Pain Management: Beyond the Basics

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Common Errors in Pain Management

- Crushing sustained release
- Rapidly titrating patch
- Combining patch and sustained release
- Parenteral/oral calculation
- Long term short acting rx.
- Routine use of opiates for CMO
- Bowel meds
- Use of naloxone

Sustained Release Tabs

- Cannot be crushed
- If unable to swallow must initiate alternative rx.
- Opiate rx can be started with low dose sustained release

Transderm Fentanyl

- Caution in opiate naïve patient
- Cannot rapidly titrate
- Ideal for stable pain in patient unable to swallow

Contraindications

In patients who are not opioid-tolerant

- In the management of acute pain or in patients who require opioid analgesia for a short period of time
- In the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- In the management of mild pain
- In the management of intermittent pain (e.g., use on an as needed basis [prn])

Combining Long Acting

- Fentanyl patch plus sustained release morphine or oxycodone
- Makes no sense
- No added benefit
- Side effects are similar

Opiates oral/IV

- Morphine, reduce dose to 1/3 of oral dose when switching to IV

Pumps

- High doses
- Difficulty with oral rx
- Take 24 hr oral dose
- Divide by 3
- Divide by 24 to get hourly rate
- Bolus=hourly dose
- Titrate by 20-30%, not>100% in 24 hrs.

Long Acting Rx

- Attempt to switch to long acting rx
- Evidence supports starting with sustained release products
- Need breakthrough medication

CMO

- Should not equate with routinely starting morphine drip
- Morphine should be started for clear indications
- Dose should be increased in response to symptoms
- Double Effect

Bowel Meds

- Scheduled opiates require scheduled bowel meds

Naloxone

- Caution in opioid dependent patient
- Especially in advanced cancer
- Is sedation due to medication or is the patient dying
- Consider low dose ie 0.1 mg if using in an opioid dependent patient

Opioid Overdose

- 50% in pts never prescribed opioids
- 20% in pts with RX from 5 or more MDs(EMR)

(Hall AJ et al, JAMA.2008;300:2613-20)

Increased risk with increased prescribed dose

Increase risk with dx of depression, substance abuse, use of benzos

(Dunn KM et al, Ann Int Med.2010;152:85-92)

Opioids in Chronic Non-Malignant Pain

- Agreement/contract in place
- Should be based on seeing improved fxn,QOL
- Without improvements, risks>benefits

Opiates and Sedatives: Effects on Survival in Terminally Ill

Double effect

- Assumes opiates and sedatives may hasten death
- Corollary: withholding these meds may prolong survival

High Dose Morphine Use in the Hospice Setting

- Bercovitch M. et al., Cancer 1999;86;871-7

Methods

- Hospice admissions over 2 years
- Cancer patients
- Retrospective chart review
- Scheduled morphine dosing
- Low dose < 300 OME
- Mod high dose 300-599
- Highest dose>599

Results

- No difference in survival between groups
- Lower doses seen in older patients
- Highest doses with GU cancers, Breast CA
- Higher doses with spinal mets
- Lower doses with lung mets
- Side effects mild, constipation

Limitations

- Retrospective
- Not a control group
- Cancer patients only

Opioid Use in Last Week of Life and Implications for End-of-Life Decision-Making

- Thorns A, Sykes N. Lancet 2000;356:398-9

Methods

- Retrospective chart review
- Inpatient palliative care unit
- 24 hr opioid doses calculated for each day on final week of life
- Increase calculated <1.5, 1.5-2, >2

Results

- No difference in survival from admission, frequency of unexpected death, or description of death between marked increase or no increase patients
- Marked increase group more likely to receive opioids for pain and to receive sedatives

Effects of High Dose Opioids and Sedatives on Survival in Terminally Ill Cancer Patients

- Morita T. Et al. J Pain Symptom Manage 2001;21:282-289.

Methods

- Retrospective data analysis/chart review
- Use of opioids/sedatives in final 48 hrs
- All sedative medications included
- 209 patients analyzed
- Inpatient setting
- Regression analysis
- OME >600, 240-599,<240 in final 48
- PME >60, 1-59,0 in final 48

Results

- 82% received opioids in final 48 hrs
- 60% received sedative medication (haloperidol, midazolam, hydroxyzine)

Results

- Palliative Performance Scale, oral intake, edema, dyspnea at rest, delirium were independent prognostic factors
- No difference in survival between opioid groups
- No difference in survival in sedative groups

Limitations

- Retrospective
- Not a control group
- Cancer patients only

Sedative Use in the Last Week of Life and the Implicatons for End-of Life Decision Making

- Sykes N, Thorns A, Arch Intern Med 2003;163:341-344

Methods

- Retrospective Chart Review
- 237 consecutive patients
- Died in an inpatient hospice
- Midazolam, haloperidol, methotrimiprazine

Methods: 4 Groups

- Little or no sedation
- Significant sedation for 7 days
- Significant sedation only in final 48 hrs
- Significant increase in dose in final 48 hrs

Results

- No survival difference between no significant sedation group and sedation in last 48 hr group
- 7 day sedation group had longer survival

Limitations

- Retrospective
- Not a control group
- Cancer only?

Patterns of High-Dose Morphine Use in a Home-Care Hospice Service

- Bercovitch M, Adunsky A. Cancer 2004;101:1473-7

Methods

- Retrospective chart review
- 661 hospice patients with cancer

Results

- Higher morphine doses associated with longer survival

Limitations

- Unclear timing of morphine dose
- Cancer only
- Retrospective
- No control group

Effects of Opioids and Sedatives on Survival in an Australian Inpatient Pallliative Care Population

- Good PD et al. Internal Medicine Journal 2005;35:512-517

Methods

- Retrospective chart review
- Inpatient hospice deaths
- Looked at sedatives and opiates
- Cancer was the most common dx.
- Looked at meds given in final 24 hrs

Results

- OME>300 mg/day had longer survival from admission
- Sedative use did not influence survival

Limitations

- Retrospective
- Diagnoses unclear
- No control group

Opioid Use and Survival at the End of Life: A Survey of a Hospice Population

Portney RK et al. Journal of Pain and Symptom Management. 2006;32:532-40

Methods

- Retrospective cohort
- National Hospice Outcomes Project
- Looked at patients on opioids who underwent a dose change
- Interval between last dose change and death was key variable of interest
- Total daily dose included prns

Methods

- 1306 patients in sample
- 1163 received opioids
- 725 had a dose change
- 640 patients had dose< 200 IVME per day
- 85 patients > 200 IVME
- 19 patients > 600 IVME

Results

- Higher dose opioid group were younger (67.1 vs 77.9)and had longer lengths of stay on hospice (46.6 days vs 28.1 days)
- 42% of patients had cancer, higher percentage in high dose group
- Higher PPS score in the high dose opioid group

Results

- Multivariate analysis:
- Absolute dose change and percent dose change not associated with survival
- Higher final dose,cancer diagnosis, unresponsiveness associated with shorter survival
- Pain score < 5 associated with longer survival
- Explained only 6% of survival variance

Summary

- ? Need to invoke doctrine of double effect
- ?Efforts to prolong survival by holding meds

Methadone

Back to the Future

History

- Germany 1938
- 1950’s re for opioid withdrawal
- 1960’s opioid addiction
- 1990’s neuropathic pain

Pharmacology

- No active metabolites
- Oral bioavailability 80% but unpredictable
- T1/2 27 hrs.
- Biphasic elimination alpha 6-8 hrs,beta 30-60 hrs.
- Beta phase prevents withdrawal but not analgesic

- Dose q 24 hrs for withdrawal q 6-8 hrs for pain
- Hepatic metabolism type 1 cytochrome P450
- Excreted via fecal route
- Urinary excretion increases with acidification
- Present in breast milk

Drug-Drug Interactions

- SSRI's increase levels
- Phenobarb, phenytoin, carbamazepine decrease

Methadone Advantages

- Renal Failure
- Cost
- Neuropathic Pain

Neuropathic Pain

- Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial
- Morley et al. Palliative Medicine 2003; 17:576-587.
- Poor responders?
- Efficacy with methadone vs placebo
- ?NMDA activity

Methadone Side-effects

- QT prolongation (? Risk of Torsades)
- Constipation(? Less)
- Nausea
- Sedation/CNS (?less)

Methadone Conversion

- Varies with opiate dose
- More potent with higher opiate dose

Methadone Conversion

- Edmonton Palliative Care Unit
- Replace 1/3 of morphine dose each day for 3 days
- Use 10/1 MS to methadone ratio

Methadone Conversion

- UK Hospice Model
- Stop opiate
- Methadone q3h prn
- Use 10/1 MS to methadone ratio
- Dose not to exceed 30 mg of methadone
- At 6 days review total daily dose and convert to bid/tid dosing

Methadone Versus Morphine As a First-Line Strong Opioid for Cancer Pain: A Randomized Double-Blind Study

- Bruera et al. J Clin Oncol 2004;22:185-192

Eligibility

- Uncontrolled pain due to advanced CA
- > 4 week life expectancy
- Normal renal and cognitive function
- Not receiving strong opioids
- No chemo or RT to improve pain

Treatment

- Methadone 7.5 mg q 12 hrs and 5 mg q 4h prn pain
- Morphine SR 15 mg q 12 hrs and ms 5 mg q 4 hrs prn pain
- Dose increase if > 2 prns daily
- Dose decrease if c/o sedation
- 4 weeks

Dosing

- Methadone mean: 20 mg qd
- Morphine mean 40 mg qd

- Breakthrough = 0 at day 29

Efficacy

- No difference in pain relief
- No difference in neuropathic pain patients

Side- effects

- Delayed sedation with methadone
- Higher drop-out rate with methadone

Conclusion

- “Methadone did not produce superior analgesic efficiency or tolerability at 4 weeks compare with morphine”

Sustained Release Oral Morphine Versus Transdermal Fentanyl and Oral Methadone in Cancer Pain Management

- Mercadante S et al
- European Journal of Pain in press

Methods

- 2003-2006
- 108 advanced cancer patients
- Had received rx including codeine, tramadol now needing strong opiods
- Excluded liver, renal disease, cognitive impairment, expected survival < 3 months, needing RT or new chemo

Methods

- 36 patients MSSR 60 mg per day
- 36 patients Fentanyl Transdermal 25 mcg/hr
- 36 patients Methadone 5 mg tid
- Given prn morphine and meds titrated based on prn use

Results

- 108 patients recruited
- 38 patients withdrew, lost to follow-up
- 22 morphine, 25 fentanyl, 23 methadone completed 4 week study
- Within groups similar losses to opioid change and loss to follow up
- Opioid increase smallest in methadone group but some required a decrease so most changes in this group

Results

- No difference in quality of life scores and side effects

- Methadone, least costly,
- Fentanyl most costly

Conclusion

- All three are effective for first line therapy with similar side effects
- Methadone, less costly, required more up/down adjustment and may require more expertise to use

Problem

- Patient can no longer swallow sustained release opiate
- How about a patch
- But the patient has advanced cancer and is very thin
- Will the fentanyl be absorbed?

Addition of Methadone to Another Opioid in the Management of Moderate to Severe Cancer Pain: A Case Series

Wallace E et al. J Palliat Med. 2013;16:305-309

- 20 patients (16 neuropathic)
- Mean morphine dose 338 mg /day
- Mean methadone dose 15.5 at evaluation
- Methadone well tolerated in 17/20
- 40% had improved pain (≥2) initially,35% at an additional time

Too thin for a patch?

Transdermal Fentanyl in Cachectic Cancer Patients

- T Heiskanen et al. Pain.2009:144;218-222

Methods

- Prospective
- Cancer patients with pain requiring opiates
- 10 normal weight, 10 cachectic patients
- Excluded: cognitive impairment, fever, pregnancy/lactation, renal, cardiac, hepatic failure, skin diseases, CYP3A4 drug use (erythromycin,diltiazem, fluoxetine, fluvoxamine, verapamil)

Methods

- Transdermal fentanyl dose based on opiates taken
- Blood levels of fentanyl tested

Results

- Transdermal fentanyl dose was higher in the cachectic patients (pt had longer duration of illness)
- Adjusted for dose the plasma fentanyl concentration were significantly lower at 48 and 72 hours
- No difference at 4 and 24 hours

Results

- No difference in local skin blood flow, skin temperature or local sweating
- Cachectic patients had thinner upper arm skin fold
- Pain scores similar in both groups

- Amount of subcutaneous tissue has not been shown to influence absorption
- Blood flow and skin permeability have been shown to influence absorption
- Skin permeability may be influenced by other factors in cachectic patients

- “not the opioid of choice for cachectic cancer patients with pain”

Topical Analgesics

NSAIDs

- Evidence for diclofenac, ibuprofen, ketoprofen
- Ibuprofen topical similar in efficacy to oral

Lidocaine

- Good evidence for post herpetic neuralgia and diabetic neuropathy
- Often used for back pain, joint pain
- Limited evidence (no controlled trials) and unclear mechanism of action

Capsaicin

- Evidence with post herpetic neuralgia and diabetic neuropathy
- Burning discomfort noted in most

Opiates

- Morphine not absorbed through intact skin
- No better than placebo when applied to painful ulcers (J Wound care 2005;4:279-283)

Neuropathic Pain

Nociceptive Pain

- Normal activation of the nociceptive system by noxious stimuli

Neuropathic Pain

- Pain due to damage to or dysfunction of the nervous system

Neuropathic Pain

- Negative and positive sensory systems
- Spontaneous pain
- Stimulus provoked pain

Allodynia

- Pain in response to nonpainful stimuli

Hyperalgesia

- Increased sensation of pain in response to painful stimuli

Nerve Injury

- Inflammation
- Hyperexciteability of primary afferent neurons (sunburn)

- Increased primary afferent nociceptor firing
- Decreased inhibition centrally, loss of inhibitory neurons
- Central sensitization (normal sensory input amplified and sustained)
- Wide dynamic range neurons in spinal cord:input from nociceptive and non-nociceptive neurons
- After sensitization mild tactile stimuli can activate spinal cord signaling
- Inhibitory neurons release serotonin and norepinephrine

Tricyclic Antidepressants

- First meds to show effect vs. placebo
- Don’t use amitriptyline
- Anticholinergic side effects

Nortriptyline

- Start 10-25 mg at hs
- Titrate to 100+ mg at hs
- Sedation, dry mouth etc.

Gabapentin

- FDA approval PHN
- Start as low as 100 mg at hs
- 100-300 mg tid
- Increase by 100-300 mg every 1-7 days
- Can load hs dose to decrease sedation
- 1800 mg/day assoc with efficacy

Gabapentin

- Need to get to therapeutic dose and maintain for > 1 week (may take 2 months)
- Side effects: somnolence, dizziness, less common GI sx., edema

5% Lidocaine Patch

- FDA:PHN
- Minimal blood levels on intact skin
- Side effects: skin rash
- Dose: up to 3 patches on for 12 hours applied to area of maximal pain
- Trial 2 weeks
- Mexilitine, IV lidocaine

Opiates

- Good evidence for efficacy
- Long acting preferred

Opiate Side Effects

- Cognitive Impairment
- Hallucinations
- Constipation
- Nausea
- Pruritis
- Myoclonus
- Sedation
- Respiratory Depression

Tramadol

- Norepi/serotonin reuptake inbitor
- Major metabolite is a mu opioid agonist
- Start at 50mg once or bid
- Maximum dose 100 mg 4 times daily
- Side effects:dizziness, nausea, constipation, orthostatic hypotension

Tramadol

- Lowers seizure threshold
- **Caution with SSRI!**

Duloxetine

- FDA:PDN
- Side effects: sedation, confusion, hypertension
- 60 mg daily

Effect of Duloxetine on Pain, Function, and Quality of Life Among Patients With Chemotherapy-Induced Painful Peripheral Neuropathy

- Smith et al. JAMA 2013;309:1359-67

- Chemotherapy induced peripheral neuropathy
- 30 mg daily for 1 week then 60 mg daily for 4 weeks vs placebo
- Decreased pain , less pain interference with fxn, higher quality of life
- Side effects slightly higher in placebo group

Pregabalin

- Side effects similar to gabapentin
- FDA: PHN. PDN
- 50 mg tid to 100 mg tid

Neuropathic Pain and Methadone

- Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial
- Morley et al. Palliative Medicine 2003; 17:576-587.
- Poor responders?
- Efficacy with methadone vs placebo
- ?NMDA activity

Opiate Neurotoxicity

- Sedation
- Myoclonus
- Delirium/agitation
- Hyperalgesia
- Allodynia
- Seizures

Opiate Neurotoxicity

Due to metabolites?

But also seen with fentanyl and methadone

Other etiologies in terminally ill

Opiate Induced Hyperalgesia

- May be seen with myoclonus,delirium
- Change in pain pattern

Hydromorphone Neuroexcitation

- Thwaites D, McCann S, Broderick P. Journal of Palliative Medicine 2004;7:545-50

TABLE 3. RELATIONSHIP BETWEEN PRESENCE OF NEUROEXCITATORYSYMPTOMS WITH DOSE AND DURATION OF CPH

	No symptoms	*Neuroexcitatory symptoms present*
• # subjects	30	18
• Mean dose (SD)	6.2	25.4
• Mean duration (SD)	8.4	27.3
• *P*<	0.001	

Dose < 20 mg/hr

- Seizures 0
- Agitation 18% (11% if< 15 days)
- Myoclonus 3% (0 if, 15 days)

Dose>20 mg/hr, >15 Days

- Agitation 50%
- Myoclonus 60%

Opioid Induced Pain

- Pain now exceeds preexisting pain without disease progression
- Pain now diffuse
- Not tolerance
- Dose increase results in no reduction of pain
- ? Less likely with methadone

Opioid Induced Pain

- Dose increase should improve analgesia at least short tem
- If not: consider dose reduction and adjuvants
- If not: consider methadone

Ketamine

- Anesthetic
- Produces analgesia
- No effect on pharyngeal-laryngeal reflexes
- Minimal respiratory depression

Ketamine

- Dissociative anesthesia
- Interrupts association pathways
- Somatesthetic sensory block
- NMDA,mu,delta,kappa receptors

Ketamine

- “Emergence reaction”
- Dream-like state
- Vivid imagery
- Hallucinations
- Delirium
- Benzos used to control this

Parenteral Ketamine as an Analgesic Adjuvant for Severe Pain: Development and Retrospective Audit of a Protocol for a Palliative Care Unit

Edward J. Fitzgibbon, Raymond Viola

Journal of Palliative Medicine Feb 2005, Vol. 8, No. 1: 49-57.

Ketamine Protocol

- Palliative Care Unit
- Terminally Ill Patients
- Uncontrolled Pain
- Contraindications: Uncontrolled Seizures, symptomatic increased intracranial pressure

Ketamine Protocol

- Primarily given sc
- Starting Dose 50-100 mg/24 hrs
- Increase by 50-100 mg/24hrs no sooner than 24 hrs after last increase
- Consider d/c if no effect with 700 mg/24 hrs
- Consider decrease in opiate by 25-50%
- Consider prophylaxis with haldol 1mg bid
- Consider prophylaxis with lorazepam 0.5mg bid

Ketamine Audit

- 16 patients in a 1 year period.
- All but 1 CA
- M/F 9/7
- 14 with some neuropathic component

Effectiveness criteria

- Pain decreased by 4/10
- Decreased prn use by 50%
- Documentation of improved comfort

Effectiveness

- All 3 criteria 11/16
- Reduced pain 15/16
- Decreased prn 12/16

Side Effects

- Drowsiness: 7/16 (resolved in <5 days)
- Hallucinations: 3/16
- Agitation:1/16
- Discontinued : 1 drowsiness,
  1 hallucinations

Safety and Efficacy of Prolonged Outpatent Ketamine Infusions for Neuropathic Pain

- Walker LR,Walker MJ. AM J Ther.
- 2006; 13 (4):300-305

- Retrospective chart audit
- 13 non-cancer patients with neuropathic pain
- Mean Dose .12 mg/kg/hr (8 mg/hr for 70 kg adult)
- Duration 5-55 days

- Supervision required first 24 hrs
- Irritation in sc patients
- 11/13 patients had improved pain
- Morphine dose decreased
- Side effects:fatigue,dizziness,confusion,spinal pain

72 yo female, Metastatic Renal Cancer

- Pain in hips, back, pelvis
- Uncontrolled on duragesic, oxycontin
- MS 4mg/hr sc to 40 mg/hr: bolus not helpful, myoclonus,paranoia
- Decadron 8mg tid, haldol 2mg tid
- Ketamine 4mg/hr to 16 mg/hr complete relief
- MS decreased to 16 mg/hr, less myoclonus

Military use of Ketamine

- Battlefield anesthetic (wound debridement/exploration, fracture/dislocation reduction
- IM 5mg/kg onset 5-10 minutes, duration 20-30 minutes
- IV 2 mg/kg over 60 seconds, onset 60 seconds, duration 5-10 minutes

Ketamine

- There is evidence for use but controlled trials would be helpful

Effective Pain Control

- May require more than one class of drugs
- Ketamine may provide relief for patients with opiate refractory pain
- May provide additional analgesia to patients in crisis ie. pathologic fracture, sudden escalation of pain