**BACLOFEN**

**THERAPEUTICS**

**Brands**
- Lioresal, Kemstro, Gablofen

**Generic?**
- Yes

**Class**
- Skeletal muscle relaxant, centrally acting

**Commonly Prescribed For**
(FDA approved in bold)
- Spasticity and spasms with concomitant pain related to disorders such as multiple sclerosis or spinal cord diseases
- Trigeminal neuralgia
- Tourette syndrome
- Tardive dyskinesias
- Chorea in Huntington’s disease
- Acquired peduncular nystagmus
- Migraine prophylaxis
- Neuropathic pain
- Alcohol dependence
- Hiccups
- Gastroesophageal reflux disease

**How the Drug Works**
- Baclofen is a GABA-B agonist, and an analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Baclofen has both presynaptic and postsynaptic actions. At the presynaptic site, baclofen decreases calcium conduction with resultant decreased excitatory amino acid release. At the postsynaptic site, baclofen increases potassium conductance, leading to neuronal hyperpolarization. Additionally, baclofen may inhibit the release of substance P. Use of baclofen appears to lead to marked facilitation of segmental inhibition. However, the exact mechanism of action is unknown but presumably related to hyperpolarization ofafferent terminals inhibiting monosynaptic and polysynaptic reflexes at the spinal level. It has CNS depressant properties

**How Long until It Works**
- Pain: hours–weeks (half-life is about 4 hours)

**If It Works**
- Slowly titrate to most effective dose as tolerated. Many patients will need gradual titration to maintain response and limit sedation

**If it Doesn’t Work**
- Make sure to increase to highest tolerated dose – as high as 200 mg/day. If ineffective, slowly taper and consider alternative treatments for pain. In general, baclofen is more effective for spasticity related to MS or spinal cord disease than other causes of spasticity

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- For focal spasticity, i.e. post-stroke spasticity, botulinum toxin is often more effective and is better tolerated
- Use other centrally acting muscle relaxants with caution due to potential synergistic CNS depressant effect
- Baclofen is usually used in combination with neuroleptics for the treatment of tardive dyskinesias or chorea
- Trigeminal neuralgia often responds to antiepileptic. Pimozide is another option. For truly refractory patients, surgical interventions may be required

**Tests**
- None required

**ADVERSE EFFECTS (AEs)**

**How Drug Causes AEs**
- Most AEs are related to CNS depression

**Notable AEs**
- Drowsiness, sedation, flaccidity, headaches, dizziness, weakness, and fatigue are most common. Nausea, constipation, hypotension, confusion, lightheadedness, weight gain, urinary retention, and sexual dysfunction

**Life-Threatening or Dangerous AEs**
- Worsening of seizure control. The most dangerous AEs occur with rapid baclofen withdrawal including high fever, confusion, anxiety, tachycardia, pruritis, seizures, labile blood pressure, hallucinations, rebound spasticity, muscle rigidity (adductor dyspnea spasms of the vocal cords), and in severe cases, DIC, rhabdomyolysis, multi-system organ failure, and death
Weight Gain
- Unusual

Sedation
- Problematic

What to Do about AEs
- Lower the dose and titrate more slowly

Best Augmenting Agents for AEs
- Most AEs cannot be improved by an augmenting agent. MS-related fatigue can respond to CNS stimulants, such as modafinil, but in most cases it is easier to temporarily lower the baclofen dose until tolerance develops

**Dosing and Use**

**Usual Dose Range**
- Spasticity
- Oral: 40–80 mg/day in divided doses (80 mg/day is the maximum daily dose in the PDR)
- Intrathecal: 300 μg – 800 μg/day, rarely more than 1000 μg/day

**Dosage Forms**
- Tablets: 10, 20 mg
- Orally disintegrating tablets: 10, 20 mg
- Intrathecal: 0.05 mg/mL, 10 mg/20mL, and 10 mg/5 mL in single-use amps

**How to Dose**
- Oral: start at 15 mg daily in three divided doses. Increase by 15 mg every 3 days as tolerated to 60 mg per day in three divided doses or until desired clinical effect. Patients may further benefit from increasing dose to 80 mg/day; usually not recommended but doses up to 200 mg/day have been used in patients that tolerate the medication well
- Intrathecal: patients must demonstrate a positive clinical response to treatment. A dose of 50 μg is given on day 1 over greater than 1 minute. Observe 4–8 hours for a clinical response. If the response is inadequate, can repeat with dose of 75 μg 24 hours later and again observe 4–8 hours for improvement. If no response, inject 100 μg on day 3. Patients who do not respond to a dose of 100 μg are not candidates for intrathecal treatment
- If the positive effect of the test dose lasts less than 8 hours, the starting dose would be doubled with the bolus dose given over 24 hours. If the response lasts over 8 hours, use the bolus dose as the original daily dose. In patients with spasticity of spinal cord origin, increase the daily dose by 10–30% after 24 hours and then every 24 hours until the desired clinical effect is achieved. In patients with spasticity related to cerebral origin and in children increase the dose more slowly – about 5–15% each increase per 24 hours until desired effect reached
- When to consider intrathecal baclofen: for treatment of spasticity related to a stable, irreversible neurologic disease or trauma that disables the patient or causes severe pain. The patient must have failed at least three to four oral medications or experience intolerable side effects at effective doses. The patient or the caregiver must understand the risks and benefits of the pump and the required follow-up care

**Dosing Tips**
- About 5% of patients will become refractory to increasing doses of intrathecal baclofen. In those patients, consider careful withdrawal and treatment with other antispasticity agents for 2–4 weeks, then restart at the initial continuous infusion dose
- Use caution in patients with chronic kidney disease

**Overdose**
- Vomiting, hypotonia, drowsiness, coma, respiratory depression, and seizures. In an alert patient induce emesis and lavage. In obtunded patients, intubation is often required

**Long-Term Use**
- Safe for long-term use. Effectiveness may decrease over time and tolerance to clinical effect occurs in about 5%

**Habit Forming**
- No

**How to Stop**
- To avoid withdrawal symptoms, taper slowly over a week or more depending on the dose and time on drug
Pharmacokinetics

- Orally: rapidly absorbed with excretion half-life 3–4 hours. Intrathecal: bolus lasts 4–8 hours, with initial onset 0.5–1 hour after bolus. Continuous infusion lasts 6–8 hours. The peak action is 4 hours after a bolus and 24–48 hours after starting continuous infusion. Excreted unchanged in the kidney.

Drug Interactions

- Use with other CNS depressants will exacerbate sedation. No hepatic metabolism, therefore no major drug interactions to consider.

Other Warnings/Precautions

- Decreased spasticity can be problematic for some patients who require tone to maintain upright position, balance, and ambulate.
- May cause an increase in ovarian cysts.
- May worsen symptoms of psychiatric disorders, such as schizophrenia or confusional states.
- May worsen control of epilepsy.

Do Not Use

- Known hypersensitivity. Never start intrathecal baclofen in patients with an active infection.

THE ART OF PAIN PHARMACOLOGY

Potential Advantages

- First-line treatment for spasticity in MS and spinal cord injury patients. Effect is maintained with extended use.

Potential Disadvantages

- Poor effectiveness and tolerability in patients with spasticity unrelated to MS or spinal cord injuries. Severe withdrawal AEs. Sedation often limits use.

Primary Target Symptoms

- Spasticity, pain.

Pearls

- Effective and important adjunctive medication for MS and spinal cord injury spasticity and pain. With slow titration, baclofen is usually well tolerated.
- Baclofen is generally not effective for spasticity related to Parkinson’s disease, stroke, and traumatic brain injury, although it occasionally is used in severe cases. In general these patients are much more susceptible to AEs.
- Do not attempt to use intrathecal baclofen before 1 year after traumatic brain injury.
- Intrathecal baclofen should be administered in centers that commonly treat MS and spinal cord disease.
- For patients on intrathecal baclofen with rapidly escalating dose requirements or new onset depression, fever, or confusion, consider the possibility of a shunt catheter malfunction.
- Some spasticity can be helpful for patients with MS or spinal cord injuries to support circulatory function, prevent deep vein thrombosis, and optimize activities of daily living.
- A second-line treatment for trigeminal neuralgia.
- Baclofen has been used off-label for many other conditions such as chorea, hiccups.

Pregnancy

- Category C: use only if benefits of medication outweigh risks.

Breast-Feeding

- Oral baclofen is excreted in breast milk. Do not use.

SPECIAL POPULATIONS

Renal Impairment

- Since baclofen is renally excreted, lower the dose with significant renal dysfunction.

Hepatic Impairment

- No known effects.

Cardiac Impairment

- No known effects.

Elderly

- Titrate carefully but no contraindications.

Children and Adolescents

- Children over age 12 have similar dose requirements as adults. Children under 12 usually have a lower dose requirement for intrathecal baclofen – on average 274 μg/day. For small children, start with a test dose of 25 μg.

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gastroesophageal reflux disease, migraine, and neuropathic pain

- Intravenous physostigmine in incremental 1–2 mg boluses may be beneficial in some cases of severe baclofen overdose
- In the United States baclofen is available as a racemic mixture, R(+-)-baclofen is the active isomer

- May inhibit cravings in the treatment of alcohol and other substance abuse
- A potential future agent currently in clinical development is arbaclofen placarbil, an R-baclofen prodrug which should have sustained action and less fluctuation in baclofen levels
- Avoid or use extremely cautiously in patients with chronic kidney disease

Suggested Reading


