Refinement: analgesia

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Useful references


http://www.ivapm.org/
Analgesia and analgesic drugs
Why it is so complicated?

• Pain management is a science

• Many drugs available

• Drugs have 2 names: molecule and brand names (sometimes more than 1 brand name!)
ex: Carprofen = Rimadyl®, Buprenorphin = Temgesic®

• Mechanism of action differ from one drug family to the other

• Dosages varies between species
  ex: Carprofen: 5 mg/kg for rats and 10 mg/kg for mice

• Some drugs will interfere with the research project
Presentation resume

Useful concepts
- Pain pathway
- Drug families
- Preemptive analgesia
- Multimodal analgesia

Common problems
- Side effects
- Drug duration of action
- Drug interaction with scientific objectives

Protocol evaluation
Protocols B, C, D
One protocol without a solution...yet

2 important elements
Pain recognition
Medical record
Pain pathway

- Periphery: pain receptors
- Pain ascends via a three-neuron chain
- Drugs can have action at one or several sites.
- Drug combination permits to act at several levels of the pain pathway.

M.E. Goldberg 2010
Analgesic drugs

4 large families:

- Non-steroidal anti-inflammatory drugs (NSAID): Aspirin, meloxicam, carprofen and others!
- Opioids: Morphine, buprenorphine, butorphanol and others!
- Local anesthetics: Bupivacaine, lidocaine and others!
- $\alpha$-2 adrenergic receptors agonists: xylazine and!

Co-analgesics

- N-methyl D-aspartate receptor antagonists (NMDA) (amantadine and ketamine)
- Gabapentine
- Etc.
Preemptive analgesia

- Application of analgesics drugs or techniques before the animal is exposed to a painful procedure
- Infiltration of the surgical site with a local anesthetic drug which blocks nerve impulses
- Analgesic given 1 or 2 hours prior to the surgery.
- Preemptive analgesia will not eliminate postoperative pain, but it will contribute in reducing the animal discomfort.
Multimodal analgesia: 2 or more analgesic drugs are given at the same time

- Some drugs will act in synergy (NSAID + opioids)
- Intervention at different levels of the pain pathway
- The use of several drugs at a lower dose will provoke less side effects than the use of one medication at a higher dose

Ex: protocol for a dog, thoracic surgery (only analgesic drugs indicated)
- Fentanyl patch 12-24 hours prior to the surgery
- Premix with butorphanol
- Carprofen prior to surgery
- Bupivacaine: Infiltration surgical site before beginning of the procedures
- Infusion per op: ketamine/lidocaine/morphine/
- End of surgery: catheter, pleural infiltration bupivacaine
- Post-op: Carprofen + fentanyl patch + morphine (rescue)
The problem of side effects

- Every drug has side effects however:
  - Will be a problem if the drug is given for a long period, ex: gastric ulceration and NSAID
  - Will not cause harm if the animal is closely monitored
- Pain causes problems too:
  - Anxiety and distress
  - Protein catabolism
  - Tachycardia, change in blood pressure, respiratory depression, sensitisation of the sympathetic nervous system, dehydration…

Generally the benefits of pain management outweigh the risks associated with analgesic drug administration. (M.E. Goldberg 2010)
The problem of drug duration of action

If we are working with an analgesic that only has a 4 - 8 hours action duration :

- No overnight analgesia for the animal who received his analgesic at the end of the afternoon
- For a rodent : No analgesia during his active period
- For a non rodent : No analgesia during sleep time

- Only some NSAID have a 24 hours action : carprofen, meloxicam...

- None of the opioids used in veterinary medicine have a duration of action than 8 hours except for the fentanyl patch. This patch is not available for rodents.

Leach MC and al. Preliminary investigation into the practicality of use and duration of action of slow-release preparations of morphine and hydromorphone in laboratory rats.
The problem of drug interaction with scientific objectives

NSAID:

Because they have an anti-inflammatory action they will interfere with protocols investigating the immune system, healing process, disease where inflammation as an important role e.g. arthritis…

Opioids:

Can affect protocols studying liver function, the nervous system (epilepsy, hepatoencephalopathies...), the immune system.

The investigator must give scientific justification for the withdrawal of analgesics

Franchi and al. 2007
Protocol category B: Experiments which cause little or no discomfort or stress

Ex: Use of female adoptive mice to save pups

- No painful procedures
- Usually no analgesia is proposed

An analgesic can be added in case of an accident (rare event) or disease

or

General SOP: Care for experimental animals
where a section describes the analgesics in use in the animal facility
Protocol category C: Experiments which cause minor stress or pain of short duration

There should be at least 1 analgesic planned:

• 1 opioid (usually buprenorphin) or 1 NSAID (usually carprofen)

• If minor surgical procedures under anesthesia: a local anesthetic should be used

• Analgesics planned should be indicated

• Modality of administration should be indicated
Protocol category C
Ex. : Technical training for animal facility and investigator personal

• Animal handling
• Administration of drugs (SC, IP, IV, per os)
• Bleeding procedures
• Number of manipulations limited to 3 /conscious animal

Extract from the protocol :

The manipulations and techniques used in this protocol are not expected to cause pain. However if an animal shows signs of discomfort or pain, it will be treated with an opioids analgesic, and NSAID or a combination of both accordingly to the veterinarian recommendation. A local anesthetic can also be used to minimized animal discomfort for certain manipulations.

Planned analgesics : carprofen, bupivacaine and buprenorphin
Protocol Category D: Experiments which cause moderate to severe distress or discomfort

- Should be at least 2 analgesics planned: 1 local anesthetic + 1 opioid (usually buprenorphin) or 1 NSAID (usually carprofen). Ideally the 3 analgesics.

- Analgesics should be administered before the painful procedures.
- Are the analgesics given accordingly to your SOPs?
- Is the analgesic drugs’ action long enough?
- Duration of the analgesia should be planned: Avoid “as needed”, it is better to put minimal duration e.g. 24h, 48h,…

- Duration: usually 48 hours or more

Is there any non-medicated procedures to prevent or reduce pain and discomfort?

Ex: Comfortable bedding, food at the level of the animal, small house in the cage, soft food, heat…
Protocol D :
Ex. Blood pressure measurement through telemetry in the rat

- A transducer is inserted in the abdominal aorta to permit the continuous acquisition of blood pressure measurements.

- The battery is installed in the abdomen. Another incision is performed on the leg so the transducer can be inserted via the femoral artery.

- Analgesics: A local anesthetic infiltration at both surgical sites
  - An opioid: buprenorphin 0.01 mg/ks sc, 1 dose at the beginning of the surgery
  - An SNAID: carprofen 5 mg/kg sc before the surgery and once daily for 2 days

- Note: Ketamine and xylazine are used in many anesthesia regimes. Both drugs have an analgesia effect, however their duration of action does not permit to ensure the post-op analgesia.
# EXPÉRIENCE: Chercheur: Implant: Pré-op set:  

# ANIMAL:  

Groupe: Post-op set:  

Souche: D.O.B.:  

Implant: Sexe: Personnes ressources:  

RECEVER:  

CHIRURGIE DE TÉLÉMÉTRIE  

Date: Chirurgien:  

Poids pré-op: g.  

Poids post-op: g.  

Anesthésie:  

- Isoflurane 2%(maintien) à 4%  
- Saline physiologique à 37°C (0,9 %)  
- Lubrifiant ophtalmique, avant la chirurgie  
- Infiltration Chlorhydrate de Bupivacaine 0,5% diluée 1/10 en pré-op  
- AIN plaie abdomen 0,5 mL S.C.  
- AIN plaie de l’aine 0,5 mL S.C.  

Analgésie:  

- Tx Carprofène en pré-op et 2 jrs post-op (Rymadil®): 5 mg/kg S.C.  
- 1 ml de carprofène dans 9 ml de saline bien mélangée. La dilution est bonne 1 semaine, conservée au frigo.  
- Buprénorphine au moment de la chirurgie: 0,01 mg/kg IP  
- Antibiotique Baytril 5mg/Kg per os dans l’eau de la bouteille (Traitement de 10 jours)  
- (Recette: Baytril concentration 50mg/mL utiliser 5 ml dilué pas 500 mL d’eau (Changer l’eau aux 5 jours))  
- Saline 0,9 % ou Dextrose 2,5 %37°C. 3cc BID S.C. si l’animal est mal en point ou anorexique, etc.  

Au besoin:  

- Verifier apporté par le biais de l’ensure et moulée, lisses dans le fond de la cage / Plaie / niveau d’activité par la posture, mouvement  

Observations:  

<table>
<thead>
<tr>
<th>Jrs</th>
<th>Date</th>
<th>Observations</th>
<th>Heure</th>
<th>Plaies</th>
<th>Saline</th>
<th>Carpro</th>
<th>Appétit</th>
<th>Ensure</th>
<th>Selles</th>
<th>Notes</th>
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<tbody>
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Légende: Ø Diamètre, CK=correcte, RAS: rien à signaler, E:Moulée en poudre+Ensure, M:moulée,BW=Poids, - pas du tout, +/- à peine, + = peu, ++=moy en, +++=beaucoup D début F: fin
**Date:**

<table>
<thead>
<tr>
<th>Doses: (mg/kg)</th>
<th>Concentrations: (mg/ml)</th>
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<tbody>
<tr>
<td>Atropine</td>
<td>0,04 0,5</td>
</tr>
<tr>
<td>Azapéroné</td>
<td>4 40</td>
</tr>
<tr>
<td>Kétamine</td>
<td>25 100</td>
</tr>
<tr>
<td>Propofol</td>
<td>1,66 10</td>
</tr>
<tr>
<td>Baytril IM</td>
<td>5 50</td>
</tr>
<tr>
<td>Baytril per os</td>
<td>5 150</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0,2 5</td>
</tr>
<tr>
<td>Morphine</td>
<td>0,2 10</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0,005 0,05</td>
</tr>
<tr>
<td>Bupivacaïne</td>
<td>2 5</td>
</tr>
<tr>
<td>Atropine</td>
<td>0,04 5</td>
</tr>
<tr>
<td>Fréquence respiratoire</td>
<td>12</td>
</tr>
</tbody>
</table>

**Masse Porc (kg):** 28

**PREPARATION**

**Medication**

<table>
<thead>
<tr>
<th>Phase of Anesthesia</th>
<th>Medication</th>
<th>Dose (ml)</th>
<th>Time</th>
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<tbody>
<tr>
<td>Pre-anaesthesia</td>
<td>Atropine</td>
<td>2,24</td>
<td>10-15 pré-op</td>
</tr>
<tr>
<td></td>
<td>Azapéroné</td>
<td>2,8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kétamine</td>
<td>7</td>
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</table>

**Régime IV**

<table>
<thead>
<tr>
<th>Solution</th>
<th>Dose (ml)</th>
<th>Time</th>
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<tbody>
<tr>
<td>NaCl.09%</td>
<td>280</td>
<td>10ml kg/hr</td>
</tr>
</tbody>
</table>

**Antibiotic**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (ml)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baytril IM</td>
<td>2,8</td>
<td>Le jour de la chirurgie, avant le début de la chx</td>
</tr>
<tr>
<td>Baytril po</td>
<td>1</td>
<td>SIDx 4 jours</td>
</tr>
</tbody>
</table>

**Analgesia**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (ml)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0,56</td>
<td>Si douleur, inconfort au réveil</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>1,12</td>
<td></td>
</tr>
<tr>
<td>Bupivacaïne</td>
<td>11,20</td>
<td>Infiltrer la plaie chirurgicale</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100ug</td>
<td>La veille de la chirurgie, mettre nv timbre 72 hres p</td>
</tr>
<tr>
<td></td>
<td>2,80</td>
<td>en bolus au début chx puis infusion 0,3ml/kg/hr</td>
</tr>
</tbody>
</table>

**Remarques**

- Donner à effet
- Bradycardie: fréquence cardiaque inférieur 60
For all protocols:
Treatment may need to be adjusted

Pain evolves in time and with the animal state

- The dose needs to be adjusted.
- We might have to change the medication
- We might have to combine drugs
- We can change the route of administration
Example of a protocol without a solution...yet
Protocol D : Collagen induced rheumatoid arthritis mouse model

- Debilitating and very painful disease
- 1 - 2 % worldwide population affected, 3/4 are women
- Complex disease, classified as autoimmune
- Severe inflammation resulting in the destruction one or more articulations
Protocol D: Collagen induced rheumatoid arthritis mouse model

- Collagen + Complete Freund Adjuvant (CFA) injected at the base of the tail
- Disease develops in 21 - 28 days
- Severity of the disease is measured with a score
  0: No sign
  1: Erythema and mild swelling of the tarsal or ankle joints
  2: Lesions extended from ankle to tarsal joints
  3: Lesions extended to the metatarsal joints
  4: Lesions at ankle, foot and digits. Limb ankylosis
Protocol D: Collagen induced rheumatoid arthritis mouse model

Problems:

• Discomfort caused by CFA → tail mutilation
• DBA/2 mice are nervous and aggressive
• When the disease develops several articulations may be affected → animal manipulation causes discomfort → administration of an analgesic may be contreproductive
Protocol D : Collagen induced rheumatoid arthritis mouse model

- Investigators are very reluctant to give analgesics
- No anti-inflammatory drugs
- Only buprenorphin (duration of action: only 6 hours and causes loss of appetite)
- Manipulation required for subcutaneous administration may cause pain if several articulations are affected

ACC required

- A reduction of the adjuvant injection volume → minor lesion to the tail
- Administration of buprenorphine if the mouse starts licking its tail
- Utilisation of female mice, less aggressive than males
Protocol D: Collagen induced rheumatoid arthritis mouse model

Endpoints

• Exposition of deep tail tissues
• 20% reduction of body weight
• Degree of inflammation: score 3 (lesions extended to the metatarsal joints)

Problems:
• Investigators disagree to use score 3 as an endpoint.
• Scoring evaluates only distal articulations. Mouse may experience pain from other articulation which are not included in the scoring system.

Solution?
Not found yet!
Keep dialogue open between investigators and ACC
Medical records

- The medical record is not an analgesic of course, however it’s an essential tool!
- Permits to ensure that the animal is receiving the right analgesic, at the right dose, the right route of administration and at the right time.
- Veterinary and investigator staff can revise observations and adjust the treatment.
- Permits to ensure that all team members know what the animal is receiving.
Animal monitoring and pain assessment

- It is important to ensure that the animal users are able to recognise clinical signs of pain

- ACC must ensure that proper training is available

- List of potential clinical signs should be included in the protocol and should also be in the medical record with instructions

Ex: If the animal cry, cannot stand up, is not using his leg, not eating...give 1 dose of meloxicam. If the animal is still uncomfortable 20 minutes after receiving the medication, give 1 dose of morphine.
Conclusion

• Evaluation of the pain management protocol is not easy
• Some key elements can help evaluating of the protocol
• Proper SOPs help to ensure that the right drugs, dosages, analgesia duration are appropriate.

• If not sure that the analgesic plan is adequate do not hesitate to ask questions or help.

• It is true that analgesic drugs will affect the protocol…pain does too.

  • Anxiety and distress
  • Protein catabolism
  • Tachycardia, change in blood pressure, cardiac debit, respiratory depression, sensitisation of the sympathetic nervous system, dehydration…
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