Disclaimers

- This is not an ACLAM sanctioned presentation
- All information is deemed reliable and correct
  - No warranty for accuracy
- No information presented is known to be specifically included in the ACLAM Board Certification Exam

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- Paul Flecknell
- Bob Meyer

Resources

- **Anesthesia and Analgesia in Laboratory Animals**
- Plan
  - Approach
    - Continuing education
    - Selected review + literature
    - Emphasis on injectables
  - Format
    - Questions ➔ audience participation
### Domain 2: Management of Pain and Distress

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### Terminology (con’t.)

- **Anesthesia**: artificially induced sleep or trance
- **Analgesia**: loss of sensation to body part or whole body
- **Sedation**: central depression with drowsiness, reduced awareness
- **Hypnosis**: loss of sensitivity to pain

### Terminology (con’t.)

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- **Anesthesia**: artificially induced sleep or trance
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- **Hypnosis**: loss of sensitivity to pain
Terminology, con't.

- Pain: an unpleasant sensory or emotional experience associated with actual or potential tissue damage
- Nociception: peripheral and central nervous system processing of information about the internal or external environment related to tissue damage

(Committee on Pain and Distress in Laboratory Animals, 1992; Flecknell and Waterman-Pearson, 2000)

Terminology, con't.

- Surgical Anesthesia = loss of consciousness and sensation, along with sufficient muscle relaxation and analgesia for painless surgery

Terminology, con't.

- General Anesthesia = loss of consciousness in addition to loss of sensation
  - Hypnosis
  - Hyporeflexia
  - Analgesia
  - Muscle relaxation

According to Antognini et al. (Compar Med 2005), which of the following is NOT a feature of general anesthesia?

A. Amnesia
B. Unconsciousness
C. Immobility
D. Analgesia

Effects of injury on pain sensation
(courtesy: Paul Flecknell)
Which of the following are physiological features of general anesthesia?

A. Respiratory depression  
B. Cardiovascular depression  
C. Decreased renal function  
D. Impaired thermoregulation  
E. Hormonal alterations  
F. All of the above

Literature Cautions

TRUE/FALSE: If it’s in the literature, it must be true.

Literature Cautions

• Definitions  
  – “anesthesia”  
  – anesthetic depth  
  – antinociceptive potency  
• Controls/baselines  
• Cardiorespiratory state, body temperature  
• Drug effect vs. general anesthesia  
• Is one article enough?

Literature Cautions, con’t.

• Animal subject variables  
  – genotype  
  – age  
  – sex  
  – body composition  
  – nutritional/disease state  
• Individual variation  
• Dosage
**Injectable “Anesthetics”**

- **Barbiturates**
- **(Other) Hypnotics**
- **Steroids**
- **Cyclohexamines**
- **Alpha-2 agonists**
- **Local anesthetics**
- **Anesthetic combinations:** above +/-
  - Opioids
  - Sedatives and tranquilizers

**Injectable “Anesthetics”**

- Alternative classification based on mechanism of action

**TRUE/FALSE:** Most injectable anesthetics act at the neuronal cell membranes to alter Na+ permeability.
Injectable “Anesthetics”

• Alternative classification based on mechanism of action

TRUE/FALSE: Most injectable anesthetics act at the neuronal cell membranes to alter Na⁺ permeability.

Which of the following is NOT a GABA agonist?

A. Ketamine
B. Metomidate
C. Propofol
D. Ethylmethyl thiourea (Inactin)
E. Diazepam

GABA Agonists

dose-dependent CNS depressants

• Barbiturates
• Chloral hydrate
• Alpha chloralose
• Tribromoethanol (Avertin)
• Propofol
• Metomidate and etomidate
• Steroids
• [benzodiazepines]
**Hypnotics – Why Use Them?**

- Dose-dependent CNS depressants
  - i.e., sleep
- Convenience
  - single injection (+/-)
  - rapidly metabolized OR “long term stable anesthesia”
- Minimal cardiorespiratory depression

**TRUE/FALSE:** Hypnotics in general are poor analgesics.

**Which of the following has been associated with pathologic changes following IP administration?**

- A. Cloral hydrate
- B. Chloralose
- C. Urethane
- D. Tribromoethanol
- E. All of the above

**Tribromoethanol**

**TRUE/FALSE:** TBE is a well-characterized, safe and effective injectable anesthetic used primarily in mice.

*See:*
**Tribromoethanol**

**FALSE:** TBE is a well-characterized, safe and effective injectable anesthetic used primarily in mice.

See:

**TBE – Why DO We Use It?**

**Hypnotics**

**Tribromoethanol**

- **Description**
  - rapid induction, short term surgical anesthesia, rapid recovery
  - common use in transgenic procedures
  - conflicting reports on efficacy and safety
  - non-pharmaceutical grade powder
  - safe use requires proper preparation and storage
  - pharmacology ??

**TRUE/ FALSE:** Chemical grade anesthetics can be used safely for anesthesia if filter-sterilized.

**MAYBE:** Chemical grade anesthetics can be used safely for anesthesia if filter-sterilized.

- Chloralose
- Urethane
- Tribromoethanol
- Inactin
Pharmaceutical-Grade Compounds in Research (Policy #3)

- Use pharmaceutical-grade medications whenever they are available, even in acute procedures.
- Use non-pharmaceutical-grade chemical compounds only with IACUC approval
  - scientific necessity
  - non-availability of an acceptable pharmaceutical-grade product.
- Cost savings alone are not an adequate justification for using non-pharmaceutical-grade compounds in regulated animals.

For which of the following would use of propofol for anesthesia be LEAST appropriate?

A. Dog  
B. Cat  
C. Pig  
D. Rabbit  
E. Rat

Which if the following best describes alphaxalone/alphadolone?

A. Barbiturate  
B. Local anesthetic  
C. Hypnotic  
D. NSAID  
E. Neuroleptanalgesic

Which of the following is NOT a characteristic of ketamine?

A. NMDA antagonist  
B. Cyclohexamine  
C. Dissociative anesthetic  
D. Sympathomimetic anesthetic  
E. Monoanesthetic

- aka: anesthetic steroid; “Saffan”
- Note: new anesthetic steroid: “Alfaxan”
Which of the following is NOT a characteristic of ketamine? (along with phencyclidine, tiletamine)
A. NMDA antagonist
B. Cyclohexamine
C. Dissociative anesthetic
D. Sympathomimetic anesthetic
E. Monoanesthetic

Cyclohexamines

**TRUE/FALSE:** Although an effective agent for chemical restraint, ketamine is considered a poor analgesic.

Which of the following is NOT an alpha2 adrenoreceptor agonist?
A. Xylazine
B. Detomidine
C. Metomidate
D. Romifidine

**Why Dexmedetomidine?**

- No medetomidine, but…
Urethane

TRUE/ FALSE: Urethane refers to a family of polymers ranging from rubbery to brittle; a versatile type of plastic material that can be manufactured into a flexible or rigid sheet, a coating, an ink, or adhesive.

- How does urethane (anesthesia) work?
- Why use urethane?

Which of the following is a carcinogen and mutagen?

A. Chloralose
B. Tribromoethanol
C. Urethane
D. Alphaxalone/alphadolone
E. Ether

Which of the following is a carcinogen and mutagen?

A. Chloralose
B. Tribromoethanol
C. Urethane
D. Alphaxalone/alphadolone
E. Ether

Which of the following does NOT have a specific pharmacologic antagonist?

A. Midazolam
B. Fentanyl
C. Medetomidine
D. Ketamine
Which of the following does NOT have a specific pharmacologic antagonist?

A. Midazolam  
B. Fentanyl  
C. Medetomidine  
D. Ketamine

Antagonists

- Midazolam: flumazenil  
- Fentanyl: naloxone  
- Medetomidine: yohimbine, atipamezole

TRUE/FALSE: Atipamezole is an effective antagonist for xylazine.

What’s a Neuroleptic?

- agent that → mental calming, decreased response to stimuli, and muscular relaxation.  
- aka tranquilizer, ataractic, antipsychotic agent  
- c/w sedative/antianxiety agent

Phenothiazines and Butyrophenones -- key points

- Dose-dependent spectrum of activity:  
  - sedation, drowsiness → ataxia, somnolence → cataleptic  
- No analgesia, but…  
- Side effects, including hypotension
**Benzodiazepines -- key points**

- Human use: sedative, hypnotic, anxiolytic, muscle relaxant, anticonvulsant
- Tranquilizing effects in animals species-variable
- Elimination T-1/2 in animals much shorter than human
- No analgesia
- Minimal cardiorespiratory depression
- Antagonist: flumazenil

**Injectable Combinations**

- Neuroleptanalgesia/Neuroleptanesthesia
  - Innovar (fentanyl/droperidol)
  - Hypnorm (fentanyl/fluanisone)
  - oxymorphone/acepromazine
  - fentanyl/midazolam

- Ketamine combinations, with:
  - xylazine or medetomidine
  - xylazine + acepromazine
  - midazolam or diazepam
  - etc.
- Tiletamine-zolazepam (Telazol)
  - TX, TKX
- Chloralose/urethane

**Injectable Combinations**

- Tribromoethanol-Medetomidine Combination Provides a Safe and Reversible Anesthetic Effect in Sprague-Dawley Rats.
  - C Gopalan et al. Contemp Topics 44(1):7- , 2005
- Etc.

**Why Inhalants?**

**TRUE/FALSE:** Inhalants are used primarily for ability to control anesthetic depth.

**TRUE/FALSE:** Inhalants are used primarily for ability to control anesthetic depth.
Why Inhalants?

- Rapid control of anesthetic depth → safety
- Rapid induction and recovery
- Defined (and measurable) level of anesthesia for duration of procedure
- Inherently safer than injectables?

Inhalants

TRUE/ FALSE: MAC = minimum alveolar concentration.

Inhalants

TRUE/ FALSE: Activated charcoal gas-scavenging units effectively prevent trace levels of isoflurane emissions.

Inhalants

TRUE/ FALSE: Activated charcoal gas-scavenging units effectively prevent trace levels of isoflurane emissions.

Inhalants

TRUE/ FALSE: MAC = Median anesthetic concentration.

(From Meyer et al., 2002; Brunson (IN Kohn et al.), 1997.)
Which of the following is a COX-2 selective drug?

A. Acetaminophen  
B. Flunixin  
C. Carprofen  
D. Meloxicam  
E. None of the above

What is celecoxib, rofecoxib

Multimodal pain therapy

• Pre-emptive analgesia  
  → decr. wind-up  
  → e.g., ketamine  
  → c/w preop ketoprofen, or meloxicam  
  → Human studies still controversial  
• Alpha-2 agonists  
• Local/regional anesthetics

Additional Analgesia prn

(allow for anesthetic sparing of preop opioids)

Nursing care

Additional Analgesia prn

Opioid or

Local Anes

Multimodal pain therapy

• Opioids (→ extended duration)  
  → transdermal fentanyl  
  → oral sustained release morphine  
  → time release pellets; osmotic pump  
  → liposomal preparations

Adapted from: Flecknell, PA and A Waterman-Pearson, eds. Pain Management in Animals, WB Saunders, 2000
Nonpharmacologic Interventions for Control of Pain and Distress

Analgesics Developed 1960-2009 and Presently in Use – drugs developed for treatment of pain

- **OPIOIDS**
  - Pentazocine
  - Fentanyl
  - Butorphanol
  - Nalbuphine
  - Buprenorphine
  - Sufentanil
  - Alfentanil
  - Tramadol
  - Remifentanil


Analgesics Developed 1960-2009 and Presently in Use – drugs developed for treatment of pain

- **NSAIDS**
  - Indomethacin
  - Mefenamic acid
  - Ibuprofen
  - Naproxen
  - Tolmetin
  - Sulindac
  - Meclofenamate
  - Piroxicam
  - Diflunisal
  - Ketoprofen


- **OTHER DRUGS**
  - Sumatriptan
  - Zolmitriptan
  - Naratriptan
  - Rizatriptan
  - Almotriptan
  - Frovatriptan


Analgesics Developed 1960-2009 and Presently in Use – drugs developed for indications other than pain, but effective...

- **ANTICONVULSANTS**
  - Carbamazepine
  - Phenytoin
  - Clonazepam
  - Valproate
  - Gabapentin
  - Topiramate


- **ANTIDEPRESSANTS**
  - Amitriptyline
  - Doxepin
  - Imipramine
  - Desipramine
  - Venlafaxine
  - Duloxetine

Analgesics Developed 1960-2009 and Presently in Use – drugs developed for indications other than pain, but effective…

- Propanolol
- Capsaicin (topical)
- Cyclobenzaprine
- Lidocaine (systemic, topical)
- Mexiletine
- Ketamine
- Dronabinol
- Dexamethasone


TRUE/ FALSE: Fish feel pain.

What is the only FDA-approved anesthetic for use in fish intended for food?

A. Ketamine  
B. Metomidate  
C. Chloral hydrate  
D. Eugenol  
E. Tricaine methanesulfonate (MS-222)

What's new with Fish?

- NOT new = MS-222
  - aka tricaine; metacaine; ethyl m-aminobenzoate; used as methanesulfonate salt
  - aka Finquel
  - Only FDA-approved anesthetic for use in fish intended for food; 21-day withdrawal
- c/w clove oil
  - mixture of eugenol, isoeugenol, and methyleugenol
  - Sladky et al., 2001. AJVR 62(3):337-
- c/w metomidate
  - Aquacalm™ is FDA-indexed for the sedation and anesthesia of ornamental finfish


http://www.vet.ed.ac.uk/animalwelfare/Fish%20pain/fish%20pain.htm
The bispectral index is used to help assess which of the following?

A. Pain
B. Distress
C. Anesthesia depth
D. Anxiety
E. Coordination

Species-Specific Summaries

- Rabbit
- Guinea Pig
- Rat
- Mouse
- Hamster
- Gerbil
- NHP

What is this piece of equipment?

A. Endotracheal tube
B. Esophageal stethoscope
C. Stomach tube
D. Laryngeal mask airway
E. Peterson-Foley catheter

The bispectral index [BIS] is used to help assess which of the following?

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What is this piece of equipment?

A. Endotracheal tube
B. Esophageal stethoscope
C. Stomach tube
D. Laryngeal mask airway
E. Peterson-Foley catheter
Species-Specific Summaries

• Guinea Pig
  - Difficult intubation
  - Palatal ostium

Species-Specific Summaries

• Rat

Species-Specific Summaries

• Mouse

Species-Specific Summaries

• Hamster

Species-Specific Summaries

• Gerbil

Species-Specific Summaries

• NHP
**Propofol**

**TRUE/FALSE:** Because of its formulation, aseptic technique is especially important in the handling of propofol.

Which of the following can significantly suppress adrenal cortical activity?

A. Ketamine  
B. Metomidate  
C. Urethane  
D. Chloral hydrate

**Propofol**

**TRUE/FALSE:** Because of its formulation, aseptic technique is especially important in the handling of propofol.

Which of the following can significantly suppress adrenal cortical activity?

A. Ketamine  
B. Metomidate *(also etomidate)*  
C. Urethane  
D. Chloral hydrate
Which of the following is NOT a characteristic of xylazine?
A. Alpha2 agonist  
B. Sedative-analgesic, muscle relaxant  
C. Sedative/hypnotic  
D. Poor analgesic  
E. Potency << medetomidine

Opioids
Morphine acts primarily at which receptor?
A. µ  
B. δ  
C. ε  
D. κ  
E. σ

Which of the following is a partial opioid agonist?
A. Buprenorphine  
B. Morphine  
C. Fentanyl  
D. Meperidine  
E. Remifentanil

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D. Meperidine  
E. Remifentanil

Butorphanol?
Which of the following is NOT a butyrophenone?

A. Azaperone  
B. Droperidol  
C. Acepromazine  
D. Fluanisone

**Neuroleptics**

**TRUE/ FALSE:** Neuroleptics do not provide analgesia.

But…

**Tail Flick Analgesia Instrument**

Test for analgesic affects; rodent’s tail is placed over window on platform while being restrained. Intense beam of light is applied to the tail (60 – 170° C) and latency period is measured until tail is flicked out of the light beam.
**Hot Plate Analgesia Instrument**

Measures latency of stereotyped paw lick response after dropping mouse or rat onto hot surface (30 – 60°C).

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**Plantar Analgesia Instrument**

Measures paw sensitivity to heat stimulation similar to Hot Plate test, however, animal is unrestrained & heat is applied to bottom of single foot after animal is at rest. Repeated testing does not result in sensitization.

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**Search for the Perfect Anesthetic**

- Elimination not dependent on metabolism
- Rapid induction, recovery, and change in depth
- Minimal cardiopulmonary depression
- Non-irritant
- Inexpensive, stable, nonflammable, non-explosive
- No special equipment
- Reversible

---

**What’s New?**

- **Equipment – General**
- **Equipment – laryngeal mask airway**
  - JC Smith et al., 2004. Contemp Topics 43(4):22-
- **Anesthetic monitoring (e.g., BIS)**
  - SA Greene et al., 2002. Compar Med 52(5):424-
  - SA Greene et al., 2004. Compar Med 54(4):397-

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Substances affecting transmission of pain signals -- Dorsal Horn

- Excitation
  - glutamate
  - substance P
  - neurokinin A
  - other neuropeptides
  - prostaglandins
  - nociceptin (?)
  - dynorphins (?)

- Inhibition
  - B endorphin
  - noradrenaline
  - dynorphins
  - endorphin
  - adenosine
  - 5HT (?)
  - GABA (?)

Substances affecting transmission of pain signals -- Nerve Ending

- Excitation/Sensitisation
  - prostaglandins
  - bradykinin
  - hydrogen ions
  - potassium ions
  - histamine
  - purines
  - leukotrienes
  - growth factors
  - substance P

- Inhibition
  - anandamide
  - B endorphin (?)

Multimodal pain therapy

- Buprenorphine?

What are the Hazards?

- Hazards posed by the animals
- Hazards posed by the facility, equipment, etc.
- Hazards posed by the experimental agents