Pain and stress in Reptiles

Case study of Python regius
Plan:

- Overview of pain and nociception in reptiles.
- Stress and pain, interactions.
- Overview of recent experiments
Pain

1988: Human anaesthetists, 80% neonates capable of experiencing pain, 52% ordered opioids after surgery.

2004: Exotic animal veterinary practitioners, 98% reptiles capable of pain, 50% used analgesia in surgery.

- Lack of objective pain assessment methods.
  - Lack of gold standard for neonatal pain expression.
  - Integration of pain assessment into daily practice remains problematic.


Pain

an unpleasant sensory and emotional experience

Nociception

the neural processes of encoding and processing noxious stimuli.

- Appropriate to species and age

What does pain do?

- Energy balance
- Immune system
- Healing
- Behavioural responses

- Increases doses needed of general anaesthetic cardio respiratory effect
- Neuro-endocrine changes affect experimental results.
Animals: pain?

(1) central nervous system,
(2) avoidance learning,
(3) protective motor reactions
(4) physiological changes,
(5) Tradeoffs between stimulus avoidance and other motivational requirements,
(6) opioid receptors and evidence of reduced pain experience if treated with local anaesthetics or analgesics,
(7) cognitive ability and sentience.

Animals: pain?

Observer effect and stress, also habitat vs lab.
Animals: pain?

Diurnal observations not reflective of nocturnal activity (Machlin 1999) and normal temperature range.
Stress and interactions with pain

• How does that effect nociceptive studies: mammals / anoles?

  e.g. Stress induced analgesia

  the effect of male experimenters on male mice nociceptive tests
  but... the effect of tonic immobility on tail flick tests in anoles

  ?the effect of long term captivity stress, replicated in pets?

• What are ways of discriminating pain from stress?

  How do we measure: physiological/behavioural
Which animals are we talking about?

- Reptiles: Physiology research (comparative and not), zoological collection, pets, conservation efforts.

  PS reptiles are VERY diverse ..............>8000 species, in 4 distinct orders
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Interval (hours)</th>
<th>References</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
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<tr>
<td>Butorphanol</td>
<td>1.0–2.0</td>
<td>IM</td>
<td>NA</td>
<td>9, 10, 39, 53, 54</td>
<td>May not be effective as an analgesic in reptiles even at excessive doses</td>
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<tr>
<td>Buprenorphine</td>
<td>0.005–0.02</td>
<td>IM, IV, SC</td>
<td>NA</td>
<td>50, 53, 54</td>
<td>Analgesic effect not clearly demonstrated</td>
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<td></td>
<td>0.075–0.1</td>
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<td>Pharmacokinetics have been determined in red-eared sliders</td>
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<tr>
<td>Morphine</td>
<td>0.05–4.0 (crocodiles)</td>
<td>IC, IM</td>
<td>NA</td>
<td>5, 7, 9, 10, 53, 54</td>
<td>May require several hours to reach peak effect</td>
</tr>
<tr>
<td></td>
<td>1.5–6.5 (turtles)</td>
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<td>Duration of action may persist up to 24 h in turtles</td>
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<tr>
<td></td>
<td>1.0 (green iguanas)</td>
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<td></td>
<td>Significant respiratory depression in turtles</td>
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<tr>
<td>Meperidine</td>
<td>1.0–5.0</td>
<td>IC</td>
<td>NA</td>
<td>7, 54, 55</td>
<td></td>
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<tr>
<td>Tramadol</td>
<td>10–25</td>
<td>PO</td>
<td>NA</td>
<td>56</td>
<td>Oral dose increased thermal nociceptive latency between 6 and 96 h</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>SC</td>
<td></td>
<td></td>
<td>SC dosing increased thermal nociception latency between 12 and 48 h</td>
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<td>Less respiratory depression than that from morphine</td>
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</tbody>
</table>
Hernandez Divers 2006

Clinical opinion – efficacy of non steroidalss via individual behaviour measurement

Also possible thermo preference data, in bearded dragons - Bertelsen.
Feeding behaviour: Lauren James

Setting up a regular feeding pattern

Analysing disruption to that pattern with
- Anaesthesia only
- Skin incision
- Muscle incision
- Capsaicin

- Change in feeding behaviour with painful stimuli, not with anaesthesia only.
Capsaicin: physiological consequences of nociception
Effect reduced by morphine and butorphanol
Conclusions

- Integrate appreciation of the effect of stress into all pain investigation
- Variable results in reptiles......are unsurprising.
- Integrating behaviour with physiology, and providing clinical rational for analgesia.
Further work

- Corticosterone measurements
- Behavioural measurements
References

NOTE!!!!  ECTOTHERM ALERT !!!

- Behaviour
- Physiological parameters
- Drug delivery
- Drug metabolism

Kischinovsky et al 2013
What options are there?

- Local anaesthetics (also used as general in amphibians)
- NSAIDS
- Opioids
- NMDA (ketamine)
- Inhalational (but wind up?)
- Administration?
What’s the evidence they work?

• How do we test nociception and/or pain?

• Amphibians: Acetic acid test (Stevens 2004 review, Guenette 2013 review)
  Hargreave’s test (Coble 2011)

• Reptiles: Surgical stimulus
  Thermal stimulus (hind limb withdrawal latency – Sladky 2008-2012)
  Chemical stimulus (capsaicin, formalin)
  Electrical stimulus

• Behavioural ethogram – in Sladky 2012 (unpublished data) and feeding behaviour: Lauren James (unpublished)
Preliminary protocol

- All should have local anaesthetic: current recommendations include using a longer acting as well as lidocaine.
- Nsaids?? Current preference for meloxicam??
- Opiates: morphine seems to be less sedative, and has less effect on resting heart rate, with significant anti nociceptive effect @ 10mg/kg...but experimental dose ONLY.
- Need dose response work.
- Do not expect everything to be applicable to everyone.