**Nuerolept Analgesia**

**Opioid Analgesics (Morphine) & Equine Colic (Butorphanol)**

**Introduction**

The primary effect of opioids is to temporarily **remove pain** when used at therapeutic levels; this is done by binding to **opioid receptors** found primarily in the **central nervous system** (some receptors are found in the gastrointestinal tract). When larger doses are given, opioids can induce beneficial and non-beneficial pharmacological effects such as **sedation, respiratory depression or constipation**. The term given to non-synthetic opioids is **opiates**; opiates are derived from the naturally occurring **opium alkaloids** found in the resin of the opium poppy.

The main uses of opioids include:

* Treatment of **acute pain** (e.g. post-operative)
* Palliative care to alleviate serve **chronic pain** (e.g. cancer)
* Surgical **premedication regimes** (due to their calming, sedative action – also reduces the amount of post pain relief required)
* **Neuroleptanalgesia** (a state of quiescence, altered awareness, and analgesia produced by a combination of an opioid analgesic and a neuroleptic – a tranquilliser). And **neuroleptanaesthesia** (a form of anaesthesia achieved by the administration of a neuroleptic agent, a narcotic analgesic, and nitrous oxide with oxygen. Induction of anaesthesia is slow, but consciousness returns quickly after the inhalation of nitrous oxide is stopped)
* **Restraint**
* **Antitussive** (the alleviating or suppressing coughing)

**Pharmacology**

The body naturally releases **endogenous opioid peptides** or **endorphins** which bind to **opioid receptors** in the body. There are three primary receptor types, each with different functional responses and these are:

* **μ** (mu) – Responsible for supraspinal (above the spine) analgesia, respiratory depression, euphoria and physical dependence of opioids (misuse and abuse of opioids)
* **κ** (kappa) – Responsible for spinal analgesia, miosis (pupil constriction of the eye) and sedation
* **δ** (delta) – Responsible for hallucinations and dysphoria (agitation and anxiety)

Exogenous opioids (synthetic or natural) **mimic** the body’s own endogenous opioids and are therefore able to bind to the above receptors – resulting in a response specific to the receptor they bound.  Opioids are able to either **stimulate or depress** the receptors, meaning opioid drugs can be classes as; **agonists, antagonists** or both – **agonists-antagonists**. Agonists bind to receptors and induce pharmacological responses whereas antagonists bind to receptors and do not produce a response, this makes them able to counteract the effect of other drugs or endogenous compounds.

Agonists are used for the primary reasons listed earlier, mainly **analgesia**. Examples of opioid agonists are:

* **Morphine**
* Pethidine
* Methadone
* Fentanyl
* Etorphine.

Antagonists are primarily used to **reverse the effects of agonists** i.e. analgesia. They do this by binding to μ and κ opioid receptors, which together are responsible for analgesia. Examples of opioid antagonists include:

* Naloxone (Narcan)

Agonists-Antagonists have both **agonistic and antagonistic properties**. This means they are able to **antagonise the pure agonists** (e.g. morphine) at μ and κ opioid receptors but they also have their own **milder agonistic effects**. The agonist effect is sufficient enough to be used as **analgesics.** Examples of opioid agonists-antagonists include:

* **Butorphanol**
* Pentazocine (Fortral)
* Nalorphine
* Diprenorphine (Revivon)
* Buprenorphine (Temgesic)

The principal usage of opioids in medication is for analgesia. Analgesia is the loss of pain perception. Opioids effect both the **physical** and **psychological** perception of pain, physically blocking or raising the threshold of pain stimulation and removing the association of pain with fear. Associated with analgesia is sedation which is not considered hazardous, respiratory depression (which can also be associated with opioid analgesia) however can be a distressing side effect. A list of unwanted opioid effects includes:

* Sedation
* Excitement
* Respiratory depression
* Cough suppression
* Nausea
* Vomiting
* Constipation

**Opioid Selection**

There are many opioids available for use, each with different properties, when selecting an opioid it is important to consider its **potency**, how quickly it acts (speed of **onset**) and how long it lasts (**duration**). The best **analgesics** are those which have a **mild potency**, **rapid onset** and a **long duration** of effect. When combining an opioid with a neuroleptic for **neuroleptanalgesia**, the desired properties of the opioid are slightly different; **strong potency**, **rapid onset** and **brief period of duration**.

As opioids can have an effect on the gastrointestinal system, (as opioid receptors are also found in the gastrointestinal tract) if they are to be given orally then they must have **low lipid solubility**.

Another point to consider is whether to use an agonist or an agonist-antagonist as both are able to produce analgesia. The main consideration is that **pure agonists** are **more reliable** and predictable than agonist-antagonists, but the **agonist-antagonists** produce **fewer side effects** such as vomiting, sedation and respiratory depression. Also as agonist-antagonists have antagonistic effects, any **further use of analgesics may be compromised**.

Below is a comparison of the **potency** of certain opioids relative to **morphine**, the most potent being **Etorphine.** Etorphine (or Immobilon) is extremely powerful and typically only used to immobilise large mammals (e.g. elephants). Due to its potency it can prove lethal to man.

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| **Drug** | **Relative Potency** |
| Meperidine | 0.1 |
| **Morphine** | **1** |
| **Butorphanol** | **1-2** |
| Hydromorphone | 10 |
| Alfentanil | 10-25 |
| Fentanyl | 75-125 |
| Remifentanil | 250 |
| Sufentanil | 500-1,000 |
| Etorphine | 1,000-3,000 |

Opioids are often used as part of a **pre-medication** routine i.e. before surgery as a pre-emptive form of analgesia. This is because once pain has been established (i.e. during surgery) pain relief drugs prove less effective. As a result **larger doses** would be needed to prevent the pain which increases the onset of associated **side effects** e.g. respiratory depression.

**Examples of Opioids and their Properties:**

**Morphine**

Morphine (**agonist**) is considered the standard opioid with all other forms of analgesia being compared against it. It is the **most potent natural analgesic**, more potent derivatives have been artificial synthesised. Morphine produces a **mixture of stimulant and depressant actions** depending on the **size of the dose** as well as the **species** and absence or **presence of pain.**

Differences between the species can be observed e.g. in the dog, the **cortex is depressed** and little excitement is produced. In the cat, very small doses are able to induce excitement and in the horse morphine will not produce excitement if no pain is present (effect is less predictable in horses however). Despite this morphine is **safe to use in all species** as long as the correct dosage is used, the presence of **excitement tends to increase with dose**.

The duration of morphine is about **4 hours** in all species, it is eventually metabolised by the liver. It is normally injected subcutaneously at a dose of around **0.1mg/Kg** (in dogs and cats).

Use of morphine can either **stimulate the medulla** (which is **followed by depression** of the medulla) or **directly depress the medulla**.

Morphine has a number of effects on the gastrointestinal tract. Initially it may invoke **vomiting and defaecation** which is followed by **constipation**. Constipation is due to local effects on the small/large intestinal opioid receptors. **Segmental tone of the intestines increases**, along with **sphincter tone** but the action **peristalsis decreases**. This **increases the time taken for intestinal contents to pass**.

Other areas affected by morphine include:

* The **chemoreceptor trigger zone** (CTZ) of the medulla is stimulated by morphine – this induced **vomiting.**
* The **occulomotor centre** is stimulated which is responsible for producing **miosis**.
* The **cough centre is depressed** – reducing coughing but making post-operation mucus accumulation a possible problem.
* The **vagal centre is stimulated**, which increases gastrointestinal activity and is responsible for the **initial defaecation**. If a large dose is administered bradycardia may be induced (slowed heart rate <60bpm) by myocardium depression.
* The **respiratory centre** is easily depressed by morphine, even with a low dose. This is due to a **reduced response to elevated CO2 levels**. The **mechanisms involved in the regulation of respiratory rhythm** are also affected – contributing to the overall depression of the respiratory centre.

**Butorphanol**

Butorphanol (**agonist-antagonist**) is a widely used sedative and analgesic in dogs, cats and horses – combined with tranquillisers for sedation. It is around 1-2 times as potent as morphine, but it does have a slightly shorter duration of action at around 2-3 hours (Morphine – 4 hours). It has a much **less profound effect on the respiratory system** as the dose increases compared to morphine.

One major use of Butorphanol is for intravenous administration in the horse (0.1mg/Kg) to alleviate abdominal pain associated with torsion, impaction, intussusception (intestinal prolapse) and **spasmodic colic**.

**Equine Colic**

The term colic can encompass all forms of gastrointestinal conditions which cause pain as well as other causes of abdominal pain not involving the gastrointestinal tract. Some examples are:

* **Spasmodic colic** – Increased peristaltic contraction
* Impactive colic – Caused by irritation to the lining of the bowel or ileum due to diet or ingestion of large amounts of sand/ dirt
* Obstructive colic – Obstruction of the bowel by large food masses
* Flatulent colic – Build of intestinal gases causing distension and pain
* Parasitic colic – Intestinal pain from parasites such as roundworm or tapeworm
* Idiopathic colic – From another cause which remains unknown

There are also many diagnostic tests for equine colic:

* Increased heart rate with decreased circulating volume
* Distinctive behavioural signs
* Auscultation – Listening to internal body sounds
* Abdominocentesis – The extraction of fluid from the peritoneum which can be useful in assessing the state of the intestines
* Nasogastric Intubation – Insertion of a tube from the nose to the stomach which can be used to drain excess liquid from the stomach – for therapeutic reasons and for diagnosis
* Rectal/Faecal examination

There are also many drugs/treatments available to treat the symptoms:

* **Analgesics**
* Spasmolytics
* Lubricants/laxatives
* Antizymotics – Used against disease producing organisms e.g. bacteria
* Anthelmintics – Used against parasites
* Fluid therapy

The major analgesics used against colic are α2-agonists (xylazine, romifidine and detomidine), **opioids** (**butorphanol**) and NSAIDs (flunixin).

Butorphanol is usually used alongside **small doses** of xylazine, romifidine and detomidine. This is because it has **minimal effects on the cardiovascular system** (which is not true for xylazine, romifidine and detomidine). Both butorphanol and the α2-agonists have a duration of around 2-3 hours and they both **reduce intestinal motility/activity.**