Respiratory Depression in the Early Postoperative Period

Toby N Weingarten, MD
Mayo Clinic
Professor Anesthesiology
Conflicts of Interest

• Medtronic
  – Chair of CEC Committee for PRODIGY Trial
• Merck
  – Investigator initiated unrestricted research grant
  – Manufacturer of sugammadex
• Previous Research Support
  – Baxter Healthcare
    • Investigator initiated unrestricted research grant
    • Manufacturer of Desflurane and Scopolamine patch
  – Respiratory Motion
    • Material support of research study
    • Manufacturer of ExSpiron monitor
• SASM
Learning Objectives:

• Incidence of postoperative hypercarbic respiratory depression

• Temporal relationship between end of surgery and development of respiratory depression

• Review risk factors for respiratory depression

• Review implications and risk factors for respiratory depression in the PACU
Postoperative Respiratory Failure

Decreased defusion
- ARDS
- Pneumonia
- Atelectasis

Decreased ventilation
- Weakness
- Drive

Failure to Rescue
Anoxic Brain Injury
Death
Hypercarbic Respiratory Failure

- Arrests from decreased respiratory drive
  - Multifactorial
    - Medications
  - Underlying comorbidities

<table>
<thead>
<tr>
<th>Analgesic Treatments</th>
<th>Year 2000</th>
<th>Year 2002</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back surgery</td>
<td>2.3 (0.28)</td>
<td>2.3 (0.38)</td>
<td>0.45</td>
</tr>
<tr>
<td>Morphine Equivalents (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40.4 ± 13.2</td>
<td>46.6 ± 20.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>33.9 ± 15.2</td>
<td>36.0 ± 16.6</td>
<td>0.03</td>
</tr>
<tr>
<td>PACU</td>
<td>6.5 ± 7.3</td>
<td>10.6 ± 10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ketorolac treatments (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

63% Increase!

Hamlin RJ Acta Chir Belg. 2013
### Rate of serious OIRD

<table>
<thead>
<tr>
<th>Study</th>
<th>Measure</th>
<th>Number</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenfeld 2016</td>
<td>Naloxone</td>
<td>108/28,151</td>
<td>0.38%</td>
</tr>
<tr>
<td>Weingarten 2015</td>
<td>Naloxone</td>
<td>134/84,553</td>
<td>0.16%</td>
</tr>
<tr>
<td>Khelemsk 2015</td>
<td>Naloxone</td>
<td>433/442,699</td>
<td>0.10%</td>
</tr>
<tr>
<td>Ramachandran 2011</td>
<td>Naloxone + CPR</td>
<td>44/87,650</td>
<td>0.04%</td>
</tr>
<tr>
<td>Gordon 2005</td>
<td>Naloxone</td>
<td>56/10,511</td>
<td>0.50%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>775/653564</strong></td>
<td><strong>0.12%</strong></td>
</tr>
</tbody>
</table>

2015 ASA Closed Claim Postoperative OIRD
Median payout of $216,750

Gupta K, abstract SASM 2017
Lee LA, Anesthesiology 2015
Postoperative Hypoxemia Very Common
CCF 1250 non-CV patients SPO2 monitored

21% 10 m/h SpO₂ <90%
8% 20 m/h SpO₂ <90%
8% 5 m/h SpO₂ <85%

Nursing records **missed 90% of cases of SPO2 <90% 1 hour!**

SpO₂ <90%,
37% episode > 1 hr
11% episode > 6 hr
SpO₂ <80%,
3% episode > 0.5 hr

Sun Z A&A 2015
Hypoxemia is underappreciated
Intermittent Nursing Checks

Nursing records **missed 90% of cases!**

Manually measured SPO2 is 6.5% (4.0-9.0%) higher than automated systems.

**WAKE UP EFFECT**

APSF rates intermittent nursing checks
- Low-moderate sensitivity, specificity and reliability,
- Slow response times

Taenzer A 2014, APSF Fall 2011 newsletter
Time of greatest risk

- ASA Closed Claims of postoperative opioid-induced respiratory depression
  - 88% happened within 1\textsuperscript{st} postoperative day

Early Events (< 4 hrs)

Later Events

Ramachandran 2011, Weingarten 2016
Many respiratory events in the closed claim analysis happened shortly after a reassuring vital sign check!

- SPO2 increases with manual vital sign checks
  - 6.5% (4.0-9.0%)

- APSF rates intermittent nursing checks
  - Low-moderate sensitivity, specificity and reliability,
  - Slow response times

Lee 2015, Taenzer A 2014, APSF Fall 2011 newsletter
Patient Factors:

NARCAN ADMINISTRATION < 48 HOURS OF PACU DISCHARGE

- **OSA**
  - 2.44 (1.15-5.19)
  - 90% cases undiagnosed
  - 20% adult surgical patients

- **CV**
  - 2.56 (1.28-5.11)

- **CNS**
  - 4.05 (1.61-10.17)

Weingarten 2015, Young T 1997, Singh M 2013
Three Emerging Phenotypes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Narcan N = 128</th>
<th>Control N = 256</th>
<th>OR</th>
<th>(95% C.I.)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>61.8 ± 14.7</td>
<td>62.0 ± 14.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>46 (35.9)</td>
<td>92 (35.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>29.0 ± 8.0</td>
<td>28.8 ± 6.7</td>
<td>1.00</td>
<td>(0.98, 1.04)</td>
<td>0.777</td>
</tr>
<tr>
<td><strong>OSA</strong></td>
<td>47 (36.7)</td>
<td>55 (21.5)</td>
<td>2.12</td>
<td>(1.33, 3.38)</td>
<td>0.002</td>
</tr>
<tr>
<td>Charlson score</td>
<td>5 [2, 7]</td>
<td>4 [2, 7]</td>
<td>1.03</td>
<td>(0.96, 1.10)</td>
<td>0.426</td>
</tr>
<tr>
<td><strong>Disability</strong></td>
<td>67 (52.3)</td>
<td>85 (33.2)</td>
<td>2.21</td>
<td>(1.43, 3.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Home Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td>42 (52.3)</td>
<td>57 (22.3)</td>
<td>1.71</td>
<td>(1.06, 2.73)</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>25 (19.5)</td>
<td>21 (8.2)</td>
<td>2.72</td>
<td>(1.45, 5.01)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Gabapentinoids</strong></td>
<td>39 (30.5)</td>
<td>27 (10.6)</td>
<td>3.72</td>
<td>(2.15, 6.43)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Deljou SASM abstract 2017*
SURGICAL FACTORS
surrogates for bigger surgeries

• Longer duration
  7% increased odds per half hour

• Long-acting vs. short-acting opioid
  – OR 2.48 (1.05-5.88)

Weingarten 2015
PERIOPERATIVE FACTORS

Type of Surgery

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Ortho</th>
<th>General</th>
<th>Uro/Gyn</th>
<th>Neuro</th>
<th>ENT</th>
<th>Thoracic</th>
<th>Vasc</th>
</tr>
</thead>
<tbody>
<tr>
<td>NARCAN (%)</td>
<td>33%</td>
<td>30%</td>
<td>15%</td>
<td>10%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>
PACU COURSE
Mayo Clinic Discharge Criteria

a) **Motor Activity**
   - 2 Active motion
   - 1 Weak motion
   - 0 No motion

b) **Respiration**
   - 2 Coughs on command
   - 1 Maintains airway without support
   - 0 Requires airway maintenance

c) **Systolic**
   - 2 ± 20 mmHg preanesthetic level
   - 1 ± 20 – 50 mmHg
   - 0 ≥ 50 mmHg

d) **Consciousness**
   - 2 Fully awake or easily aroused
   - 1 Responds to stimulus
   - 0 No response or absent protective reflexes

e) **Oxygen saturation**
   - 2 Sat ≥ 93% (or preop) without O₂
   - 1 Sat ≥ 93% (or preop) with O₂
   - 0 Sat ≤ 93% (or preop) with O₂

Patient can be discharged with score ≥ 8 unless there is a 0 in any category
Respiratory Specific Events

• Hypoventilation
  – 3 episodes < 8 breaths per minute

• Apnea
  – 1 episode ≥ 10 seconds

• Desaturations
  – 3 episodes Pulse Ox < 90% or preop saturation with or without $O_2$

• Pain Sedation Mismatch
  – 1 episode RASS < -1 and Pain Score > 5

Gali 2007, Gali 2009
<table>
<thead>
<tr>
<th>Evaluation Period</th>
<th>Initial Period 30 minutes</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Eval Period 60 minutes</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Eval Period 90 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 8 respirations/minute (3 episodes needed for yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hypoventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episode of hypoventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 seconds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(only 1 episode needed for yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Apnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episode of Apnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desaturations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Ox&lt;90% or pre-op saturation with or without oxygen (3 episodes needed for a yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Desaturation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episode of Desaturation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain/sedation mismatch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RASS score -2 through -5 and pain scale score &gt;5 (only 1 episode needed for a yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain/sedation mismatch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episode of pain/sedation mismatch</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patient monitored in the PACU for longer duration (> 30-60 min after modified Aldrete criteria met)

- Known OSA
  - Non-compliant with PAP
  - AHI > 30 (Severe OSA), or
  - Recurrent PACU Respiratory Event (30-min block)³
    - Oxygen saturation < 90% on nasal cannula (3 episodes)
    - Bradypnoea < 8 breaths / min (3 episodes)
    - Apnea ≥ 10 s (1 episode)
    - Pain sedation mismatch (high pain and sedation scores concurrently)

- Suspected OSA (≥2 on STOP, ≥3 STOP-Bang)
  - Recurrent PACU Respiratory Event (30-min block)#
    - Oxygen saturation < 90% on nasal cannula (3 episodes)
    - Bradypnoea < 8 breaths / min (3 episodes)
    - Apnoea ≥ 10 s (1 episode)
    - Pain sedation mismatch (high pain and sedation scores concurrently)

- No
- Yes

  - AHI 16-30 (Moderate OSA)
  - Postoperative parenteral opioids
  - Postoperative oral opioids (>codeine 60 mg q4h or equivalent)

  - No
  - Yes

Consider discharge to home if minor surgery.

Consider postoperative PAP and care in a monitored bed.†

Consider discharge to home if minor surgery or postoperative care on the surgical ward.

Consider postoperative care on the surgical ward.
Algorithm for OSA patient triage

CPAP

Known OSA

Suspected OSA

Non-compliant with CPAP
Severe (AHI > 30)

Recurrent respiratory events

Consider CPAP
Considered advanced monitoring

Seet E 2010
OSA and PACU Respiratory Depression

OR 5.11 (2.32-11.27) of receiving naloxone after PACU Discharge

PACU naloxone administration had OR 3.39, 95 % CI 2.22-5.23, P < 0.001 for adverse events

# ICU Admissions and PACU Respiratory Depression

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Respiratory Events</th>
<th>ICU Admissions</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Event</td>
<td>Event Free</td>
</tr>
<tr>
<td>TJA (n=11,970)</td>
<td>2,836 (23.4%)</td>
<td><strong>189 (6.8%)</strong></td>
<td><strong>121 (1.3%)</strong></td>
</tr>
<tr>
<td>Laparoscopic &gt; 90</td>
<td>1,311 (15.3%)</td>
<td><strong>101 (7.7%)</strong></td>
<td><strong>407 (5.6%)</strong></td>
</tr>
<tr>
<td>(n=8,567)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weingarten 2015, Cavalcante 2017
PACU episodes of respiratory depression fits into early warning theory

Taenzer Anesthesiology 2011
Hypoxemia in PACU

• 137,757 patients 2007 – 2013 @ Vanderbilt
  – Hypoxemia < 90% for 2 minutes

• 11% patients had a hypoxic event
  – 66% only had 1 event
  – 70% had event > 30 minutes

• 0.1% reintubated
  – 63% > 30 minutes

# Rates of PACU Respiratory Depression at Mayo

<table>
<thead>
<tr>
<th>Population</th>
<th>Hospital</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip/Knee TJA (6,467)</td>
<td>A</td>
<td>31%</td>
</tr>
<tr>
<td>Laparoscopic &gt;90 min (5,412)</td>
<td>A</td>
<td>19%</td>
</tr>
<tr>
<td>Laparoscopic &gt;90 min (3,258)</td>
<td>B</td>
<td>9%</td>
</tr>
<tr>
<td>General Surgery (3,137)</td>
<td>B</td>
<td>8%</td>
</tr>
<tr>
<td>Laparoscopic Bariatric (781)</td>
<td>B</td>
<td>4%</td>
</tr>
</tbody>
</table>

Multimodal Analgesic Therapy With Gabapentin and Its Association With Postoperative Respiratory Depression

Alexandre N. Cavalcante, MD,* Juraj Sprung, MD, PhD,† Darrell R. Schroeder, MS,† and Toby N. Weingarten, MD*

Rates of Respiratory Depression

19.2%  9.0%

Practice Differences

<table>
<thead>
<tr>
<th></th>
<th>Hospital</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISOFLURANE</td>
<td>53%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>MIDAZOLAM</td>
<td>78%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>GABAPENTIN</td>
<td>26%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

Time to DC Criteria Met

n = 8,670
PACU Respiratory Depression Risk Factors

Patient
• Older Age
• Lower BMI
• OSA not a factor

Anesthetic
• Opioids
• Non-opioid analgesics
  – Gabapentinoids
  – Ketamine
• Volatiles
• NMBD
Opioids

• Higher doses = greater risk
  – 1 - 2% increase risk per 1 IVME mg
  – Potentiated by midazolam with induction

• Preop sustained release oxycodone for TJA
  – 10 mg dose = OR 1.178 (1.030,1.347)
  – 20 mg dose = 1.294 (1.068, 1.566)

Sustained Release Oxycodone

- $T_{\text{max}}$ 157±64 minutes
- Mean time of surgery was 121±49 minutes

Gabapentinoids

• Knee/Hip TJA (n = 6,467)
  – 300 mg = 1.216 [0.982, 1.505]
  – 600 mg = 1.455 [1.255, 1.687]

• Laparoscopic > 90 minutes (n = 8,670)
  – 1.47 [1.22, 1.76]

• Naloxone < 48 hours of surgery*
  – Continuation of home gabapentinoids
    • OR 6.3 (2.38, 16.66), P=0.001

Gabapentinoids & Respiratory Depression?

- 12 ASA I 20 – 26 yo DB cross over
  - Pregabalin vs Placebo
    - 150mg 13 hr and 1 hr before study
  - Remifentanil infusion vs Placebo

Myhre M, Anesthesiology 2016
Gabapentin, opioids, and the risk of opioid related death: A population-based nested case ± control study

1,256 regular opioid users who died of opioid-related causes were matched 4:1 of regular opioid users who did not die of opioid-related causes

<table>
<thead>
<tr>
<th></th>
<th>No. Exposed Cases</th>
<th>No. Exposed Controls</th>
<th>Unadjusted Odds Ratio</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Analysis</strong>*:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent Gabapentin Use</td>
<td>155 (12.3%)</td>
<td>313 (6.8%)</td>
<td>1.99 (1.61 to 2.47)</td>
<td>1.49 (1.18 to 1.88)</td>
</tr>
</tbody>
</table>

| **Sensitivity Analysis: Overlapping Gabapentin Use*** | | | | |
| Gabapentin Overlapping Index | 121 (9.6%)       | 240 (5.2%)           | 1.98 (1.56 to 2.50)   | 1.46 (1.12 to 1.89) |

| **Secondary Analysis: Gabapentin Dose** | | | | |
| High Dose                  | 57 (4.5%)        | 101 (2.2%)           | 2.20 (1.58 to 3.08)   | 1.58 (1.09 to 2.27) |
| Moderate Dose             | 57 (4.5%)        | 111 (2.4%)           | 2.05 (1.46 to 2.87)   | 1.56 (1.06 to 2.28) |
| Low Dose                  | 41 (3.3%)        | 101 (2.2%)           | 1.70 (1.17 to 2.48)   | 1.32 (0.89 to 1.97) |

| **Neutral Exposure*** | | | | |
| Recent NSAID Use         | 480 (38.2%)      | 1647 (35.7%)         | 1.11 (0.98 to 1.27)   | 1.14 (0.98 to 1.32) |

*1,256 cases and 4,619 controls; Reference Group: no gabapentin use

** Low dose: <900mg/day; moderate dose: 900-1799mg/day; high dose: ≥1800mg/day; Reference Group: no gabapentin use

† Reference Group: no NSAID use

Gomes T PLoS Med 2017
Volatiles

• Hip/Knee TJA
  – Desflurane = 0.839 [0.718, 0.979]
• Laparoscopic > 90 minutes*
  – Isoflurane = 1.31 [1.15, 1.50]

Open Eyes

Consciousness Recovered

Change in anesthetic management
Comparison 2 six month epochs

Weingarten BMCA2015
Median Decrease in PACU stay

Respiratory depression decreased 7.8% to 5.1%, P<0.001
35% decrease

72 [50, 102] minutes

62 [44, 90] minutes

14% Decrease!
Postoperative Respiratory Depression Risks Lessons from Inpatient Observations

• Develop early postoperative period
• Patient factors:
  – OSA,
  – CNS/CV disease or frailty
  – Tolerance
• Surgical factors
• Anesthetic factors:
  – Longer acting anesthetics
  – Sedating medications