

# **Toxicology Conference**

## **Skeletal muscle relaxants**

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# The case

- A 12 year old boy with CP is brought to the ED by his grandma
- He is obtunded, and has intermittently stopped breathing according to grandma
- Earlier that day he had an appointment and was then dropped off at grandma's house by his mother
- He was acting fine when he first arrived at grandma's

# The case

- The triage RN comes back to the B pod where you are drinking coffee out of an approved container
- The patient is sick
- Grandma is frazzled
- You are as cool as the other side of the pillow



# The case

- Grandma is calling mom on her pink RAZR for his medical information
- Meanwhile as you prepare to examine him he stops breathing again and you call a medical team



# Physical exam

- T-36.5 HR-80 BP-68/49 RR 0 spontaneous
- Sat-89% with BMV
- Unconscious, no response to painful stim
- Pupils 3mm b/l and sluggish
- No evidence of head trauma, mmm
- Coarse breath sounds b/l
- Heart exam was unremarkable, 1+ pulses
- You feel a hard LLQ mass the size of a hockey puck on abdominal palpation
- No spontaneous movement, increased muscle tone

# In the Trauma Bay

- He is intubated for lack of spontaneous respirations
- IV access is established
- Narcan is discussed, but not given
- You order 40ml/kg over the Belmont infuser
- Initial ISTAT
  - pH 7.21
  - pCO<sub>2</sub> 66
  - Base deficit -2
- His glucose is 88, other values are unremarkable

# In the Trauma Bay

- After 40ml/kg he is still hypotensive, and another bolus is given
- The chest Xray is unremarkable, and the ETT placed by the PL3 is in good position
- You start dopamine in consultation with the PICU and his BP improves
- Your CBC, B/C, and urine studies are in the lab
- He has received Cefotaxime

# More history

- As you are about to take him to the CT scanner Mom arrives and gives you some more information
- He has a h/o CP, a ventriculoperitoneal shunt placed at birth and last revised at age 5
- He also had an intrathecal baclofen pump implanted at age 5
- It was replaced at age 8
- He goes to grade school and gets straight A's
- His meds include only baclofen and miralax
- Today he was seen in the multidisciplinary clinic where his baclofen pump reservoir was filled



# The case continued

- After an unchanged CT scan he is admitted to the PICU
- His coverage was broadened with the addition of Vancomycin
- His BP stabilized on Dopamine, but he was still not arousable
- Neurosurgery was consulted, and in conjunction with Rehab, the source of his symptoms was finally elucidated

# Skeletal muscle relaxants

- Act as sedative-hypnotics to indirectly provide skeletal muscle relaxation
- Prescribed for muscle spasm in chronic pain conditions, as well as in patients with spasticity
- Examples include;

**Baclofen**

**Carisoprodol**

**Cyclobenzaprine**

**Methocarbamol**

**Tizanidine**

**Orphenadrine**

**Lioresal**

**Soma**

**Flexeril**

**Robaxin**

**Zanaflex**

**Norflex**

# Mechanism of toxicity

- Generalized CNS depression
  - **Baclofen** is a GABA<sub>B</sub> agonist causing CNS and respiratory depression, but also paradoxical muscular hypertonicity
  - **Soma** can cause spastic encephalopathy
- Cardiovascular effects
  - Hypotension
  - **Baclofen** causes bradycardia in 30% of OD
- Pharmacokinetics
  - $t_{1/2}$ s vary, up to 24-72 hours for **Flexeril**

# Toxic dose

- It varies between agents, but generally 3-5x normal dose is enough
- Co-ingestions (ethanol) obviously play a large role
- In a few case reports toddlers have required mechanical ventilation after ingestion only 700mg (2 tablets) of **Soma**



# Clinical presentation

- CNS depression is usually seen within 30-120 minutes of ingestion
- Other symptoms include;
  - Lethargy
  - Slurred speech
  - Ataxia
  - Coma
  - Respiratory arrest

# Specific drugs

- **Soma (carisoprodol)**
  - Hyperreflexia, opisthotonus, and increased muscle tone



Sir Charles Bell's portrait of a man with generalized tetanus, opisthotonus, and rhisus sardonicus

# Specific drugs

- **Flexeril** (cyclobenzaprine) and **Norflex** (orphenadrine)
  - Can also produce anticholinergic symptoms
    - Tachycardia, dilated pupils, delirium
  - Though structurally similar to TCAs **Flexeril** does not appear to have the same cardiotoxicity
  - **Norflex** however can cause ventricular tachycardia

# Specific drugs

- **Zanaflex (tizanidine)**
  - Similar to clonidine
  - Can cause coma, profound hypotension, and bradycardia
  - SA and AV node dysfunction has also been reported





# Treatment of overdose

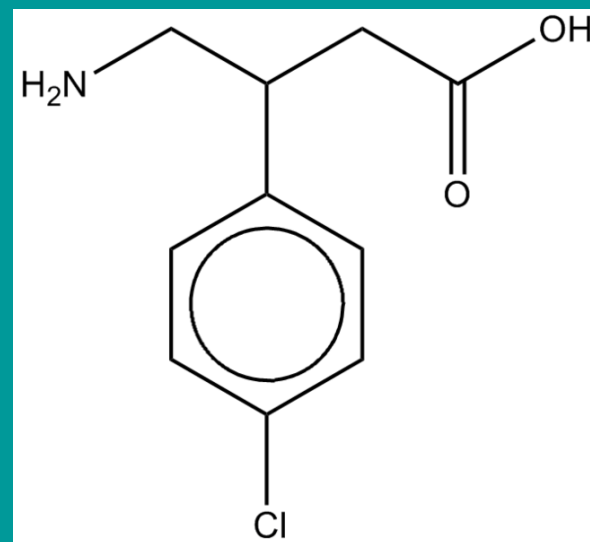
- ABCs
- Treat coma, hypothermia, hypotension
- Monitor patients for at least 6 hours after ingestion, as some agents have delayed absorption
- GI decontamination
  - Use activated charcoal if conditions are right
- These drugs have extensive tissue distribution, so dialysis isn't likely to be effective

# Treatment of overdose

- Specific antidotes?
  - Sorry, there are none
  - Flumazenil is a benzodiazepine receptor specific agent (not the type of GABA these drugs interact with)
    - Though it has been reported to be effective in **Soma OD**
  - Physostigmine may reverse anticholinergic Sx of **Flexeril** and **Norflex** – but may also cause seizures, and is generally not necessary

# Baclofen

- A skeletal muscle relaxant used to decrease spasticity in patients with CP, MS, spinal cord injury, and other disorders
- It is an analog of GABA, and binds to the GABA<sub>B</sub> receptors and inhibits calcium influx therefore preventing the release of excitatory neurotransmitters (glutamate and aspartate)



# Baclofen

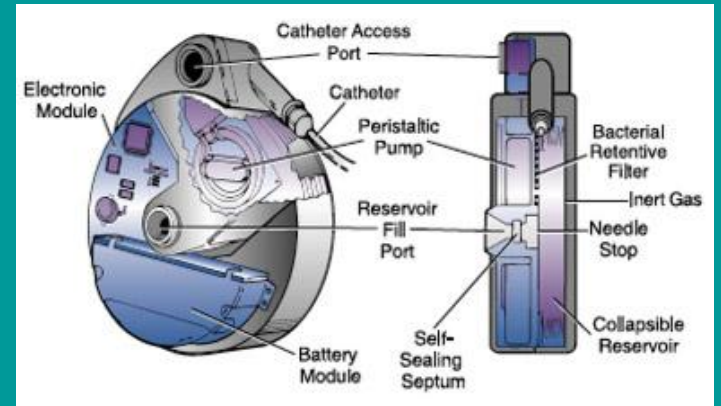
- Pharmacokinetics
  - Oral
    - Muscle relaxation effects require 3-4 days and maximal clinical effects are not seen for 5-10 days
  - Intrathecal
    - Onset 30-60 minutes
    - Max effect 4 hours, duration 4-8 hours

# Baclofen pumps

- Intrathecal pumps are useful for patients with spasticity that does not respond to oral doses, or to those who have significant side effects at therapeutic PO doses
- There are over 15,000 patients in the world with intrathecal baclofen pumps

# Baclofen pumps

- The pump is inserted into a subcutaneous pocket on the anterior abdominal wall
- It is connected to a catheter that passes subcutaneously around the flank before being inserted into the lumbar thecal sac
- It is inserted either by needle or laminotomy



# Baclofen pumps

- Typical doses are between 100 to 900 micrograms/day
- Initially a 25-100 ug dose is given, and then titrated to muscle spasticity
- A computer is then used to set the continuous infusion rate
- Every 6 to 12 weeks the reservoir is filled with a new supply of baclofen
- The pump itself (not the catheter usually though) is replaced at 3 to 5 year intervals

# Baclofen Overdose

- Signs of overdose
  - Drowsiness
  - Dizziness/Lightheadedness
  - Slow and shallow breathing
  - Seizures
  - Loss of consciousness and coma
  - Autonomic instability
  - Cardiac conduction abnormalities
  - Nonreactive pupils (because it affects the brainstem)



# Baclofen Overdose

- Management of overdose
  - ABCs
  - Empty pump and stop drug flow
  - Physostigmine may reduce central side effects including somnolence or resp depression
    - Acetylcholinesterase inhibitor
    - It can cause bradycardia, incr seizure risk, and incr resp secretions
- There is no specific antidote for baclofen

# Baclofen Withdrawal

- Signs of withdrawal
  - Pruritis
  - BP changes
  - Spasticity
  - High fever
  - Altered mental status
- The spasticity has the potential to lead to rhabdo, multi-system organ failure, and death

# Baclofen Withdrawal

- Management of withdrawal
  - ABCs
  - If the patient has an intrathecal delivery system
    - Call their rehab MD or neurosurgeon
    - High dose oral/enteral baclofen
    - Restore intrathecal infusion if stopped
    - IV benzodiazepines
    - Note that oral baclofen should not be relied upon as the sole therapy for withdrawal in patients receiving intrathecal therapy

# Back to the case

- The neurosurgery NP (luckily it was before 5PM) uses a portable programming device to stop the patient's baclofen pump
- Further workup showed a normal shunt series
- His EEG was normal except from some slowing that was attributed to the sedative meds given to him while he was intubated
- His CSF was normal, and 30ml of CSF was removed upon LP in order to decrease intrathecal baclofen levels
- Physostigmine was not given because his vitals normalized

# The case continued

- On HD #2 he starts to cough with deep suctioning
- CSF baclofen level came back at 7471ng/mL (no reference levels – but trust me, that's high)
- Serum baclofen level 0.38ug/mL (0.08-0.40)
- All Cx were negative at 48hrs and antimicrobials were stopped
- His BP normalized and he was weaned off dopamine
- Neurosurgery emptied his baclofen pump

# The case continued

- By HD #4 his sedation was weaned, and he responded to simple commands
- He was successfully extubated
- On HD #5 he became tachycardic, and hyperthermic
- He complained of headache and dizziness
- Baclofen withdrawal was suspected, and he was started on appropriate oral doses of baclofen
- His symptoms improved by HD #6

# The case continued

- On HD #9 he underwent a pump revision
- He was D/C on HD #10
- It was ultimately determined that during the filling of the pump the baclofen was injected into the subcutaneous pocket in which the pump was situated, as opposed to the reservoir itself
- The baclofen was then rapidly absorbed into the systemic circulation