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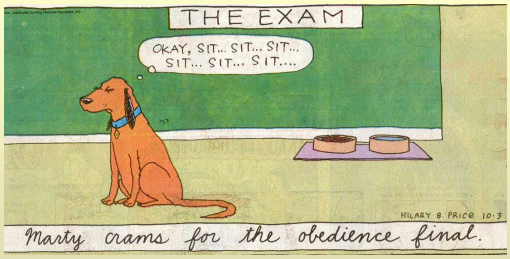

Anesthesia & Analgesia

Workshop in Laboratory Animal Medicine
Raleigh, NC
May 13, 2010

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College of Veterinary Medicine

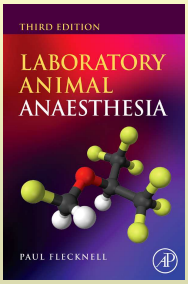
Disclaimers

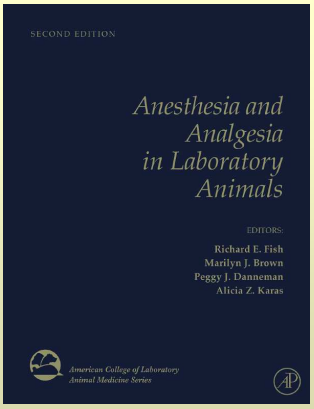
- This is not an ACLAM sanctioned presentation
- All information is deemed reliable and correct
  - No warranty for accuracy
- No information presented is known to be specifically included in the ACLAM Board Certification Exam

Acknowledgements!

- Thanks to the following sources for the images used in this presentation:
  - Diane Forsythe and Mary Grant – National Institute for Environmental Health Sciences
  - US Army
  - Sue Spray and Tim Barker – Scripps Institute
- Paul Flecknell
- Bob Meyer

Resources





Plan

- Approach
  - Continuing education
  - Selected review + literature
    - Emphasis on injectables
- Format
  - Questions → audience participation

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Domain 2: Management of Pain and Distress	10%
Tasks	*Knowledge Topics*
T1. Recognize pain and/or distress	TT2.1. anatomy and physiology of pain and distress as they pertain to laboratory animals
T2. Minimize or eliminate pain and/or distress	TT2.2. patient monitoring as it pertains to laboratory animals
T3. Euthanatize (Euthanize)	TT2.3. critical and post-procedural care techniques as they pertain to laboratory animals
	TT2.4. assessment of pain and distress (e.g., behavior which is a sign of pain and/or distress; physiologic changes; pain and distress scoring systems)
	TT2.5. causes of pain
	TT2.6. causes of distress
	TT2.7. effects of pain and distress on normative physiology and on research studies
	TT2.8. pharmacological interventions for pain and distress and their effects on physiology, including age and species differences for such interventions, and depth and duration of analgesia provided by such interventions
	TT2.9. nonpharmacological interventions for pain and distress and their effects on physiology, including age and species differences for such interventions
	TT2.10. euthanasia
	TT2.11. humane endpoint criteria

Terminology

- **Anesthesia**
- **Analgesia**
- **Sedation**
- **Hypnosis**

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

Terminology, con't.

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- **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)

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

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

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

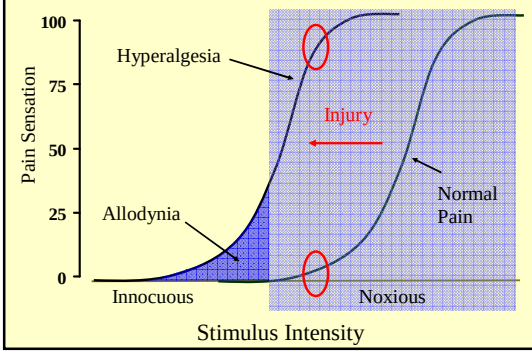
A. Amnesia
B. Unconsciousness
C. Immobility
D. Analgesia

According to Antognini et al. (Comp 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

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Literature Cautions

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

Literature Cautions

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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

Why Injectables?

TRUE/FALSE: Injectable anesthetics are used primarily because they provide general anesthesia of superior quality.

Why Injectables?

FALSE: Injectable anesthetics are used primarily because they provide general anesthesia of superior quality.

but…

Why Injectables?

- Default: habit, familiarity
- Decreased equipment
- Difficulty of intubation
- Safety
- Preserve physiological reflexes/cardio-respiratory function

Why Injectables?

- Specific antagonists
- Balanced anesthesia: = ??
  - combination of drugs, each → specific pharmacological effect
    - Tranquilization
    - Hypnosis
    - Analgesia
    - Muscle relaxation
    - Amnesia?
  - N2O + opioid + NMB, +/- sub-MAC inhalant and midazolam
- TIVA
  - e.g., propofol/remifentanil

Injectable "Anesthetics" (classification)

- 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.

Injectable "Anesthetics"

- GABA agonists
- NMDA antagonists
- Alpha$_2$ agonists
- Miscellaneous
- Local anesthetics
- Neuroleptic/antipsychotic agents
- Injectable combinations

Which of the following is NOT a GABA agonist?

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

Which of the following is NOT a GABA agonist?

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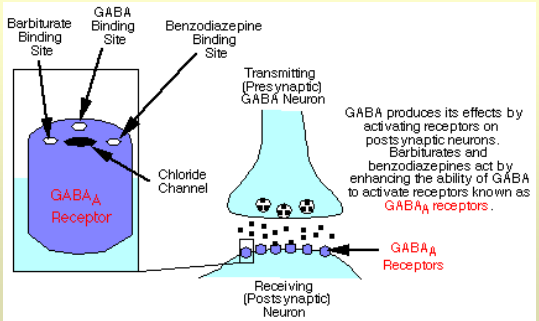
D. Ethylmethyl thiourea (Inactin)
E. Diazepam

GABA Agonists

(*dose-dependent* CNS depressants)

- Barbiturates
- Chloral hydrate
- Alpha chloralose
- Tribromoethanol (Avertin)
- Propofol
- Metomidate and etomidate
- Steroids
- [benzodiazepines]

GABA agonists



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.

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

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:

- RE Meyer and RE Fish. (2005). A review of tribromoethanol anesthesia for production of genetically engineered mice and rats. Lab Anim (NY). 34, 47-52.)
- CC Lieggi et al. (2005). Efficacy and safety of stored and newly prepared tribromoethanol in ICR Mice. Contemp Topics 44(1): 17- , 2005.

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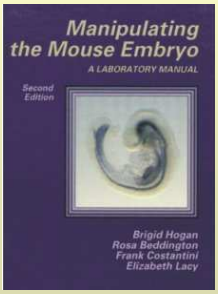
- CC Lieggi et al. (2005). Efficacy and safety of stored and newly prepared tribromoethanol in ICR Mice. Contemp Topics 44(1): 17- , 2005.

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 ??

Hypnotics

Tribromoethanol

- Reported pharmacologic effects
  - generalized CNS depression
  - cardiorespiratory depression at increased dosage
  - analgesia?
  - postanesthetic complications
    - decomposition products +/or decreased pH
    - increased dosage
    - repeated use

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.

Examples?

- 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

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 if the following best describes alphaxalone/ alphadolone?

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

- aka: anesthetic steroid; “Saffan”
- *Note*: new anesthetic steroid: “Alfaxan”

Which of the following is NOT a characteristic of ketamine?

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

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.

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

Which of the following is NOT an alpha2 adrenoreceptor agonist?

A. Xylazine
B. Detomidine
C. Metomidate
D. Romifidine

don't confuse with medetomidine

Why Dexmedetomidine?

- No medetomidine, but…

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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.

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.

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

Sedatives and Tranquilizers

- Phenothiazines
  - acepromazine
- Butyrophenones
  - droperidol
  - azaperone
  - fluanisone
- Benzodiazepines
  - diazepam
  - midazolam
  - zolazepam

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

Injectable Combinations

- 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.

Why Inhalants?

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 = Median anesthetic concentration.

Inhalants

TRUE/ FALSE:

MAC = minimum alveolar concentration.

AGENT	VAPOR PRESSURE	MAC	BLOOD:GAS SOLUBILITY	BIOMETABOLISM (%METABOLITES)
Nitrous oxide	39,500	136-235	0.5	0.004
Diethyl ether	450	3.2	15.2	20
Methoxyflurane	23	0.3	15.0	40-50
Halothane	244	0.8-1.2	2.5	15-20
Enflurane	172	2.2	2.0	2.4
Isoflurane	240	1.2-1.5	1.5	0.2
Sevoflurane	160	2.4-2.5	0.7	3.0
Desflurane	664	5.7-7.1	0.4	0.02

(from Meyer et al., 2002; Brunson (IN Kohn et al.), 1997.)

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.

- JC Smith et al., 2003. Contemp Topics 42(2): 10- .

Which of the following is a COX-2 selective drug?

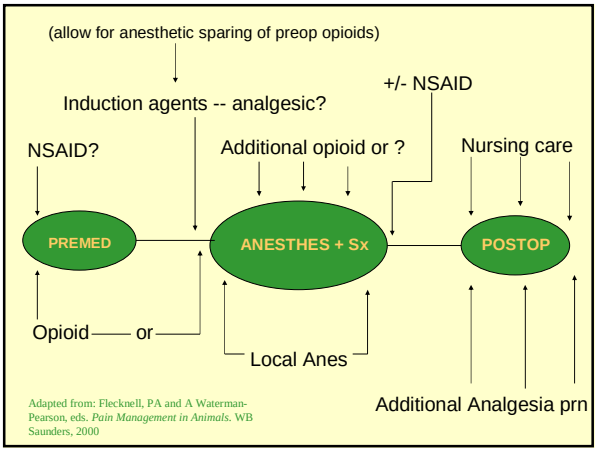
A. Acetominophen
B. Flunixin
C. Carprofen
D. Meloxicam
E. None of the above

Which of the following is a COX-2 selective drug?

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

What is? celecoxib, rofecoxib

What is multimodal pain therapy?



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

Multimodal pain therapy

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

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

(Kissin, 2010. The development of new analgesics over the past 50 years: A lack of real breakthrough drugs. Anesth Analg 110:780-9.)

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

- NSAIDS
  - Indomethacon
  - Mefenamic acod
  - Iburpofen
  - Naproxen
  - Tolmetin
  - Sulindac
  - Meclofenamate
  - Piroxicam
  - Diflunisal
  - Ketoprofen
  - Diclofenac
  - Fenoprofen
  - Flurbiprofen
  - Nabumetone
  - Oxaprozin
  - Ketorolac
  - Bromfenac
  - Celecoxib
  - Meloxicam
  - Nepafenac

(Kissin, 2010. The development of new analgesics over the past 50 years: A lack of real breakthrough drugs. Anesth Analg 110:780-9.)

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

- OTHER DRUGS
  - Sumatriptan
  - Pentosan
  - Zolmitriptan
  - Naratriptan
  - Rizatriptan
  - Almotriptan
  - Frovatriptan
  - Eletriptan
  - Ziconotide
  - Pregabalin

(Kissin, 2010. The development of new analgesics over the past 50 years: A lack of real breakthrough drugs. Anesth Analg 110:780-9.)

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

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

(Kissin, 2010. The development of new analgesics over the past 50 years: A lack of real breakthrough drugs. Anesth Analg 110:780-9.)

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

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

(Kissin, 2010. The development of new analgesics over the past 50 years: A lack of real breakthrough drugs. Anesth Analg 110:780-9.)

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

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

(Kissin, 2010. The development of new analgesics over the past 50 years: A lack of real breakthrough drugs. Anesth Analg 110:780-9.)

TRUE/ FALSE: Fish feel pain.

(LU Sneddon, 2009. ILAR J 50:338-342; DL Neiffer and MA Stamper, 2009. ILAR J 50:343-360.)

TRUE/ FALSE: Fish feel pain.

http://www.vet.ed.ac.uk/animalwelfare/Fish%20pain/fish%20pain.htm

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

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

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

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

The bispectral index [BIS] 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

Species-Specific Summaries

- Rabbit
  - No Telazol?
  - No propofol?
  - Difficult intubation
  - Hypercapnia?
  - Hypotension?
  - Atropine
  - Subclinical respiratory disease (?)

What is this piece of equipment?

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

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A. Endotracheal tube
B. Esophageal stethoscope
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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

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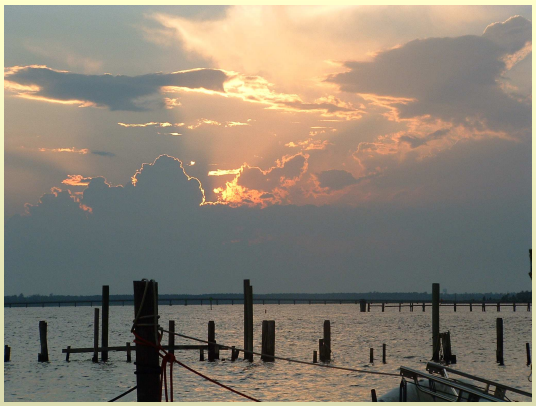

Propofol

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

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

Which of the following can significantly suppress adrenal cortical activity?

A. Ketamine
B. Metomidate *(also etomidate)*
C. Urethane
D. Chloral hydrate

CL Davis
5/13/10

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

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Opioids

Morphine acts primarily at which receptor?

A. μ
B. δ
C. ε
D. κ
E. σ

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Which of the following is a partial opioid agonist?

A. Buprenorphine
B. Morphine
C. Fentanyl
D. Meperidine
E. Remifentanil

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Butorphanol?

Which of the following is NOT a butyrophenone?

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

Which of the following is NOT a butyrophenone?

A. Azaperone
B. Droperidol
C. Acepromazine *(=phenothiazine)*
D. Fluanisone

Neuroleptics

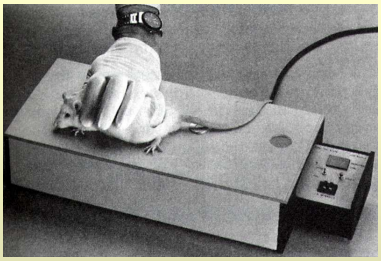
TRUE/ FALSE: Neuroleptics do not provide analgesia.

Neuroleptics

TRUE Neuroleptics do not provide analgesia.

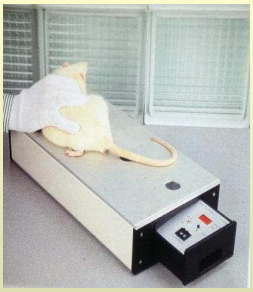
But…

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 – 170º C) and latency period is measured until tail is flicked out of the light beam.

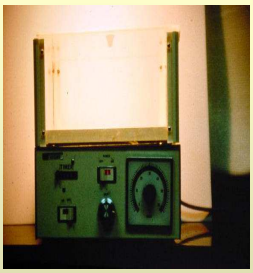
Tail flick (hot)

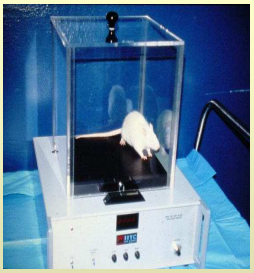


Hot Plate Analgesia Instrument

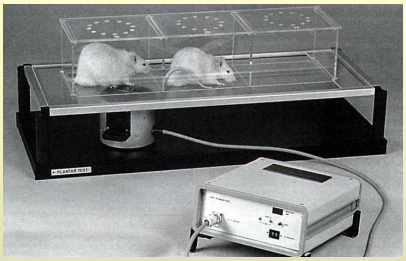
Measures latency of stereotyped paw lick response after dropping mouse or rat onto hot surface (30 – 60º C).

Hot plate





Plantar Analgesia Instrument



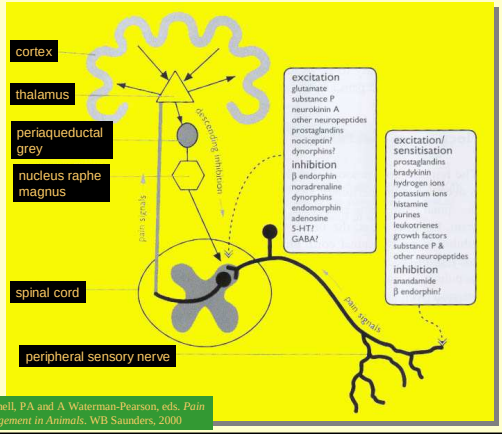
Measures paw sensitivity to heat stimulation similar to Hot Plate test, however, animal is unrestrained & heat is applied to bottom of single foot after animal is at rest. Repeated testing does not result in sensitization.

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
  - Matthews, NS, ed. Clinical Anesthesia. Vet Clin N Am/ Sm Anim Prac 29(3), May, 1999.
- Equipment – laryngeal mask airway
  - JC Smith et al., 2004. Contemp Topics 43(4):22- .
- Anesthetic monitoring (e.g., BIS)
  - JE Heavner, 2001. Compar Med 51(6):500- .
  - SA Greene et al., 2002. Compar Med 52(5):424- .
  - SA Greene et al., 2004. Compar Med 54(4):397- .



Flecknell, PA and A Waterman-Pearson, eds. *Pain Management in Animals*. WB Saunders, 2000

Substances affecting transmission of pain signals -- Dorsal Horn

- Excitation
  - glutamtae
  - substance P
  - neurokinin A
  - other neuropeptides
  - prostagalndins
  - nociceptin (?)
  - dynorphins (?)
- Inhibition
  - B endorphin
  - noradrenaline
  - dynorphins
  - endomorphin
  - 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?
  - Roughan and Flecknell, 2002. Buprenorphine: a reappraisal of its antinociceptive effects and therapeutic use in alleviating post-operative pain in animals. Laboratory Animals, 36, 322-343.

What are the Hazards?

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