Medicolegal Issues in Opioid Misuse

Richard F. Clark
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
Lethal morphine intoxication in a patient with a sickle cell crisis and renal impairment: case report and a review of the literature.

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Abstract
Morphine-6-glucuronide, the active metabolite of morphine, and to a lesser extent morphine itself are known to accumulate in patients with renal failure. A number of cases on non-lethal morphine toxicity in patients with renal impairment report high plasma concentrations of morphine-6-glucuronide, suggesting that this metabolite achieves sufficiently high brain concentrations to cause long-lasting respiratory depression, despite its poor central nervous system penetration. We report a lethal morphine intoxication in a 61-year-old man with sickle cell disease and renal impairment, and we measured concentrations of morphine and morphine-6-glucuronide in blood, brain and cerebrospinal fluid. There were no measurable concentrations of morphine-6-glucuronide in cerebrospinal fluid or brain tissue, despite high blood concentrations. In contrast, the relatively high morphine concentration in the brain suggests that morphine itself was responsible for the cardiorespiratory arrest in this patient. Given the fatal outcome, we recommend to avoid repeated or continuous morphine administration in renal failure.
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 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
**CYP2B6 and OPRM1 gene variations predict methadone-related deaths.**

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**Abstract**

The largest proportion of methadone-associated deaths occurs during the drug induction phase. We analysed methadone-related fatalities for gene variations linked with methadone action. A significant association between high methadone concentrations and the CYP2B6*6 allele characteristic of the slow metabolizer phenotype was identified. We suggest that the risk of methadone fatality may be predetermined in part by the CYP2B6*6 allele. A significant correlation was also observed between post-mortem benzodiazepine concentrations and the OPRM1 A118G allele GA in methadone-related fatalities. Screening for these susceptibility variations prior to methadone prescription could assist in reducing the potential for serious adverse effects.
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.
Invasion of the Pill Mills in South Florida

By THOMAS R. COLLINS / FORT LAUDERDALE  Tuesday, Apr. 13, 2010
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
The Alchemy of OxyContin

By Paul Tough
Published: July 29, 2001

Paula is taking me on a driving tour of Man, the tiny West Virginia town where she has spent her entire life. Because I don't know my way around the hollows and gullies and creeks that carve through these hills, Paula is at the wheel. And because Paula isn't a morning person, we've set out on our tour at midnight. It's dark; the only illumination comes from our headlights cutting through the mist that rolls down from the hills.

The tour Paula is leading isn't sanctioned by the local chamber of commerce; there are no stops at Civil War plaques or scenic vistas. It's a pillhead tour: an addict's-eye view of the radical changes that a single prescription drug, called OxyContin, has brought to the town of Man. OxyContin abuse started in remote communities like this one more than two years ago; more recently, it has spread beyond its origins in Appalachia and rural Maine to affect cities and suburbs across the eastern United States. I came to Man to try to understand how America's latest drug problem started, to see its roots and trace how it has spread.
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
• 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
Postoperative respiratory compromise in children with obstructive sleep apnea syndrome: can it be anticipated?

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Abstract

OBJECTIVE: The aim of this research was to describe the postoperative respiratory complications after tonsillectomy and/or adenoidectomy (T and/or A) in children with obstructive sleep apnea syndrome (OSAS), to define which children are at risk for these complications, and to determine whether continuous positive airway pressure (CPAP) is an effective strategy for dealing with these complications.

METHODS: The data for this study were gathered through a retrospective chart review of all children 15 years of age or younger with polysomnographically (PSG) proven OSAS who had a T and/or A at Hennepin County Medical Center between January 1985 and September 1992. Particular attention was paid to factors that contributed to the OSAS, postoperative respiratory complications, and intervention strategies for dealing with these complications.

RESULTS: The charts of 37 children with OSAS documented by preoperative PSG who later had a T and/or A were reviewed retrospectively. Ten of these children had significant postoperative respiratory compromise secondary to OSAS that prolonged their hospital stay from 1 to 30 days and caused symptoms ranging from O2 desaturation < 80% to respiratory failure. These children were younger and had significant associated medical problems that contributed to or resulted from their OSAS in addition to large tonsils and adenoids. The associated medical problems included craniofacial anomalies, hypotonia, morbid obesity, previous upper airway trauma, cor pulmonale, and failure to thrive. The children with postoperative respiratory complications also had more severe apnea on their preoperative PSG. One child had a uvulopalatopharyngoplasty (UPPP) in addition to the T & A. Taken together, the history, physical and neurological examination, and the PSG were able to identify successfully the children who subsequently developed respiratory compromise secondary to OSAS after a T and/or A. Nasal continuous positive airway pressure (CPAP) and bilevel CPAP was used successfully to manage the preoperative and/or postoperative upper airway obstruction in five of these children.

CONCLUSIONS: Based on these findings, overnight observation is recommended with an apnea monitor and oximeter for patients undergoing a T and/or A who have OSAS and meet any of the following high-risk clinical criteria: (1) < 2 years of age, (2) craniofacial anomalies affecting the pharyngeal airway particularly midfacial hypoplasia or microretroglenathia, (3) failure to thrive, (4) hypotonia, (5) cor pulmonale, (6) morbid obesity, and (7) previous upper airway trauma; or high-risk PSG criteria: (1) respiratory distress index (RDI) > 40 and (2) SaO2 nadir < 70%; or undergoing a UPPP in addition to the T and/or A. Nasal CPAP/bilevel CPAP can be used to manage the preoperative and/or postoperative upper airway obstruction in patients with OSAS undergoing a T and/or A.
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
Central Sleep Apnea Induced by Acute Ingestion of Opioids

Mohammed Mogri, MD; Mohammed I. A. Khan, MD; Brydon J. B. Grant, MD, FCCP; and M. Jeffrey Mador, MD

Objectives: Three cases are presented in which patients were using opioids as required for nonmalignant pain management and significant central sleep apnea developed. Patients in the first two cases had no evidence of sleep-related breathing disorders on polysomnography until they ingested an opioid for treatment of chronic pain during the night and severe central sleep apnea developed. The patient in our third case had established obstructive sleep apnea but experienced a significant number of central events after the ingestion of an opioid analgesic, leading to worsening severity of his underlying sleep-related breathing disorder. Conclusion: The short-term ingestion of opioid analgesics can precipitate central sleep apnea in patients with chronic pain receiving long-term opiate therapy who otherwise show no evidence of central sleep apnea and have no cardiac or neurologic disease that would predispose them to central sleep apnea.

(CHEST 2008; 133:1484–1488)

Key words: central sleep apnea; chronic pain; complex sleep apnea; opioids; sleep apnea
Sleep-disordered breathing and chronic opioid therapy.

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Abstract

OBJECTIVE: To assess the relation between medications prescribed for chronic pain and sleep apnea.

DESIGN: An observational study of chronic pain patients on opioid therapy who received overnight polysomnographies. Generalized linear models determined whether a dose relation exists between methadone, nonmethadone opioids, and benzodiazepines and the indices measuring sleep apnea.


PATIENTS: Polysomnography was sought for all consecutive (392) patients on around-the-clock opioid therapy for at least 6 months with a stable dose for at least 4 weeks. Of these, 147 polysomnographies were completed (189 patients declined, 56 were directed to other sleep laboratories by insurance companies, and data were incomplete for seven patients). Available data were analyzed on 140 patients.

OUTCOME MEASURES: The apnea-hypopnea index to assess overall severity of sleep apnea and the central apnea index to assess central sleep apnea.

RESULTS: The apnea-hypopnea index was abnormal (> or =5 per hour) in 75% of patients (39% had obstructive sleep apnea, 4% had sleep apnea of indeterminate type, 24% had central sleep apnea, and 8% had both central and obstructive sleep apnea). 25% had no sleep apnea. We found a direct relation between the apnea-hypopnea index and the daily dosage of methadone (P = 0.002) but not to other around-the-clock opioids. We found a direct relation between the central apnea index and the daily dosage of methadone (P = 0.008) and also with benzodiazepines (P = 0.004).

CONCLUSIONS: Sleep-disordered breathing was common in chronic pain patients on opioids. The dose-response relation of sleep apnea to methadone and benzodiazepines calls for increased vigilance.
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
Transdermal Fentanyl
An Updated Review of its Pharmacological Properties and Therapeutic Efficacy in Chronic Cancer Pain Control

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Fig. 2. Fentanyl transdermal system. Schematic representation of the delivery system (not to scale) and the pathway of absorption across the skin.[7]
Table II. Pharmacokinetic values after the first 72 hours of transdermal fentanyl application (US prescribing information, number of individuals or status not reported)\(^ {16}\)

<table>
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<tr>
<th>Dosage (µg/h)</th>
<th>Patch size (mg/24h)</th>
<th>Patch size (cm²)</th>
<th>C(_{\text{max}}) (µg/L)</th>
<th>t(_{\text{max}}) (h)</th>
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<td>25</td>
<td>0.6</td>
<td>10</td>
<td>0.6</td>
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<tr>
<td>50</td>
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<td>20</td>
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<td>75</td>
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<td>30</td>
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<tr>
<td>100</td>
<td>2.4</td>
<td>40</td>
<td>2.5</td>
<td>36.8</td>
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C\(_{\text{max}}\) = maximum plasma concentration; t\(_{\text{max}}\) = time to C\(_{\text{max}}\).

Fig. 3. Mean plasma fentanyl concentration in 10 patients with cancer or intractable pain who wore two consecutive transdermal fentanyl patches (25 µg/h; 72 hours each). Unpublished data previously reviewed by Jeal and Benfield.\(^ {7}\)
DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that:
**Boxed Warning**

DURAGESIC® (fentanyl transdermal system) CII contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that:

- Requires continuous, around-the-clock opioid administration for an extended period of time, and
- Cannot be managed by other means such as nonsteroidal analgesics, opioid combination products, or immediate-release opioids

DURAGESIC® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/hr. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, DURAGESIC® is contraindicated:

- 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])

(See CONTRAINDICATIONS section of the full Prescribing Information for further
Duragesic and Fentanyl: FDA Resources & the Black Box Warning

In July 2005 the FDA issued a safety advisory emphasizing the safe use of the fentanyl pain patch also known by the brand name Duragesic and other generic pain patches. Despite this advisory, a large number serious adverse reactions and deaths continue to happen.

On December 21, 2007 the FDA issued another fentanyl safety advisory.

The fentanyl patch contains fentanyl, a very potent narcotic pain medicine which is only intended for treating persistent moderate to severe pain in patients who are opioid-tolerant. It is extremely important that patients be opioid tolerant because of the dangerous side effects of the fentanyl patch.

For patients who are not opioid-tolerant, the amount of fentanyl in one fentanyl patch of the lowest strength is enough to cause dangerous side effects, such as severe respiratory distress or very slow or shallow breathing and death.

Do You Have a Duragesic and Fentanyl Lawsuit? »
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), trazedone, 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”
Buprenorphine and midazolam act in combination to depress respiration in rats.

Gueye PN, Borron SW, Risède P, Monier C, Buneaux F, Debray M, Baud FJ.
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Abstract
High dose buprenorphine is used as substitution treatment in human heroin addiction. Deaths have been reported in addicts using buprenorphine, frequently in association with benzodiazepines. In the current study, we observed the effects of buprenorphine and midazolam alone and in combination on arterial blood gases. Four groups of 10 male Sprague-Dawley rats received a parenteral injection of aqueous solvent, buprenorphine (30 mg/kg, iv), midazolam (160 mg/kg, ip), or buprenorphine (30 mg/kg, iv) plus midazolam (160 mg/kg, ip). Serial blood gases were obtained over 3 hours. There was a mild but significant effect of buprenorphine alone in comparison with the aqueous solvent on PaCO2 at 60 min (6.24 vs. 5.65 kPa, p< 0.01). There was also a mild but significant effect of midazolam alone in comparison with aqueous solvent on arterial pH at 90 min (7.33 vs. 7.41, p< 0.001) and PaCO2 at 60 min (6.52 vs. 5.65 kPa, p< 0.01). The combination of midazolam and buprenorphine produces a rapid, profound, and prolonged respiratory depression, as demonstrated by an increase in PaCO2 at 7.65 +/- 0.12 kPa at 20 min and a decrease in arterial pH at 7.25 +/- 0.02 at 20 min, with appearance of delayed hypoxia with a decrease in PaO2 at 8.74 +/- 0.20 kPa at 120 min. These data show that high doses of midazolam and buprenorphine alone have limited effects on arterial blood gases in rats while midazolam and buprenorphine appear to act in an additive or synergistic fashion to depress ventilation in rats.
Effects of various combinations of benzodiazepines with buprenorphine on arterial blood gases in rats.

Pirmay SO, Mégarbane B, Borron SW, Risède P, Monier C, Ricordel I, Baud FJ.
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Abstract
Fatalities have been attributed to combinations of high-dose buprenorphine with benzodiazepines. In rats, high-dose buprenorphine combined with midazolam was shown to induce sustained respiratory acidosis, while buprenorphine alone did not. However, the effects of buprenorphine combined with pharmacological doses of benzodiazepines remain unknown. Our objective was to compare the acute effects of four selected benzodiazepines used intravenously at equi-efficacious doses in rats, alone and in combination with buprenorphine on sedation, respiratory rate and arterial blood gases. Buprenorphine (30 mg/kg) did not significantly modify sedation level or respiratory rate, but induced mild and transient effects on pH and PaCO(2) (P < 0.05). Similarly, despite having no effects on respiratory rate, nordiazepam (10 mg/kg), bromazepam (1 mg/kg) and oxazepam (12 mg/kg) mildly and transiently altered pH and PaCO(2) (P < 0.05), whereas clonazepam (5 mg/kg) did not. Buprenorphine combined with each benzodiazepine induced no significant effects on respiratory rate or blood gases, in comparison with buprenorphine alone. However, combinations of oxazepam or nordiazepam with buprenorphine significantly deepened sedation. While both combinations reduced respiratory rate, buprenorphine + 30 mg/kg clonazepam significantly increased PaCO(2) and buprenorphine + 30 mg/kg nordiazepam decreased PaO(2). In conclusion, not all benzodiazepines induce significant respiratory depression at therapeutic doses. We were unable to demonstrate significant effects on rat ventilatory parameters of buprenorphine combined with equi-efficacious pharmacological doses of benzodiazepines in comparison with buprenorphine alone. Our results may suggest that effects of these combinations are rather mild. Respiratory failure may, however, result from the association of buprenorphine with elevated doses of benzodiazepines.
• 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
Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer.

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Abstract
We present a case of a 29 months old previously healthy child who experienced apnea resulting in brain injury following a dose of acetaminophen and codeine 2 days after an uneventful anesthetic for tonsillectomy. A genetic polymorphism leading to ultra-rapid metabolism of codeine into morphine resulted in narcosis and apnea. This paper discusses the use of codeine for pain relief, obstructive sleep apnea, the alteration of the CYP2D6 gene and the resulting effect on drug metabolism.
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