Medicolegal Issues in Opioid Misuse

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Lecture outline

- Morphine
- Methadone
- Oxycodone
- Sleep apnea and opioids
- Buprenorphine
- Codeine

Opioids

- Analgesics are perhaps the most commonly prescribed medications in the world
- Opioids are the most effective for moderate to severe pain
- High abuse potential
- Potential adverse outcomes are severe (death)
- Liability issues common
Morphine

- 45 yo bipolar female has routine bunion surgery. Received several doses of morphine during and after surgery in hospital
- Admitted post op to rehab hospital
- Podiatrist accidentally orders 50 mg Q4hr of morphine instead of meperidine.

Morphine

- Pharmacy called nursing staff and said dose seemed wrong
- Nurse consulted with doctor who said the patient was in pain and needed the medicine
- Nurse received 25 mg morphine from pharmacy and administered IM at 2000 at night
- Pt was fine when checked by nurse and friend at midnight. Nursing staff documented vital signs normal including respirations at 0400

Morphine 1

- Patient found with sonorous and slow respirations at 0800 next day
- Resuscitated initially and believed to be intact but deteriorated over 1-2 weeks to become altered with significant mood and cognition deficits from baseline
Morphine 2

• 46 yo f with history of obesity and hypertension goes into hospital for colon resection for colon cancer
• Post-op maintained on morphine PCA
• Switched over to Percocet on post-op day 4
• No observance of medication-induced problems while hospitalized
• No more morphine after post-op day 3

Morphine 2

• Discharged on the evening of post-op day 4
• Next day is fine and “normal” according to daughter who is nursing student and giving patient her meds at home
• Last reported dose of Percocet at 2000 at home (post-op day 5)
• Found dead in bed at 0800 on post-op day 6
• Family sues surgeon and hospital for excessive narcotic prescribing

Morphine 2

• Autopsy shows morphine in blood at “therapeutic” concentrations
• Zero acetaminophen found in blood
• Zero oxycodone found in blood (small amount in liver)
• No PE found
Morphine
what happened?
• Can be given IV or IM
• Oral immediate release morphine with variable bioavailability (15-64%)
• Half life 1.5-7 hours
• Peak concentrations with IM dosing in 10-20 minutes
• Exhibits post mortem redistribution (PMR) averaging 2.2 (1-6)

Morphine
metabolism
• 5% of a dose demethylated to nor-morphine
• 2 glucuronide metabolites:
  – Morphine-3-glucuronide (inactive)
  – Morphine-6-glucuronide (potentially active)
• 3-glucuronide is concentrated in bile and recirculated
• 6-glucuronide renally eliminated
• Autopsy results often detect and report only “total” morphine

Morphine
6-glucuronide
• Due to renal elimination, 6-glucuronide may accumulate in renal insufficiency
• Although not as active an analgesic, the 6-glucuronide may lead to respiratory depression
• At autopsy, if concentrations of only free morphine are measured, this may not accurately reflect metabolites
Morphine

- Eating food containing poppy seeds can give serum morphine concentrations as high as 0.100 mg/L (codeine 0.007 mg/L) with urine concentrations of 4.5 and 0.2 mg/L
- Analyzing urine for thebaine (not present in pharmaceutical morphine) has been suggested as means to differentiate

Methadone

- 32 year old male heroin user decides to kick heroin
- Enrolls in local methadone treatment program, started on 80 mg methadone daily
- Returns on schedule each day for methadone dose, gradually titrated up 10 mg each day due to feelings of withdrawal
- On 4th day presents sedated, still given dose
- On 5th day found dead at home
Methadone 2

- 31 yo substance abuser presents to urban ED complaining he is out of pain meds for chronic neck pain, demanding methadone
- Found to have empty prescription bottle of methadone filled in Mexico
- Abusive to staff and security, eventually walks out when physicians refuse to refill methadone

Methadone 2

- Patient then presents to nearby ED 4 hours later by ambulance saying he is in methadone withdrawal
- Stated his dose is 40 mg BID
- Given a dose in ED and a prescription for 3 days at same dose

Methadone 2

- Same patient presents back to the same ED 4 days later with altered LOC
- Given naloxone in field with improved mental status but develops withdrawal symptoms
- Patient tells ED staff and physician his dose is 80 mg BID
- Given dose of 80 mg in ED, discharged with 3 day prescription of 80 mg BID
Methadone 2
- Patient found dead in apartment 2 days later
- Found in kneeling position at foot of bed, unclear how long dead
- Autopsy showed methadone concentration within range of that “in previously reported fatal ingestions”
- Decedent’s father, a physician, sued the ED doctor and hospital

Methadone
- First synthesized as morphine substitute in Germany during WWII, made available in US in 1947
- Analgesic activity found to dissipate faster than respiratory effects
- Due to half life it can accumulate with repetitive dosing
- In 1965 was marketed in the US for narcotic maintenance programs for heroin addicts

Methadone
- Usually sold as d/l racemic mixture, but the l isomer is the major active component
- Half life 15-55 hours, genetically dependent on CPY activity
- Whereas tolerant individuals will require 150 mg or more per day for maintenance, 50 mg orally or less can be fatal in those non-tolerant
Methadone metabolism

- Metabolized largely by demethylation (CYP2B6)
- None of metabolites felt to have any significant pharmacologic activity
- Most significant urinary excretion products are methadone, EDDP and EMDP
- As maintenance continues, higher concentrations of EDDP are found in urine

Methadone interpreting levels

- Almost impossible to interpret serum concentrations at autopsy (minimal PMR)
- Span of fatal acute overdose concentrations completely overlaps that of methadone maintenance patients due to tolerance
- Some experts have suggested that measuring EDDP concentrations can predict prior methadone use and suggest tolerance

Methadone problems

- At the end of the 1990s, OxyContin developed a bad reputation leading insurance companies to stop covering it
- Many primary care providers switched their chronic pain patients to methadone, resulting in an epidemic of fatal cases
Methadone problems

- 2 main problems:
  - Build-up of serum and brain concentrations due to genetically slow metabolizers, leading to "stair-step" increases
  - QT prolongation leading to dysrhythmias
- Publications have noted 2 "golden periods" during maintenance therapy where fatalities most likely:
  1) between 3 and 14 days
  2) >1 month or more

Oxycodone

- Semisynthetic derivative of thebaine
- Used clinically since 1939
- Half life 3-6 hours
- Half life prolonged for parent drug in both renal and hepatic failure
- Metabolized by demethylation, one metabolite, oxymorphone is very potent analgesic
Oxycodone

- Commercial opiate assays have 1-18% cross-reactivity with oxycodone and oxymorphone
- PMR averages about 2
- Seems to cross blood brain barrier almost as rapidly as heroin, leading many IV, inhaling or insufflating users to compare them favorably

Oxycodone

- Oxycontin released to market in 1990s
- Heralded as one of the first long-acting opioids by Purdue Pharmaceuticals and heavily marketed
- Rapid escalation in use
- Abusers soon found out that crushing or cutting pills could rapidly release oxycodone in system.
Oxycodone 1

• 25 year old male at party in WVA gets his prescription of Oxycontin and throws a party
• He and other guests crush pills and snort oxycodone, he then decides to melt them down and begin injecting them
• Found dead by fellow partiers later that night
• His attorney sues Purdue

Oxycodone 1

• Plaintiff attorney states drug company knew how addicting their drug was and should have done more to warn public and health care providers
• Further stated Oxycontin was too easy to crush and abuse
• Patients couldn’t help themselves from abusing it once they tried it
Oxycodone 2

- 13 year old boy underwent outpatient tonsillectomy
- Uncomplicated procedure, discharged home after short observation with Rx for Percocet, 1-2 every 4-6 hours PRN.
- Takes nap after meds that evening and found unresponsive and in cardiac arrest by mother at 1800

Oxycodone 1

- Family sued surgeon and medical center
- Stated child had a history of sleep apnea, one of the reasons he required tonsillectomy
- Said child should not have been sent home on opioids due to his history and this caused his death
Opioids

sleep apnea

- Adverse reaction with opioids in patients with sleep apnea becoming more recognized
- Potential for prolonged apneic spells when opioids given to these patients or combined with other sedating meds
- Has led to at least overnight observation of post-op patients who receive opioids to assess tolerance

Opioid-induced sleep apnea

Central Sleep Apnea (induced) by Acute Ingestion of Opioids

Adverse reaction with opioids in patients with sleep apnea becoming more recognized
- Potential for prolonged apneic spells when opioids given to these patients or combined with other sedating meds
- Has led to at least overnight observation of post-op patients who receive opioids to assess tolerance
Fentanyl

- 75 year old female falls at home.
- Seen in ED and diagnosed with fractured humerus
- Pain not helped much with 2 injections of morphine, 4 and 8 mg
- Good pain relief from 40 mcg fentanyl IV
- Placed in shoulder immobilizer

Fentanyl

- 40 mcg fentanyl patched placed before discharge by physician’s assistant (PA)
- Patient admitted to rehab hospital
- Family instructed that the rehab doctors will have to reassess her pain
- Patient somewhat confused the following day (day 1, 24 hours after patch applied) and examined by rehab facility MD
- VSS, respirations and O2 sat normal, pt refused to go to ED for further evaluation

Fentanyl

- Unremarkable day 2 (48 hours) after patch applied, nursing notes patient with normal mental and respiratory status
- Found dead in bed the morning of 3rd day after patch first placed (about 61 hours after patch placed)
- No autopsy performed, body cremated
- Family sued doctors and hospital
Fentanyl transdermal

- Patches contain 2.5-10 mg fentanyl
- Provide dose of 25-100 mcg/hr
- Usually replaced every 72 hours
- With removal of patch serum concentrations decline with average half life of 17 hours
- Package insert warns against external heating that may increase absorption and serum levels
Buprenorphine
Subutex

- 45 year old male with history of hydrocodone, carisoprodol and ethanol abuse checks into a detox facility
- PMH with chronic back pain, hypertension, diabetes
- Placed on buprenorphine, SL, 2 mg Q4hrs for first 2 days, along with regular meds: fluoxetine, ropinirole (Requip), trazadone, mirtazapine (Remuron), metformin and lorazepam

Buprenorphine

- On day 2, told his wife by phone he was “deathly sick” with vomiting all night and severe headache
- On day 3 he received his dose of 2 mg at 0400, but the second dose was held due to lethargy and sedation
- He was restarted on buprenorphine again at 2000 on day 3 with 2 mg SL, then another dose of 2 mg at 0400 the next day (day 4)
- At 0700 of day 4 he was found in bed unresponsive

Buprenorphine

- Resuscitated and taken to an ED
- CT done and found to have cerebral edema, uncal herniation and SAH.
- Urine toxicology screen done and found positive only for benzos.
- Died the next day
Buprenorphine

- Autopsy showed cerebral edema and hypertrophic cardiomyopathy
- Buprenorphine level drawn on arrival to ED (antemortem) of 2.4 mg/mL
- Coroner concluded: “The concentration (of buprenorphine) is within the range previously associated with fatalities...and is also within generally accepted therapeutic concentrations in opiate dependent individuals.”
- Toxicology screening at autopsy negative for other drugs, including benzos

Buprenorphine

- Lab noted: “The SL administration of 2 mg buprenorphine produced mean peak blood concentrations of 1.6 ng/mL at 1.3 hours. And “A 4 mg SL dose gave a peak concentration of 3.3 mg at 0.8 hours.”

Buprenorphine

- Synthetic thebaine derivative
- Analgesic and opioid antagonist properties
- Said to be 25-40 x more potent than morphine as analgesic and equipotent to naltrexone as antagonist
- Comes in patches, pills, film, parenteral
- Metabolized by dealkylation (CYP3A4) to norbuprenorphine (active)
Buprenorphine

• Subutex: sublingual tablet, 2 mg and 8 mg buprenorphine
• Suboxone: sublingual tablet, 2 and 8 mg buprenorphine with 0.5 and 2 mg naloxone
• Suboxone film now in same doses as tablet
• Naloxone added to Suboxone is supposed to prevent injection

Buprenorphine

• Partial mu-opioid agonist
• Package insert material note to administer 4 mg as starting dose when opioid withdrawal sx develop
• Give second 4 mg dose if no withdrawal is precipitated by first dose
• Then a third dose of 4 mg if needed on day 1

Buprenorphine

• Then increase by 2-4 on day 2 for total dose of 10-12 mg
• If withdrawal sx are still present, increase dose by another 2-4 mg on day 3, shooting for stable target dose of 10-16 mg after day 3
• Continue this dose for 3-7 mg, then decrease dose by 2mg “at a time”


**Codeine**

- 5 yo child seen in ED for URI
- Full examination and chest radiograph unremarkable
- No laboratory test performed
- Child discharged with parents with prescription for Robitussin AC
Codeine

• Child administered 3 doses at home by parents, last dose at 2200 that day
• Slept well over night but found “barely breathing” in the morning by parents, resuscitated in the ED with naloxone
• Toxicology screening of the child’s blood identified normal codeine concentrations consistent with dosing, but elevated levels of morphine

Codeine

• Genotyping of patient’s blood finds her to be homozygous for CYP2D6, ultra-rapid genotype
• This is suggestive that she is ultra-rapid metabolizer of codeine to morphine
• This can potentially be dangerous in breast-fed infants of mothers taking codeine containing products
**Issues with Opioids**

- Tolerance
  - Affects interpretation of blood levels
  - Affects dose requirements
- Clearance affected by renal and hepatic dysfunction
- Clearance somewhat determined by genetic differences
- Some have active metabolites
- Abuse potential high