RODENTS: ANESTHESIA, ANALGESIA, EUTHANASIA

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- Division of Animal Care
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EXPERIMENTAL/STUDY PRINCIPLES

- BIG difference between humans & animals
- Informed consent ≠ animals
- Checks and Balances govern studies
- Responsible study of animals is acceptable
3 BROAD RODENT TOPICS

• Anesthesia
• Analgesia
• Euthanasia
ANESTHESIA

Loss of sensation affecting the entire body and accompanied by loss of consciousness.
ANALGESIA

- Insensibility (lack of) to pain without loss of consciousness.
EUTHANASIA

- The practice of permitting or causing death in a relatively painless way.
- Literally = easy death
EASIER IF:

- Acclimate -- Vanderbilt recommends 1 week
- History -- check animal daily /EOD/routinely

What is normal? (aggressive, social, lethargic, grooming, fighting, agitated)
- After anesthetic event – anesthesia vs. normal?
- After procedure – painful?
- Is it time to euthanize? -- humane endpoints
ANESTHESIA

- Surgical procedures
- Extrapolation: “If I did this to a human....”
- “Momentary” pain or distress
- Risk management
ANESTHESIA

- Surgical procedures
- Extrapolation: “If I did this to a human....”
- “Momentary” pain or distress
  - Injections:
    - tail vein, subcutaneous (SQ), intraperitoneal (IP)
  - gavage
  - blood draws – submandibular, retro-orbital
  - microchip implant - pets
  - subcutaneous pellet implant (hormone, Rx)
- Risk management
ANESTHESIA—“MOMENTARY” PAIN OR DISTRESS
Open (abd or skin) deposit, close (sew)

Anesthetic choices
- Inhalant
- Injectable
- Local
- Hypothermal
ANESTHESIA- ALZET PUMPS/TUMOR IMPLANT

- Anesthetic choices
  - Inhalant - (isoflurane, sevoflurane)
  - Injectable - (Ketamine, Propofol)
  - Local – (lidocaine, dentist)
  - Hypothermal – (ice bath – seldom, never used)
**Table III. Anesthetics and Analgesics used in Mice**
Vanderbilt University (VU) provides the following table as a reference only, for use by VU faculty and staff.
Note: Mice have a relatively small total muscle mass and are prone to develop muscular atrophy or nerve damage following IM injections. The IM route should be avoided in mice. If drugs must be administered via the IM route, minimal injection volumes (≤0.05 ml), and a 27-30-gauge needle should be used.

<table>
<thead>
<tr>
<th>Anesthesia in Mice</th>
<th>Dose &amp; Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane (Forane®)</td>
<td>To effect. In general, 3-5% induction, 1-3% maintenance; inhalation</td>
<td>Precision vaporizer, adequate ventilation or scavenging essential</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>40 – 70 mg/kg IP</td>
<td>Caution! Potentially significant cardiovascular and respiratory depression, variable response</td>
</tr>
<tr>
<td>Tribromoethanol (Avertin)</td>
<td>125-250 mg/kg IP</td>
<td>Store at 4°C; dark conditions</td>
</tr>
<tr>
<td>Ketamine + Xylazine</td>
<td>90-120 mg/kg (K) + 10 mg/kg (X) IP</td>
<td></td>
</tr>
<tr>
<td>Ketamine + Medetomidine</td>
<td>50-100 mg/kg (K) + 1.0 mg/kg (M) IP</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analgesia in Mice</th>
<th>Dose &amp; Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1 – 10 mg/kg SC</td>
<td>Up to 3 hours of analgesia</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>0.05 mg/kg SC</td>
<td>Up to 3 hours of analgesia</td>
</tr>
<tr>
<td>Butorphanol (Torbutrol® 0.5mg/ml)</td>
<td>0.05 – 5.0 mg/kg SC</td>
<td>1 – 2 hours of analgesia</td>
</tr>
<tr>
<td>Buprenorphine (Buprenex®)</td>
<td>0.05 – 0.1 mg/kg SC</td>
<td>8-12 hours of analgesia; do not use with tribromoethanol</td>
</tr>
<tr>
<td>Carprofen</td>
<td>5-10 mg/kg SC</td>
<td>From 12 - 24 hours of analgesia</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>5-10 mg/kg SC</td>
<td>From 24 hours of analgesia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sedation in Mice</th>
<th>Dose &amp; Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medetomidine</td>
<td>30 – 100 μg/kg SC</td>
<td>Reverse with Atipamezole @ 1.0 μg/kg SC, IP, or IV</td>
</tr>
<tr>
<td>Ketamine</td>
<td>44 mg/kg SC</td>
<td></td>
</tr>
</tbody>
</table>
Injectable - Ketamine + Xylazine

+ 90-120 mg/kg (K) + 10 mg/kg (X) IP
+ Onset: 1-3 minutes
+ Duration: 30-40 min
+ Recovery: 10-15 minutes

(+): easy, mobile, cheap, effective
(-): DEA license (ketamine difficulty), redosing, precision, longer recovery
ANESTHESIA- PROSTATE TUMOR IMPLANT

- Open (abd cavity) implant tissue, close (sew)
- Anesthetic choices
  - Inhalant
  - Injectable
  - Local
  - Hypothermal
ANESTHESIA- PROSTATE TUMOR IMPLANT

- Inhalant: Isoflurane
  - induction box, mask (1-4% gas in oxygen)
  - Onset: 1-3 minutes
  - Duration: as much as you need
  - Recovery: 1-5 minutes

  (+)-very precise, safer, quick recovery, NO DEA (little/no addiction potential)

  (-) – hood/ventilation – gas scavenge, equipment cost & maintenance-vaporizer
Anesthesia: Inhalant: Isoflurane
ANESTHETIC SUPPORT

- Are you asleep? (surgical plane of anesthesia)
  - humans – many monitors
  - rodents – palpebral reflex, pain withdrawal (pinch)
  - consciousness versus movement
- Monitoring – recommend check (record) each 5 min
- Are you warm? 37°C
  - (+) – re-circulating water blankets
  - (+) – chemical pillows
  - (-) – heat lamps -temperature monitoring
ANESTHETIC SUPPORT

Deltaphase ® Pads
ANESTHETIC RECOVERY

- Are you hydrated? – subcutaneous fluids
- Until Sternal
- Purposeful Movement
ANALGESIA

- Surgical procedures
- Extrapolation: “If I did this to a human....”
- “Momentary” pain or distress
- Risk management
  - (+)analgesia › (-) administration
    -- cotton rats, grass hopper mice, schizophrenic mice
- Why not?
  -- Study contradiction (organ of metabolism, pain study, fever study)
ANALGESIA

- Risk management
  - (+) analgesia › (-) administration
    -- cotton rats, grass hopper mice, schizophrenic mice
**ANALGESIA-USAGE/APPLICATION**

- **Pre-emptive**
  - Recommended /required before painful procedure.
    - Wind-up – once nerves signaling pain, more effort to calm down
    - At induction/at incision

- **Post-operatively**
  - By extrapolation – humans?--Q 12 hours x 48 hours
  - As needed-more difficult in animals
    - Clinical signs – when in doubt, give medication unless approved otherwise
      - eating, drinking, active, hunched, fighting
  - porphyrin staining – rats
  - How do they normally act?
ANALGESIA- ROUTE

- Injectable
  (+) – controlled and DONE
  (-) – more work
- Oral – Per OS (mouth)
  (+) – cheap & easy – Children’s Motrin in H2O
  (-) – dose? – H2O tastes funny
- Transdermal – limited application
ANALGESIA - STRUCTURE

- Opioids –
  - Morphine – classic – Not used
  - Partial agonist/antagonist – (yes/no)
    - Buprenorphine/Buprenex
    - Tramadol (next generation)
- NSAIDS – NonSteroidal Anti-Inflammatory Drug
  - Aspirin /Ibuprofen/Naproxen (Aleve) - human
  - Ketofen/Ketoprofen
    - shuts down inflammatory cascade & prostaglandins
- [Sidebar – NEVER give steroids (prednisone, dexamethasone) and NSAID = stomach ulcerations]
Euthanasia

- Ethical culture/ethical industry
- Emphasis
  - Don’t waste life – (there is a reason)
  - Minimize (or eliminate) pain/distress
  - Death itself is not so bad
- Objective (quick, painless, useful/value)
EUTHANASIA: APPROACHES/METHODS

- Many methods have been studied
  - Compare-ethical debate—human capital punishment (electrical, chemical, physical—firing squad, hanging)
- The AVMA Guidelines on Euthanasia (formerly the 2007 Report of the AVMA Panel on Euthanasia)
EUTHANASIA: TYPES

- Inhalant
- Chemical (Rx)
- Physical
- Combinations, secondary methods
EUTHANASIA: TYPES

× Inhalant

extrapolation from anesthesia
most common = CO2 (carbon dioxide)

(+ – quick, no DEA, relatively safe, cheap
(-) – can be aesthetically unpleasant
10-15sec -unconscious w/brainstem activity/movement

× Chemical (Rx)

× Physical

× Combinations, secondary methods
EUTHANASIA: INHALANT
EUTHANASIA: TYPES

- **Inhalant**

- **Chemical (Rx)**
  - Barbiturate- (Nembutal, Fatal Plus – pentobarbital)
    - (+) – peaceful, aesthetically pleasant (mostly)
    - (-) – impact on study (?), expensive, DEA,

- **Physical**

- **Combinations, secondary methods**
EUTHANASIA: TYPES

- Inhalant
- Chemical (Rx)
- Physical
  - Decapitation
    - (+) – quick, clean(er) tissue collection
    - (-) - aesthetically unpleasant
  - Terminal bleed (used in combination)
  - Cervical Dislocation
    - Often used as 2\textsuperscript{nd} method, upcoming requirement
- Combinations, secondary methods
EUTHANASIA: TYPES

- Cervical dislocation
  Under anesthesia unless IACUC exemption
  Death is immediate
  Spinal cord is severed. 2-4 mm space is created between the base of the skull and first cervical vertebra.
EUTHANASIA: TYPES

- Inhalant
- Chemical (Rx)
- Physical

Combinations - Anesthesia coupled with:
  - terminal bleed
  - thoracotomy
  - decapitation
  - perfusion
Closing: - end on positive note
+ Yes industry uses animals – value, ethically, humanely
+ Benefit to both humans and animals
  ❖ Ex: chemotherapy/radiation therapy in canines
+ Minimize pain/distress - experience momentary pain/distress
+ Some advantages when compared to ‘natural’ lives of rodents or humans
+ Especially true/correct with effective use of
  ❖ Anesthesia
  ❖ Analgesia
  ❖ Euthanasia
THE END

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Questions, Comments, Concerns