Module 09 – Analgesia

The objectives of this module are:

- to define analgesia
- to define nociception
- to outline the anatomy and physiology of nociception
- to discuss the major groups of pain relieving drugs; their properties, limitations and side effects
- to discuss the legal requirements in using controlled drugs for analgesia

We should try to relieve pain in animals because:

a. We expect to have our own pain relieved
b. Animals feel pain
c. Pain has an effect on many body systems and so may distort research results
d. We have an obligation to avoid causing unnecessary pain and suffering to animals
e. The Canadian Council on Animal Care Guidelines require the use of analgesics
f. We have an obligation to avoid causing unnecessary pain and suffering to animals

Pain may originate from a variety of sources and while the pain of surgical wounds may be the most common source, we should not forget other causes. The signs of pain will vary from species to species and with the source of the pain. Highly localized pain may cause signs restricted to that locality e.g., the signs of pain from a sore foot may be restricted to the same leg while a generalized infection will provide more widespread evidence of pain.

Introduction to Analgesia in Experimental Animals

We have an obligation to reduce or abolish pain in animals whenever it occurs and particularly if it occurs in research, teaching or testing.

Many investigations that use animals for research and testing have the potential to cause pain or suffering that should be alleviated. When studies may result in pain, the principal investigator should include a plan of action to use analgesic agents, including contingency plans for unexpected events. Veterinary expertise should be consulted.

Some experimental situations are obvious candidates for pain therapy. Pain occurs following most surgical procedures, but the severity depends on the invasiveness of the surgery, the organs involved, post surgery complications, etc. In some cases, the pain is of relatively short duration in the immediate post-operative period, while in other cases pain may last considerably longer.

For example, animal models of arthritis should be considered painful as the human diseases that they model are known to be painful. Similarly, some forms of cancer in humans are painful, particularly those that are found in bone. However, even solitary tumours may induce pain, depending on their site. Those that ultimately ulcerate through the skin may have been causing pain for a considerable time.

Infectious diseases result in a range of pain and distress symptoms. Fever and pain in muscles and joints, "flu-like" symptoms, may be experienced in a variety of viral infections. Gastrointestinal diseases, urinary tract diseases, hepatitis, peritonitis, respiratory diseases, abscesses, conjunctivitis, may all be painful. Antibody-antigen interactions, as in allergies or following immunization, may be itchy or painful.

The examples given above provide concrete indications for pain therapy. In very painful states, this may include the use of the most potent analgesic agents, the opioids. However, if we consider our own situations, there are also less serious conditions that have us reaching for the medicine cabinet.

We are used to thinking of pain relief in terms of a single analgesic. However, as we learn more about the nature of pain, it is clear that effective pain control may depend on using a number of drugs. Pain can also vary with time, and the pain treatment should match the situation. This may involve using different drugs at different times in the course of treating pain in an

animal. The usefulness of local anaesthetics in providing short-term pain control should not be forgotten.

In addition, we should examine the timing of analgesic administration. The use of analgesics before surgery has been reported to lessen the need for post-surgical pain control although there is still some controversy over the effectiveness of this approach.

For the most part we are the cause of pain and distress in experimental animals and we should alleviate that pain and distress as completely as possible using all the tools at our disposal.

Concern Over The Impact Of Analgesics On Research Results

Although some investigators may worry about the effects of pain relieving drugs on their experimental model, the effects of the pain and distress that the animal may suffer are of greater concern. The physiological and neuroendocrine effects of unrelieved pain and distress may be extensive. More consistent results will probably be obtained from an experimental model when the animal is not experiencing pain and distress. It is a moot point then, whether the risk of side effects from drugs is a greater threat to the experimental protocol than the problems associated with extensive pathophysiology. Further, the side effects of most drugs are quite well known and with careful selection acceptable pain relief can be achieved with a minimum of interference with the investigation.

Analgesia in Laboratory Animal Models

Analgesia Means "Without a Sensation of Pain"

Analgesic drugs, with the exception of local anaesthetics, usually do not completely abolish painful sensations but reduce the intensity of the pain and make it tolerable. Nearly everyone has taken an analgesic for a painful condition (e.g., severe headache; after a tooth extraction) and has found the pain diminished and more tolerable. The same effect probably occurs in animals although it is difficult to be certain of this. The approach to pain therapy should be a balance between providing the animal with adequate pain relief without causing the animal further problems. Pain relieving drugs have side effects that must be considered. For example, under certain conditions, many non-steroidal anti-inflammatory drugs (NSAIDs) may

cause gastric ulcers and renal damage. Many people are unable to take pain-relieving doses of aspirin for this reason and this has fuelled the search for new NSAIDs.

Administering Analgesics to Laboratory Animals

Oral administration of drugs in food or water may seem attractive as there will be minimal interference with the animal. However, it does depend on the animal eating or drinking a required amount to obtain sufficient drug and this does not always happen. The taste of the drug may discourage the animal from eating it. Water consumption in normal rodents is quite variable and so accurate dosing of any compound in drinking water is difficult. It should be remembered that some analgesics, particularly the opioids, suppress appetite.

Although each class of analgesic drug is considered separately, this does not mean that only one should be used at a time. However, care must be taken to ensure that there are few or no reactions between the drugs that would either increase the side effects or diminish the analgesic effects. There are many factors to be considered in choosing an analgesic drug including those listed below. Many of these factors will be discussed in greater detail in the ensuing text. However, each situation should be evaluated separately and a decision made to minimize the pain experienced by the animal.

- Species
- Cause of the pain
- Severity of pain
- Route of administration
- Volume required
- Duration of effect
- Potential side effects of drug, good or bad
- Effects on study
- Effects of administration on animal

Analgesic Drugs

There are three major groups of analgesic drugs:

- Opioids
- Non-steroidal anti-inflammatory drugs (NSAIDs)

- Local anaesthetics

There are also several useful drugs that do not fit into these groups:

- Alpha-2 adrenergic receptor agonists
- N-methyl-D-aspartate (NMDA) receptor antagonists

Opioids

Drugs of this classification act on one or more of the principal receptors and their subtypes in the brain. The activity is either stimulation (agonist), partial stimulation (partial agonist) or blocking (antagonist) of the receptor. Stimulation of some receptor types may produce unwanted side effects (e.g., respiratory depression) and so the goal of manufacturers is to produce opioids that give good analgesia without the side effects. Some of these drugs are described as agonist/antagonists, indicating that they stimulate some receptors while inhibiting others. One group of opioids, the opioid antagonists, is important for its ability to reverse most of the effects of opioids.

Effects of Opioids: The effect of opioids on any particular system varies markedly depending on the drug and the species of animal. The following effects are seen to a greater or lesser degree with all opioids.

Sedation: Opioids produce sedation in some species but in others may cause increased activity, especially with higher doses (e.g., cats may become excited if given high doses of morphine and rats may show increased activity including pica with higher doses of buprenorphine).

Cardiovascular effects: Usually there is slowing of the heart (bradycardia) and a fall in blood pressure (hypotension). Dilation of peripheral blood vessels, as well as changes to the heat regulation centre in the hypothalamus, may contribute to heat loss and result in hypothermia.

Respiratory effects: Respiration is usually depressed through reductions in respiration rate and tidal volume with a decrease in the respiratory centre sensitivity to carbon dioxide. Some opioids inhibit ciliary activity in the trachea and this may be significant for an animal recovering from anaesthesia.

Gastrointestinal effects: Gastrointestinal propulsive movements (peristalsis) are reduced. Appetite is suppressed and animals may be unwilling to eat.

Immune system effects: Opioids have been shown to have subtle effects on the immune system (e.g., suppression of cytotoxic activities of natural killer cells).

Analgesia and pain tolerance: This is due primarily to stimulation of μ receptors although other receptors are known to have analgesic effects. All of the commonly used opioid analgesics are μ receptor agonists or partial agonists. The effects of opioids described above do not represent any single drug or animal species. There is considerable variation between species and among the different opioids. For this reason, it is important to consult with a veterinarian.

As with other drugs, the actions described are for normal healthy animals. Pre-existing conditions may increase the level of the responses and may result in severe reactions in the animal. Care should be taken to identify any potential side effects in compromised animals.

Duration of Action of Opioids

The effects of opioids are quite short in animals following a single injection (one to three hours for most drugs, with species variation). Buprenorphine may provide effective analgesia for a longer period of time.

Routes of Administration of Opioids

Opioids are usually given by subcutaneous injection but may be given by other routes, including intravenously. Patches impregnated with the opioid fentanyl are available to provide continuous absorption of the drug through the skin over a prolonged period. Epidural use of opioids provides prolonged analgesia in some species, including man, without the usual side effects. Epidural administration of drugs is difficult in small animals. (Link to diagram of epidural injection). Opioids may also be given orally, but their effectiveness is lessened by the degree of metabolism associated with the first pass through the liver. Buprenorphine has been incorporated into instant jelly powder such as Jell-O® for administration to rats.

Opioids in Combination with Other Drugs

Opioids are sometimes administered in combination with other drugs and the combined effects may or may not be beneficial. For example, fentanyl may be combined with the tranquilising drug droperidol or fluanisone to provide short-term anaesthesia. However, the effect of the fentanyl is of much shorter duration than the tranquilliser and so the animal may remain sedated for quite a long time but not have the benefit of the analgesia. Care should be taken when giving an opioid with any other drug which depresses respiration or encourages heat loss because the effect of the two will be more profound than for either alone.

Adverse Reactions Caused by Opioids

The most life-threatening effects of opioids involve the depression of the respiratory and cardiovascular systems. These are particularly important if the opioids are being used in conjunction with other drugs known to have similar effects (e.g., anaesthetic agents). The loss of body heat that occurs when opioids are used may further compromise the respiratory and cardiovascular systems and for this reason, animals should be kept warm when they are recovering from anaesthesia, with or without opioids. Some animals respond to opioids with excitation, rather than sedation. In these species (e.g., swine, sheep) the occurrence of convulsions would also represent a life-threatening situation. Specific antagonists to the opioids may be used to counteract the respiratory and cardiovascular depression. Naloxone, for example, may be used but the analgesic effects of the opioids will also be reversed.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs reduce pain by interfering with the production of prostaglandins from arachidonic acid. Prostaglandins, produced at a site of inflammation, sensitize pain receptors in the area. NSAIDs block prostaglandin production from arachidonic acid through the inhibition of the enzymes cyclo-oxygenase 1 and 2 (COX-1 and COX-2). COX-1 occurs normally in the body e.g., in the stomach and kidney, while COX-2 is produced at sites of inflammation. It is desirable to inhibit COX-2 only but most of today's NSAIDs block both enzymes, leading to some undesirable side effects. There are now some selective COX-2 inhibitors on the market.

Effects of NSAIDs

NSAIDs provide analgesia for mild to moderately painful conditions, although their effect on visceral pain is considered to be poor. As with the opioids, different animals react differently to NSAIDs. NSAIDs have two other desirable effects, namely they reduce fever and inflammation. These effects, along with fewer side effects than the opioids, have led to the widespread use of NSAIDs for treating acute or chronic pain (e.g., headaches or arthritis). There are few effects on the cardiovascular or respiratory systems.

Gastric ulceration is possible with most NSAIDs especially when given orally. This effect is least with p-aminophenol derivatives of which acetaminophen (Tylenol©) is the best known. Acetaminophen has the least anti-inflammatory activity of the NSAIDs.

Interference with platelet aggregation occurs with all NSAIDs. It persists for the life span of affected platelets following acetylsalicylic acid (aspirin) administration. This effect can result in prolonged bleeding but it is useful in reducing intravascular clotting in some studies. Interference with prostaglandin mediated renal function occurs because the NSAIDs block prostaglandin production in the kidneys (and in the gastric mucosa) where prostaglandins are important for normal function. Animals with already impaired renal function may be pushed to renal failure following the administration of NSAIDs in the event of fluid or blood loss.

Duration of Action of NSAIDs

The duration of action depends on the effect being considered and the specific NSAID. For the more commonly used NSAIDs (e.g., flunixin, ketoprofen, meloxicam) the analgesic effect may last for about 24 hrs. There are species differences also in the excretion of NSAIDs and so veterinary advice should be obtained before long-term therapy is initiated.

Routes of Administration

NSAIDs may be given by oral, intramuscular and subcutaneous routes. It is often convenient to give these drugs to small animals in their drinking water. However, in some cases, the taste may discourage the animals from drinking normally and so the required dose may not be ingested.

NSAIDs in Combination with Other Drugs

NSAIDs are seldom given in combination with other drugs in animal care although there are some products available for human use (e.g., acetaminophen plus codeine for more severe pain or acetaminophen plus pseudoephedrine for cold symptoms). However, care should be taken when giving an NSAID with some other drugs that have complementary effects. For example, NSAIDs may cause gastric ulceration and this will be made worse if the animal is receiving a corticosteroid at the same time. Similarly, the use of an NSAID at the same time as other anticoagulation therapy may result in unexpected bleeding.

Adverse Reactions to NSAIDs

The major adverse reactions to NSAIDs given at therapeutic doses come from their ability to cause gastric ulceration and kidney toxicity. This varies from drug to drug and from animal to animal. Animals with gastric ulceration may show signs of abdominal pain and have blood in their feces, however these signs may not be obvious so appropriate monitoring is necessary. These problems are more frequently seen with prolonged administration of NSAIDs. Overdoses of NSAIDs may also include respiratory signs and persistent bleeding due to platelet inhibition.

Local Anaesthetics

Local anaesthetics provide pain relief by blocking pain stimuli from reaching the central nervous system (brain and spinal cord). They differ from the previously discussed opioids and NSAIDs in that they abolish pain rather than diminish it and make it more tolerable. However, they are limited in their usefulness by the need to reach the activated pain receptors or the nerves leading from these receptors to the brain or spinal cord. An advantage of local anaesthetics is their local activity with few systemic effects. This allows for local pain relief without distorting other physiological systems that could interfere with the experiment.

The primary use of local anaesthetics in analgesia therapy is in the relief of pain in the skin. Wound edges infiltrated with local anaesthetics provide relief for up to about six hours after surgery, the time over which the acute pain of surgical wounds is at its greatest and when there is the greatest need for pain relief. Local anaesthetics may also be infiltrated around nerves if the

opportunity arises. Intercostal nerves, for example, may be blocked to relieve pain following a thoracotomy and to permit better respiration.

Duration of Effects

Local anaesthetics last for up to six hours, depending on the agent. The effects will be prolonged if the preparation included epinephrine. Topically applied local anaesthetics may last for less than one hour.

Routes of Administration

Local anaesthetics may be given by several different routes depending on the objectives. Local infiltration may be used to block receptors in the skin and underlying tissues, or to block nerves coursing through the area. In the latter case, anaesthesia (and paralysis) is provided at a site remote from the injection site. Topical application on mucous membranes or subcuticular structures will effectively block receptors in these areas. For example, local anaesthetic sprays are used to block receptors on the vocal cords to prevent spasm during endotracheal intubation. When given into the spinal epidural or subarachnoid spaces, all activity in the nerves will be blocked, so that there will be a loss of sensation and a loss of motor function.

Local anaesthetics are poorly absorbed through intact skin. One preparation that is absorbed through skin is a mixture of prilocaine and lidocaine, however absorption is relatively slow and anaesthesia is limited to about five millimeters under the skin. This is enough to anesthetise the cutaneous receptors. The preparation requires a minimum of 30 minutes to penetrate the skin and will require longer achieving maximum penetration. This is effective when applied to the surface of the rabbit's ear over the artery or vein and wrapping with an occlusive bandage for 30 minutes before injecting or taking a blood sample.

Local Anaesthetics in Combination with Other Drugs

Frequently epinephrine is added to local anaesthetics to cause local vasoconstriction and to slow the uptake of the local anaesthetic and increase the effective duration. Although the amounts of epinephrine are small, they may be sufficient to cause an elevation of blood pressure and heart rate. This effect is well recognized by dentists who use this type of preparation.

Adverse Reactions to Local Anaesthetics

Overdoses of local anaesthetics may cause convulsions in people and animals. In general, the more potent the anaesthetic, the lower the toxic dose. Procain, prilocaine, lidocaine have low relative anaesthetic potencies and high toxic doses while tetracaine and bupivacaine have a high relative anaesthetic potency and low toxic doses. Toxic doses vary between animal species and range from 1-5 mg/kg to 15-25 mg/kg. These figures usually refer to local anaesthetics injected intravenously; however, toxic levels may be achieved following administration by other routes.

Special care must be taken when giving local anaesthetics to small laboratory animals, as it is very easy to exceed the toxic dose. Injectable local anaesthetics come in solutions of 0.5-5.0%. Even the lowest concentration has 5mg/ml and for the least toxic local anaesthetic, 0.1 ml could be toxic for a 20g mouse. Inadvertent intravenous injection of local anaesthetic may cause a decrease in cardiac function with a fall in blood pressure.

Summary of Major Effects of the Above Three Groups of Analgesic Drugs

The following table summarizes the major effects of the three main groups of pain relieving drugs. These are general effects and are applicable, more or less, to all of the drugs in each group. However, they should be considered guidelines only. More detailed descriptions will be found in pharmacology texts or in texts dealing with pain relief. A veterinarian should be consulted to assist in the selection of the most appropriate analgesia regimen.

Table: Summary of Major Effects of Analgesic Drugs

	Opioids	NSAID	Local Anaesthetics
	For severe pain	For mild to moderate level pain and for chronic pain	Block all painful stimuli for duration of anaesthesia
Nervous System	Sedation depending on drug, dosage and species; may cause excitation	No effects at normal doses	No sedation; excitation and convulsions with overdose
Cardiovascular	Fall in blood pressure and heart rate; dilation of peripheral blood vessels	No general effect; some may cause platelet changes and a possibility of bleeding	May cause some vascular changes due to added epinephrine
Respiratory	Depressed respiration rate and depth; cilia activity in trachea inhibited	No general effect; overdoses may affect respiration	No effect unless nerves associated with respiration are involve
Gastrointestinal	Appetite suppression; gastrointestinal movements reduced	May cause ulcers in stomach	No effects
Immune system	Subtle effects on some cells of the immune system	May inhibit the immune system	No effects demonstrated
Other	Behavioural changes	Hypersensitivity	

Alpha 2-Adrenergic Receptor Agonists

The alpha2-adrenergic receptor agonists have been used extensively in animals to supplement other anaesthetic agents and to provide increased analgesia. While they provide sedation in most species, the level of analgesia is quite variable, depending on the species, and

the dose of the drug. Alpha2-adrenoreceptors are found throughout the body, particularly in the vascular system. Stimulation of these receptors results in an initial increase in blood pressure followed by a fall in blood pressure and heart rate. This lowering effect on blood pressure and heart rate is one of the important side effects limiting the use of these drugs to the healthiest animals. Respiration rates are reduced and this results in an elevation of carbon dioxide and a lowering of oxygen in the blood.

The most commonly used drugs of this group are xylazine and medetomidine. They are sometimes used in combination with other drugs (e.g., ketamine) to produce general anaesthesia (although it is preferable to use inhalation anaesthetics in most cases). Specific antagonists are available (e.g., atipamezole) so the depressant effects on the cardiovascular systems and the respiratory systems can be reversed if clinical problems arise.

NMDA Receptor Antagonists

N-methyl-D-aspartate (NMDA) receptors are important for the transmission of some aspects of pain in the central nervous system. In particular, they appear to be involved in the development of hypersensitivity that accompanies injuries or inflammation.

The main NMDA receptor antagonist in use at present is Ketamine. It is used as an anaesthetic agent in conjunction with other analgesics, particularly the alpha-2 adrenergic agonists. Less than anaesthetic doses are required to block central sensitisation but the duration of action is short and it is not yet a practical means of controlling pain. Dextromethorphan is also an NMDA receptor antagonist but its use has been primarily as a cough suppressant.

The NMDA receptor antagonists prevent the development of wind-up and may also prevent the direct transmission of pain from the viscera.

Ketamine is the only commonly used member of this group of drugs. It is an anaesthetic with relatively poor analgesic qualities. It has not been used extensively to provide pain relief, for example, after surgery because of its short duration of action. Dextromethorphan, commonly used as a cough suppressant, also blocks NMDA receptors and may have a role in pre-emptive analgesia. (Articles on pre-emptive analgesia may be found in a number of journals, particularly those that deal with pain and anaesthesia.)

Administration of Analgesic Drugs

These drugs may be given by a variety of routes. The route of administration and the frequency should not be stressful to the animal. They no more enjoy getting injections than we do. The volume of injections should be considered. Very small volumes to very small animals increase the risk of inaccuracies and the chance of an accidental overdose, thus a dilution of the drug may be needed before it is given to the animal. Large volumes injected into muscles may be painful and so cause the animal more stress. The following website has some useful information on recommended volumes to be given by a variety of routes to research animals. These volumes are considered to be the maximum that should be given in one site.

Legal Requirements Associated with Use of Analgesics

Opioids: Many of the opioids are very potent compounds that have the potential to be addictive. They are controlled drugs. Only qualified persons may prescribe them. Careful record must be kept of each dose given. The records are subject to examination by the inspectors from the Office of Controlled Substances of Health Canada.

NSAIDs: Many NSAIDs are available as over-the-counter drugs (e.g., aspirin™, acetaminophen). Some of the newer compounds may require a prescription for acquisition. Although there is not a legal requirement to keep a record of administration, this should be standard practice.

Local anaesthetics: Local anaesthetics are available on prescription. Although there is not a legal
requirement to keep a record of administration, this should be standard practice.

The alpha2-adrenergic receptor agonists: the alpha2-adrenergic receptor agonists are available on prescription. Although there is not a legal requirement to keep a record of administration, this should be standard practice.

NMDA receptor antagonists: The NMDA receptor antagonists are available on prescription.

Although there is not a legal requirement to keep a record of administration, this should be standard practice.

Summary Statement

The relief of pain both in people and animals is an inexact science. Evidence of pain is sometimes difficult to demonstrate but the relief of that pain may be even more difficult to confirm. There are many analgesic drugs and their effects differ from species to species and even within a species. The side effects of the drugs may make it difficult to be certain that pain has been relieved. Nevertheless, we must try to relieve pain, particularly that which we have caused.