Official Newsletter of the **Utah Poison Control Center**

TOXICOLOGY TODAY

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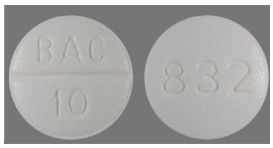
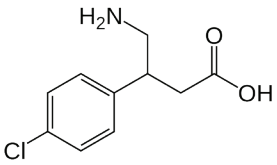
Baclofen

By Rachel Allen, MD, Chronic Pain Fellow, University of Utah



Baclofen 10 mg oral tablet
NLM https://pillbox.nlm.nih.gov



Skeletal formula of baclofen

INTRODUCTION

Baclofen is a synthetic drug derived from the inhibitory neurotransmitter γ-aminobutyric acid (GABA).[1,2] It is used for a variety of disorders related to muscle spasticity and spasm, including spinal cord injuries, multiple sclerosis, traumatic brain injury, dystonia, and complex regional pain syndrome, for which it has FDA approved uses.[3] As a muscle relaxant it also has an additional off-label use for back pain.[2] However, the most supported clinical use of baclofen is for treating spasticity of spinal origin. When used intrathecally via an implanted reservoir system, it has been shown to reduce spasticity, contractures, and pain—thus improving quality of life.[3] The abrupt discontinuation or accidental overdose of baclofen has serious ramifications, and the symptoms associated with both have some overlap, making it difficult to distinguish between too much or too little baclofen. Timely identification and treatment of overdose or withdrawal is imperative for improved outcomes.

Mechanism of Action

Baclofen—β-(4-chlorophenyl)-γ-aminobutyric acid—is a $GABA_B$ receptor agonist at known spinal sites.[4] It is postulated that there are also supraspinal sites of action. However, the exact mechanism by which baclofen reaches these sites remains unknown.

Baclofen blocks mono- and polysynaptic reflexes by inhibiting the release of excitatory neurotransmitters.[5] This blockade is mediated through the activation of the G-protein-linked $GABA_B$ receptor, which increases K^+ permeability, causing Ca^{2+} efflux and hyperpolarization of cell membranes. This results in the reduction of excitatory neurotransmitters such as glutamate and aspartate.[6] Additionally, baclofen is postulated to inhibit the release of the excitatory neurotransmitter, substance P, at the afferent terminals in the spine.

Administration and Pharmacology

Baclofen can be administrated orally (PO) and intrathecally (IT). Compounding pharmacies may also create a transdermal topical product with baclofen, and often other medications, to treat localized pain. The onset after oral ingestion is usually within 60 to 90 minutes, with 100% bioavailability and no reduced absorption due to food

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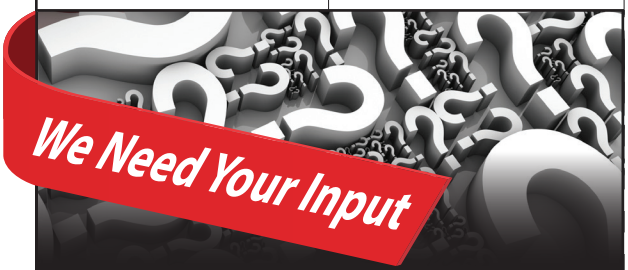

Environmental toxins are a leading concern for pediatric healthcare providers. The Utah Poison Control Center is collaborating with the Rocky Mountain Pediatric Environmental Health Specialty Unit to survey providers about their most pressing education needs related to this issue.

Please take 1-2 minutes to complete the survey by October 15, 2016.
Survey Link: http://goo.gl/azVau3

OUTREACH EDUCATION

Protect Against Insect Bites

By Sherrie Pace, MS, MCHES

Throughout the United States and the world, diseases may be transmitted through insect bites, including the West Nile virus, Dengue, and Zika virus, among others. Insect repellents can be very effective at reducing the risk for a bite and therefore the transmission of a disease. There are several types of repellents on the market that may offer protection from bites, including IR3535, Picaridin, and oil of lemon eucalyptus (OLE)*. However, those containing diethyltoluamide (DEET) are the most effective and are recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) to prevent insect-related diseases. DEET offers protection against insect bites such as mosquitos and ticks. Concentrations of DEET in repellents can range from 4% to 100%, and the amount in a product can be found on the label. Studies have shown that there is no significant difference in the effectiveness of products that contain greater than 50% concentration of DEET.

Using DEET or other repellents can increase the amount of time individuals spend outdoors when disease-carrying insects are most prevalent and reduce the chance of contracting insect-borne illness. However, it is not as effective as barrier protections, such as long-sleeved shirts and pants or using mosquito netting in sleeping areas. Other methods to avoid bites include staying inside from dusk until dawn and removing standing water where mosquitos lay their eggs. However, Zika may be transmitted by bites at all hours of the day because of different feeding habits of the mosquitos harboring the virus.

When using DEET, consumers should follow directions on the product label. When traveling to a country that has reported cases of Zika or Dengue, use insect repellent when going outdoors all the time and a mosquito net when sleeping. In addition, avoid spraying insect repellent in enclosed areas or around food, applying to eyes or mouth, or applying on cuts or wounds or on irritated skin. DEET should be applied on top of clothing rather than underneath.

The guidelines for using insect repellent on children differ from adults. Insect repellent should not be used on infants under 2 months old. Instead, they should be protected by draping mosquito netting, preferably with an elastic edge for a tight fit, over their carrier or car seat. For children over 2 months old, adults should apply insect repellent with a DEET concentration no greater than 30% by applying it to their own hands and then gently spreading it over the child's exposed skin. Avoid applying to children's eyes, mouth, and hands.

*"Pure" oils of lemon eucalyptus (essential oil) have not been tested by the EPA for safety and effectiveness and are not recommended by the CDC.

Resources: CDC, AAP

TOXINS IN THE NEWS

Fentanyl

By B. Zane Horowitz, MD

Fentanyl abuse is becoming more prevalent in America. Diverted pharmaceutical fentanyl is usually not the problem; instead it is the imported raw materials of fentanyl and several derivatives: acetyl-fentanyl, butyr-fentanyl, and furanyl-fentanyl. Carfentanyl, a large animal veterinary product, has even appeared in some cases.

Most heroin in the Western United States is black tar heroin that is dark in color and sticky in consistency. Fentanyl and derivatives are generally sold as loose white power. In addition to being sold to heroin users who inject the drug, fake fentanyl disguised as prescription medications is being sold by street entrepreneurs. Fentanyl and derivatives have been found in fake oxycodone, Norco® (hydrocodone and acetaminophen), and even Xanax® tablets.

While fentanyl itself is known to be very potent, with 75 mcg equivalent to 10 mg of morphine, the relative potency of these new derivatives, and sometimes mixtures of derivatives, is unknown and not studied. Carfentanyl is 10,000 times more potent than morphine. A number of deaths in Northern California earlier this year were linked to overdoses of fentanyl disguised as Norco® (MMWR April 29 2016). Fentanyl-containing pills have also been confiscated in Utah.

Clinicians should be on heightened alert for fentanyl overdoses. In patients who use heroin, ask about changes in color or consistency of their "heroin." If a tablet seems flimsy, don't assume it's the real medication, but ask the patient where he or she obtained it. Unless they got it directly from a pharmacy with a valid prescription, consider that it may be a new fentanyl. As with all opioids, treatment for respiratory depression includes supporting their breathing and administering naloxone to counter the opioid effects. Larger doses of naloxone may be necessary to reverse the effects of fentanyl, and repeat doses, or a constant infusion may be necessary despite what we know about the short duration of pharmaceutical fentanyl.

Cetylev™: A New Oral Acetylcysteine Dosage Form for the Treatment of Acetaminophen Toxicity

By Kaitlyn Brown, PharmD, Clinical Toxicology Fellow

Cetylev™ (acetylcysteine tablet, effervescent) is a new oral dosage form of acetylcysteine, FDA approved in March 2016 for the treatment of acute and chronic acetaminophen toxicity. It is supplied as a lemon-mint-flavored effervescent tablet. Cetylev™ follows the same dosage regimen as 72-hour oral acetylcysteine therapy: a 140 mg/kg loading dose, followed by 70 mg/kg maintenance doses every 4 hours for a subsequent 17 doses. The tablets are available as 500 mg and 2.5 g dosages and are to be dissolved in water. Each 2.5 g acetylcysteine tablet contains 438 mg of sodium, and each 500 mg tablet contains 88 mg of sodium. The package insert contains a weight-based dosing chart detailing the number of tablets needed to prepare the loading dose and maintenance doses. The loading dose is dissolved in 300 mL of water while maintenance doses are dissolved in 150 mL of water. This dosage form is marketed as a more palatable alternative to the classic acetylcysteine oral solution.

Adverse Events

The most common adverse reactions reported with Cetylev™ are nausea, vomiting, other gastrointestinal symptoms, and rash with or without fever.[1] However, the incidence of these adverse events is not described. Historically, oral acetylcysteine sodium has a 20% incidence of nausea and vomiting.[2] The high incidence of adverse effects is likely due to the strong sulfuric odor and unpleasant taste associated with acetylcysteine solution. The tolerability of Cetylev™ has not been studied in patients with acetaminophen toxicity.

Table 1. Average Wholesale Price (AWP) for a Full Course of Acetylcysteine Therapy in a 70 kg Patient*

Dosage Form	20% Acetylcysteine, Oral	Cetylev™	20% Acetylcysteine, IV
AWP[5]	30 mL (6g): $43.74	2.5 g tabs, box of 20 tabs: $433.96 500 mg tabs, box of 20 tabs: $86.80	120 mL (24g): $902.40
Full Course of Therapy	$678.00	$912.00	$790.00

** Does not account for an extra 2 days in the hospital for oral protocol over IV protocol.*

Use Cetylev™ with caution in patients requiring sodium restriction. When treating with the recommended dosage regimen, a 60 kg patient will receive 7 g of sodium on the first day, 5.3 g on the second day and 4.4 g on the third day.[1] These quantities exceed the American Heart Association's daily recommended[3] sodium intake of 1.5 g.

IV vs. Oral Acetylcysteine

IV and oral acetylcysteine are equally efficacious when administered within 8 hours of acute ingestion.[4] Thus, decision to use oral or IV acetylcysteine depends on tolerability, duration of therapy, and cost. Intravenous therapy is typically preferred over oral because it is better tolerated and its approved duration of administration is shorter.[4] However, oral acetylcysteine is preferred for patients unable to tolerate intravenous infusion due to anaphylactoid reactions.

The acquisition cost of the different acetylcysteine formulations varies by institution. Table 1 lists average wholesale prices for acetylcysteine dosage forms and the estimated cost based on the FDA approved full course of acetylcysteine therapy in an average-sized adult. Cost of therapy does not include preparation and administration fees, hospital length of stay, and readministration of doses.

The Bottom Line

Cetylev™ is a new flavor of an old antidote. It is not known whether it is more tolerable than diluting the current formulation used orally with a citrus-flavored beverage intended to mask the taste and smell.[6] Additionally, its very high sodium content may provide a new set of challenges for therapy, especially in patients with cardiac disorders. Therefore, the Utah Poison Control Center will continue to recommend IV acetylcysteine as first-line therapy for patients presenting with acetaminophen toxicity.

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intake. The oral half-life is 3–4 hours with a large variation from 0.9–5 hours and may last longer in overdose. Baclofen, when taken orally, undergoes 80% renal excretion and 15% hepatic metabolism.[7] Thus, one should exercise caution when prescribing baclofen to patients with renal impairment.

Intrathecal baclofen administration is 10 times more potent than oral administration and allows for more effective spinal treatment and reduced systemic side effects such as drowsiness, sedation, vertigo, fatigue, and confusion. The intrathecal half-life is 1.5 hours and is based on bulk clearance of the CSF.[5]

Baclofen Toxicity & Treatment

Baclofen may cause side effects at therapeutic doses and may be abused for its sedative effects. Since it is chemically and pharmacologically similar to GHB, a club drug of abuse, serious overdoses may occur. In one such event of intentional misuse, Perry reported 14 adolescents who became seriously ill after ingesting between 60-600 mg of baclofen at a party.[8] The most common clinical findings were hypothermia, bradycardia, hypertension, hyporeflexia, and coma, with two of the adolescents requiring endotracheal intubation. Coma can mimic brain death, and EEG tracings should not be utilized to determine brain death until the drug has been cleared completely. Other signs and symptoms of overdose are listed in Table 2.

There is no specific antidote to baclofen toxicity. Treatment is supportive care and symptomatic treatment.[9] Admission to a hospital or even intensive care unit is likely necessary, as intubation and mechanical ventilation might be needed for respiratory failure. Activated charcoal can be used for oral ingestion once the airway is protected by intubation. Symptomatic treatments include intravenous fluids to maintain renal function and blood pressure, atropine for symptomatic bradycardia, and benzodiazepines for seizures.

Table 2.

Baclofen Toxicity: Signs & Symptoms

Mild/Moderate

- Mydriasis (rare cases of miosis)
- Dizziness
- Weakness/hypotonia
- Hyporeflexia
- Vomiting
- Bradycardia
- Hypotension
- Hypothermia
- Sedation/somnolence

Severe

- Respiratory depression
- Seizures
- Coma
- Death

Baclofen Withdrawal and Treatment

Baclofen withdrawal can be potentially life-threatening following both intrathecal and oral administration. In most cases following cessation of intrathecal baclofen, withdrawal symptoms appear in 1–3 day(s).[10] This can be caused by intrathecal pump malfunction, programming error, catheter obstruction, low pump reservoir or other mechanical errors.

Prolonged baclofen use is proposed to cause downregulation of $GABA_B$ receptors. Cessation of baclofen after chronic intrathecal use leads to hyperactivity of afferent nerve impulses, resulting in the clinical features of muscle spasms, seizures, and agitation.[9, 12] Other withdrawal symptoms include changes in mental status, hallucinations, hyperthermia, anxiety, tremors, and rhabdomyolysis (Table 3). It is important to note that these symptoms can mimic other clinical scenarios such as sepsis, neuroleptic malignant syndrome, meningitis, illicit drug use, serotonin syndrome, and autonomic dysreflexia.

Early diagnosis of baclofen withdrawal is critical. If a patient is known to have a baclofen pump or a pump is suspected due to a healed abdominal incision or palpated abdominal mass, X-rays can be obtained to identify the presence and position of the pump and whether the catheter is intact.

Table 3.

Baclofen Withdrawal: Signs & Symptoms

- Hallucinations (auditory, visual, tactile)
- Altered consciousness
- Agitation/delirium
- Seizures
- Spasticity/rigidity
- Autonomic instability
- Tachycardia
- Tremors
- Hyperthermia
- Rhabdomyolysis
- Death

The ideal initial treatment is restoration of baclofen therapy, using the prior dose and route.[10] Oral administration of baclofen is not always feasible or practical, especially in the critically ill or intubated patient. Oral baclofen is not always effective in the early stages of withdrawal. In the case of a patient with a known baclofen pump, a skilled provider proficient in intrathecal baclofen pump management can assist with reinitiation of baclofen therapy.

While early restoration of baclofen therapy is critical, symptomatic treatment should be commenced immediately. This includes minimizing muscle spasticity and preventing and/or treating central nervous system complications (e.g., seizures). Treatment options include $GABA_A$ agonists such as *(cont. on pg. 5)*

(cont. from pg. 4)

Baclofen

IV benzodiazepines, which act to reduce spasticity and rigidity by pre- and postsynaptic mechanisms different from baclofen.[10] Sustained muscle contraction can lead to dangerous rhabdomyolysis with subsequent renal failure and, in rare cases, disseminated intravascular coagulation or even death. Aggressive restoration of intravascular volume and renal perfusion are key to initial management. In severe cases with acute kidney injury and hyperkalemia, hemodialysis may be required.

Hyperthermia should be managed with active cooling. The apparent similarities between baclofen withdrawal and malignant hyperthermia (MH) as well as neuroleptic malignant syndrome (NMS) have led to the use of dantrolene for the treatment of muscle rigidity and hyperthermia seen in baclofen withdrawal. Dantrolene binds to skeletal muscle ryanodine receptors, preventing the release of calcium into the cytosol from the sarcoplasma reticulum, effectively decoupling excitation and contraction. This suppresses contraction and thermogenesis of repeated muscle contraction.[11]

Other drugs such as tizanidine and cyproheptadine have been tried to decrease the central excitatory output in the treatment of baclofen withdrawal. As an α-2 agonist, tizanidine decreases excitatory input to alpha motor neurons to reduce muscle spasticity. Cyproheptadine is a potent serotonin antagonist that may decrease the excitatory output through serotonin pathways.[11]

Summary

Baclofen is used to treat a variety of disorders, with the strongest evidence for its treatment of spasticity of spinal origin. Overdose and withdrawal can have significant morbidity and mortality. Prompt diagnosis and treatment is key with close monitoring in a hospital setting needed. Supportive care is the mainstay of baclofen overdose, with restoration of baclofen administration being a critical component to prevent withdrawal.

Naloxone

Utah ranks 4th in the nation for drug overdose deaths, and most of them are from opioids. Deaths from opioids occur during use, misuse, or abuse of prescription opioids as well as heroin. Naloxone, a competitive antagonist at the opiate receptor, can rapidly reverse respiratory depression caused by opioids. A law passed in 2014 allows physicians to prescribe naloxone to be used by a layperson in the event a loved one or even a complete stranger appears to be experiencing an opioid overdose.

If opioids are in the home, then naloxone should be there too. Teens and young children are at risk for unintentional overdose when opioids are in the home. For a toddler, as little as a single tablet can be fatal.

We strongly urge you to consider coprescribing intranasal naloxone 4 mg for all patients on long-acting opioids such as methadone or long-acting preparations of morphine or oxycodone. We also recommend naloxone for patients taking greater than 50 mg morphine or hydrocodone per day or 33 mg oxycodone per day.

When naloxone is dispensed, it should include instructions for use and instructions to call 911 and/or the Poison Control Center when naloxone is administered. Education materials are available from the Utah Department of Health:

- Pocket card for drug overdose prevention (English and Spanish)
- Written instructions for administering Naloxone

Additional resources are available from http://health.utah.gov/vipp/topics/prescription-drug-overdoses/resources.html.

Patients and family members can obtain naloxone directly from pharmacies that currently have collaborative practice agreements with a prescriber, through Utah Naloxone or via a standing order. Currently naloxone is available through many pharmacy locations, including the University of Utah Health Care Community Pharmacies, Intermountain Healthcare, VA medical center, CVS, and many Associated Foods stores. For questions, call the Utah Poison Control Center at 1-800-222-1222.

Table 4. Oral Morphine Equivalents

Opiate	Some Trade Names	Mg	Mg*	Mg*
Morphine	(MS Contin, Kadian, Roxanol)	30	50	90
Oxycodone	(Oxycontin IR)	20	33	60
Hydrocodone	(Zohydro, Norco, Lortab)	30	50	90
Hydromorphone	(Dilaudid)	7.5	13	22.5
Oxymorphone	(Opana)	10	17	30
Tramadol	(Ultram, Ryzolt)	120	200	360

**Any patient on 90 mg morphine equivalents chronically or 50 mg acutely, should be prescribed home naloxone for rescue resuscitation by bystanders.*

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M-44 Sodium Cyanide

The United States Department of Agriculture, Animal and Plant Health Inspection Service, Bureau of Wildlife Services would like us to remind you that the M-44 sodium cyanide device is used in Utah. The ejector device contains a capsule of sodium cyanide, which is baited with meat and placed in the ground. This device is used in specific situations to control coyotes, red foxes, gray foxes, and wild dogs to protect livestock and endangered species and to prevent the spread of disease. This device is primarily used on private lands but may also be used on federal land in any county in the state. Areas where the M-44 sodium cyanide device is used are marked with signs. While human exposure to this device is extremely unlikely, be aware this device contains 91% sodium cyanide for which there is an antidote. Please report any exposure to this device to the Utah Poison Control Center at 1(800) 222-1222.

Meet the UPCC Staff

Simón Rodriguez, BS began working at the Utah Poison Control Center in December of 2014. He received his bachelor's degree in Exercise Physiology at the University of Utah and is currently in his last year of pharmacy school at the University of Utah. Simón was raised in Salt Lake City and has several hobbies, including taekwondo. He is a two-time US Collegiate National Team Member and has fought internationally in countries from Spain to Korea. His toxicology interests include plants and drugs of abuse.

Ben Davies, BS started working at the poison control center as a Poison Information Provider (PIP) in December of 2014. He received his bachelor of science from Brigham Young University and is currently a P3 student at the University of Utah Pharmacy School. Ben was born and raised in Spanish Fork, Utah. Ben enjoys the unique opportunity the UPCC provides student in taking incoming calls and helping people through their poisoning exposures. In his spare time, Ben enjoys reading, exercising, playing the piano, traveling, and spending time with family and friends. His toxicology interests include tricyclic antidepressants, fluoride, and hydrofluoric acid exposures.

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**Certified Specialist in Poison Information*
*** Diplomate of the American Board of Applied Toxicology*

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

POISON Help
1-800-222-1222

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