Titrating Your Anesthetic

The “Bookends” of Safety

Dean Mazurek, CRNA
All about me
• Independent Contractor since 2004

• Chairman, AANA Nominating committee, 2008
  • Member, 2006

• Member, AANA Programs Committee 2008

• Member OSHA committee 2004-2005

• Member SODC\SRF committee 2003

• Member PR committee 2001-2002

• Secretary-treasurer for NJANA 1998-2004
“Mr. June 2008”
My patient
Agenda

- Examine incidence of awareness under anesthesia
- Discuss causes and long term consequences
- Review literature surrounding “too much anesthesia”
- Other longer term effects
Anesthetic Depth and Recall

- Awake
- Explicit Memory
- Responsiveness to Commands
- Implicit Memory
- Movement
- Fully “Anesthetized”

Increasing Anesthetic Depth
“I’ve never had an awareness case in all my years of giving anesthesia.”

- a frequent comment by anesthesia providers
When are you asking the question?
Incidence of Awareness With Recall

- **11,785 patients**
  - Interviews at PACU discharge, 1-3d, 7-14d
  - Only 33% of awareness cases (6/18) were detected in PACU, others detected later
  - Awareness: 0.18% with NMB – more severe
  - Awareness: 0.10% without NMB – less severe

**Implications:**
- Avoiding NMB does not prevent awareness
- Awareness with paralysis increases severity
- PACU screening misses most awareness episodes
- 39% had benzodiazepines (*little insurance*)

How are you asking the question?
Suggested Post-op Questions

1. Last thing you remember before you went to sleep?
2. First thing you remembered when you woke up?
3. Remember anything between these two periods?
4. Dreams during operation?
5. Worst thing about the operation?

Incidence of Awareness

- General Incidence 0.1-0.2% (>40,000 in US?)
  - Ghoneim *Anesthesiology* 92:597, Feb 2000 (review)

- Obstetrics
  - 0.9% recall and 6.9% dreams (Lyons 1991)

- Cardiac
  - 1.1% recall (Phillips 1993)
  - 0.3% recall (Dowd 1998)
Awareness in the US

- Goal: determine incidence of awareness in US
- Large, prospective, multicenter study
- 19,576 Patients interviewed
  - Postoperatively
  - After one week
- Convenience sampling of all patients types

The findings from this US multi-center study are similar to previously reported awareness incidence reports from Australia and Sweden. **Awareness during anesthesia is a ubiquitous phenomenon** occurring at an incidence between 1-2 cases per 1000. *Sebel et al, Anesth Analg. 2004; 99: 833-9*
Experiences During Awareness

- Sounds, conversation
- Intubation/ endotracheal tube
- Sensation of surgery
- Sensation of paralysis
- Anxiety and panic
- Helplessness and powerlessness
- Pain
“Awareness” – A Self Report

“I share my experience as a general practioner, awake but paralyzed whilst undergoing a laparoscopic cholecystectomy . . .”

“I could feel the cool iodine being sponged onto my abdomen. I was terrified as I realized I had sensation and was going to feel the surgery…. The first umbilical incision, although only a few centimeters long felt like a huge incision across my abdomen”

Rowan, Anaesth Intensive Care 2002; 30:505-6
Jeanette M. Liska, PhD.

Silenced Screams

Surviving Anesthetic Awareness During Surgery: A True Life Story

AANA Publishing Inc, Park Ridge IL. 2002
What Causes Awareness?

- Selection of inadequate anesthetic dose
- Resistance to anesthetics
- Mechanical malfunction or misuse of anesthetic machine

Inadequate anesthetic dose

---

CLINICAL CONCEPTS AND COMMENTARY

Richard B. Weiskopf, M.D., Editor

Anesthesiology
2000; 92:597-602
© 2000 American Society of Anesthesiologists, Inc.
Lippincott Williams & Wilkins, Inc.

Awareness during Anesthesia

M. M. Ghoneim, M.D.*
Awareness: A DOSING Problem

Sevo 3 - 2%
Sevo 0.8%
Sevo 1.3%
Sevo 1.7%
On CPB Iso 2%

Incision & Sternotomy

Anesth Analg 2001; 93:798-799
Awareness: A DELIVERY Problem

Noted that the anesthetics were "backed up" in the IV line. Patient was unparalyzed but did not move during this time.

Luginbühl, M and Schnider T. Detection of Awareness with the Bispectral Index: Two Case Reports. Anesthesiology 2002;96:241-243
~40 yo female, 53 kg

PSH: Anterior lumbar fusion as well as 2 prior lumbar lamis

60 mg Oxycontin BID with adjuncts

Now presenting for ACDF with SSEP monitoring

Received in OR

- 5500 mg propofol for 2.5 h procedure
  - 691 µg/kg/min!
- 1250 µg fentanyl (25 ml)
- 17 mg midazolam
Resistance to Anesthetics
Resistance to Anesthetics

Extubated in OR
C/o pain in Recovery Room
Treated with Morphine 20 mg
What are the Consequences of Awareness?

**CLINICAL CONCEPTS AND COMMENTARY**

Richard B. Weiskopf, M.D., Editor

Anesthesiology 2000; 92:597–602
© 2000 American Society of Anesthesiologists, Inc.
Lippincott Williams & Wilkins, Inc.

**Awareness during Anesthesia**

M. M. Ghoneim, M.D.*

---

Department of Psychiatry
Post-traumatic Stress Disorder Clinic
Consequences: PATIENT

- 18 cases of Awareness –
  - Initial Treatment (up to 3 weeks): Discussion/support
    - Patient satisfied: “All symptoms had disappeared”
    - Patient considered further contact unnecessary
    - All declined referral to psychiatrist

2 yr Follow-up:
- 6/18 – Refused interview
  - Avoidance as part of PTSD?
- 9/18 patients – Located and agreed to interview
  - 4/9 – psychiatric sequelae with severe disability
    - All with ANXIETY, One with PAIN during Awareness Episode
  - 3/9 – Less severe, transient disability
  - 2/9 – Denied any sequelae

Lennmarken et al, Victims of awareness
Acta Anaesthesiol Scan 2002; 46:229-231
Sentinel Event Alert

Preventing, and managing the impact of, anesthesia awareness
Anesthesia awareness, also called unintended intraoperative awareness, occurs under general anesthesia when a patient becomes cognizant of some or all events during surgery or a procedure, and has direct recall of those events. Because of the routine use of neuromuscular blocking agents (also called paralytics) during general anesthesia, the patient is often unable to communicate with the surgical team if this occurs.

The frequency of anesthesia awareness has been found in multiple studies to range between 0.1 percent and 0.2 percent of all patients undergoing general anesthesia. (1,2,3) The administration of general anesthesia to 21 million patients annually in the United States translates to the occurrence of 20,000 to 40,000 cases of anesthesia awareness each year. Patients experiencing awareness report auditory recollections (48 percent), sensations of not being able to breathe (48 percent), and pain (28 percent). (1) Over 50 percent of these patients are reported to experience mental distress following surgery, including an indeterminate number with post-traumatic stress syndrome. (2,3) Some patients describe these occurrences as their “worst hospital experience,” and some determine to never again undergo surgery.

The incidence of awareness is reported to be greater in patients in which the dose of general anesthetic must be smaller and carefully titrated to decrease significant side effects, for example, a patient who is hemodynamically unstable. Procedures typically identified as falling into this category are some cardiac, obstetric and major trauma cases. (4) Factors contributing to the risk...
Does Brain Function Monitoring (BFM) make a difference in awareness?
Intraoperative Awareness: How Effective are Hemodynamic Markers?

ASA Closed Claims Review

- 15% - hypertension
- 7% - tachycardia

Recent Awareness Studies

- **Impact of BFM Monitoring**
  - **B-Aware Study** *(Myles et al. Lancet. 2004; 363:1757-63)*
SAFE-II: Study Design / Results

- 5057 consecutive patients > age 16
- GAs w/ relaxant technique
- All BIS-monitored
- Post-op interviews conducted for potential awareness (3 over 14 days)
- Results compared with historical data

BFM Use Reduces Awareness

78% reduction

―The incidence found is the lowest ever reported in a reasonably large study‖

SAFE-2 Awareness Cases: High BIS Values

Case 1: KLR 71

Case 2: KLR 2506

B-Aware Trial: Study Design

- Prospective, randomized, double-blind, multi-center
- 2,500 high-risk adult patients
  (c-section, high-risk cardiac, trauma, rigid bronchoscopy, prior awareness experience)
  - randomized into 2 groups: BIS-guided and routine care
- Blinded observer assessment for recall at 3 regular intervals after surgery
- Blinded adjudication committee determined status:
  - awareness/possible awareness/no awareness

Myles et al. Lancet 2004
BFM Reduces Awareness

Prospective, Randomized, Double-blinded, Multicenter Study

- Adult Patients at High Risk for Awareness
- Total Patients Enrolled: 2503

82% reduction

P=0.022; 95% CI 17-98%

Myles et al. Lancet 2004
B-Aware: BIS Monitored Cases

Two awareness cases in the BIS guided treatment group

Heard voices and sternal saw, with some pain. BIS recorded as 55-59, > 60 for 9 minutes

Brief recollection of rigid bronchoscopy with slight pain. BIS recorded at 79-82; BIS > 60 for 5 minutes
“Monitors by themselves are not therapeutic – they require understanding and interpretation, after which a rational action must be undertaken.”

What are the long term effects of general anesthesia, especially “too much anesthesia”?
Apoptosis: (defn.) cell self-destruction, a physiologic process eliminating DNA-damaged, superfluous or unwanted cells. Also called programmed cell death.
Widespread nonphysiologic apoptosis and neurodegeneration have been observed in laboratory rodent fetal brains after short-term anesthetic exposure.

Even in mature brain, the transition of immature cells into more highly differentiated neurons with the complex synaptic structure needed for learning could be compromised by routine anesthetic exposure.
Some preliminary clinical data could also be interpreted to support the hypothesis that anesthetics have intrinsic potential neurotoxicity. In elderly surgical patients, for example, deeper levels of inhalational anesthesia are associated with more severe early postoperative cognitive impairment.

This suggests that in individuals with limited nervous system reserve or impaired tolerance for oxidative stress, prolonged exposure, or higher anesthetic concentrations could be, in effect, neurotoxic.
FDA Conference

Brain Growth Spurt (BGS) period a time of synaptogenesis (neural synapse formation)

The BGS period occurs in different species at different times relative to birth.

“Window of Vulnerability”

**Rodent:** First three weeks after birth.

**Human:** From mid-gestation to several years after birth.

*Dobbing & Sands, Early Human Dev., 3, 79, 1979*
All general anesthetics used in obstetric and pediatric medicine incorporate mechanisms which lead to neuroapoptosis.

- We have demonstrated that exposure for 6 hrs to an anesthetic cocktail used commonly in pediatric anesthesia (midazolam, nitrous oxide, isoflurane), triggers extensive neuroapoptosis in the developing rat brain, followed by learning/memory deficits at 30 days of age which persist into adulthood.

Jevtovic-Todorovic et al. J. Neuroscience, 2003
Alternative Therapies For Children

- Neuraxial/regional/local anesthesia
- Opioid anesthesia
- No anesthesia
- Delay surgery

- Will we be seeing “black box” warnings on volatile anesthetics?
### Anesthetic Exposure & Alzheimer’s Disease

**No Clinical Association?**

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>YES</th>
<th>NO</th>
<th>Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prior exposure of general anesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>208</td>
<td>44</td>
<td>1.28 [0.82-2.00]</td>
</tr>
<tr>
<td>Control</td>
<td>199</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Six or more prior events of general anesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>25</td>
<td>227</td>
<td>1.44 [0.77-2.71]</td>
</tr>
<tr>
<td>Control</td>
<td>18</td>
<td>234</td>
<td></td>
</tr>
<tr>
<td>&gt;Ten cumulative hours of general anesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>8</td>
<td>244</td>
<td>1.63 [0.53-5.04]</td>
</tr>
<tr>
<td>Control</td>
<td>5</td>
<td>247</td>
<td></td>
</tr>
</tbody>
</table>

(*80% power, alpha = 0.05)
General Anesthesia and Breast Metastases

- Retrospective Clinical Analysis
  - 129 consecutive breast cancer patients
  - Mastectomy + Axillary Node Dissection
  - Same anesthesia provider, same surgeon, same oncologist caring for all the patients within the study

- Non-randomized:
  - 79 pts: GA only
  - 50 pts: Paravertebral + GA

- Follow-up: 32 ± 5 months
<table>
<thead>
<tr>
<th>Metastasis-free survival (%)</th>
<th>24 mo</th>
<th>36 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paravertebral</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>GA</td>
<td>82</td>
<td>77*</td>
</tr>
</tbody>
</table>

*p = 0.012

This retrospective analysis suggests that paravertebral anesthesia and analgesia for breast cancer surgery reduces the risk of recurrence or metastasis during the initial years of follow-up.

Exadaktylos, Anesthesiology. 2006;105:660-4
Breast Cancer

• The stress response impairs numerous immune functions including a marked attenuation of natural killer cells
  • Natural killer cells are thought to play a central role in preventing tumor dissemination and establishment

• Experimental studies show that surgical stress is attenuated better by regional anesthesia than by GA and that consequently, natural killer cell function is better preserved and metastatic load is reduced.

Exadaktylos, Anesthesiology. 2006;105:660-4
Anesthetic Management and One-Year Mortality After Noncardiac Surgery

Terri G. Monk, MD, MS*, Vikas Saini, MD, FACC†, B. Craig Weldon, MD*, and Jeffrey C. Sigl, PhD‡

*Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, †The Cardiovascular Specialists LLC, Hyannis, Massachusetts, ‡Aspect Medical Systems, Newton, Massachusetts
“The original study was designed to have cognitive decline at 3 months and a secondary endpoint of survival at one year...

There have been several longitudinal studies of aging - the Berlin Aging study and the Seattle Aging Study that have shown that abrupt cognitive declines for any reason are associated with an early death - thus, I put the survival end point in to see if the patients who had cognitive decline after surgery were more likely to die. There was a significant association between cognitive decline at 3 months after surgery and death in the first year after surgery.”

Personal communication with Dr. TG Monk, 2/14/2006
Anesthetic Management and One Year Mortality after Non-Cardiac Surgery

- 1064 Patients
- Prospective Design
- Overall Mortality 5.5%
- Mortality 10.3% if age > 65
- 3 independent variables were predictive of mortality:
  - Co-morbidity
  - Cumulative intraoperative hypotension
  - Cumulative deep hypnotic time (BIS<45)

Monk TG, et.al. Anesth Analg; 100:4-10
## Independent Multivariate Predictors of One-Year Mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative Risk [Bootstrapped 95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson Comorbidity Score (3+ vs 0-2)</td>
<td>16.116 [10.110 – 33.717]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypotension SBP &lt; 80 mm Hg (per minute)</td>
<td>1.036 [1.006-1.066]</td>
<td>0.0125</td>
</tr>
<tr>
<td>Cumulative Deep Hypnotic Time (BIS &lt; 45) (per hour)</td>
<td>1.244 [1.062-1.441]</td>
<td>0.0121</td>
</tr>
</tbody>
</table>

c-statistic: 0.847 [95%CI: 0.788-0.906, p < 0.001]

Monk et al. Anesth Analg 2005; 100:4-10
### Independent Multivariate Predictors of One-Year Mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative Risk [Bootstrapped 95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson Comorbidity Score (3+ vs 0-2)</td>
<td>16.116 [10.110 – 33.717]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypotension SBP &lt; 80 mm Hg (per minute)</td>
<td>1.036 [1.006-1.066]</td>
<td>0.0125</td>
</tr>
<tr>
<td>Cumulative Deep Hypnotic Time (BIS &lt; 45) (per hour)</td>
<td>1.244 [1.062-1.441]</td>
<td>0.0121</td>
</tr>
</tbody>
</table>

c-statistic: 0.847 [95%CI: 0.788-0.906, p < 0.001]

Monk et al. Anesth Analg 2005; 100:4-10
Is “Depth of Anesthesia” Associated with One-Year Mortality?

- Multi-center Prospective Trial (Sweden)
  - 5,057 General Anesthetics, Non-cardiac Surgery
- 1 Year Mortality Rate = 5.6%
  - vs. 5.5% in Monk Study
- Deep Anesthesia Time:
  - Significant Independent Predictor Of Mortality
  - Increased Relative Risk: 19.7% / Hr
  - vs. 24.4% in Monk Study

Lennmarken et al, Anesthesiology 2003; 99:A-303
This collaborative conference provided the opportunity to examine a variety of issues. One had to do with surprising - but very preliminary - data regarding post-surgical survival that might affect the lives of tens of thousands of patients each year. These new data showed an unexpected correlation between the time a person spent at more profound levels of 'brain wave' changes during anesthesia and the likelihood of their dying within the first year after their surgery from causes totally unrelated to the surgery.

http://www.apsf.org/initiatives/outcomes.mspx
Inflammation has been implicated in many disease processes and it is definitely possible that there exists a relationship between inflammation and the long-term outcomes associated with surgery and anesthesia. But much remains to be determined to see if this linkage is present, and if so its strength and what can be done about it. Studies are needed both on the basic biology of inflammation, and on the specifics of this biology in the setting of anesthesia and surgery.

http://www.apsf.org/initiatives/outcomes.mspx
Points to Ponder

- Can’t we just stop giving anesthesia?
  - Can we delay when it is given?
- Can we give less anesthesia?
- What is the best choice of anesthesia for any particular patient?
Conclusion

- All Truth Goes Through Three Stages
  - First it is ridiculed
  - Then it is violently opposed
  - Finally, it is accepted as self-evident

- Arthur Schopenhauer (1788 - 1860)
  German philosopher
Thank You
References

Anesth analg. 2006 Aug;103(2):403-409
Neubauer, Journ Amer Phys Surg, Vol 10, No 1, Spring 2001 22
http://www.apsf.org/initiatives/outcomes.mspx
Taggart DP Heart. 2003 Aug;89(8):897-900
http://Seattletimes.rwsource.com/html.healthscience/134569552_brainfog05.html
Arch Gen Psychiatry 1976 Feb;33(2) 255-9
Monk TG et al. ASA abstracts, 2002 A-40
Chan Anesth Analg 2004; 98:S126
Monk TG et al. Anesth Analg. 2005 Jan;100(1):4-10. Anesthetic management and
one-year mortality after noncardiac surgery
Lennmarken et al, Anesthesiology 2003; 99:A-303
general anesthesia.
AANA Committees

- We’re looking for “a few good CRNA’s”
  - Nominating Committee
  - Resolutions committee
Regional Director
Nominating Committee

- Nominating Committee is responsible for preparing the official ballot and reviewing candidate submissions. Includes eliminating candidates and recruiting candidates as necessary.
The Nominating Committee meets 1 day twice a year

- Annual Meeting and typically the first Saturday in March in Chicago

- The Nominating Committee usually holds 3-5 one hour conference calls during the fiscal year. The dates of the calls are predetermined

- All expenses are paid for March meeting
The Resolutions Committee is responsible for reviewing proposed resolutions for proper format and studying the proposed resolution for the purpose of making a recommendation to the membership at the annual Business Meeting.
Resolutions Committee

- The Resolutions Committee may meet twice during the year, typically on a conference call and at the Annual Meeting in August, if there are resolutions to consider.
Recommended Talents
Resolutions and Nominating Committee

- Talents include, but are not limited to:
  - Problem evaluation
  - Problem solving
  - Decision-making ability
  - Ability to work with others
  - Respect among peers
  - The ability to present a position to the membership
Cleveland Clinic Study

- General Anesthesia
  - 900 patients
  - BIS monitoring
  - “Aggressive” glucose control
  - Dexamethasone
  - Neurocognitive testing
  - One year survival
Questions?