Drug-Drug interactions and Anesthesia

Serotonin Syndrome
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Lecture objectives
• Have a better understanding of Serotonin Syndrome
• Be able to recognize signs and symptoms
• Be able to provide treatment/supportive care

Case 1:
• 69 year old female presenting for mid thigh lipoma resection under Local/MAC
• 1st case of the day
  • PMH
    • 67kg
    • GERD- Ranitidine
    • Depression- Effexor
    • Multiple lipomas resected in the past

Case 1:
• Once in the operating room pt received
  • 2 mg Midazolam
  • 100 mcg Fentanyl
  • 20 mg Ketamine
  • Propofol infusion titrated as needed
  • Local Anesthetic by Surgeon
  • 4 mg of Zofran at the end of the case

Case 1:
• At the conclusion of surgery
  • Pt was awake
  • Comfortable
  • Alert/Oriented
  • Vital Signs Stable
  • She was discharged to Phase 2 Recovery

Case 1:
• Shortly after presenting to Phase 2 recovery covering anesthesiologist was paged overhead to quickly report to a bay where our discharged pt was recovering
  • Nurse States-“I think the patient is having some sort of allergic reaction”
Case 1:
- First look at the patient
  - Confused/Agitated
  - Trying to crawl out of bed
  - Moaning for help
  - Slight flushing over the chest
  - BP 210/100 HR 95
  - Rhythmic myocloning jerking in hands and feet

Case 1:
- Unsure what was causing her symptoms
- Differential Diagnosis
  - Unpleasant Reaction to Ketamine
  - Possible Serotonin Syndrome

Case 1:
- Symptomatic Treatment
  - Multiple doses of Versed 2 mg each
  - Labetalol to keep BP <160mmHg
  - Benadryl
- Following Versed and Labetalol administration pt became somnolent and BP stabilized
- However, myoclonic jerking in all 4 extremities persisted
- Pt was transferred to internal medicine service for further care and observation

Case 1:
- 4 hours later the patient regained consciousness, myoclonic jerking disappeared and patient was discharged to home with follow up care with her primary care physician
- Pt had no recollection of any of the events

Literature Search

Case 2:
- 40 year old male
- 85 kg
- Hernia repair
- Under general anesthesia
- Unremarkable medical history
  - Treated depression
  - Prozac (Fluoxetine)
Case 2:
- Uneventful standard general anesthetic
  - Lidocaine
  - Propofol
  - Fentanyl
  - Rocuronium
  - Zofran
  - Muscle relaxation reversed at the end of the case with
    - Neostigmine/Glycopyrrolate

Case 2:
- Extubated and taken to the recovery room
- Alert, oriented, comfortable and VSS
- Pt reported that his feet started to involuntarily move/twitch and that he feels a little restless

Case 2:
- Over the next 5-10 minutes patient developed agitation and confusion
- Myoclonic jerking developed in all four extremities
- He rapidly progressed to being diaphoretic, hypertensive and tachycardic with normal SpO2 readings
- In addition he had ocular movement/twitching
- Generalized muscle twitching/fasciculations

Case 2:
- Completely unresponsive
  - Occasional bursts of moaning and grunting
  - He also developed severe muscle rigidity

Case 2:
- Serotonin Syndrome was suspected
  - Oxygen was applied via CFM
  - Multiple doses of Midazolam and Labetalol administered
    - However, no improvement was seen
  - Pharmacist was contacted in regard to availability of Cyproheptadine (A known antidote for SS)
    - Available as a pill by mouth

Case 2:
- Crushed 12 mg of Cyproheptadine buccally
  - Rapid improvement w/in 5-10 minutes
  - Additional crushed 12 mg was given
  - Pt regained consciousness and neuromuscular symptoms disappeared
  - He was observed for hours and discharged
What is Serotonin Syndrome?

- SS is a potentially life-threatening condition that results from excessive accumulation of neurotransmitter serotonin in the CNS.

- This increase in serotonin level is not a natural phenomenon but is attributed to certain medication use or synergistic interaction between multiple classes of medications that exert their affect on serotonin release, reuptake or breakdown.

Serotonin Syndrome

- Usually presents with a range of symptoms that vary in severity from mild to life threatening.
- 3 Categories of symptoms:
  - Mental Status Changes
  - Autonomic Hyperactivity
  - Neuromuscular abnormalities

Serotonin Syndrome

- Has been observed in:
  - Newborn
  - Children
  - Adults
  - Elderly
- It is encountered in all areas of healthcare:
  - Outpatient/Inpatient
  - ER visits
  - Perioperative/Anesthesia

Incidence

- Unknown
- Many case reports
  - Probably more common than we think as many cases are not reported

Serotonin Syndrome

- When properly recognized and treated most patients experience full recovery.
- Severe cases can have mortality as high as 2-10%.
- Can lead to end organ damage:
  - Rhabdomyolysis-kidney damage
  - DIC
- Prolonged hospital stay
- Increased cost of healthcare
- Disrupt surgical schedule

Serotonin Physiology

- Serotonin mediates excitatory neurotransmission through its action on G-protein-coupled/ligand channels.
- It is a monoamine neurotransmitter that is derived from tryptophan.
- 7 different receptors for serotonin: 5HT1-5HT7.
Serotonin function outside the CNS

- GI system
- Peristalsis
- Platelets
  - Promotes aggregation
- Blood vessels
  - Vasoconstriction
- Uterine tone/Bronchoconstriction

Serotonin function in the CNS

- Serotonin Stimulates Postsynaptic neurons
  - 5-HT1A and 5-HT2A receptors
- Serotonin plays a role in
  - Regulating mood
  - Personality
  - Appetite
  - Wakefulness
  - Temperature
  - Sexual behavior

Pharmacology

- These CNS receptors are important in psychiatric pharmacology as their stimulation has been found useful in management of multiple psychiatric disorders
  - Depression
  - Anxiety
  - Eating disorders

Pharmacology

- Multiple classes of Psychiatric Medications
  - Selective serotonin reuptake inhibitors
  - Serotonin/norepinephrine reuptake inhibitors
  - Monoamine oxidase inhibitors
  - Serotonin releasing agents

**Play a role in serotonin production, release reuptake and breakdown**
SSRIs/Pharmacology

- Higher concentration leads to stimulation of serotonin receptors at the CNS and outside the CNS

Prescribed Predisposing medications

- SSRIs: Fluoxetine, Fluvoxamine, Paroxetine, Citalopram, Sertraline, Escitalopram
- SNRIs: Trazodone, Duloxetine, Venlafaxine
- MAOIs: Phenelzine, Tranylcypromine, Turmeric
- Serotonin releasing agents: Fenfluramine, Amphetamines, Ecstasy, LSD
- Miscellaneous (Serotonin receptor agonist): Lithium, Tryptophan, St. John’s Wort, Turmeric, Tramadol, cough suppressants, Buproprion, L-Tryptophan, Xarelto

Synergistic perioperative medications

- Opioids (Weak SSRIs): Fentanyl, Sufentanil, Alfentanil, Remifentanil (Meperidine derivative), Oxycodone-mimics serotonin activity
- Anti-Emetics (5HT3 blocker): Granisetron, Ondansetron
- Antibiotics: Linezolid – Strong MAOI inhibitor
- Dyes: Methylene Blue – Strong MAOI inhibitor

Serotonin Syndrome

Onset, Clinical findings, Diagnosis

- Usually following a change in dose or addition of synergistic serotonergic medications
- With in 24 hours
- Rapid symptom progression
- Diagnosed on clinical findings

Clinical findings

<table>
<thead>
<tr>
<th>Mental Status</th>
<th>Neuro/Muscular</th>
<th>Autonomic Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Startles easy</td>
<td>Mydriasis</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Anxiety/agitation</td>
<td>Hyperreflexia</td>
<td>BP fluctuation</td>
</tr>
<tr>
<td>Delirium/confusion</td>
<td>Tremor</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td>Visual Hallucinations</td>
<td>Rigidity</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Trismus</td>
<td>Temp &gt;38</td>
</tr>
<tr>
<td>M utilis</td>
<td>Myoclonus</td>
<td>Flushed skin</td>
</tr>
<tr>
<td>Coma</td>
<td>Ocular movements</td>
<td></td>
</tr>
</tbody>
</table>

Hunter Serotonin Syndrome Criteria

- One of the following
  - Spontaneous clonus
  - Inducible clonus and agitation/diaphoresis
  - Ocular clonus and agitation/diaphoresis
  - Tремор
  - Hyperreflexia
  - Temp >38 and inducible clonus or ocular clonus

True positive 84%
True negative 97%
The most important clinical signs
• Spontaneous
  • inducible clonus, + Babinski Sign
• Generalized hyperreflexia
• Rigidity in the lower extremities

Signs and symptoms under anesthesia
• Delayed emergence from anesthesia
• Hyperthermia, tachycardia hypertension
• Increase in EICo2
  • Due to hypermetabolic state
  • Increased muscle activity
• Neuromuscular excitation
  • Clonus/jerking movements if pt not paralyzed
  • w/spinal anesthetic symptoms above block

Lab evaluation
• No single lab that will confirm a diagnosis
• Complete blood count- WBC
• Basic Electrolytes
• BUN/Creatinine
• Creatine Phosphokinase-
• Liver labs
• Coagulation studies-Coagulopathy

Untreated Serotonin Syndrome
• Coma
• Intravascular clotting
• DIC
• Elevation of creatinine/renal failure
• Hypertension that leads to shock
• Metabolic acidosis
• Rhabdomyolysis/Myoglobinuria
• Multiorgan failure

Serotonin Syndrome Management
Supportive care
• Symptom management

Administration of Antidote
• Cyproheptadine administration

Supportive Care/Symptom management
• Administration of oxygen and IV fluids
  • Increased metabolic demand
• Continues cardiac monitoring
• Chemical restraint for agitated patients
  • Diazepam/ Midazolam
**Hemodynamic management**
- Initially hypertensive and tachycardic
- Will progress to wide swings with severe hypotension
- Manage severe hypertension/tachycardia
  - Nitroprusside and Esmolol
  - Avoid long acting beta blockers
- Manage severe hypotension with direct acting
  - Phenylephrine/Epinephrine

**Hyperthermia management**
- Very critical to control hyperthermia
  - >41 Celsius (No role for Tylenol)
- Involves eliminating excessive muscle activity
  - Muscle paralysis/intubation
  - Sedation
- Active cooling
- Aggressive control of hyperthermia will minimize progression to
  - Coma, DIC, Metabolic Acidosis, V-tach.

**Serotonin Syndrome Management**
- Supportive care
  - Early Cyproheptadine administration
- Administration of Antidote
  - Observation

**Antidote = Cyproheptadine**
- Many reports of successful rapid treatment of Serotonin Syndrome w/Cyproheptadine
- Cyproheptadine (Literature gold standard)
  - 1st generation histamine-1 receptor blocker
  - Also antagonist at 5HT-1a and 5HT-2a
  - FDA approved for
    - Allergic reactions
    - Appetite stimulation
    - Carcinoid syndrome management

**Cyproheptadine Drug Facts**
- Available 4mg pill or 2mg/ml syrup
- Initial dose 12mg by mouth, may repeat 12 mg to a max dose of 0.5mg/kg per day
  - 2 mg every two hours following improvement
  - If pt is in a coma crush it and administer via OG

**Cyproheptadine side effects**
- Sedation
- May produce transient hypotension due to reversal of serotonin mediated vasoconstriction
- Weak anticholinergic activity
  - If initial diagnosis is incorrect will worsen hyperactive anticholinergic syndrome
Other possible antidotes
- Naloxone
  - Case report from Mayo Clinic
  - Fentanyl induced SS prior to anesthetic
- Famotidine
  - Single case report
- Treatment with Dantrolene not recommended
  - Many cases of SS that were misdiagnosed as MH

Differential diagnosis
- Anticholinergic Syndrome
- Hyperactive form
- Neuroleptic Malignant Syndrome
  - Develops over days to weeks
- Malignant Hyperthermia
  - The key is lack of clonus/hyperreflexia
- Sedative/Hypnotic Withdrawal
- Meningitis/Encephalitis

Why do some patients develop SS and some don’t?

ASA 3 pt with many meds +Anesthesia
- Metoprolol
- HCTZ
- Tramadol
- Amitriptyline
- Zolpidem
- Neurontin
- Diazepam
- Loperamide
- Omeprazole
- Tramadol
- Fish oil
- Baclofen
- Neurontin
- Baclofen
- Many OTC meds

ASA 1-2 pt with 1 medication +Anesthesia
- Prozac + Zofran + Fentanyl = Dealing with a problem

Medication overdose
- Patients with SSRI overdose 10-14% incidence of Serotonin Syndrome
  - High plasma concentration of a medication
Slow Drug Metabolism
- Pharmacogenetics

Drug Metabolism
- CYP 450- More than 50 different enzymes
  - CYP1A2
  - CYP2C9
  - CYP2C19
  - CYP2D6 - Breaks down most SSRIs
  - CYP3A4 (majority of medications)
  - CYP3A5
- Mostly in the liver, but also occur in GI, lungs, kidneys

CYP2D6
- Largest variability in metabolism
- Multiple Alleles
- Prevalence of poor metabolizers in white population is 6-10%
- African Americans are greater than whites
- Asians 2%

Pt with many drug allergies
Pharmacogenomic testing

SSRI Metabolism
- SSRIs-Metabolized by CYP2D6
  - SSRIs also inhibit CYP2D6
  - High Active drug concentration
- Zofran and many other medications are also partially metabolized by CYP2D6

Additional pro-serotonergic meds given
Therapeutic level
Pharmacogenetics workup
• Dr. Beatty case report
  - Pt tested was shown to be slow metabolizer
• 2004 Mayo Clinic Proceedings case report
  - 39 year old with multi organ failure and SS clinical picture
  - Tested was a slow metabolizer

References
References


