

Analgesia in Small Mammals

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Disclosure

I, Miranda Sadar, declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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Objectives

- The pharmacist should be able to:
 - Interpret the facial grimace scale for a rabbit, ferret, rat, or mouse
 - Recall what analgesics would be appropriate for a case of gastrointestinal hypomotility in a rabbit
 - List at least one example of pharmacodynamic modeling for opioids and nonsteroidal anti-inflammatory drugs
- The pharmacy technician should be able to:
 - Recall the differences between pharmacokinetic and pharmacodynamic studies
 - Interpret the facial grimace scale for a rabbit, ferret, rat, or mouse
 - Memorize the most commonly used analgesics in small mammals

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Recommended Texts



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Pain in Small Mammals

NC 3R^s
National Centre for the Replacement, Refinement & Reduction of Animals in Research


- Prey species
- Body position/posture
- Activity and attitude changes
- Unkempt hair coat
- Appetite and fecal production
- Facial expression/grimace scale
 - Mice, Langford et al. 2010
 - Rats, Sotocinal et al. 2011
 - Rabbits, Keating et al. 2012
 - Ferrets, Reijgwart et al. 2017
 - Guinea pigs, unpublished


Not Present
"0"



Moderate
"1"







Obvious
"2"



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Grimace Scale: Orbital Tightening


- Partial or complete eye closure or eye "squeezing"
- Wrinkle may be visible around the eye

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Grimace Scale: Nose/Cheek Changes

- Ferrets/Mice:
 - Bridge of nose bulges
 - Contour of cheeks become visible
- Rabbits/Rats:
 - Flattening of the cheeks
 - May have a sunken look



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Reijgwart et al. 2017 www.nc3rs.org.uk

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Grimace Scale: Ear Changes

- Fold, curl into a pointed shape
- Angle forwards, outwards or pulled back against the body




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Grimace Scale: Whisker Changes

- Move forward, away from the face, and bunch to make them appear to be standing on end
- Ferrets: pulled back against the cheeks, whiskers clump together

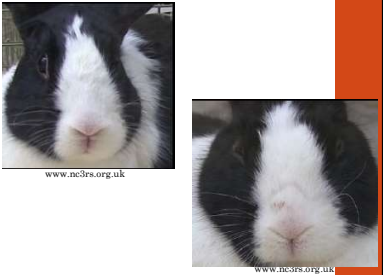


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Grimace Scale: Nostril Shape

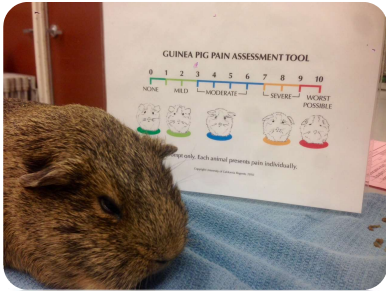
- Nares drawn vertically to form a "V" rather than a "U" shape



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Guinea Pig Facial Pain Scale



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Normal or Abnormal?



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Question Time!

Which of the following components of the facial grimace scale is used in rabbits, ferrets, rats, and mice?

- A. Orbital tightening
- B. Cheek flattening
- C. Ear curling
- D. Nostril shape

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Question Time!

Which of the following components of the facial grimace scale is used in rabbits, ferrets, rats, and mice?

- A. **Orbital tightening**
- B. Cheek flattening
- C. Ear curling
- D. Nostril shape

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Definitions

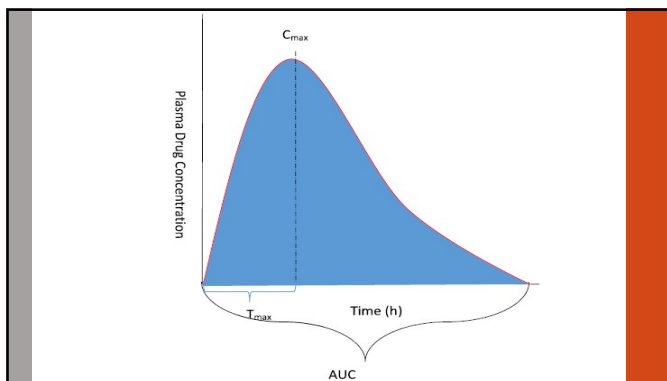
1. Pharmacokinetics are the study of what?
 1. Bodily absorption, distribution, metabolism, and excretion of drugs via mathematical modeling
 2. Measures the concentration of a drug or its metabolites in blood, tissue, feces, or urine over a set period of time
 3. Aka the body's effect on the drug
2. Pharmacodynamics are the study of what?
 1. Effects of a drug on the body and depends on the dose-response curve
 2. Aka the drug's effect on the body

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Definitions

1. All PK parameters are determined by plotting the plasma drug concentrations versus time
2. Some can be identified by visually examining the plot
 1. C_{max} , T_{max}
3. What is the definition of C_{max} ?
 1. Maximum concentration that a drug achieves after it has been administered
4. What is the definition of T_{max} ?
 1. Time after administration of a drug when the maximum plasma concentration is reached – i.e. when rate of absorption equals rate of elimination

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Other Definitions

1. What is the area under the curve?
 1. Actual body exposure to drug after administration of a dose
 2. Representation of BOTH concentration and time
2. What is elimination half-life?
 1. Time it takes for the concentration of the drug in the plasma to be reduced by 50%
3. What is "F" and when do we use it?
 1. Bioavailability
 2. Absolute F compares IV administration to any other route (PO, IM, etc.) and relative bioavailability compares any 2 extravascular routes to each other

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Now For Pharmacodynamics

1. What are some example of pharmacodynamics models for opioids?
2. For NSAIDs?
3. For sedatives?
4. For antibiotics, antifungals, antiparasitics?

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Question Time!

Which option describes a component of pharmacodynamic testing?

- A. Measures concentration of a drug
- B. Evaluates drug absorption and excretion
- C. Measures metabolites of a drug in the blood
- D. Evaluates the effects of a drug on the body

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Question Time!

Which option describes a component of pharmacodynamic testing?

- A. Measures concentration of a drug
- B. Evaluates drug absorption and excretion
- C. Measures metabolites of a drug in the blood
- D. Evaluates the effects of a drug on the body**

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Another Question

Which of the following would be an example of a pharmacodynamic model used for evaluating nonsteroidal anti-inflammatory drugs?

- A. Thermal threshold backpack
- B. Sodium urate joint injections
- C. Acute pain in a fracture model
- D. Minimum inhibitory concentrations

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Another Question

Which of the following would be an example of a pharmacodynamic model used for evaluating nonsteroidal anti-inflammatory drugs?

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- C. Acute pain in a fracture model
- D. Minimum inhibitory concentrations

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General Recommendations

- Small creature = small muscle mass = use caution with injection volumes
 - May need multiple sites
- Requires effective restraint
- IM locations:
 - Epaxial muscles
 - Quadriceps mm. – **why not hamstrings?**
- Short needles – 3/8"



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Analgesia - Opioids

- Don't fear μ opioids!
- Utilize in situations similar to small animals, as few studies have been performed (PK vs. PD)
- Varying routes available depending on goals:
 - IV, IM, SC for sedation
 - IV, IM, SC for hospitalized patients
 - OTM – use caution and remember there are limitations!
- Rats, mice: Morphine 1-2 mg/kg q 2-3 hrs


Species	Hydromorphone (IV, IM, SC)	Buprenorphine (IV, IM, SC)	Tramadol (PO)
Ferrets	0.1 mg/kg q 1-2 hr*	0.04 mg/kg q 4-6 hr*	4-5 mg/kg q 8-12 hr
Rabbits	0.2-0.3 mg/kg q 4 hr	0.05-0.1 mg/kg q 4-6 hr*	10-20 mg/kg q 8-12 hr*
Guinea pigs	0.3 mg/kg q 4 hr*	0.2 mg/kg q 4-6 hr*	15 mg/kg q 8-12 hr
Chinchillas	2 mg/kg q 4 hr*	0.2 mg/kg q 4 hr*	Not recommended*
Rats, mice, hamsters	0.2 mg/kg q 4 hr	0.2 mg/kg q 4-6 hr	15-30 mg/kg q 8-12 hr*
Hedgehogs	0.1 mg/kg q 4 hr	0.03-0.05 mg/kg q 48 hr*	4-5 mg/kg q 8-12 hr
Sugar gliders	0.05 mg/kg q 4 hr	0.03-0.05 mg/kg q 6 hr	2-5 mg/kg q 8-12 hr

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Analgesia – More Buprenorphine

- What about OTM buprenorphine?
 - Ferrets: proposed 0.04-0.06 mg/kg q 6-8 hr
 - Limitations
 - Guinea pigs: 0.2 mg/kg q 3-6 hr*
 - Alkaline pH in mouth
 - Rabbits: 0.15 mg/kg not sufficient = not recommended
- High concentration and sustained release formulations
 - Rabbits: 0.24 mg/kg q 42 hr (HC)*, 0.12 mg/kg q 72-96 hr (SR)*
 - Guinea pigs: 0.3 mg/kg q 24-72 hr (SR)*
 - Rats: HC not recommended due to adverse effects

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Analgesia - Opioids

- Fentanyl CRI
 - Ferrets: Loading dose 2-5 $\mu\text{g}/\text{kg}$; intraop 5-10 $\mu\text{g}/\text{kg}/\text{hr}$; postop 1.25-5 $\mu\text{g}/\text{kg}/\text{hr}$
 - Rabbits: intraop 15-60 $\mu\text{g}/\text{kg}/\text{hr}$; postop 1.25-5 $\mu\text{g}/\text{kg}/\text{hr}$
 - Guinea pigs: Loading dose 5-10 $\mu\text{g}/\text{kg}$ IV; intraop 10-30 $\mu\text{g}/\text{kg}/\text{hr}$; postop 1.25-5 $\mu\text{g}/\text{kg}/\text{hr}$

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Question Time!

Which analgesic drug is uncommonly used in small mammals, due to its impact on the gastrointestinal tract, respiratory tract, and cardiovascular system?

- Hydromorphone
- Butorphanol
- Morphine
- Buprenorphine

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Question Time!


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- Hydromorphone
- Butorphanol
- Morphine**
- Buprenorphine

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Analgesia - NSAIDs

- Meloxicam most commonly utilized
- PD studies lacking in ECM species
- Few PK studies performed, but most single dose
- Tolerated well longer PK in rabbits
 - 29-day study – no drug accumulation, no toxicosis in liver, urinary bladder, GI tract, kidneys – Delk et al. 2014
 - Limitation – used only young, healthy rabbits



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Analgesia - NSAIDs

- Dosages commonly utilized in ECM:
 - Ferrets: 0.1-0.2* mg/kg q 24 hr
 - Rabbits: 1 mg/kg q 24 hr* OR 0.5 mg/kg q 12 hr
 - Chinchillas, guinea pigs: 0.5-0.75 mg/kg q 12 hr; 1.5 mg/kg q 12 hr (GP*)
 - Rats, mice: 1 mg/kg q 12 hr*
 - Hedgehogs: 0.2 mg/kg q 24 hr
 - Sugar gliders: 0.2 mg/kg q 24 hr



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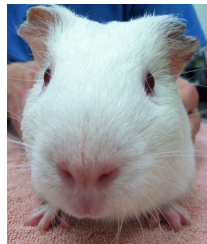
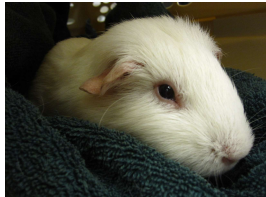
Analgesia - Others

- Gabapentin
 - Minimal data for PK and PD
 - Ferrets: 5-10 mg/kg PO q 8-12 hr
 - Rabbits: 10-15 mg/kg PO q 8-12 hr; 25 mg/kg PO*
- Lidocaine
 - Rabbits: 50-100 µg/kg/min IV
- Maropitant
 - Rabbits: 1 and 10 mg/kg SC evaluated; dermal reactions
 - Rats: 10 mg/kg IV – not recommended



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Describe Grimace Questions?




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Putting Things Into Practice

- 3 YO FS Holland lop rabbit with anorexia and decreased defecation x 12 hours
- PE: QAR, BCS 5/9, 98.8 F, 320 bpm, 60 brpm, pale pink mucous membranes, CRT 2 seconds, painful abdominal palpation, palpable fecal pellets in colon
- Stabilize before diagnostics – what do you want to use?

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Analgesic Options

- Isotonic fluids – shock dose, then move to 100 mL/kg/day IV
- Lidocaine 50-100 $\mu\text{g}/\text{kg}/\text{min}$ IV
- Hydromorphone 0.05 mg/kg/hr IV
- +/- meloxicam 0.5 mg/kg SC q 12 hr
- Maropitant 4 mg/kg SC q 24 hr

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Ready For Diagnostics!



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Sedation Options


- IV option: midazolam 1 mg/kg with continued hydromorphone CRI
- IM option: midazolam 1-2 mg/kg, alfaxalone 2-3 mg/kg
- Determine there is a liver lobe torsion – surgery is elected and performed, what to use postop?



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Post-operative Care

- Maintained on fentanyl 5 $\mu\text{g}/\text{kg}/\text{hr}$ IV and lidocaine 50 $\mu\text{g}/\text{kg}/\text{min}$ IV after surgery, but dislodged catheter at 5 am
- Administered meloxicam 0.5 mg/kg SQ after surgery at 4 pm and planned oral gabapentin to begin in the morning
- You arrive at 7 am and your rabbit looks like this:



Describe your interpretation of these findings

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Adjusted Analgesic Plan

- Hydromorphone 0.2 mg/kg IM q 4 hr to start, then transitioned to SC
 - Transitioned to tramadol 15 mg/kg PO q 8 hr to go home
- Continued meloxicam 0.5 mg/kg PO q 12 hr and gabapentin 15 mg/kg PO q 8-12 hr

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Questions?

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