Inflammation is...

- a complex immunological response of the body to various stimuli
- Inflammatory mediators are its humoral messengers
- Promotion or inhibition of the inflammatory response may be a therapeutic goal

Anti-inflammatory Agents Used in Practice

- Glucocorticoids ('corticosteroids' or 'steroids')
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- (Antihistamins)
Aspect One: Anti-Inflammatory Therapy

Physiology of Glucocorticoids I.

- The release of endogenous GC-s is controlled by the hypothalamus (CRH)- anterior pituitary gland (ACTH)-adrenal gland (cortisol) axis (HPA)
- Receptor numbers vary with tissue and cell type
- Altered cellular gene transcription (differences between species)
- Therapeutic use: metabolic, anti-inflammatory and immunosuppressive effects

Pharmacology of Glucocorticoids I.

- Modifications: mineralocorticoid or glucocorticoid potency, receptor binding strength
- Bound to transcortin and albumin

Physiology of Glucocorticoids II.

- Synthetic glucocorticoid drug preparations are derivatives of endogenously produced adrenal hormone cortisol
- Pharmacologic derivatives of cortisol exert a similar negative feedback on the HPA-axis

Physiology of Glucocorticoids III.

- Metabolic effects:
  - catabolic effect, insulin antagonism, glycogen formation, 1GNG.
- Anti-inflammatory effects overlapping with immunosuppressive effects: inhibit liberation of arachidonic acid to diminish production of eicosanoid proinflammatory mediators (PG)
  - Stress leukogram altered membrane expression
  - affect cell mediated immune response diminished mononucl. phn. function, altered cytokine production (IL-1, IL-6, TNFa), affect on humoral immunity is indirect and not as pronounced

Pharmacology of Glucocorticoids II.

- HPA axis suppression:
  1. Short acting: suppression is less than 12hrs
  2. Long acting: suppression is more than 48hrs
  3. Intermediate acting
Correlation of Structure and Action of Synthetic Glucocorticoids

<table>
<thead>
<tr>
<th></th>
<th>Anti-Inflammatory Action</th>
<th>Mineralocorticoid Action</th>
<th>Relative Dosage</th>
<th>Biological Half-Life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>20 mg</td>
<td>8-12</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>0.8</td>
<td>25 mg</td>
<td>8-12</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>5 mg</td>
<td>12-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
<td>4 mg</td>
<td>12-36</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>0</td>
<td>4 mg</td>
<td>12-36</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25</td>
<td>0</td>
<td>0.75 mg</td>
<td>36-54</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0</td>
<td>0.75 mg</td>
<td>36-54</td>
</tr>
<tr>
<td>Cortivazol</td>
<td>60</td>
<td>0</td>
<td>0.3 mg</td>
<td>above 60</td>
</tr>
</tbody>
</table>

Pharmacology of Glucocorticoids III.

Pharmacokinetics
- Most water soluble: rapid absorption and action
- Poorly water soluble
- Least water soluble: slow absorption

Clinical Utility of Glucocorticoids

Anti-Inflammatory Therapy I.
- Identify and eliminate the underlying cause of inflammation
- Rule out infectious causes of inflammation
- Exceptions to the rule: Otitis externa, Mycoplasma hemofelis/Babesia caused AIHA

Clinical Utility of Glucocorticoids

Anti-Inflammatory Therapy II.
- Desired rapidity of action and expected duration of therapy
- When the initial inflammation is suppressed, the dose is reduced to the lowest necessary level
- Repository therapy

High Dose-Short Term Therapy
- Single dose
- Rapid onset of action is required
- Acute spinal cord injuries (within 8 hrs of injury): methylprednisolone sodium succinate
  15-40 mg/kg iv. repeated boluses of 15 mg/kg every 2-6 hrs later, followed by boluses of 7.5 mg/kg/6 hrs for 24 hrs or 24 h CRI of 2.5 mg/kg/h
Adverse Effects of Glucocorticoids

- Conditions exacerbated by glucocorticoid effects: infections, diabetes mellitus, pancreatitis
- Adverse effects: PU/PD, polyphagia, iatrogenic hyperadrenocorticism, GI side effects, dermatological side effects, delayed wound healing, infections, muscle atrophy, etc.

Glucocorticoid Reduction Protocols

- The lowest dose possible to achieve the desired effects
- When administered >2 weeks, reduce slowly
- Clinical condition should be monitored
- Prolonged dosing intervals (Every other/third day)

Aspect Two: Pain Management

Eliminating or suppressing pain and promoting normal vocalization

Perioperative Pain Management

Aim of Pain Relief

- Improving quality of patient care as well as surgical outcome
- Prevention of arising chronic pain
- Eliminating or suppressing pain and promoting normal behaviour
- Removing stress or distress

Pain Assessment I.

- Behavioral and physiologic characteristics associated with pain in cats and dogs
  - Abnormal posture
  - Tremor
  - Abnormal gait
  - Abnormal movements
  - Vocalization
  - Poor general health
  - Physiologic signs
Pain Assessment II.

- Pain associated with surgical procedures, illness, or injuries
  - 1. severe: cervical intervertebral disk herniation, pathologic fracture, multiple fracture repair, bone cancer
  - 2. moderate to severe: osteoarthritis, acute polyarthritis, fracture repair, limb amputation, laparotomy, thoracotomy, total ear canal ablation, glaucoma, uveitis, corneal abrasion, ulceration
  - 3. moderate: laparotomy, ovariohysterectomy, castration
  - 4. mild to moderate: some ophthalmic surgical procedures, lacerations, some dental procedures
  - 5. mild

Aspects of Classification of Pain

- Intensity: (see previous slide)
- Chronicity: acute/chronic
- Origin: somatic/visceral
- Type: nociceptive/inflammatory

Keep in mind:

There is more to pain management than NSAIDs!

See previous slide (Dr. Dunay)

Principles of Perioperative Pain Management

- Pre-emptive analgesia
- Multimodal analgesia

Drugs Used to Treat Pain

- Opioids
- NSAIDs
- Local anaesthetics
- Analgesic adjuvant agents

Effects of NSAIDs

- Anti-inflammatory effect
- Analgesic effect
- Antipyretic effect
NSAIDs

- Analgesia: anti-inflammatory effect
- Main component of postoperative pain: inflammation
- Toxicity and side effects

Plateau (ceiling) effect
- Restricted to animals in mild to moderate pain
- In combination: the base of multimodal pain therapy
- Potentiates opioid-induced analgesia (enhanced pain relief, reduced opioid requirement, less side effects)

Classification of NSAIDs I
Chemical Structure
- Acetic acid derivatives (diclofenac)
- Salicylic acids (acylsalicylic acid)
- Propionic acids (carprofen, ketoprofen, ibuprofen, naproxen)
- Pirazolones (phenylbutazone)
- Oxicams (meloxicam, piroxicam)
- Sulfanilamides (nimesulide)
- Coxibs (celecoxib, rofecoxib, valdecoxib)
- Other (paracetamol)

Classification of NSAIDs II
Biological Action
- A. Central/peripheral
- B. Non-selective/selective (COX-1, COX-2)

General Consideration
- Cats and dogs are more susceptible than people to the adverse effects of NSAIDs. Therefore the reported safety of any drug approved for humans should not be assumed to be safe in dogs or cats.

Indications for NSAID Administration
- Postoperative pain
- Inflammatory conditions (meningitis, soft tissue inflammation, polyarthritis, cystitis, arthritis, dermatologic disease, injuries, animal bites, etc.)
- Miscellaneous conditions (panostitis, hypertrophic osteodystrophy, cancer pain especially of bone, radiation induced stomatitis in cats, dental pain, etc.)
- Osteoarthritis
- Antipyretic therapy (most veterinary approved NSAIDs, as well as aspirin and nonsteroidal anti-inflammatory drugs)

Do NOT use paracetamol in cats!
### Most Commonly Used NSAIDs in Small Animal Practice

- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Noraminophenazon
  - Acetylsalicylic acid
  - Ketoprofen
  - Carprofen
  - Meloxicam
  - Derac/Firo/Robena/Mavacoxib
  - Tolfenamic acid
  - Tepoxalin

### Suggested Dosage of Some NSAIDs

- **Meloxicam**
  - Ca: ≤0.2 mg/kg, sc, po 1x ≤ 0.1 mg/kg, sc, po 1x daily for up to 4 days
  - Fe: ≤0.2 mg/kg, sc, po 1x ≤ 0.1 mg/kg, sc, po 1x daily for up to 3 days
  - ≤ 0.025 mg/kg, sc, po 2–3x weekly

- **Carprofen**
  - Ca: ≤ 2.4 mg/kg, sc, po 1x ≤ 2.2 mg/kg, sc, po every 12 or 24 hours
  - Fe: ≤ 4 mg/kg, sc 1x daily
  - Single dose preoperatively

- **Tolfenamic acid**
  - Ca, Fe: ≤ 4 mg/kg, sc, po 1x daily for up to 4 days, can be repeated once after 3 days

- **Ketoprofen**
  - Ca, Fe: ≤ 0.2 mg/kg, iv, im, sc, po 1x daily
  - ≤ 0.1 mg/kg, iv, im, sc, po 1x daily for up to 4 days
  - Not suggested for long-term administration

### Adverse Effects of NSAIDs

- **NSAIDs are not harmless**
- Common adverse effects include:
  1. GI irritation, vomiting, ulceration (especially with simultaneous corticosteroid administration)
  2. Renal adverse effects
  3. Clotting disorders
  4. Cartilage
  5. Bone healing
  6. Cardiovascular

### Contraindications to the Use of NSAIDs

- Active GI disease or recent GI surgery
- Renal insufficiency and decreased renal blood flow
- Shock
- Long-term glucocorticoid administration
- Ongoing NSAID therapy
- Active haemorrhage
- Pregnancy

### Remember:

NSAIDs alone can only alleviate mild to moderate pain. Use opioids, adjuvants, local anaesthetics and NSAIDs in combination!
Thank You!