecognized clinically in a chemically paralyzed patient [119]. Electroencephalography monitoring is recommended if these patients are chemically paralyzed. Succinylcholine use should be limited; it should not be administered to patients who may have been comatose for prolonged periods, who have neuromuscular diseases, or who are suspected to be at risk of rhabdomyolysis or trauma. Patients with neuromuscular disease have altered muscle fiber receptors, resulting in hypersensitivity to hyperkalemia that may follow succinylcholine administration. Cardiac arrest may occur in these patients after the administration of succinylcholine [130, 131] [Level III].

Common Errors in Baclofen Poisoning

Failure to appreciate airway compromise

Failure to recognize the danger of succinylcholine administration in patients with neuromuscular disease

Failure to use short-acting agents when treating hypertension or hypotension and tachycardia

Failure to recognize nonconvulsive (akinetic) status epilepticus

Failure to consider the potential for prolonged, profound CNS depression with overdose

Failure to differentiate between toxicity, withdrawal, and infection

Failure to resume baclofen treatment after acute or chronic toxicity resolves, precipitating withdrawal

Withdrawal from intrathecal baclofen may be resistant to various treatments and may require reinstitution of intrathecal baclofen [68, 117, 126]. Case reports suggest that dantrolene may be helpful in treating baclofen withdrawal, but this is not well established [132]. It seems more sensible to resume baclofen promptly rather than initiate dantrolene therapy [115, 119]. Cyproheptadine has also been used in the treatment of baclofen withdrawal in both children and adults given its resemblance to serotonin syndrome in some cases [123, 133] [Level III].

Infectious

Pump infections may be treated by removal of the pump and intravenous antibiotic administration. Alternatively, antibiotics may be administered via the pump [77, 85] [Level III].

Specific Antidotal Treatments

In prior case reports of baclofen overdose, physostigmine has been administered as an antidote [96, 125, 134, 135]. Additionally, flumazenil has been given alone [65, 92, 103, 136, 137] or with physostigmine [56] in similar reports of baclofen poisoning. However, at this point, there is no clear evidence that either agent is advantageous, and further study would be warranted to support specific indications for use in baclofen poisoning. Ondansetron also has been reported as an antidote in a case report, but this agent has not been studied further [91]. In a single study, intravenous lipid infusion was trialed in dogs for treatment of baclofen poisoning and seemed to have a favorable outcome [138] [Level III].

Criteria for ICU Discharge in Baclofen Poisoning

Resolution of altered mental status and seizures

Resolution of blood pressure, pulse, and temperature abnormalities

Resumption of baclofen initiated without evidence of withdrawal

Special Populations

Pediatric Patients

Respiratory arrest occurred in a 22-month-old infant who ingested 10.9 mg/kg of baclofen [27]. Six children, age 2–6 years, presented after oral baclofen overdose; two children required intubation, and one child experienced seizures. Signs and symptoms were similar to those reported in adults [129]. An 8-year-old child presented with diminished responsiveness and vomiting then hypothermia, bradycardia, flaccidity, and areflexia after an intrathecal baclofen overdose [99]. In a case series of adolescents ingesting baclofen, 9 of 14 required intubation; their symptoms were similar to the symptoms seen in adults [65]. Another case involving an adolescent describes exam findings of coma and bradycardia in addition to seizures after abusive oral baclofen use [64]. Baclofen withdrawal syndrome also presents similarly in children and adults [57].

Pregnant Patients

Pregnant women and nursing mothers generally are excluded from baclofen treatment [5]. However, cases of intrathecal baclofen administration during pregnancy have been reported in the literature [139–141]. If a pregnant woman presents with baclofen toxicity, she should be treated supportively, as recommended for nonpregnant patients.

Elderly Patients

Peak plasma concentrations occur later after ingestion in elderly patients [43]. This delay may prolong the clinical course in elderly patients.

Other Patients

Patients with impaired renal function are at risk for developing toxic symptoms soon after initiating even low-dose baclofen. Patients on stable regimens of baclofen may develop toxicity if creatinine clearance declines [49, 94, 127, 142]. Serum creatinine levels may remain normal, despite diminished creatinine clearance [49].

Key Points in Baclofen Poisoning

1. Patients who receive aggressive supportive care generally survive baclofen toxicity.
2. There is no clinically available antidote that reliably reverses baclofen toxicity.
3. Seizures, resulting from either toxicity or withdrawal, generally respond to benzodiazepines.
4. Differentiating between baclofen toxicity and withdrawal can be difficult.
5. Generally, hypothermia suggests toxicity, whereas hyperthermia suggests withdrawal or possibly infection.
6. Baclofen toxicity can mimic brain death clinically.
7. Prompt resumption of baclofen administration is often essential for the prevention and treatment of baclofen withdrawal.

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