

Pharmacology-Premedication

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Introduction

- Preanesthetic medication or ‘premedication’ is used to help both the anesthetist and the animal.
- Premedication implies administration of sedatives, tranquilizers and analgesics with or without anticholinergics before anesthetic induction.
- Premedication is aimed to
 - relieve anxiety thus apprehension, fear and resistance to anesthesia
 - counteract unwanted side effects of agents used in anesthesia
 - reduce the dose of anesthetic.
 - provide extra analgesia
- Modern methods of obtaining balanced anesthesia have “clouded the issue” as to the aims and the exact nature of premedication, because they have, to some extent, made difficult the definition of anesthesia. For example, if a low dose of medetomidine and ketamine combination is given IM to a cat then, once the cat is sedated prior to anesthetic induction/maintenance, this mixture is a premedicant. However, if a high dose of medetomidine and ketamine combination is given IM and the cat becomes anesthetized, is the mixture still a premedicant?
- The definition is unimportant, as long as the part which each drug (premedicant or anesthetic) plays in the production of suitably balanced anesthesia, and in the reduction of unwanted side effects.
- The sedative and anxiolytic drugs play the major role in premedication by improving the quality of anesthesia and recovery and counteracting unwanted side effects such as ketamine-induced muscle rigidity.
- The type of sedative drug chosen for premedication depends on a variety of factors such as species, health status, procedures and age.
- Anticholinergics such as atropine and glycopyrrolate may be used as premedicant to avoid excessive salivation, bradycardia and hypotension.
- There is no premedicants or combination of drug protocols that can be safely and routinely administered to all patients
- Type of surgery, duration of procedure, anticipated complications, postoperative needs, age, temperament and physical condition should all be carefully considered in the choice of premedicants.
- Sound understanding of premedication pharmacology helps avoid dangerous dosing and choice, and increase the safety of anesthetic management
- In clinical situation, what is most commonly practiced in preanesthetic medication is to provide more than one class of drugs to achieve sedation and analgesia.
- This technique is termed as NEUROLEPTANALGESIA, which is defined as “a state of quiescence, altered awareness, and analgesia produced by the administration of a combination of a neuroleptic agent and a narcotic (opioid) analgesic”.
- This lecture provides a brief pharmacological description of various drugs used as premedicants

Phenothiazines

- Some examples of the phenothiazines in veterinary use are acepromazine, promazine, chlorpromazine, propiupromazine and triflupromazine of which acepromazine is the most commonly used in veterinary medicine.
- Can be given, orally, subcutaneously, intramuscularly, or intravenously.
- Some examples of butyrophenones in veterinary use are droperidol, azaperone and lenperone.
- Although the phenothiazines and butyrophenones differ in chemical structure they share many similar pharmacological properties, so these two will be discussed together.
- These agents are classified as major tranquilizers (neuroleptics).
- They induce sedation by depressing brain stem and the neuronal signal transmission to the cerebral cortex, and also by antagonizing dopamine (a multipurpose neurotransmitter) excitatory receptors through inhibiting dopamine release at the neuronal synapses.
- Major clinical indications for their use are to provide anxiolysis, reduce the concurrently administered anesthetic dose when used as part of pre-anesthetic medication, or provide additional sedation synergistic with other prescribed sedatives or analgesics.

Cardiovascular effects

- A well known side effect is a tendency to cause hypotension due to alpha-1-adrenergic blockade.
- Therefore, its use is contraindicated in shocky, hypotensive, or anemic patients.
- phenothiazines posses antiarrhythmic effects.

CNS effects

- Phenothiazine derivatives induces CNS depression by affecting the basal ganglia, hypothalamus, limbic system, brain stem and reticular activating system.
- They lack any generalized hypnotic effect and do not produce analgesia
- they block dopamine receptors and the action of 5 hydroxytryptamine
- They act centrally on the chemoreceptor trigger zone as well as the vomit center in the medulla to induce antiemesis.
- Thermoregulation is depressed
- Other side effect includes lowering seizure threshold, so avoid using it in patient that is likely to induce seizure (e.g. myelogram).

Respiratory effects

- At therapeutic dose there is negligible respiratory effects
- They may decrease rate, but this is usually compensated with increase in tidal volume, and the minute volume is maintained

- Large dose can depress ventilation
- When combined with opioids and hypnotics, the phenothiazines have additive effect and respiratory depression may occur.

Other physiological effects

- Some skeletal muscle relaxation
- delayed gastric emptying time
- decreased packed cell volume and total plasma protein and increase in plasma volume as a result of peripheral vasodilation and subsequent shifts of extravascular water into the vascular space
- Decreased body temperature as a result of peripheral vasodilation, reduced skeletal muscle tone and depressed thermoregulatory center

Metabolism and excretion

- Biotransformation include oxidation, conjugation with glucuronic acid in the liver
- Metabolites are excreted in urine for several days
- No specific antagonists are available, so depend on metabolism and excretion when overdosed
- Although the manufacturer's recommended dose for acepromazine found in the package insert ranges 1- 2 mg/kg, these doses are rarely prescribed in the clinical situation.
- Most common clinical dose in the dogs and cats ranges between 0.01 to 0.1 mg/kg and doses exceeding this range will simply increase the duration, incidence of hypotension without much benefit in the degree of sedation.

Other useful characteristics

- Most of these agents have relatively long acting duration of drug effect lasting for several hours. Elimination of the drugs is mainly through hepatic metabolism.
- Some owners report unhappily that their dog is still sedate a day after a dose of acepromazine.
- It is more likely easily noticed in larger breed dogs when they are sedate and groggy compared to small toy breeds under similar influence, which explains why the complaints usually come from large breed dog owners.

Butyrophenones

- Three butyrophenone derivatives are used in veterinary medicine: droperidol (Inapsine®), azaperone (Stresnil®), and lenperone HCl (Elanone-V®)
- Butyrophenones have very similar physiologic effects to the phenothiazines
- Droperidol (0.4 mg/ml) is combined with fentanyl citrate (20 mg/ml) to form Innovar-Vet®. The combination has little to no effect on cardiac output, but decreases arterial

blood pressure, systemic vascular resistance and heart rate. This product is no longer marketed in the US.

Benzodiazepines

- These provide minor tranquilization at clinically used dose.
- Diazepam (Valium®), midazolam (Versed®), and zolazepam (in Telazol®) are most commonly used agonist in this class in veterinary practice.
- Although specific antagonists such as flumazenil (Romazicon®) and sarmazenil (Sarmasol®) are available, its use is limited by the expense and lack of enough clinical information.
- Benzodiazepine agonists bind at benzodiazepine receptor sites in the CNS and these receptors potentiate the effects of GABA (gamma-amino butyric acid, an inhibitory neurotransmitter) which lead to enhanced function of chloride ion channel gating.
- The resulting enhanced opening of the chloride ion channel leads to hyperpolarization of cell membranes, making them more resistant to neuronal excitation.
- These mechanisms explain how the central nervous depression is achieved with use of the drugs.
- Despite less degree of sedation compared to more potent sedative (e.g., acepromzinae or alpha 2 agonists) benzodiazepines are favored in animals that are in increased risk of cardiopulmonary failure.
- The cardiopulmonary effect from these drugs is very minimal, although accompanies occasionally mild hypotension and respiratory depression.
- Mild to moderate sedation is achieved, but clinically it is rarely given as the sole sedative. For synergistic effect it is most commonly combined with opioid analgesics (in dogs) or dissociatives (in cats), which provides greater degree of sedation as well as analgesia.
- Other common use of this class of drug is to treat seizure. In some dogs paradoxical excitement or aggression can be observed when given alone, believed to be through disinhibition of suppressed behavior.
- The excitement is seen most notably in hyperactive and young animals, but less frequently in depressed and geriatric animals. Co-administering the drug with opioids or dissociatives should avoid incidence of such adverse behavioral alteration.
- The sedative effect lasts shorter than phenothiazine class drugs, ranging from 30 minutes to a few hours at most.
- The drugs are eliminated due primarily to hepatic metabolism with renal and fecal excretion.

Diazepam

- Physico-chemical characteristics
 - insoluble in water; needs propylene glycol to increase solubility (irritating to tissues, erratic absorption from IM injection, often incompatible with other solutions).

- 0.2 – 1.0 mg/kg IV, SQ in the dog and cat
- IV should be injected slowly to prevent pain and venous thrombosis
- Propylene glycol is a cardiopulmonary depressant and rapid infusion may cause hypotension, bradycardia, and apnea
- the sedative effect varies considerably among individuals

- CNS effects
 - Works primarily on parts of the limbic system, the thalamus and the hypothalamus.
 - It may produce calming, or taming effects in animals, but paradoxical excitement is also a possibility.
 - It is known to be amnesic in human.
 - Anxiety is reduced without marked sedation.
 - Benzodiazepine receptors appear to have wide spread distribution in the brain; however, these receptors appear to be lacking in the white matter.
 - Anti-convulsant.
 - Muscle relaxing effect is believed to occur at the spinal cord level and at the reticular formation of the brain stem.
 - A number of neurotransmitter systems including acetylcholine, glycine, serotonin, gamma-amino butyric acid (GABA) may be involved in the CNS effects produced by benzodiazepines.
 - Could be used as appetite stimulant in cats and dogs

- Cardiopulmonary effects
 - At clinical dose, minimal cardiopulmonary effects prevail
 - High IV dose may produce respiratory depression and decreased blood pressure

- Metabolism and excretion
 - Up to 96 % of diazepam is protein bound
 - Diazepam is metabolized in the liver to N-desmethyldiazepam, 3 hydroxydiazepam and oxazepam, all of which are pharmacologically active
 - Most metabolites go through renal excretion.

Midazolam

- Physico-chemical characteristics
 - It is water soluble and has a pH of 3.5. At a pH above 4.0, it turns into lipid soluble form.
 - It is 2-5 times more potent than diazepam, but the unit cost is still more expensive.
 - The typical clinical dose is 0.1 – 0.5mg/kg in dogs and cats.
 - It has a faster drug onset time than diazepam.

- Due to a good water solubility, it is well absorbed from IM or SQ injections, and physically compatible with many other solutions (unlike diazepam, it lacks the irritant solvent, propylene glycol).
- Cardiopulmonary effects
 - It has similar cardiovascular effect to diazepam with minimal alterations in this.
 - It may be more respiratory depressant than diazepam.
- Metabolism and excretion
 - It is similar to diazepam in this respect.
 - Clinical duration of midazolam is shorter than diazepam, but onset of clinical effects are more predictable.

Zolazepam

- This is only used in combination with tiletamine in Telazol (Class III)
- Each vial contains powder of 250 mg of zolazepam and 250 mg of tiletamine, and typically is reconstituted to make 5 ml solution (therefore 100 mg/ml of zolazepam-tiletamine mixture)
- This mixture is essentially identical to Ketamine-diazepam (Ket-Val) mixture in many pharmacological aspects.
- Their use is popular for exotic species.

Alpha-2 adrenergic agonists

- Examples
 - xylazine (Rompun®)
 - medetomidine (Dormitor®)
 - detomidine (Dormosedan®, Domosedan®)
 - romifidine (Sedivet®)
 - clonidine (Catapres®)
- The alpha 2 adrenoceptor is a subclass of the alpha adrenergic receptors
- The prejunctional inhibitory receptors exist within the sympathetic nervous system.
- Alpha 2 receptors are found in the CNS, gastrointestinal tract, uterus, kidney and platelets.
- Mild analgesia is also achieved.
- Mechanism of action
 - Similar to opioids.
 - When alpha 2 or mu opioid agents are bound to their specific receptors, the membrane G-proteins are activated.
 - Activated G-proteins open potassium channels in the neuronal membrane, hyperpolarizing the neuron.

- The neuron become unresponsive to excitatory input, and blocks the neurotransmission.
- Primary clinical effects are sedation, analgesia and muscle relaxation.
- Good muscle relaxation is usually present. Among the alpha 2 agonists, medetomidine and xylazine are the most commonly used in small animals.
- These drugs provide moderate to heavy sedation. Animals appear very sedate but still respond to stimuli (Beware, aggressive dogs should still be muzzled when handled, and horses may still kick in response to sudden touch).
- Alpha 2 antagonists such as atipamezole (Antisedan®), yohimbine and tolazoline are available to reverse the alpha 2 agonistic side effects such as excessive CNS or CVS complications.
- Cardiovascular effects include initial transient hypertension followed by prolonged hypotension (biphasic changes), bradycardia and second degree atrioventricular block, and decreased cardiac output.
- Respiratory effects include decreased respiratory rate, with a variable effect on tidal volume, but at clinically useful dose it is of minor concern.
- Other effects of clinical importance are increasing blood glucose level, decreasing intestinal motility, increasing urine production, increasing uterine contractions which may lead to premature delivery or abortion, and inducing vomiting.
- The drug's mechanism of action is mainly through its agonist activity at presynaptic alpha-2 adrenergic receptors that results in decrease in release of norepinephrine from adrenergic nerve terminals in CNS and periphery.
- This causes sedation, decreased sympathetic activity, analgesia, and hypotension.
- Main clinical uses are to decrease anxiety, provide chemical restraint with relatively dependable sedation (addition of opioids recommended for more predictable outcome), potentiate effects of other drugs and provide analgesia.
- The duration of action is dose dependent, and typically lasts 10 to 30 minutes of sedation and restraint for xylazine and 1 to 3 hours for medetomidine.
- The drugs are metabolized by the liver, and undergo urinary and biliary excretion.
- One good advantage of this class of drugs is its ability to enable pharmacological reversal with alpha-2 adrenergic antagonists: atipamezole (20- 100 mcg/kg), yohimbine (0.05-0.3 mg/kg) and tolazoline (0.5-1.5 mg/kg)

Xylazine (20 mg/ml or 100 mg/ml)

- A thiazine derivative that has sedative, analgesic and muscle relaxant effect
- Onset of effect is within 3-5 minutes following IV administration, and 5 – 15 minutes following IM administration.
- Typical dose is 0.1 – 1.0 mg/kg in dogs and cats, 0.5 – 2.0 mg/kg for horses, but lower in ruminants in the range of 0.05 – 0.2 mg/kg.
- Analgesic effect is relatively short lived (15-30 minutes), but sedation outlasts this.
- Initial increase in blood pressure is due to intense peripheral vasoconstriction, but this is followed by prolonged hypotension (biphasic BP) due to decrease in sympathetic outflow and decrease of norepinephrine from sympathetic nerve terminal.

- Single therapeutic dose does not induce much respiratory depression, but at large dose and concurrent administration (opioids, inhalants and injectable anesthetics), significant respiratory depression may occur.
- Xylazine causes laryngeal relaxation and cough suppression.
- Vomiting is frequently seen in the cat and the dog due to central alpha 2 activation.
- The thermoregulatory center is depressed and hypothermia is observed.
- Hyperglycemia and glucosuria are due to depressed insulin release in the pancreas.
- Inhibition of ADH release results in diuresis.
- Xylazine goes through extensive hepatic metabolism, and metabolites are excreted mainly in the urine.
- Xylazine has marked emebolic effects and should not be used in the last third of pregnancy (nor at conception: for example in ovum transplants)
- Combining with anticholinergics is not recommended due to excessive hypertension and tachydysrhythmia.

Medetomidine

- It is the most potent and specific of this group
- It has displaced the use of xylazine in the dog and the cat.
- It causes marked ataxia in the horse even at low doses.
- Its alpha-2 to alpha-1 ratio is 1620 in comparison to 160 of xylazine, thus making it approximately 10 times more potent than xylazine.
- Dose is arroximately 5-30 mcg/kg IM, SQ, IV

Detomidine

- It is potent alpha 2 agonist, primarily used in the horse.
- In horses maximum sedation effect is achieved 20 mcg/kg IV (equipotent of 1 mg/kg of xylazine) or 40 mcg/kg IM.
- It has less emebolic effect than zylazine, so is preferred over xylazine in late pregnancy
- Dose requirement is similar for horses and cattle.

Alpha 2 antagonists

- Example
 - atipamezole (Antisedan®)
 - yohimbine (Yobine®)
 - tolazoline (Tolazine®)
 - idazoxan
- Alpha 2 agonistic side effects such as excessive sedation or bradycardia can be reversed using the antagonists.
- Atipamezole has alpha 2 to alpha 1 seletivity ratio of 200 to 300 times higher than yohimbine or idazoxan.
- Equal volume of atipamezole (5 mg/ml) is administered to reverse medetomidine (1 mg/ml).

- Reversal is also possible for other alpha 2 agonists using atipamezole, but is more costly than using telazoline or yohimbin.
- Atipamezole has no activity at beta-adrenergic, histaminergic, serotonergic, dopaminergic, GABAergic, opioid, or benzodiazepine receptors.
- Rapid IV administration is associated with hypotension and excitatory emergence. Slow titrated IV dosing or IM/SQ administration will minimize these.

Opioids

- Detailed pharmacologic information about opioids will be presented in the pain lectures.
- Examples of drugs in this class are morphine, fentanyl, oxymorphone, meperidine, butorphanol, pentazocine, buprenorphine, nalbuphine, and naloxone.
- The drugs bind to opioid receptors in the CNS which usually have inhibitory effects on neurons.
- Opioids are classified into agonist, agonist-antagonists, partial agonist and antagonist depending on the pharmacological effect.
- Main clinical uses are to decrease anxiety, provide sedation/chemical restraint (variable, depends on species, agent and dose), provide analgesia, and decrease doses of other agents for synergism.
- The cardiopulmonary effects include bradyarrhythmias - usually easy to correct with anticholinergics, minimal effect on blood pressure and cardiac output.
- The respiratory depression accompanies with opioid agonist administration and is dose dependent (plateau effect with partial agonists).
- Respiratory rate may decrease or increase and induce compensatory changes in tidal volume. The opioids raise chemoreceptor threshold to P_aCO_2 , thereby further exacerbating the respiratory depression.
- Other effects include vomiting, defecation (initial effect), urinary retention/constipation with continued use, excitatory effects at high doses in some species (cat, horse, pig); best used with neuroleptics to avoid the excitement, reset thermoregulatory center panting in dogs.
- Duration of action depends on the type of agents used as well as dose and route of administration, widely ranging from 30 minutes (fentanyl) to several hours (buprenorphine).
- These drugs are metabolized by the liver (extensive first pass metabolism, hence not very effective orally administered) and excreted in bile and urine.
- The pharmacological reversal of agonists is achieved by antagonistic effects with a pure antagonist (e.g. naloxone), but due to short duration of action, be aware relapse to the agonistic effect (monitor closely, particularly respiratory depression).
- Partial agonists (e.g. butorphanol, nalbuphine) can reverse some of the effects (e.g. sedation, excitement, respiratory depression).
- Combination of opioid with tranquilizer is the most popular practice for sedating or chemically restraining animals (neuroleptanalgesia). These combinations provide heavy sedation and analgesia for minor surgical procedures or allow endotracheal intubation (airway support or anesthetic induction).

- It is noted that patients may be hyperresponsive to noise, so quiet surrounding is desirable.
- Some examples of commonly used combinations are:
 - morphine + acepromazine
 - morphine + diazepam
 - morphine + medetomidine
 - butorphanol + medetomidine
 - butorphanol + diazepam
 - hydromorphone + acepromazine
 - hydromorphone + diazepam
 - hydromorphone + medetomidine
 - oxymorphone + acepromazine
 - oxymorphone + diazepam
 - oxymorphone + medetomidine
 - fentanyl + droperidol
 - etc...

Dissociatives

- The examples of dissociative agents in veterinary use are ketamine and tiletamine.
- These are generally classed as anesthetic agents rather than sedatives but at low doses and particularly used in combination with another sedatives, these can produce very useful premedication particularly in intratable cats or very aggressive dogs.
- More detailed pharmacologic information will be provided in “Induction Agent and Dissociates” lecture.
- The mechanism of action is through its NMDA (n-methyl-d-aspartate) – glutamate antagonistic effect which inhibits neurotransmission, and causes a variety of pharmacological effects. It is described as having cataleptic, analgesic and anesthetic action.
- Spontaneous involuntary muscle movement and hypertonicity are not uncommon.
- The dissociative agents are highly abused, and there have been sporadic reports of break-ins of the veterinary practices.

Ketamine

- This is the most commonly used dissociative used in veterinary medicine
- At sedative doses (5-10 mg/kg) the effects of ketamine alone on the cardiovascular system is minimal.
- Although ketamine can be used by itself in small animals as a sedative for procedures which do not require muscle relaxation, for example radiography, it is commonly combined with other sedatives for synergistic effect and to counteract muscle rigidity.
- The useful adjunct sedatives include, but are not limited to, acepromazine, xylazine, medetomidine, diazepam and midazolam.

Anticholinergics

- Its vagolytic effect induces decreased salivation, bronchodilation, decreased gastrointestinal motility and tachycardia.
- Its routine use as premedication is not recommended, but still is a useful agent in procedures that may cause vagal stimulation (e.g., ocular surgery)
- Its use is contraindicated in patients with preexisting tachycardia.

Atropine sulfate (0.54 mg/ml for small animals, 2 or 15 mg/ml for large animals)

- Atropine is belladonna alkaloid that blocks acetylcholine at the postganglionic terminations of cholinergic fibers in the autonomic nervous system
- Atropine does not inhibit Ach release
- When administered rapidly IV, initial bradycardia may be observed due to vagal stimulation, which is then followed by cholinergic blockade and tachycardia.
- Atropine crosses blood-brain barrier and placenta barrier
- Relaxation of iris sphincter muscle induces dilation of the pupils. Therefore, it is contraindicated in patient with glaucoma and synechia.
- Works as antidote for overdose of cholinergic drugs such as neostigmine and edrophonium.
- Works as antidote for organophosphate poisoning
- Typically used in the dose range of 0.02 – 0.04 mg/kg IV, IM, SQ in dogs and cats, but at a lower dose than 0.02 mg/kg in large animals.
- Duration is between 60 – 90 mins.
- Rabbits and rats have atropinase in the liver, so higher dose is needed in this species.

Glycopyrrolate (Robinul-V® (0.2 mg/ml))

- Large synthetic quaternary ammonium molecular size prevents easy crossing of the blood-brain barrier and placental barrier.
- Therefore, it may be a better choice for CNS diseased patients or in pregnant animals than atropine.
- The mechanism of action is similar to atropine and duration is longer, lasting 90 – 180 minutes.
- Typical dose is in the range of 0.005 – 0.01 mg/kg, IV, IM, SQ.
- Tachycardia is not as prevalent as seen with atropine, and is less arrhythmogenic.
- It is more expensive than atropine.

Clinical Notes

- A number of agents and techniques are available for premedicating animals, however obviously the choice would depend on the patient's physical state and the type of procedure.

- It must be remembered numerous combinations exist depending on the circumstances, and a good review of the major pharmacological features of the drugs, as well as the important concerns for the fragile patient will help guide the practitioner in avoiding complications.
- In animals under premedication that are still conscious, anesthetic monitoring is not usually carried out to the standard applied in animals under general anesthesia (see Anesthetic monitoring notes).
- However vigilant monitoring of cardiopulmonary system is encouraged as often as possible in severely sedate or unconscious animals under the influence of premedicants.