Introduction

Despite tremendous advances in medicine from non-invasive imaging to minimally invasive surgical techniques, improvements in pain medicine have been seemingly slow to develop or when introduced, to gain widespread acceptance in our medical practices. At first look, perioperative pain control appears to be dominated by only a few therapeutic agents, namely: local anesthetics, opioid analgesics and/or non-steroidal anti-inflammatory agents - NSAIDS. In spite of this, physicians and other health care providers are expected to effectively manage pain under increasingly difficult clinical circumstances.

We are now facing a growing crisis of global proportions – safely and effectively managing pain in obese patients with sleep apnea.

1. Obesity and Sleep Apnea – “Coming to a patient near you!”
   a. Terminology - Over Weight, Obese, Morbidly Obese, Super Obese
   b. Rates of obesity continue to climb – going global
   c. Incidence of Sleep Apnea – What is the ‘real’ percentage?

2. Types of Sleep Apnea - Does it really matter?
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   b. Central Sleep Apnea
   c. Mixed OSA + Central

3. How to make a difficult situation (a lot) worse – OPIOIDS
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   b. Risk factors for perioperative respiratory depression
   c. Opioids and Sleep Apnea
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   e. Opioids: Is there both a safe and effective choice?
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   a. Surgical Approach
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d. Alpha -2 agonists  
e. NSAIDS / Cox-2 inhibitors  
f. Acetaminophen

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1. Obesity and Sleep Apnea – “Coming to a patient near you!”

a. Terminology - Over Weight, Obese, Morbidly Obese, Super Obese  
i. Obese: BMI > 30 kg/m2.  
ii. WHO Ladder of obesity:  
   - Simple obesity (30-34 kg/m2)  
   - Severe Obesity (35-40)  
   - Morbid Obesity (40-45)  
   - Super Morbid Obesity (> 45-50 kg/m2)  
   (Luc EC De Baerdemaeker, et al BJA: CEACCP 2004; 152-155)

b. Rates of obesity continue to climb – Going Global !  
i. Currently 1/3 of the USA adult population is considered Obese and nearly ¼ of children + adolescents are obese. Estimated that 50% of Adults will be obese by 2030 in the USA (CDC web site: http://www.cdc.gov/obesity/data/trends.html)  

2. Types of Sleep Apnea - Does it really matter?  

Is obesity, per se, the primary factor for hypoxia - with or without OSA? Morbidly obese patients experience multiple episodes of post – operative desaturation despite supplemental oxygen. (Ahmad, S. et al. Anesth. Analg. 2008; 138-43.)

a. Obstructive Sleep Apnea (OSA)  

   Risk Factors: Obesity, Thick / fat neck, Micrognathia, Large tongue, Enlarged tonsils, Nasal obstruction  
i. Patients studied for evidence of airway obstruction found a reduction in the pharyngeal area and that fat deposition had occurred within these tissues. (Homer et all, Eur Resprie J. 613-622, 1989) (Thorax 1992; 47:101-105).
Under restorative sleep, a relaxation of the pharyngeal musculature occurs that will lead to obstruction. Normally, a series of mini arousal events activate the pharyngeal muscles that open the airways. – “snorting” noises. (Lofsky et al, Anesthesia Patient Safety Foundation Newsletter Summer 2002;12:24-25.)

b. Central Sleep Apnea


ii. A major etiology of opioid-related death is respiratory suppression via opioid-induced central sleep apnea. Opioids prolong non-REM sleep by decreasing REM sleep duration, accentuating nocturnal breathing risks. With chronic opioid use with morphine-like opioids, there is a decrease in stage N3, REM sleep, and prolonged REM latency. Ventilation is both consciously and reflexively controlled in the medulla. Nocturnal drive is purely reflexive. Nocturnal opioid ingestion can enhance the risk of nighttime hypoxemia with possible respiratory failure. (Geller AS et al JAMA 2011; 306: 380-1)

c. Mixed OSA + Central

i. Most commonly, a patient with OSA that is on either acute or chronic opioid therapy. (Benumof J. Clin Anesth 2001; 13,144-156).

d. Incidence of Sleep Apnea – What are the percentages?

i. Obesity is the leading cause of OSA

ii. 80-90 % of OSA remains undiagnosed

iii. Estimates of sleep apnea in obese patients (male or female) approach 50%

iv. Prevalence of OSA in another hospital population is at least 60% (Frey et al, Obes Surg 2003;13,678-683).

3. How to make a difficult situation (a lot) worse – OPIOIDS

a. The growing tide of prescription opioid associated deaths

i. In 1997, the American Academy of Pain Medicine and the American Pain Society issued a consensus statement that advocated liberalization of opioids for chronic pain management. Since the statement was published, the use of methadone and oxycodone has increased by 824% and 660%, respectively.
ii. In the United States, the most common non-illicit drug poisonings resulting in death are those related to the use of prescribed opioids, and their incidence has increased over the past decade.

b. Risk factors for Perioperative Respiratory Depression


Additional risks:

Use of hydromorphone
Age over 65
Chronic obstructive pulmonary disease (COPD)
Kidney disease – ESRD
Congestive heart failure
Sleep apnea

ii. Increased Risk with Type of Opioid Analgesic

(Odds Ratio)

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>.31 (.13–.78)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2.93 (1.28–6.70)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.55 (.42–5.80)</td>
</tr>
</tbody>
</table>

>1 route or drug 7.76 (.93–65.12)

c. Opioids and Sleep Apnea

i. OSA appeared to be the predominant form of sleep apnea in patients with chronic opioid use with only 15% having central sleep apnea.

ii. CPAP may not be an effective treatment option for Central Sleep Apnea due to long-term opioid use.


d. PCA - 7th Top Health Technology Hazard of 2011 ECRI Institute Report Nov, 2010
i. “The use of PCA is a complex, high risk treatment that is associated with harmful events and death” (Hicks et al m. J. Health Syst. Pharm. Mar 2008; 65 429-440)

e. Rethinking Opioid choices and delivery by PCA devices

Respiratory pauses (with delays in expiration), irregular and periodic breathing rate and frequency, and decreased or normal tidal breaths have been observed with acute opioid use during wakefulness. The central drive for ventilation to pCO$_2$ may be blunted with opioid use while the peripheral hypoxic drive to breathe continues to operate.

ii. In one series, twenty-one percent of obese patients used narcotic analgesics for pain. (Raebel MA et al; Arch Intern Med 2004; 164: 2135-40)

iii. There is significant variability in opioid-induced antinociception in the morbidly obese after surgery with up to 10-fold variation observed in opioid requirements not related to body surface area, sex, age, dose per injection or anesthetic agent. (Bennett R. et al., Pharmacotherapy 1982;2: 50-3)

iv. Little is known about the consequences of bariatric surgery on intestinal absorption of drugs, especially that of morphine. In the setting of PCA opioids, PCA might be safe for an individual post bariatric surgical patients when a number of criteria are met that includes dosing on “ideal body weight”, essentially reducing the opioid dose by at least one half. (Anesthesiology. 2004;101:603-13)

v. In a PACU based study over a period of nearly 3 years, obesity was significantly associated with a larger number of critical respiratory events than in non-obese subjects.

Although there is no convincing study that has shown a clinical advantage of one opioid (morphine, hydromorphone, fentanyl) over another in the treatment of acute post operative pain (Hill HF. Et al, Anesth Analg 1991;72:330-6), Hydromorphone been increasing use of hydromorphone to manage acute post operative pain in the opioid naïve patient. This goes against its historical use in opioid tolerant patients, cancer pain patients and those who cannot tolerate morphine or cannot achieve adequate analgesia with morphine. In fact, the concentrated form of hydromorphone (10mg/cc) was approved for use only in opioid tolerant patients (FDA product insert).

The author has a growing perception that indiscriminant use of hydromorphone and/or other opioids can lead to untoward and/or life threatening respiratory events. Such a view is gaining strength based on an informal review of National patient safety web based – bulletins such as:
- The Pennsylvania Patient Safety Web Advisory – 2011, who have focused on the realization that does equivalencies may be wrong or misleading.

- The Anesthesia Patient Safety Foundation notes that the risk of serious injury from PCA in the postoperative period includes a low, unpredictable incidence of life threatening, opioid-induced respiratory depression (RD) in young, healthy patients. Respiratory depression based on bradypnea was many orders of magnitude greater than the 1 to 2 percent widely reported in the literature. MEDMARX and U.S. Pharmacopeia (USP) data show that when PCA pumps are involved, the chance for patient harm increases more than 3.5 times (APSF).

ASA Closed Claims Studies:

.. “Identified 13 additional acute pain management cases found in respiratory or cardiac arrest, but no preceding signs of respiratory depression were noted. On-site reviewers judged that better use of monitoring devices (particularly pulse oximetry or capnography) may have prevented the complication in .. 63 percent of PCA/other claims”

The claims review found poor outcomes (death and brain damage), particularly in the PCA group. Interestingly, obesity was a factor noted in a number of our respiratory depression claims, consistent with an increased risk of opioid-induced respiratory depression in the obese patient with obstructive sleep apnea. [http://depts.washington.edu/asaccp/ASA/Newsletters/asa71_8_3.shtml]

- Commonwealth of Massachusetts: Patient Care Assessment Division Advisory 2007. Patient Safety Concerns with Hydromorphone versus Morphine

“Hydromorphone is also often prescribed at upper limits with little reference to the patient’s opiate tolerance level”.

- Case Series: “Three of the four deaths occurred within the first 24 hours postoperatively ..and three of the four deaths occurred between midnight and 6 AM. Five of the 32 events occurred in the PACU and the rest (27) occurred on general surgical floors.” ..many of the events occurred at relatively modest opioid dosages and when pain levels were still significant. That suggested that some might have an increased opioid sensitivity. ...the authors speculated about the potential role of obstructive sleep apnea (OSA) in many patients. Two of the deaths occurred in patients with known OSA. The association with acute renal failure also suggested reduced opioid clearance or global organ dysfunction as contributing factors.” (Ramachandran SK, et al. J Clin Anesth 2011;23: 207-213)

Although not focused on the obese patient population, inter-patient differences in opioid mediated analgesia and/or side effects can be and have been documented. This has been a particular issue in determining equipotent dosing between morphine and hydromorphone in opioid naive patients, where conversion ratios of 5:1 to 8:1 have been published. For example, morphine 10mg iv would then be considered to be equivalent to either 1.3mg or 2 mg of iv hydromorphone – a significant difference. Moreover, most providers would be very hesitant to give a post operative patient 10mg of Morphine as a single iv push, yet they appear much more willing to prescribe a dose greater or equal to 1 mg of iv hydromorphone in a single dose. Therefore, although there are no systematic difference between morphine and hydromorphone in opioid-related side effects (Hong D
et al, Anesth Analg. 2008;107:1384-9), on closer inspection, unique aspects of hydromorphone must be taken into account in opioid naïve patients. If we add the additional complexities of a provider’s experience prescribing hydromorphone under conditions of morbid obesity, concurrent renal and/or liver failure, the clinical outcome could be disastrous.

Importantly, the pharmacokinetics of hydromorphone are affected by renal impairment where there is a 2 fold increase in plasma levels in patients with moderate renal impairment (CLcr = 40 - 60 mL/min) where as there is a 4 –fold increase with severe renal impairment (CLcr < 30 mL/min). In addition, hydromorphone appears to be more slowly eliminated under conditions of renal failure with a longer terminal elimination half-life (40 hr) compared to patients with normal renal function (15 hr). Therefore, it is recommended that patients with renal impairments a started one-fourth to one-half the usual starting dose. Patients with renal impairment should also be closely monitored during dose titration (FDA product insert).

e. Perioperative OSA protocols – Do they help?


ii. Several treatment strategies: Different noninvasive positive airway pressure devices, including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP) therapy, and adaptive servo-ventilation (ASV) have been tried to treat opioid-associated SDB, with conflicting results. Overall, the limited evidence shows that BPAP with a back-up rate may be reasonable treatment to consider in patients with sleep apnea related to long-term opioid use(Gallagher et al., J Surgical Research 2010;159: 622-626).

f. Monitoring – Where are the guidelines?

i. Unfortunately there is no evidence based guidelines or protocol that will ensure a ‘safe’ post PACU discharge to an unmonitored unit. However, monitoring end-tidal C02 / transcutaneous may allow providers to intervene earlier. (Gali et al., J. Clin Sleep Med. 2007, 3: 582-588) (Gali et al Anesthesiology 2009;110: 869-877).

ii. Is there value in a CPO – a late landing “safety net”?

iii ASA Guidelines: For patients with OSA, if there is a respiratory event in the PACU, additional monitoring is recommended including up to an additional 7 hrs after the last
observed event ..until room air SPO2 is normal in a quiet environment with pain controlled.

iii. Acute OSA related desaturation is different than persistent hypoventilation which may be gradual in onset / offset and with PaCO2 40-80 mmHg. In the OSA population studied, never measured a significant change in PACO2 as a sign of an upcoming event. Desaturation occurred in all patients, with or without O2. Mean percentage of time that a patient was at a O2 sat of <90% was 18% +/- 4 percent of the study period. All desaturations were unsuspected. Usually pulse ox checking (every 4 hours) did not catch any of them.

iv. Capnography was more effective than pulse oximetry in providing early warning of respiratory depression in patients receiving supplemental oxygen. Capnographic monitoring and automatic pausing of patient-controlled analgesia improved postoperative outcomes in situations that could have otherwise been fatal. (McCarter, T et al June 2008, www.ahdbonline.com)

4. How to make a difficult situation better – MULTI MODAL

a. Surgical Approach
   i. Laparoscopic

b. Epidural / Regional
   
   

C. Wound infiltration / infusion
   i. Some benefit of local anesthetic infiltration of laparoscopic surgical sites (Schumann et al. Anesth Anlag.2003; 96 469-74).
   
   ii. Effectiveness for a soaker catheter system on recovery of bariatric surgery patients using 0.2 % ropivacaine, Open Roux-en –Y, small study, no difference in morphine requirements, pain scores or length of stay. Patients did ambulate more quickly (Surgery for Obesity and Related Diseases 2010;6,181-84).

d. Alpha -2 agonists
   i. Most show an opioid sparing effect post operatively
e. NSAIDS / Cox-2 inhibitors
   i. Chochrane Systematic review “Update on Best Practices recommendations for anesthetic perioperative care”.
      (Schumann et al. Obesity 2009; 17:889-894)

f. Acetaminophen
   i. Approved by the US Food and Drug Administration (FDA) for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever.

   ii. Use with caution in patients with a history of: Hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, severe renal impairment (creatinine clearance ≤ 30 mL/min).

      227 completed 24 hours of treatment
      2 dosing regimens
      4 groups: IV acetaminophen 1000 mg q6h;
      IV acetaminophen 650 mg q4h
      IV placebo q6h
      IV placebo q4h

      The morning after abdominal laparoscopic surgery procedure, subjects' PCA was withheld until pain intensity (PI) was moderate (2) or severe (3). Results: Both intravenous acetaminophen dosing regimens were associated with significantly reduced pain intensity (SPID24) compared with placebo (1000 mg q6h, P < 0.007; 650 mg q4h, P < 0.019).

      Administration of a normal adult dose of acetaminophen to an obese patient should yield plasma concentrations in the same range as the non-obese. Dosing according to Total body weight than ideal body weight could lead to toxic effects. However, there is little evidence of acetaminophen associated hepatic toxicity when used judiciously. (Rumack BH., Hepatology 2004, 40, 10-15) (Benson et al., AM J Ther 2005;12:133-141)