Pharmacology-Premedication

Lyon Lee DVM PhD DACVA

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

Phenothiazines

Some examples of the phenothiazines in veterinary use are acepromazine, propazine, chlorpromazine, propiopromazine 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 phenothazines 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 the anesthetic medication, or provide additional sedation synergistic with other prescribed sedatives or analgesics.

Caridovascular 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

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 at 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 dissociates (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
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- Due to a good water solubility, it is well absorbed from IM or SQ injection, 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®)
- deaTj EM4osedan®, >>B1j EM4osedan®)
- rTj EM4(a)a1f(a)a197 0 Tm [(T)ID 62Se
- clonidine (Catapres®)

The alpha 2 adrenoceptor is a subclass of the alpha adrenergic receptors
The prejC /uncl 7 0 Tmh7receptors exist within the sympathetic nervous system.
Alpha 2 recep3C /Trs are found 7 0 Tm 3C /he CNS, gas3C /rT7 0 Tm3C /esl 3C /racusay platelets.
Mild analgesia is also achieved.
Mechanism of action
- Sr to opioids.
- When alpha 2 Tr j EM4u opiagen3C /s are bound 3C /T 3C /heiC /r speca(a)a1crecep3C membrane G-proteins are activated.
- Aivated G -pro3C /e open po3C /ass7 0 Tuj EM4 chanm [(TlC /s)-1(7 0 Tm 3C /he)4(m hyperpolC /ar(a)a1zi 3C /he meuron.

- 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 vomition.
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: atipamizole (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 (~30 minutes), but sedation outlasts this.
Initial increase in blood pressure is due to intense peripheral vasoconstriction, but this is followed byprolonged hypotension (biphasic BP)

Single therapeutic dose does not induce much repiratory 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 ecbolic 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 alpha2 to alpha1 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 ecbolic 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, serononeric, 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 CO_2, thereby further exacerbating the respiratory depression.
Other effects include vomition, 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 rout 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

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

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.