Nurse Practitioner Case Study Review

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Samaritan Evergreen Hospice
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The presenter has nothing to disclose.
Objectives

- This case study involves ketamine - goal is to familiarize participants about this medication that can be used in diverse ways.

- Discuss briefly myoclonus its causation in hospice and the most effective treatment.

- Review Ketamine medication profile in pain, depression, and topical wound care.

Allergies: morphine, hydrocodone, codeine, oxycodone: All=urticaria

Sign on to Hospice: 3 months prior to admit to Hospice House

Caregiving: Daughter was primary CG, his wife worked fulltime

Pain management: He reported his pain to be in his mid back and neck, he did have eruption of tumor in his midback that was very painful for him. The day prior to his pain crisis he was seen by home RN, he stated pain was a little worse but would not extrapolate, he was up and about during visit and out to back porch to smoke. RN did note that he was experiencing more open skin sites where tumor had erupted, most notably on his neck and face.
Medications

1. Related to His Pain management:
   › Hydromorphone per CADD IV
     • 25 mg basal with BTD of 15mg
   › Dexamethasone 16 mg daily
   › Ketamine 50 mg at HS for depression and pain adjunct.
   › Lorazepam 2mg 3x/day and prn
Pain Crisis

Daughter notifies on call RN at 0500 states he has been having increasing pain x12 hours and she has been using his bolus dose as often as she could. She reported 1760 mg on CADD given in last 24 hrs since last RN visit. She also had administered lorazepam, ketamine, and trazodone. He was sleepy but not comfortable. He was starting to have twitching and this was very painful.
Transported to hospice house with daughter. He did not want to come in but she assured him she would come with.

Assessment on arrival:
- Dusky with circumoral cyanosis, RR 24, HR 80. Sats 73% on 4Lnc. Writhing in bed. Picking at air and confused but able to report: pain “10” mostly in his chest and back. Myoclonic jerking with very limited release time, almost constant.
- He did report to me that everytime he jerked it felt like his tendons were being ripped out of his body.
- Morphine CADD is: 25mg basal, 17 mg bolus
What to do first??

- Treat pain but also need opioid rotation
  - Remember his allergies!
- Treat myoclonic activity- this will also help with pain
- Address delirium
- Support to family
- Anything else?
What is available?

- Midazolam IV 10mg/ml
- Phenobarbital 130mg IV and PO
- Ketamine 100mg/ml IV
- Fentanyl TDP
- Haldol PO and IV
- Chlorpromazine PO and IV
- Hydromorphone PO and IV
- Morphine PO and IV - allergy
- Oxycodone PO - allergy

I also contacted MSW and chaplain - which the daughter declined.
What did I do?

- For pain: I placed 2-100 mcg Fentanyl patches on (that was all we had in stock).
  - Conversion would be: 1760 mg of hydromorphone in 24hrs: at 80% crossover about 14,000 mcg/hr
  - How ridiculous is that???? Theoretically I could have covered him head to toe....

- Discussion with his daughter and wife about sedation and the need to stop the myoclonic activity. His daughter was distraught and continued to keep pushing his BTD button, she could not understand that this may be causing his myoclonus.
He did not have another port on his CADD access so we gave Midazolam SQ until we could switch lines.

- 0705 - 5mg Midazolam SQ
- 0715 - 5mg Midazolam SQ and Ketamine 5 mg SQ
- 0725 - 10mg Midazolam IV - he was still having myoclonic activity but he was sedated.
- 0750 - 5 mg Midazolam IV and Ketamine 10mg IV - still some myoclonus. So I added phenobarbital 135mg SQ and scheduled this every 6 hrs.
- 0800 - Midazolam 5mg IV and started CADD IV at 10mg/hr with 5mg BTD every 5 min
- 0810 - Less myoclonus activity - sedated - ordered Ketamine 10mg/hr SQ or IV.
- 0900 - Better but still twitching much less amplitude - titrating down hydromorphone CADD.
- 1000 - still occasional twitching but pink, warm, dry. Sedated
- 1100 - No further twitching. Sedated.

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Was he comfortable?

- Yes - RR 18, HR 70, Pink, warm dry. Occasional twitching activity (nursing care needs) that responded to BTD of midazolam prior to care.

Drugs

- Midazolam 10mg/hr IV with BTD of 5mg every 5 minutes prn.
- Phenobarbital 130mg SQ every 6hrs
- Ketamine 10mg/hr SQ
- Hydromorphone tapered to 20mg/hr
- Fentanyl TDP 200 mcg
What could be causing the myoclonus?

- Opioids—especially high dose
- Recent addition of a new drug or recent drug increase
- Hypoxia ongoing and posthypoxic brain injury
- Renal Failure
- Hepatic Failure
- Glycemic Disturbances—Hyper or Hypo
- Hyperthyroidism
- Metabolic alkalosis or acidosis
- Electrolyte imbalance—hyponatremia, and glycemias

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Secondary Myoclonus

- This type of myoclonus occurs in the context of an underlying neurological or nonneurological disorder and is the most common form of myoclonus.
  - The etiology includes posthypoxic myoclonus, drug-induced myoclonus, toxic–metabolic causes, myoclonus due to focal nervous system damage, neurodegenerative diseases and hereditary metabolic diseases.

- A useful approach to the treatment is to first establish the physiology of myoclonus (cortical versus subcortical or spinal), because different drugs will work in different types of myoclonus.
Subcortical Myoclonus=Toxic metabolite causation

- One single agent can seldom completely control myoclonus; therefore multiple drug trials and combination of drugs are necessary, often in large dosages.

- In general, antiepileptic drugs such as valproate, levetiracetam and piracetam are effective in cortical myoclonus, but ineffective in other forms of myoclonus.

- Clonazepam is helpful in all types of myoclonus (Kojovic, Cordivari, & Bhatia, 2011)
Ketamine for Pain?

- I used Ketamine for pain adjunct - did I give the correct dose?
  - I gave 10mg SQ per hour

- Review Ketamine dosing guidelines:
Generic Name: Ketamine Hydrochloride
Brand name: Ketalar, Ketaset, Ketanest
Legal status: Schedule III controlled substance
Drug classes: NMDA receptor antagonist, General anaesthetic
Other drugs in same class: Propofol, Nitrous oxide, Etomidate
Supplied: Liquid form only in: 50mg/ml or 100mg/ml concentrations
Street Drug: Special K, Kitty, Ket, K, Vitamin K
**Pain:** Ketamine is used as an adjunct medication for opioid refractory pain or intractable side effects of opioids, particularly if the pain is neuropathic in nature or a high degree of morphine tolerance is suspected. As an adjuvant agent it can reduce the amount of narcotic required.

**Depression:** Ketamine is used for refractory depression and/or anxiety as it works in hours to days versus SSRI’s which can take weeks.

**Palliative Sedation:** Can be considered for PS in patients refractory to midazolam or in situations when respiratory depression or suppression of airway protective reflexes is to be considered.

**Dyspnea:** Ketamine has also been used for terminal dyspnea as in does not cause respiratory or cardiovascular depression.

**Seizures:** In some NICU’s ketamine has been used in cases of prolonged seizures. Some evidence indicates the NMDA-blocking effect of the drug protects neurons from glutamatergic damage during prolonged seizures.
Ketamine is classified as a “dissociative anesthetic” meaning the patient appears to remain awake but is actually unconscious and feels no pain when given in full anesthetic doses.

Ketamine is a non-competitive N-methyl-D-aspartate receptor (NMDA) antagonist that blocks the release of excitatory neurotransmitter glutamate. Ketamine also interacts with cholinergic, nicotinic, muscarinic, and opiate receptors and possibly inhibits the synaptic re-uptake of monamines.

It has potent multifactorial analgesic properties when given at sub-anesthetic doses.

Ketamine is useful as it dose not suppress respiratory drive of decrease protective airway reflexes.
1. Ketamine is metabolized in the liver by cytochrome P450 enzyme system. CYP3A4 is the major enzyme involved. Chronic ketamine administration increases the activity of the enzymes involved in its own metabolism and may modify the response with repeated administration. Tolerance has been reported.

2. Ketamine is highly lipophilic and rapidly crosses the blood-brain barrier providing quick onset of action. Its distribution half-life is approximately 7-11 minutes. Ketamine has a wide therapeutic index, so there is low chance of lethal overdose.

3. The main metabolite norketamine does have analgesic properties and is produced in great quantities when taking oral ketamine related to high first pass hepatic metabolism. Norketamine is 1/3 to 1/5 as potent as ketamine resulting in lower oral dosing of 25-50% than parenteral. Oral bioavailability is 15-20%.

4. The elimination half-life is 2-3 hours for ketamine and approximately 4 hours for norketamine.

5. Less than 10% of the drug is excreted unchanged; 5% in the feces, 5% by the kidneys. Impaired renal function does not prolong the effect of the drug.
Dizziness and a dream-like feeling. Start low and Go Slow. These effects also tend to go away as tolerance develops.

Hallucinations and vivid dreams when emerging from full anesthetic doses. Hallucinations and the re-emergence syndrome are usually preventable with co-administration of:
*benzodiazepine or haldol prior to or while giving ketamine*

Side effects with higher doses can include: tachycardia, hypertension, pelvic pain, diplopia, and nystagmus which all resolve after lowering or cessation of the drug.

Contraindications in Palliative Care:
Intracranial hypertension, neurological impairment, hypertension, cardiac failure, CVA.
Ketamine is supplied as injection solution in 50mg/ml and 100mg/ml multi-dose vials. Ketamine is highly lipophilic, the solution can be given: **PO/SL/SQ/IM/IV/PR/Intranasal**.

The injection solution has a bitter taste that can be disguised with flavorings when given orally.

Ketamine can be irritating to skin so SQ sites may need to be rotated daily.
## Ketamine

<table>
<thead>
<tr>
<th>Route of Admin.</th>
<th>IV</th>
<th>IM</th>
<th>SQ</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>1 min</td>
<td>5 min</td>
<td>15-30 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Duration</td>
<td>10-15 min</td>
<td>15-30 min</td>
<td>30-60 min</td>
<td>2-4 hrs</td>
</tr>
</tbody>
</table>
Ketamine can be given in “burst” style technique IV-similar to steroid burst. Ketamine is administered IV with titration upwards for 3-5 days then it is discontinued. Continue on opioids only again.

Effects of “burst” control may be effective for up to 6 weeks.
Consider reducing opioid by 25-50% at initiation of ketamine, and then every 6-12h by another 25-50% prn.

Next are two different protocols that are used. #1 by VCU Massey Cancer Center and #2 by Comfort Care Choices by Dr. Robert Webb (see reference pages).
## IV Dosing of Ketamine

<table>
<thead>
<tr>
<th>VCU Massey</th>
<th>Comfort Care Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>A trial of 5-10mg IV is considered with repeat in 15-30 min</td>
<td>Initiate at 4mg/hr (100mg/24hr) Some other reports say 50-150mg/24hr</td>
</tr>
<tr>
<td>Starting infusion is .2mg/kg/hr can increase by .1mg/kg/hr every 6 hrs, with upward titrations to .5mg/kg/hr</td>
<td>If not effective in 24hrs go to 12mg/hr (300mg/24hr). If not effective after another 24hrs go to 20mg/hr (500mg/hr)</td>
</tr>
<tr>
<td>Not to exceed 800mg in 24hrs</td>
<td>Continue rate at which pain control is satisfactory and stop 3 days after last increment. If no pain control at 500mg/24hr for a full day, stop infusion.</td>
</tr>
</tbody>
</table>

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What about PO dosing?

- A suggested conversion dose of oral ketamine would be 30-40% of the effective parenteral dose.

- The elimination half life of oral ketamine is 2-3 hrs and up to 4 hours of norketamine.
### PO Dosing Suggestions

<table>
<thead>
<tr>
<th>VCU Massey</th>
<th>Comfort Care Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mask taste with flavor syrup</td>
<td>Mix in fruit cordial to mask taste</td>
</tr>
<tr>
<td>Consider decreasing opioid by 25-50%</td>
<td>Consider decreasing opioid by 25-50%</td>
</tr>
<tr>
<td>Start dose is 10-15mg po every 6 hrs</td>
<td>Test dose of 25mg is given</td>
</tr>
<tr>
<td>Dosing may be increased daily by 10mg every 6hrs until pain relieved or side effects occur. Do not increase dose more freq than every 24hrs</td>
<td>If no adverse reaction and/or pain is reduced, continue 25mg 4x/day and prn. MAX dose is 200mg/day</td>
</tr>
<tr>
<td>Doses as high as 1000mg/day have been reported. Avg dose is 200mg/day in divided doses.</td>
<td>Give smaller dose more often if drowsiness occurs and doesn't improve with reduction of opioid.</td>
</tr>
</tbody>
</table>
Studies have shown that patients who also receive daily oral and IM ketamine experienced a robust antidepressant and anxiolytic response with few adverse events. This is especially useful in the setting of end of life care where treatment needs to be rapid and effective.

Ketamine targets the excitatory glutamate neurotransmitter. Methylphenidate is also used for antidepressant effects but mechanistically the psychostimulant blocks reuptake of dopamine and inhibits reuptake of serotonin or norepinephrine as does SSRI’s, it can also cause anxiety.
### Oral Dosing in Depressive Disorder

<table>
<thead>
<tr>
<th>Description</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>.5mg/kg of IV solution mixed in flavoring once daily PO at HS</td>
<td>If you see an decrease in benefit increase dose by 20%</td>
</tr>
<tr>
<td>If side effects occur, administer lorazepam or haloperidol at HS</td>
<td>May also adjust dose lower or decrease frequency to 3-4x/week</td>
</tr>
</tbody>
</table>

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Topical Administration

- There were no RCT or clinical trials using ketamine in fungating or open wounds except for one....

- The data I found was use on hospice and palliative care blogs and websites.

- Our compounding pharmacist had used it before as a wound spray and suggested:
Topical Spray for Wound Care

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine 5% or 10%</td>
<td>Compound all 3 meds with normal saline in a 30ml or 60ml atomizer spray bottle. Apply compound to entire wound bed prior to dressing changes and up to 3-4x daily prn.</td>
</tr>
<tr>
<td>Lidocaine 1%</td>
<td></td>
</tr>
<tr>
<td>Morphine 1% or 5%</td>
<td></td>
</tr>
<tr>
<td>Metronidazole 500mg paste</td>
<td>May follow with metronidazole 500mg paste for odor control.</td>
</tr>
</tbody>
</table>
Evaluation is ongoing for dyspnea control with ketamine; it shows promise in that there are bronchodilation effects, along with analgesic and anesthetic effects without respiratory or cardiovascular depression.

There is one study by Abhijit, that trialed ketamine .2mg/kg and midazolam .02mg/kg (mainly for negation of undesirable side effects of ketamine) to evaluate the efficacy of low dose ketamine in relieving terminal dyspnea.

The study showed excellent symptomatic relief of dyspnea but it was short lived (36.7 min on average). This study was done in India where they report consistent shortages of opioids thus attempting to find an alternative.
REFERENCES


THANK YOU!!!!

- If you would like an electronic copy of my ketamine guidelines...

- Please email me at:
  - khoffman@samhealth.org