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

Yo, it’s Dolores, where you at?
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
  pCO2 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:

<table>
<thead>
<tr>
<th>Baclofen</th>
<th>Lioresal</th>
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<tr>
<td>Carisoprodol</td>
<td>Soma</td>
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<tr>
<td>Cyclobenzaprine</td>
<td>Flexeril</td>
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<tr>
<td>Methocarbamol</td>
<td>Robaxin</td>
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<tr>
<td>Tizanidine</td>
<td>Zanaflex</td>
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<tr>
<td>Orphenadrine</td>
<td>Norflex</td>
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Mechanism of toxicity

• Generalized CNS depression
  – **Baclofen** is a GABA\textsubscript{B} agonist causing CNS and respiratory depression, but also paradoxic 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, ophisthotonus, 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\textsubscript{B} 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
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