Numerous clinical entities have pain and is a challenge and a necessity for the veterinarian to control or neutralize it, our first mission is to alleviate suffering; other situations, in chronic disease, where relieving the pain we can usefully augment the life and the productivity of the animal, and we also find ourselves in situations, where controlling pain will be fundamental for allowing the handling and the continuation of therapy, for situations of intense visceral pain, in which the patient becomes unmanageable, endangering our safety and their own and preventing any possibility of therapy. Therefore, it is necessary to continue the search for potent analgesics, that will allow us to combat pain in its various manifestations, obtaining with it an important relief to our patients and a greater success in our fight against this disease. Many drugs are able to alter or eliminate pain and we can use them according to the circumstances, alone or in combination with other drugs.

The types of drugs that we can use as palliatives for pain are:
- Analgesic types such as NSAIDs, anti-inflammatory drugs, analgesics and antipyretics, non-steroids, with extensive use for visceral pain and also for musculoskeletal pain. Acts in the point of inflammation, intervening in the production of prostaglandins.
- Opioid Analgesics, in its different variations - pure agonists, mixed agonists, etc - preferably used for visceral analgesia or intraoperative, they are hypno-analgesics that act at the central level, of the pain receptors, miming the action of endogenous opioids. They are potent analgesics, but they have drawbacks that affect the central nervous system, causing general depression, although in some cases also excitability.
- Analgesics of the Alpha-2 agonists group, drugs that in addition to its sedative, exercise an important analgesic action, also a visceral preference, that inhibits the central level of the alpha-2 adrenergic receptors.
- Local anesthetics, are drugs that are able to prevent or relieve pain by producing a reversible block of the conduction nerve, they have a limited use as analgesics, but in some clinical situations, they are an important tool in controlling musculoskeletal pain.
- Neurolytics, substances used to alter nerve conduction, during long periods of time, they are general irritants that alter the medullary sheath, impeding normal transmission of the nerve impulse, they are used as palliatives for pain in chronic infections of the musculoskeletal system.
PAIN
Sensation or pain nociceptors are classified according to their origin and characteristics in several categories. Depending on their origin, visceral pain is classified when it originates from the distension of the viscera and in somatic pain when it is situated in the soma. Somatic pain can be classified in surface pain if it comes from the skin, and deep pain when it comes from the muscles, bones, joints and connective tissue.

Depending on its characteristics it can be classified in fast pain as being a sensation that is very well localized in the area of origin, which disappears quickly when the stimulus is eliminated and its transmission is relatively fast. On the other hand, slow pain appears more delayed in time and can be very intense and prolonged, it is perceived in a more diffused way and its transmission is slower.

MECHANISM OF ACTION

Types of nociceptors

Pain receptors are nociceptors, which encode the intensity of the stimulus through a firing frequency code of action potentials. They suffer from the process of sensitization for which a stimulus subthreshold of intensity produces pain and one of threshold intensity that produces a greater intensity of pain. Nociceptors are nerve endings widely distributed throughout the skin; they are abundant in certain internal tissues (bone tissue, peritoneum, skeletal muscle, articular surfaces, cranial cavity and arterial walls) and very rare in the rest of the internal tissues. According to the nature of the stimulus we can classify nociceptors in:

- Polymodal Nociceptors that respond to mechanical, electrical, thermal or chemical stimuli of high intensity. They are innervated by non-myelinated type-C fibers.
- Mechanisensitive nociceptors that respond only to mechanical stimuli of high threshold. They are innervated by type-A myelinated fibers.

Nociceptor stimulation:
Pain receptors also have their own transmission routes that differentiate from those that direct to other sensations. Chemical nociceptors are stimulated by numerous chemical substances such as:

- Neurotransmitters: acetylcholine.
- Prostaglandins E2 (PGE2).
- Autocoids: Bradykinin, 5-hydroxytryptamine: (5-HT), histamine, potassium ions and proteolytic enzymes.
- Acids: Lactic acid.
- Cytokines: Tumor necrosis factor, Interleukin 1,6,8 and peptide that is related with the calcitonin gene.

These substances also reduce the threshold of excitability of the other two types of nociceptors, the mechanical and thermal sensitivities. The mechanical
nociceptors are stimulated by stress, stretching, compression and flattening. Mechanical stimuli act through the deformation of the membrane channels and the chemical and thermal stimuli produce an ion channel activation. This way thermal stimulation of high intensity also stimulates thermal nociceptors through the damage of parallel tissue, that will induce the release of chemical substances that stimulates the chemical nociceptors and will decrease the threshold of mechanical and thermal sensitivity.

**VISCERAL PAIN**

Very localized in viscus injuries and do not usually cause severe pain, however a diffuse stimulation of the nociceptors from a viscus produce severe pain. There is an interaction between the intensity of the injury and the origin of pain.

The most frequent causes of visceral pain are:

- Tissue ischemia.
- Spasm of the smooth muscle of a hollow viscus (ureters, gall bladder or intestine).
- Excessive distension of a hollow viscus.
- Chemical stimuli such as gastric acid.
- Released chemical substances that mediate inflammation conditions (bradykinin, prostaglandins, leukotrienes, serotonin, histamine,..)

Referred pain: is produced when there is a genuine (unrelenting) visceral pain which also produces a painful sensation in its own viscera, it is perceived as pain in a part that is far away from the tissues that are producing the specific painful sensation.

This is because when the fibers of visceral pain are stimulated some signals can be taken by second-order neurons that normally carry cutaneous nociceptor signals. Because of this the (CNS) central nervous system interprets the pain that comes from a surface area and not a viscus.

**PATHWAYS FOR TRANSMISSION OF SOMATOSENSORY INFORMATION**

Somatic information of the truncus and extremities that reaches the spinal cord through the spinal nerves, and visceral information that goes through the nerves of the autonomic nervous system. Information originating from the head goes through the cranial walls that lead to the brainstem. Sensory fibers that carry information of the visceral origin because of sympathetic and parasympathetic afferences. The sympathetic leads the afferences of the visceral sensations and the nerves of the parasympathetic that transmit the reflex and regulatory functions of the viscera. Information of the somatovisceral recipients of the truncus and extremities is lead by the primary sensory neurons (with its neural body in the spinal ganglia) up to the spinal cord and from there it leads up to the encephalon.

**OPIOIDS**

Opioid drugs reduce the sensation of pain. They are effective in almost all types of acute and chronic pain, although their effectiveness is often limited in
neuropathic pain.
There are three types of opioid receptors that exist, the mu, kappa and delta receptors. It has shown its existence in the CNS and in other areas such as the stomach, intestine, adrenal medulla, heart, etc.
The analgesic effects of opioids are produced by the union of these receptors.

**MU RECEPTORS**
They are primarily located in the brain, whose stimulation causes supraspinatus analgesia, respiratory depression, hypothermia and myosis, also other effects such as brachycardia, euphoria and physical dependence.

**KAPPA RECEPTORS**
Basically located in the spinal medulla which when stimulated results in analgesia, sedation and miosis, in the absence of respiratory depression.

**DELTA RECEPTORS**
They are probably the most important at the peripheral level, but they can also contribute to analgesia, there are few selective delta agonists that exist. There are two other receptors that exist that are called the Sigma and Epsilon. The first is actually classified by the majority of authors as a non-opioid receptor; now it appears that other drugs such as phencyclidine, may also act through this receiver and the second is responsible for additive effects on the Sigma during syndromes of abstinence and dependency on certain morphemic drugs. All opioid agonist drugs that present agonist activity on mu receptors are analgesics and the majority of opioids used in veterinary are in this group.

**CLASSIFICATION**
Opioid drugs may be classified according to their receptor selectivity and may be active at one, two or all of the receptors. The activation of a determined subtype of receptors in general are associated to a pharmacological profile in particular. Effective analgesic drugs in the clinical practice are those that act selectively on mu receptors, some of them are morphine, methadone, oximorphone, fentanyl, sufentanil, remifentanil and buprenorphine. Butorphanol, which is active in mu receptors, has also significant activity in kappa receptors, and is widely used in the clinical practice. Opioids are also classified as agonists, partial agonists, mixed agonists-antagonists or antagonists, which describe their ability to induce a response once linked to a receptor. Agonists can induce a maximum response, whereas partial agonists cannot, independently of the dose, and antagonists that are linked to receptors do not bring on any type of response. Therefore the effectiveness of opioid drugs varies in different types of receptors.

**PURE AGONISTS**
This group includes in the majority of drugs an action similar to morphine. They all have a high affinity by the mu receptor, and a variable affinity by kappa and delta receptors.

**MORPHINE:**
For extended use, it is a selective mu agonist with minimum action over other receptors.

- **PHARMACOKINETICS AND METABOLISM**
  Despite its widespread use, clinical pharmacology data in animals are not complete. Morphine presents good distribution, quick clarification and a relatively short half-life.
  Morphine is an excellent analgesic drug for the treatment of moderate to severe pain in many species of animals, whether it is used in intramuscular (IM) injections or in postoperative periods as infusion.
  Morphine is used more frequently in small animals, and although it has been described for use in horses it is not usually included in the protocols for the treatment of pain in this species due to the frequently observed motor effects.
  It causes euphoria, especially in horses and cats. It induces vomiting and may inhibit gastrointestinal motility. It is a powerful respiratory depressor and can induce hypotension.

**METHADONE:**
Is a selective agonist of mu receptors.

- **PHARMACOKINETIC AND METABOLISM:**
  Has similar effects to that of morphine but with a slightly higher duration of action
  Unlike morphine it does not cause an important emetic effect.
  In respiratory depression inducement is less severe than that of morphine.
  Used in combination with neuroleptics to produce deep sedation.

**PETHIDINE:**
Is a selective mu agonist.

- **PHARMACOKINETICS AND METABOLISM:**
  Is less potent than morphine, it is eliminated more rapidly from the organism especially in large animal species. In the treatment of horses and ruminants the duration of the action is less than 30 minutes. It is frequently used as a part of the premedication regime, it does not induce vomiting and is an effective and a reliable analgesic drug.
  The beginning time to action is short after intramuscular injection and is useful in treating acute trauma and surgical pain. However, the short duration may be a drawback in the treatment of pain after moderate or severe surgery. Should be administered through intramuscular injection seeing that the recommended dosage for subcutaneous injection does not get the therapeutic levels of the drug and IV injection may cause severe hypotension.

**FENTANYL:**
Is a powerful mu agonist receptor.

- **PHARMACOKINETICS AND METABOLISM:**
  Is administered through syringe IV injection, intermittent IV injection or infusion. It presents a large volume of distribution and has a high value of clarification, although its half-life is relatively short.
  As a result of its high solubility it has a wide uptake in the tissues of the body, which limits infusion time due to the possibility that it will produce drug accumulation with long periods of infusion.
  The initial action of fentanyl is fast, from 2 to 5 minutes after IV injection.

**ALFENTANIL:**
Is a mu selective agonist with a potent analgesic effect. It is the same as fentanyl, it brings forth respiratory depression and in clinical doses, marked brachycardia. In small animals it is used through IV infusion. It has a fast and extensive distribution.

- PHARMACOKINETICS AND METABOLISM:
Experiences a rapid and almost complete absorption after IM or subcutaneous injection. It is an lipophil drug and is well distributed throughout the body. It has a half-life of short elimination. Butorphanol clearance is very fast in cows and dogs, but is slower in the horse.
The intensity of the analgesia can be variable and its use is best limited to animals with mild to moderate pain. The potency of butorphanol in a considerable manner has tranquilizer properties of acepromazine in animals. In the horse when butorphanol is administered by itself it only produces an increase in motor activity and in this specie it is often used more in combinations with sedatives or tranquilizers.
It is an effective antitussive drug and is authorized for use with this indication in small animals.

SUFENTANIL:
Is an opioid analgesic derived from fentanyl, with a higher potent mu agonist. It has no widespread use in veterinary medicine, it is administered through syringe IV injection or IV infusion, as well as in epidural administration, the initial action is very fast with excellent spinal anesthesia.

BUTORPHANOL:
Is an agonist of the mu and kappa receptors.

+ MIXED AGONIST-ANTAGONISTS
They combine a degree of agonist and antagonist activity in different receptors.

BUPRENORPHINE:
Is a partial selective agonist for the mu receptor.

- PHARMACOKINETICS AND METABOLISM:
It has a particularly high affinity for its receptor. The association of the drug with its receptor is slow, which is reflected in the slowness of the beginning action of the drug (45-60 min).
It has a slow elimination and is not due to enterohepatic recirculation, it is probably a result of the return of buprenorphine from a deep tissue compartment, such as fat. It is a highly lipophilic drug that penetrates well in the CNS.
The oral bioavailability of buprenorphine is very low, at 3-6%.
Doesn't appear to induce vomiting in pet species for this it is a very useful analgesic.

PENTAZOCINE:
Is a mu antagonist and kappa agonist.

NALBUPHINE:
Is structurally related to naloxone and oximorphone.
Spectrum is an opioide of quantitatively effects similar to that of pentazocine,
however, it is a more potent antagonist of mu receptors and are less likely to produce dysphoric side effects as that of pentazocine.

ANTAGONISTS:
- NALOXONE: is an opioid antagonist used in medical and veterinary practice to change the effects of complete or partial agonists.

-PHARMACOKINETICS and METABOLISM:
Has a short duration, approximately 30-60 minutes, and when used for reversing toxic side effects of opioid drugs in animals, specialists must be prepared to repeat the doses at frequent intervals.

LOCAL ANESTHETICS:
Local anesthesia consists of loss of feeling in a body part without loss of consciousness nor alteration of the central control of the vital functions.

Chemical aspects:
The molecules of local anesthetics consist of an aromatic part that is connected by an ester or amide link in the lateral alkaline chain. The only exception to this structure is benzocaine, which lacks the core group. The rest of local anesthetics are weak bases with pKa values, generally in the 8-9 range, so these compounds are in its main part, although not totally, ionized at the physiological pH. This fact is important in relation to the capacity of these substances through the nerve sheath and of the axonal membrane. As molecules of local anesthetics they are composed of an aromatic hydrophobic group joined to a basic hydrophilic group, these compounds tend to accumulate in aqueous-nonaqueous interfaces (meaning, that local anesthetics tend to reduce surface tension).

The presence of an ester link or an amide in the molecules of local anesthetics (in addition to assume that the classification base of this group of drugs) is important that these links are susceptible to metabolic hydrolysis. Substances presenting the ester link will frequently inactivate in the plasma and in the tissues (especially in the liver) through non-specific estearases. Amides are allot more stable and are characterized for having a longer plasma half-life than those of the previous anesthetics.

Action Mechanism:
Local anesthetics prevent the generation and conduction of the nervous impulse. At the molecular level, they act on Na+ channels depending on the voltage, inhibiting the entrance of the said cation (ion).

Blocking is exerted using two ways:
- via hydrophilic: where the pore is accessed from inside of the cellular interior. The anesthetic, that is in the pH extracellular is mostly ionized, it must cross the plasma membrane in a non-ionised form. Once in the cytoplasm it must reionize, it is in this form that it can access the pore when open. Once inside the pore, it'll only bind to the same area when the channel is found in an inactivated state. So, when the greater the number of depolarizations that the neuron suffers, the more anesthetic molecules can access the interior of the pore and block it (dependency on usage).
- via hydrophobic: from the plasma membrane is where the pore is reached. In this case it is not required that a channel opens up to penetrate it, it can also be joined with the anesthetic when the channel is in a closed state.

Not all nerve fibers have the same susceptibility to the action of local
anesthetics (LAs), however the susceptibility depends on the diameter of the fiber and if it is mielinizada or not. LAs block the duct in the following order: small myelinated axons, non-myelinated axons, and large myelinated axons. Therefore, the transmissions that they block first are the nociceptors and the sympathetic. On a practical level, the order of sensation loss is pain, temperature, touch, deep pressure, and finally, it alters the motor function.

EFFECTS OF LAs ON OTHER PHYSIOLOGICAL SYSTEMS:

The main physiological systems that are affected by LAs are the CNS and the cardiovascular system.

The main effect of LAs on the CNS is stimulate; they produce tremors and restlessness, with the appearance of subjective effects that can range from mere confusion until it reaches major agitation. An increase in doses leads to depression of the CNS and the main risk factor is derived from the depression of the respiratory system that is produced during this phase. The only LA with different CNS effects from those that causes compound remains is cocaine.

Cardiovascular effects of LAs are mainly myocardial depression and vasodilatation.

The reduction of the contractility of the myocardium is resulting, likely and indirectly, of the partial inhibiting of the Na+ current in the heart muscle. The decrease in the entry of Na+ leads to a decrease of the [Na +]i, which, in turn, reduces intracellular calcium deposits, which causes the decrease in contraction strength.

Vasodilation caused by LAs is due, in part, to a direct effect on the smooth musculature of the blood vessels, and in part, to inhibition of the sympathetic nervous system, as much as the central level as the ganglionic. It mainly affects the arterioles.

The combination of the effects; vasodilation and myocardial depression, causes a drop in blood pressure that can appear suddenly and present risk factors. Cocaine is an exception in terms of cardiovascular effects due to its peculiarity to inhibit the reuptake of noradrenaline (NA).

Side Effects:
The more dangerous side effects of LAs are the actions of these substances at the level of the CNS and the cardiovascular.

They can develop, although rarely, hypersensitivity reactions that take the form of allergic dermatitis, although occasionally cases of acute anaphylactic reaction have been reported.

Pharmacokinetic aspects:

When the anesthetic is injected in a certain place, a part of it diffuses to the nerve fibers, where it must pass through the connective tissue sheaths that they surround and the plasma membrane of the same, in a non-ionized form. When the anesthetic molecules are inside the nerve fiber they exert their action. From the injection site, another part of the anesthetic diffuses into the bloodstream, distributing throughout the whole organism. In the bloodstream the majority of LAs that have an amide bond are rapidly hydrolyzed by plasma cholinesterase, so its half life plasma is short. Anesthetics with amide bonds
metabolize primarily in the liver, undergoing, by a general rule, an N-dealkylation and later, hydrolysis. The anesthetic effects of these drugs end when anesthetic molecules leave the nerve fibers. This happens because there is a balance between the anesthetic that is in the extracellular space and is located in the nerve fiber. As the anesthetic that is outside the cell diffuses into the bloodstream, the balance is maintained at the expense of the anesthetic that is found in the neurons that they had started to abandon. For this, the more hydrophobic anesthetics there are, the more potent they are and have a longer duration of action, as they tend to concentrate on the inside of the cell and have a harder time leaving the nerve fibers.

**Ways to administrate LAs**

1. Topical or superficial anesthesia: is effective in the mucous membranes, such as the bronchial tree, and on surfaces such as the cornea. It consists of direct application of LAs on the mucous membrane that is to be anesthetized.
2. Anesthesia by infiltration: consists of direct LA injection in the area of interest. It can be very superficial, including only the skin, or can affect deeper structures, if they are to be infiltrated. Infiltration anesthesia is effective for many regions, but there can be necessary high doses of anesthetic. Vasoconstrictors may be used (ex: adrenaline) to delay absorption.
3. Regional block anesthesia, is performed by applying a proximal LA in where you want to anesthetize. The area of nerve trajectory has to be well known, seeing that the anesthetic is injected close to them. With this technique, using low amounts of anesthetic, you can anesthetize a larger area than that of infiltration.
4. By nerve block anesthesia: the LA is applied individually around the peripheral nerves or nervous plexus, which obtains a larger area of anesthesia than in the previous technique.
5. Intravenous regional anesthesia: is used in the limbs. The LA is injected in the distal portion of a cuff which is applied to a limb to leave the anesthetic restricted to the periphery. Systemic effects can occur after the withdrawal of the cuff.
6. Spinal or rachidian anesthesia: in this case the LA is injected into the subarachnoid space of the spinal canal at the lumbar level. A large area of the organism is anesthetized with low doses of anesthesia.
7. Epidural anesthesia: the anesthetic is injected in the extradural space. This technique is used in the sacrum areas (caudal anesthesia), lumbar, thoracic or cervical.

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