Objectives:

• How to evaluate pain in reptiles
• Preemptive analgesia is more successful than pain management in response to pain
• Multimodal analgesia since one agent can’t do it all
• Common analgesics utilized in reptiles
• Use medications that can be reversed when possible
• Considerations to take prior to anesthesia
• Intubation or face mask induction, maintenance
• Monitoring of anesthesia
References:
What is pain?
The old saying “It was fine before I went to sleep and was dead when I woke up” is true.

In reptiles probably weeks to months

This remphasizes the importance of preventive exotic animal medicine!
Balanced graced anesthesia

Preemptive analgesia
- Administer medication before, rather than after injury, whenever possible
- Prevents “pain windup” by preventing noxious stimuli from reaching the CNS

Multimodal analgesia
- Mechanisms of pain involve multiple pathways and a variety of neurotransmitters
- No one drug or class of drugs can be used to treat all pain
- Relies on drug combinations to provide greater pain relief
- By combining agents often uses lower doses, reduces the risk of undesirable side effects

Use a relatively short-acting opioid like butorphanol concurrently with an NSAID to provide more prolonged analgesia.
Many opioids act rapidly within 10-15 m from injection whereas it can be 1 h before significant analgesic effects from NSAID
Pain

- Do reptiles feel pain?
- Perhaps, more importantly, can we recognize pain in reptiles?
- Is the perception of pain by a reptile equivalent to that of a mammal?
- We will never be able to objectively answer whether reptiles feel pain because they simply cannot communicate with humans.
Like mammals, reptiles have all of the anatomical structures considered critical for the recognition of pain:

- Peripheral nociceptors, appropriate CNS structures and pathways
- Opioid receptors and endogenous opioids
- Reduction of nociceptive response with analgesics (although data are sparse)
- Pain avoidance learning, and suspension of normal behavior with pain
Research in fish, amphibians, reptiles & birds has demonstrated that the transmission of peripheral sensory signals, via the spinal cord to midbrain and forebrain regions is homologous to mammalian cortical and limbic structures.

Veterinarians should err on the side of a reptile patient’s well-being and assume that conditions considered painful in humans and other mammals should be assumed to be painful across other vertebrate species.
Measuring nociception & antinociception in reptiles

- **Nociception**: sensory nervous system's response to certain harmful or potentially harmful stimuli
- **Antinociception**: reduce sensitivity to pain
- Understanding of normal species-specific behavior within the environmental context in which that behavior is being displayed
- E.g., the behavior of a bearded dragon in its home cage may be different from its behavior in a hospital cage
- Evaluate pre and post op behaviors
- Hard since most are sick upon presentation

Colour change may serve a thermoregulatory function
Alternative to studying postsurgical pain is to measure pain under strictly controlled laboratory conditions.

Established behavioral models during which noxious stimuli (mechanical, thermal, chemical) are applied to an anatomic location on the reptile subject.

Some might argue that a withdrawal response to a noxious stimulus is not equivalent to pain.

Evidence in a number of animal species that noxious thermal stimulation does cause molecular and cellular changes in the CNS.
NSAIDS?

- Meloxicam commonly used, why???

- No evidence for their efficacy in reptiles

- Green iguanas single .2mg/kg PO yielded excellent bioavailability, suggesting that plasma concentrations associated with analgesia in other species can be obtained for 24 h

- 0.1 mg/kg inadequate for loggerhead sea turtles

- 0.3 mg/kg did not provide analgesia in ball pythons
(Royal 2012)
- One study successfully demonstrated COX expression in reptiles
- Did not demonstrate the end products (PGE, TXA, PGF, PGD or PGI) which are the primary mediators of inflammation & pain production associated with increased COX expression
- Recommended to use nonselective instead of COX-2-selective

(Tuttle 2006)
- PK, Ketoprofen 2 mg/kg IV green iguana long half-life of 31 h vs. in mammals
- 2 mg/kg IV q 24 h
- Bioavailability after IM only 78%, and half-life only 8.3 h

(Hannon 2015)
- Ketoprofen has been used effectively in sea turtles at 2 mg/kg IM
- Duration of administration should be limited to 3 to 5 d
Opioid and opioid-like drugs

- Receptors must be present so drugs to have a beneficial analgesic effect
- The opioid receptors (μ, κ, and δ) are highly conserved across multiple vertebrate orders
- Two snake species have endogenous brain opiates, and RES have both proencephalan-derived peptides and functional and μ and δ opioid receptors in the brain
- Butorphanol 0.02 to 25 mg/kg ???
- No clinical data to substantiate that butorphanol was an effective analgesic drug in reptiles
- Has been use by most clinicians for many years
- Buprenorphine- NO
Opioids: Hydromorphone

- BD 0.5 mg kg SC q24 h, RES 0.5 mg kg SC q12–24 h (Hawkins 2019)
Anesthetic considerations

- Always premedicated SC/IM/IN
- Inhalation anesthetic compounds are associated with struggling and breath-holding
- Apnea > bradycardia, hypercapnia and hypoxemia
- Allows for a smooth anesthetic induction
- Minimal cardiorespiratory side effects
- Can combine with opioid to provide additional analgesia
- Flumazenil reversal
- It can be combined with other alpha-2-agonists to provide adequate sedation and analgesia
Transdermal fentanyl patches have been applied to prehensile-tailed skinks and ball pythons, and plasma concentrations were detectable in both species.

We primarily use SC and local/locoregional...
Tramadol

(Baker 2011)
- Red-eared sliders thermal withdrawal study 1, 5, 10 & 25 mg/kg PO
- 5 & 10 mg/kg provided good analgesia, 25 mg/kg caused flaccid limbs and necks in 4/11 turtles and severe respiratory depression
- SQ slower to take effect, had decreased duration of action, and less overall analgesic effect
- 5 mg/kg PO affected thermal nociception for 12 - 24 h, while higher doses of 10 or 25 mg/kg had effects from 6 - 96 h

(Giorgi 2015)
- PK yellow-bellied sliders 10 mg/kg IM either a forelimb or hindlimb
- Significant changes in limb withdrawal were noted from 0.5 - 48 h HL and 8 - 48 h in the FL
- Maximal blood concentrations of tramadol were achieved within 1.7 h HL injections and 0.7 h FL injection
- Both max effect at 24 h
- Possible there is significant first by pass effect in the liver leading to higher conversion of tramadol or its metabolite
Tramadol

- Loggerhead sea turtles PO 5mg/kg q48 h and 10mg/kg q72 h (Norton 2015)
- Bearded dragons 5-10mg/kg (Greenacre 2008)
Lidocaine considerations, cat study

- A previous study showed topical 2% as effective as 10% to facilitate intubation
- 2% lidocaine lower maximum plasma concentrations; is recommended
- Topical alone or in combination with intratesticular results in dose-dependent increases in maximal plasma concentrations
- Recommended doses of 2% are 0.1 mL (≈0.6 mg/kg) administered topically on the larynx and 0.1 mL/kg administered intratesticularly, adjust for smaller patients
- Although time to reach peak plasma concentrations does not significantly differ between topical application alone or in combination with intratesticular
- Plasma concentrations may be affected by other patient factors and should be considered on an individual patient basis
- Must know max dose recommended!

Plasma concentrations of lidocaine following laryngeal administration or laryngeal and intratesticular administration in cats. (Soltaninejad 2018)
Local/locoregional anesthesia
(species varibilities)

- Topical local analgesics questionable d/t poor absorption across the skin
- Injectable is preferred
- Incisional line blocks, local infiltration, ring blocks, splash-blocks, conductive nerve block and intra thecal anesthesia
- Mandibular nerve block in crocs, using a nerve locator and infusing mepivacaine (Wellehan 2006)
- Wait 5 minutes
- Lidocaine 2-6 mg/kg (10?), can be buffered 1:1 with NaHCO3
- Bupivacaine 1-2 mg/kg (4?), 2x potency
- Mixing?
- Scarce data, no published toxic doses
Intrathecal (subdural) administration of anesthesia & analgesia

- Turtles/tortoises, novel technique for the induction of spinal anesthesia & analgesia
- Possible indications include surgeries of the tail, phallus, cloaca & hind limbs
- IT injections are performed at the level of the coccygeal vertebrae
- RES IT administration of preservative free lidocaine 4 mg/kg & bupivacaine 1 mg/kg
- Provides regional anesthesia of the tail, cloaca and hind limbs for about 1 & 2 h, respectively
- IT morphine provides regional analgesia for up to 48 h
Strict aseptic techniques should be used to avoid iatrogenic complications.

Only preservative-free drugs should be injected into the intrathecal space so that spinal toxicity and secondary neurologic complications are avoided.
Methylene blue dye injected into the intrathecal (subdural) space surrounding the spinal cord in RES

(A) Cross-section proximal tail base, close proximity of the skin overlying the neural arch dorsally can be noted

(B) Sagittal view of the spinal canal at the level of the last dorsal and sacral vertebrae
Analgesics recommended for reptiles

- Having plasma concentration does not equal analgesia
- Ketoprofen
- Meloxicam? IM/SC q24
- Hydromorphone .5-1mg/kg SC q24
- Methadone 3-5mg/kg SC q24
- Tramadol 5-10mg/kg PO q48-72, snakes?
- Lidocaine 1-2 mg/kg ?
- Bupivicaine 1-2mg/kg ?
- NSAIDs ?
- Dexmedetomidine
Alfaxalone
“or together with something else”

- Neurosteroidal anesthetic
- Excellent sedative effects across a wide range of reptiles
- 8–15 mg/kg IV and 10–20 mg/kg IM have been used in snakes, lizards & chelonians
- Primarily for sedation to perform diagnostic tests (e.g., imaging), intubate animals, or for minor procedures with local anesthesia (e.g., lidocaine or bupivacaine) with good results
**α2-adrenergic agonists**

Xylazine, dexmedetomidine

- Used with other analgesics primarily for the sedative effects
- Thought to have analgesic effects in reptiles, widely documented analgesic effects observed in humans and mammal
- Only one study exists evaluating the analgesic properties of α2s, efficacy?
- Leopard geckos showed that dext 0.1 & midazolam 1mg/kg SC initial sedation was noted at 3 m
- Profound **sedation** was achieved 7/9, lost righting reflex (Doss 2017)
- Tegus dext. 0.2mg/kg IM did not cause sedation & were highly responsive to stimulus, when midazolam was added sedation was achieved (Bisetto 2018)
α2-adrenergic agonists (Bunke 2018)

- Ball pythons dext. 0.1 or 0.2 mg/kg SC
- Increased thermal withdrawal latency which indicated that antinociception was present x 8 h
- Minimal changes in behavior, indicating that sedation did not occur
- Did cause respiratory depression, but did not cause long bouts of apnea
- The decrease in breathing frequency was compensated by an increase in tidal volume

Intracloacal study YBS (Morici 2017)

- Dexmedetomidine 0.2 mg/kg & ketamine 10 mg/kg
- Unpredictable results, maybe just for sedation
(Schnellbacher 2012)

- #8 YBS dexmedetomidine .2 and ketamine 10 mg/kg IN
- Provided a level of sedation to perform PE and minor clinical procedures
- IN atipemazole, up in 18 m

(Emery 2014)

- RFTs dexmedetomidine and midazolam IN didn’t cause sedation
Anesthesia

- Inhalants Sevo/Iso most common for maintenance
- CRI not practical or much data
- Sevo rapid induction & recovery, differences may be inapparent (1–3 m) to most clinicians
- Good tech > any monitoring equipment
- Get a baseline HR, RR & Temp prior to anesthesia
- Monitor physiologic parameters throughout the anesthetic period (pre/during/post)
- Loss of reflexes - Cranial to caudal - most of the time
- Loss of palpebral reflex in lizards, chelonians
Administer pre-warmed fluids

- Maintenance requirements estimated 10-30 ml/kg/day
- Vol for rehydration: % deficit x BW (kg) x 1000 ml
- Replace deficits over 48-96 h
- Plasma osmolarity may be helpful in the selection of fluids that will be isotonic for an individual patient
- Fluids may be given SC/PO for mild-moderate dehydration
- Fluids IC, IV, IO for moderate-severe dehydration
Majority of crystalloids used in mammals may be hypertonic or hypotonic depending on the individual reptile.

Signs of overhydration:
- Serous nasal discharge
- Jugular venous distension (when visible)
- Tachypnea secondary to pulmonary edema
- Peripheral edema
- Weight gain
<table>
<thead>
<tr>
<th>Species</th>
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<tr>
<td>Bearded dragon</td>
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<td>Green iguana</td>
<td>330</td>
</tr>
<tr>
<td>Red-eared slider</td>
<td>260</td>
</tr>
</tbody>
</table>
Vascular access

**IV:**
- Coccygeal, jugular, cephalic, or ventral Ab. v. can be used but may be difficult to place

**IO:**
- Lizards: proximal tibia, distal femur or proximal humerus, or ulna
- Chelonians: the gular plastron can be used depending on patient size
- Snakes do not have a good site
Induction/Intubation

- Always premed
- Mask > chamber
- Intubation can be challenging, protect tube
- Trachea- Complete chelonians & crocs vs. incomplete in snakes & lizards
- Intubation, don’t cause trauma to the anesthetist or patient, splash lidocaine
Maintain in their POTZ, ~85-90F most

Poikilotherms use external sources to maintain body Temp., which in turn affects the anesthesia

Drug absorption and excretion will be affected by Temp.

Temp. will affect the metabolic demands of the patient

Comorbidity and poor husbandry also can have an effect on anesthetic quality

Hypothermia > immunosuppression

Hyperthermia > decreased anesthetic duration & vasodilation
Monitoring: doppler

Remember that heartbeat does not equate to being alive in reptiles!!!

- Most have a 3-chambered heart
- Some monitor spp. efficient CV systems, like mammal physiology
- Functional cardiac separation
- Shunting of blood from lungs
- L > R by passes the systemic system
- R > L by passes the pulmonary system
- Renal portal system
- Avoid injection of anesthetic drugs to the caudal half the body since they may go through renal and/or hepatic first pass effect
Monitoring: ECG

- Thick, scaly skin of snakes & lizards limits the sensitivity of ECG leads
- Effective signal conduction requires alligator clips be attached to needles or SS suture
- Adhesive patches can be used on smooth-scaled reptiles
- Lack of normal values, however typical tracing may include an SV wave that precedes the P wave
- SV wave - depolarization of the sinus venosus, which serves as a pacemaker of the 3-chambered heart in most reptiles
- Heart often continues to contract for long periods of time following death, so use caution interpreting ECG findings as an
Monitoring: Blood Pressure

- Not routinely performed
- Chelonians have the lowest MAP of 15-30 mm Hg
- Resting MAP in the Green iguanas 40-50 mm Hg
- Varanid lizards MAP similar to mammals, 60-80 mm Hg
- Indirect BP correlates poorly with direct arterial BP
- Limited value, can provide information on trends
Lungs more fragile than mammalian, care not to induce barotrauma

Lizards & chelonians paired air-sac like lungs

Snakes functional R. in most spp. of pythons & colubrids

Some spp. of boids have more functional L. lung

Physiologic apnea and episodic breathing
Monitoring: Respiratory

- Active respiration: Intercostal muscles and limb movement to produce negative pressure for breathing
- No functional diaphragm, Crocs diaphragmaticus m.
- Ventilation driven by $\text{PaO}_2$ and mediated by changes in pH, $\text{PaCO}_2$ & Temp.
- Dive reflex and shunting
- pH: metabolic acidemia and anaerobic metabolism
- ETCO2 can be useful to monitor but not validated in most species
- Evidence of cardiac shunting can be seen with a drop of ETCO2
- SPO2 not validated, trends

Sidestream > Mainstream capnography (slide)

Provide IPPV 2-3/min
Example protocols

Chelonians:
- Dexmedetomidine 0.05–0.1, ketamine 10-15, midazolam 0.5–2 mg/kg SC/IM
- Lidocaine around tracheal opening, 5 min, intubate IPPV
- Tortoises lower dose range, box & semi-aquatic turtles higher end

Snakes: (big fat require lower dosages vs. ie. cornsnake)
- Hydro, midazolam SC depending on attitude
- Lidocaine around tracheal opening, 5 min, intubate and IPPV

Lizards:
- Hydro, midazolam SC depending on attitude
- Lidocaine in glottis, 5 min, intubate and IPPV or mask down
Recovery, can be lengthy….

- Recover intubated reptiles with room air or air < 100% O2
- Otherwise may take hours to recover
- Can bypass standard metabolism requiring O2
- If they do not breathe on their own or are provided IPPV, can revert to utilizing the effective but energy inefficient option of anaerobic respiration
- Not only does this patient not getting O2, but also not getting anesthetic and will respond to noxious stimuli such as cutting during surgery
- Do not schedule late in the day
• ASA your patient, premeds, Iso/Sevo
• Keep warm before, during & after
• Always premed prior mask induction
• Use reversibles when possible reverse ASAP
• Microdose naloxone reverses sedation > analgesia
• Rely on local blocks
• Microdoses of ketamine are analgesic > anesthetic
• Have colloids/fluids pre drawn warm & handy
• Have ER drugs pre drawn
• 1 good technician > any monitor
Conclusion

› Very limited PK & PD studies available in the majority of reptilian species
› Studies in species such as RES, green iguanas, bearded dragons, ball pythons, etc., we can extrapolate doses & anesthetic plans
› These studies should be used with care but not avoided
› Experience and future research with continue to advance the care of reptiles
› “Many” options that will need to be weighed out in the individual reptile patient
› Attend CE wet labs to enhance skills
› Thank the internet for some great images
› Publish what you see, it is easier than you think
Questions!