BACLOFEN

Introduction

Baclofen is an anti-spastic agent, that acts to reduce **skeletal muscle spasticity**.

Its action is sometimes referred to as "muscle relaxant" however this is misleading terminology as this term is also applied to depolarising and non-depolarizing skeletal muscle **paralysing** agents used in anaesthesia.

Baclofen does *not* result in skeletal muscle paralysis. The terminology **anti-spasticity agent** is a more accurate description of the action of baclofen.

Baclofen is used for chronic spasticity or muscle spasm resulting in painful or debilitating symptoms, in association with some neurological conditions including:

1. Neurodegenerative disorders:
    - MS
2. Spinal cord lesions (of any causation)
3. Cerebral palsy

Sudden cessation of baclofen therapy may precipitate a withdrawal syndrome, which can be life-threatening.

Large ingestion overdose can result in life-threatening seizures/ coma.

See also separate document on Baclofen Overdose (in Toxicology folder).

History

Baclofen was initially designed as an anti-epilepsy agent.

It was developed by the Swiss chemist Heinrich Keberle, in 1962.

It was not satisfactory as an anti-epilepsy agent, but it was found that in some people, spasticity was decreased, and so it gained value for this indication.

Chemistry

Baclofen it is a synthetic structural analogue of GABA.

Classification

There are a number of drugs which act by different mechanisms to reduced skeletal muscle tone.

The most commonly used include:

1. **Baclofen**
2. Dantrolene
3. Orphenadrine

Note that these agents are *not* related to the depolarising and non-depolarizing skeletal muscle paralysing agents used in anaesthesia.

Preparations

Baclofen as:

Tablets:

- 10 mg
- 25 mg

Ampoules:

- 0.05 mg/mL, in 1 mL
- 0.5 mg/mL, in 20 mL
- 2 mg/mL, in 5 mL
- 2 mg/mL, in 20 mL

Mechanism of Action

At therapeutic doses, baclofen acts principally on **spinal** GABA-**B** receptors, *inhibiting the release* of the excitatory amino acids - glutamate and aspartate.

In overdose it causes effects on **brain** GABA receptors resulting in *inhibition* of CNS excitatory neurotransmitters leading to sedation and coma.

Pharmacodynamics

Baclofen is an effective anti-spastic agent with a spinal site of action.

Baclofen also has central sites of action and has general CNS depressant properties.

In neurological diseases associated with spasm of skeletal muscles, clinical benefits can include:

- Reduced reflex muscle contractions
- Relief from painful spasm, automatism and clonus.

Baclofen, where indicated, improves the patient's mobility, making for greater independence, and facilitating passive and active physiotherapy.

Maximal clinical benefit may take up to **6 - 8 weeks of achieving the maximum**

Pharmacokinetics

Absorption

- Baclofen can be administered orally or intrathecally.

  Baclofen is rapidly and completely absorbed following ingestion.
- Peak serum concentrations occur within 2 hours.

Distribution

- The volume of distribution is 0.7 L/Kg.
- Baclofen readily crosses the blood brain barrier.
- Protein binding is modest at around 30%.
- It is thought likely that baclofen crosses the human placenta.
- Baclofen is distributed into human breast milk in small amounts only.

Metabolism and excretion

- About 15% is metabolised in the liver to inactive metabolites.
- About 85% is excreted unchanged in the urine.
- The elimination half life is ranges from 4 -7 hours.

Indications

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Contra-indications/precautions

These include

1. Known allergy
2. Psychiatric disorders
    - Risk of aggravation of symptoms.
3. Epilepsy
    - Risk of aggravation.
4. Cerebrovascular disease
5. Parkinson's disease
    - Risk of aggravation of symptoms.
6. Respiratory disease
7. Hypertonic bladder sphincter
    - Risk of aggravation.
8. Diabetes
    - Risk of increased blood glucose concentration.
9. Renal impairment:
    - Primarily renally excreted; so reduce initial dose in renal impairment.

      Toxicity has occurred after low doses in patients with severe renal impairment.
10. Hepatic impairment:

- Use with caution in hepatic impairment; increased risk of adverse effects; monitor liver function.

11. Peptic ulcer:

- The manufacturer advises caution in patients with a history of peptic ulcer; however, reports of gastric acid-related adverse effects in humans are **lacking**.

Pregnancy

Baclofen is classified as a category B3 drug with respect to pregnancy.

Category B3 drug are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Most case reports have described normal pregnancy outcomes following maternal use of baclofen.

However, a single case of late onset neonatal convulsions caused by baclofen withdrawal has been reported. In addition, ongoing baclofen use during pregnancy until delivery may cause neonatal withdrawal symptoms.

If baclofen is the medicine of choice, treatment should not be withheld because of pregnancy. However, follow-up and monitoring of both maternal and fetal wellbeing by a multidisciplinary team is recommended.

Breast feeding

There is limited safety information available following the use of baclofen during breastfeeding.

Small amounts of baclofen are excreted into breast milk, but adverse effects have not been noted in breastfed infants.

If maternal baclofen is stopped suddenly, a severe withdrawal syndrome may occur.

Therefore, if baclofen is the medicine of choice, use the lowest effective daily dose possible and observe the breastfed infant for potential adverse effects such as excessive drowsiness, poor feeding and restlessness.

Adverse Effects

These include:

1 GIT upset:

- Nausea / vomiting / constipation / diarrhoea.

2. Neurological:

- Sedation
  - ♥ Can cause synergetic CNS depression with other CNS depressants, including alcohol.
- Lowered seizure threshold
- Confusion
- Mood changes; euphoria / depression,
- Hallucinations
- Ataxia / tremor / nystagmus
- Tinnitus
- Visual disturbances
- Dyskinesia
- Dysarthria
- Paraesthesiae

3. Muscle weakness

4. Respiratory depression.

5. Increased blood glucose levels.

6. Hepatic:

- Elevated liver function tests

Baclofen withdrawal syndrome:

This may occur between 24 and 48 hours post **abrupt** cessation of baclofen.

Baclofen withdrawal can be **life-threatening**

It is characterised by:

- Delirium / hallucinations
- Visual disturbances
- Seizures
- Dyskinesia
- Hyperthermia

Management essentially involves reinstating baclofen. This should be discussed with a clinical Toxicologist.

Dosing

Slower dose titrations of baclofen may minimise adverse effects (e.g. drowsiness).

If no benefit is apparent within **6 - 8 weeks of achieving the maximum** dosage, a decision should be made on whether to continue treatment with baclofen.

Discontinuation of the treatment should always be gradual by successively reducing the dosage over a period of approximately 1 - 2 weeks, except in overdose-related emergencies, or where serious adverse effects have occurred

Adults:

Usual adult dosing is:

- Oral, initially 5 mg tds;

  Increase gradually by 15 mg daily every fourth day until therapeutic effect is obtained.

  Usual range, **10 - 25 mg 3 times daily**.

- Doses up to 120 - 150 mg daily may be given in hospitalised patients.

Renal impairment:

Oral, initially 5 mg once daily;

Then titrate dose cautiously according to response.

Give after dialysis.

Elderly:

Oral, initially 5 - 10 mg daily in divided doses;

Increase by smaller increments and at longer intervals.

Children:

Oral, initially 0.75 mg/kg daily in 3 or 4 doses;

Increase gradually every 3 days to 2 mg/kg daily in 3 or 4 doses.

Maximum 40 mg daily for children < 8 years or 60 mg daily for children 8 - 10 years.

Intrathecal administration:

Intrathecal administration is sometime used in people who fail to respond to oral administration or cannot tolerate high doses orally.

References

1. eTG - October 2019

2. Baclofen in Australian Medicines Handbook Website, Accessed October 2019.

3. Baclofen in MIMs Website, 1 September 2019.

4. Baclofen in RWH Pregnancy & Breastfeeding Guidelines, 30 October 2018.

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