UNDERSTANDING THE UNWANTED SIDE EFFECTS OF THE ANESTHESIA DRUGS
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All of the anesthetic drugs produce desired effects and can positively contribute to patient care. Unfortunately, they also produce dose dependent, unwanted side effects. It is important to understand what the most common unwanted side effects are and how to formulate protocols that limit the potential for adverse side effects to contribute to patient morbidity and mortality.

PRE-ANESTHETIC DRUGS

ANTICHOLINERGIC DRUGS

Anticholinergic drugs (glycopyrrolate, atropine) are administered to treat vagal induced bradycardia or to prevent the development of vagal induced bradycardia in the peri-anesthetic period. Routine administration of anticholinergic drugs in pre-medication protocols is no longer recommended; however, use of these drugs on a case by case basis is still indicated. The co-administration of anticholinergic drugs and dexmedetomidine is contraindicated due to the development of myocardial hypoxemia.\(^1,2\)

Glycopyrrolate is less arrhythmogenic than atropine while still preventing bradycardia precipitated by other drugs. It decreases salivary and respiratory secretions, does not cross blood-brain barrier or placenta. Glycopyrrolate may cause tachycardia (do not use in patients with pre-existing tachycardia). The traditional dose is 0.01 mg/kg SQ, IM, IV in dogs and cats. However, if administered IV, only 0.0025 mg/kg may be needed for an appropriate effect. Vagal inhibition lasts 2-3 hours and secretions are decreased up to 7 hours. Application of eye ointment immediately after administration and every two hours for seven or eight hours after Glycopyrrolate may be beneficial at preventing corneal damage, especially if blink reflexes are obtunded by sedatives (ketamine) or the primary problem. Glycopyrrolate is compatible in the same syringe with butorphanol, oxymorphone, hydromorphone, and midazolam.

Atropine also decreases salivation, prevents bradycardia and will precipitate bronchodilation and decrease GI secretions and motor function. The duration of effect of atropine is approximately 1 hour. Atropine will cross the blood-brain barrier and placenta (overdose may cause seizure) and may cause profound tachycardia (do not use in patients with pre-existing tachycardia). Do not use atropine in patients with glaucoma or synechia. Atropine also decreases tear formation (especially in dogs) for several hours.
after administration. Traditional dosing of atropine is 0.04 mg/kg SQ, IM and 0.01 mg/kg IV in dogs and cats. If administered IV, only one-fourth the calculated dose may be necessary to achieve the desired effect without causing profound tachycardia. Atropine is compatible in the same syringe with butorphanol, oxymorphone, hydromorphone, and midazolam. Atropine Overdose should be treated with Physostigmine 0.02 mg/kg slowly IV.

Opioid analgesics are appropriate additions to any sedation protocol because they will balance the combination, providing mild to moderate sedation and appropriate analgesia. Opioid analgesics preserve cardiovascular stability better than other sedative/analgesics (alpha-2 agonists) and have a low occurrence of unwanted side effects when dosed appropriately. Cerenia® (maropitant) has been shown to obtund opioid induced vomiting when administered SQ 45 minutes prior to opioid premedication.

Morphine provides excellent analgesia in moderate to severe pain states and has very little effect upon cardiovascular function. It may precipitate panting in dogs and may cause bradycardia at higher doses. If bradycardia occurs, it is easily treated with an anticholinergic. Morphine must be given slowly IV as it may cause histamine release and precipitate hypotension. In dogs, morphine is traditionally dosed 0.5 to 2 mg/kg IM and 0.05 to 0.2 mg/kg SLOWLY IV. Duration of analgesia is 2 to 4 hours. Morphine can also be administered as a constant rate infusion (CRI) at 1 to 3.5 mcg/kg/min IV. In cats, morphine has been traditionally dosed at 0.1 to 0.4 mg/kg IM. Dysphoria in cats due to opioid administration is rare when opioids are dosed appropriately, especially if a balanced drug protocol is used. Withholding analgesic drugs (opioids) because of the minimal potential for dysphoria lacks validity. Cats should receive opioid analgesics when they are an appropriate part of the sedation/analgesia protocol as determined by the presenting problem. Morphine can be partially reversed with butorphanol 0.4 to 0.6 mg/kg slowly IV and completely reversed (including analgesia) with Naloxone 0.04 mg/kg IM or IV.

Oxymorphone and Hydromorphone also provide excellent analgesia, mild sedation, and are appropriate to include when moderate to severe pain is present. They have little effect upon cardiovascular function when used at appropriate doses. Both drugs may precipitate panting in dogs and may cause bradycardia at higher doses. Bradycardia is easily treated with an anticholinergic. Both drugs are dosed at 0.05 to 0.2 mg/kg SQ, IM, IV in dogs and cats. Duration of analgesia is 4 to 8 hours. These drugs are compatible in the same syringe with: atropine, glycopyrrolate, and midazolam.
Inadvertent overdose may be partially reversed with butorphanol 0.4 to 0.6 mg/kg slowly IV or completely reversed (including analgesia) with Naloxone 0.04 mg/kg IM or IV.

Fentanyl may be appropriate in a sedation protocol that is best administered as a CRI. After a loading dose of 5 to 20 mcg/kg slowly IV, the CRI is started at 2 to 10 mcg/kg/min IV. Fentanyl provides excellent analgesia in moderate to severe pain states and has very little effect upon cardiovascular function. It may precipitate panting in dogs and may cause bradycardia at higher doses. If bradycardia occurs, it is easily treated with an anticholinergic. After a single IV bolus, fentanyl’s duration of effect is less than 30 minutes, making it better suited for administration by CRI.

Buprenorphine is a partial mu opioid agonist with a reasonably long duration of effect, between 4 and 6 hours. Analgesia and sedation are mild at best. It is a good choice if sedation and analgesic needs are minimal. For patients requiring moderate to heavy sedation/analgesia, morphine, oxymorphone, hydromorphone, and fentanyl are better choices.

Butorphanol is an opioid mu antagonist that provides sedation only and will interfere with analgesia/sedation provided by other opioids and it may reverse any analgesia provided by endogenous opioids. If a patient needs sedation only and no analgesia is required, butorphanol may be a good choice. Doses for sedation in dogs are between 0.2 to 1 mg/kg IM or IV. Sedation in cats is minimal at best and a more potent opioid (oxymorphone, hydromorphone) are better choices when devising balanced protocols for cats. Sedation may last 1 to 2 hours. Butorphanol is also used as a cough suppressant. Butorphanol is a good sedative and doses of other tranquilizers can be markedly reduced or eliminated when it is included in balanced protocols. It has very little effect upon cardiovascular function. Butorphanol will partially reverse analgesia provided by endogenous opioids (endorphins) and should be used cautiously in patients with pain present longer than 24 to 48 hours. Butorphanol may actually increase pain in these patients. Butorphanol is compatible in the same syringe with atropine, glycopyrrolate, and midazolam.

Acepromazine provides tranquilization, sedation, decreased epinephrine induced myocardial arrhythmias, has antiemetic and weak antihistiminic properties. Acepromazine has no intrinsic analgesic properties, it will provide muscle relaxation to augment analgesia provided by opioids but caution must be exercised because this drug can obtund a patient’s ability to indicate that it is experiencing pain. Acepromazine should not be used in hypovolemic patients and patients in shock. Acepromazine should
be used cautiously in patients with cardiac dysfunction, decreased cardiac reserve, hepatic dysfunction, or general debilitation. Pediatric patients are quite susceptible to the hypotensive effects of acepromazine. In geriatric patients, very low doses have been associated with prolonged drug effects. Low doses have also resulted in prolonged recoveries in large and giant breed dogs. Acepromazine precipitates profound hypotension, hypothermia, alpha-adrenergic blockade causing epinephrine reversal (circulatory collapse may occur in catecholamine loaded patients), has a slow onset of action: may take 30 to 60 minutes for peak drug effects, decreases PCV by up to 50% within 30 minutes of administration, decreases ventilation, potentiates organophosphate toxicity, and can be easily overridden by catecholamines, making it unpredictable when used as a sole restraining drug. Traditional doses of acepromazine in dogs and cats are between 0.02 to 0.075 mg/kg SQ, IM, or IV up to a maximum of 3 mg regardless of patient size. Duration of sedation in normal patients is 8 to 12 hours. In debilitated patients duration may be longer than 24 to 48 hours. Dosing should be markedly reduced in unstable patients if acepromazine is the only tranquilizer available. Acepromazine is compatible in the same syringe with: atropine, glycopyrrolate, butorphanol, oxymorphone, hydromorphone, and midazolam. Acepromazine Overdose should be treated with Phenylephrine 0.15 mg/kg (0.075 mg/lb) slowly IV.

Benzodiazepine tranquilizers include diazepam and midazolam. These drugs have virtually no effect upon cardiac function and have a reasonably short duration of effect making them more suitable tranquilizers than the phenothiazines. They possess no intrinsic analgesic activity. When formulating balanced drug protocols, the addition of an opioid analgesic is appropriate when using a benzodiazepine. Sedation will be more predictable and patients are more comfortable. The benzodiazepines will disinhibit and patients may become unruly if benzodiazepines are used alone in patients without altered mentation. Inhibitory behaviors tend to keep our veterinary patients under control. Disinhibition by benzodiazepines is similar to how alcohol disinhibits people; their behavior can become quite unruly after a few drinks. Therefore, it is better to use these drugs within a balanced protocol that includes drugs with other mild to moderate sedative properties (i.e. opioids). The benzodiazepines can be reversed with Flumazenil 0.1 mg/kg (0.05 mg/lb) IV.

Diazepam is used primarily for sedation and to relieve status epilepticus. It is only useful if administered IV. It should be drawn immediately prior to administration because it adsorbs to plastic syringes within a few minutes. After a short time, the diazepam has
adsorbed to the plastic and only the propylene glycol carrier base is administered to the patient. Because of the propylene glycol base, diazepam is not compatible when physically mixed with any other drugs or solutions. Traditional dosing of diazepam in dogs and cats is between 0.1 to 0.6 mg/kg IV. The propylene glycol base is not water soluble and will not permit the uptake of diazepam after SQ or IM injection. Duration of effect is 20 to 30 minutes. Because the benzodiazepines decrease May cause excitement if used alone.

Midazolam is water soluble and is suitable for both IV and IM administration. Midazolam is rapidly and almost completely absorbed after IM administration. Duration of effect is 20 to 30 minutes. Traditional doses of midazolam for dogs and cats are between 0.07 to 0.4 mg/kg IM or IV. Midazolam is compatible in the same syringe with atropine, glycopyrrolate, butorphanol, oxymorphone, hydromorphone and acepromazine.

Alpha-2 Adrenergic Agonists have both sedative and analgesic properties. The duration of analgesia is considerably shorter than the sedative effects. The use of anticholinergic drugs with alpha-2 agonists is contraindicated due to the development of myocardial hypoxemia. Both xylazine and dexmedetomidine have been shown to significantly decrease arterial oxygenation. After dexmedetomidine administration IV, pulmonary hypertension with or without pulmonary hemorrhage has been shown to occur at doses as low as 0.002 mg/kg IV. Alpha-2 agonists can be overridden by excitement and are not reliable as sedatives on their own. These drugs can cause profound bradycardia, profound hypertension followed by profound hypotension, can cause pulmonary edema, higher doses have a prolonged duration of effect, profound respiratory depression and cyanosis may occur, they precipitate hypothermia, diuresis and hyperglycemia, cause muscle twitching, second degree heart block, and circulatory failure can occur in apparently healthy animals. The alpha-2 agonists are not considered appropriate drugs for use in unstable patients because of the multitude and severity of potential unwanted side effects unless doses are reduced considerably. These drugs are reversible with Atipamizole 0.04 to 0.5 mg/kg in both dogs and cats.

DexMedetomidine is a highly selective alpha-2 agonist compared to xylazine. It is considered to have a relatively narrow margin of safety because doses two times the published dose will cause circulatory collapse. Traditional doses of dexmedetomidine in dogs and cats are between 0.0005 to 0.005 mg/kg SQ, IM, or IV. This dosing in stable, healthy patients may decreases the amount of inhalant anesthetic necessary to maintain unconsciousness by up to 50%. In unstable patients, doses may need to be reduced to
0.00005 to 0.00025 (0.05 to 0.25 mcg/kg) to prevent severe unwanted side effects. Dexmedetomidine is compatible in the same syringe with butorphanol, oxymorphone, hydromorphone and ketamine. Dexmedetomidine overdose should be reversed with Atipamizole 0.04 to 0.5 mg/kg ½ IV and ½ IM.

Xylazine hydrochloride is a mixed alpha_2/alpha_1 agonist with an alpha_2:alpha_1 selectivity ratio of 160:1. It was first synthesized in the 1960's as an antihypertensive but was found to have potent sedative effects in animals. Xylazine can be administered IP, SQ, IM, or IV. Xylazine is supplied in 20 mg/ml and 100 mg/ml concentrations and care needs to be exercised by being certain of the product concentration before drawing xylazine into a syringe. The onset of action following SQ or IM administration is approximately 10 to 15 minutes, and following IV administration is 3 to 5 minutes.

Xylazine should be used cautiously in patients with pre-existing cardiac disease and those with ventricular arrhythmias, hypotension, shock, respiratory dysfunction, hepatic or renal insufficiency, pre-existing seizure disorder or if debilitated. Because the alpha_2 agonists may increase uterine tone, xylazine should not be used, or be used with extreme caution, during pregnancy. Xylazine depresses thermoregulatory mechanisms and either hypothermia or hyperthermia may occur depending upon ambient temperature. This effect may last beyond the sedative and analgesic effects of xylazine. Patients may be aroused by sharp auditory stimuli and fractious patients may not be adequately sedated with xylazine alone. Increasing the dose of xylazine does not generally increase the level of sedation but prolongs the duration of effect.

Xylazine's effects upon the cardiovascular system include an initial increase in total peripheral resistance with increased blood pressure followed by a longer period of hypotension. Bradycardia may be seen and some patients develop second degree heart block. Cardiac output may be decreased up to 30%. Xylazine has been shown to potentiate the arrhythmogenic effects of epinephrine. Respiratory function is usually not effected with clinically useful doses of xylazine. Pulmonary edema has been reported after xylazine administration in some species.

Decreased gastroesophageal sphincter pressure has been reported in dogs following xylazine administration and may increase the likelihood of gastric reflux. Vomiting is common in cats and is usually seen within 3 to 5 minutes after administration. Xylazine also prolongs gastrointestinal transit time in dogs. Acute abdominal distention may occur in large dogs (25 kg or greater). This may be caused by aerophagia or by parasympatholytic gastrointestinal atony with accumulation of gas.
Sedation with xylazine may not be appropriate for upper GI imaging. The manufacturers warn against using xylazine in conjunction with other potent tranquilizers (e.g. acepromazine). Xylazine and opioid analgesic combinations have less effect upon cardiopulmonary function. Traditional doses of xylazine in dogs and cats are between 1.1 and 2.2 mg/kg IM and IV. Doses may need to be lowered considerably in unstable patients.

Dissociative anesthetics exert their effects at the NMDA, glutamate, and aspartate receptors in the CNS, depressing the thalamoneocortical system while activating the limbic system. Dissociatives inhibit the binding of GABA and may also block serotonin, norepinephrine and dopamine in the CNS.

Ketamine is frequently used in combinations designed for sedation. The use of ketamine alone for sedation is not recommended, but combining ketamine with a benzodiazepine or opioid/benzodiazepine combination is acceptable. Ketamine can be administered IM or IV. The pH of ketamine is very acidic and this drug causes pain at the injection site. Administration of ketamine results in a central release of catecholamines that indirectly stimulates cardiovascular function. Ketamine increases cardiac output, heart rate, and blood pressure in normal patients. However, patients that are catecholamine depleted (exceptionally stressed) will experience negative inotropic (decreased force of myocardial contraction) effects due to ketamine's direct effects upon the heart.

Increased muscle tone and hypersalivation are also associated with ketamine. Pinnal, palpebral, laryngeal, and pharyngeal reflexes are not abolished. The eyes will remain open and should be protected with sterile lubricant. Ketamine can also cause increases in intracranial and intraocular pressure. Traditional doses of ketamine in dogs and cats are between 2 to 10 mg/kg IM or IV. Ketamine can be administered as a CRI with a loading dose of 1 to 4 mg IV followed by a CRI of 0.1 to 0.6 mg/kg/hour IV.

The proprietary combination of the dissociative tiletamine and benzodiazepine zolazepam (Telazol®) can also be used to premedicate dogs and cats. This drug combination may provide enough sedation to decrease the dose of subsequent anesthetics by 50% or more. Patients receiving this drug combination may experience vomiting, salivation, excess respiratory secretions, muscle twitching or rigidity, and pain at the injection site. They may vocalize or experience erratic or prolonged recoveries. Telazol® provides only mild analgesia and should not be used alone for procedures that precipitate moderate to severe pain (i.e. ovariohysterectomy, castration, feline
onychectomy, severe laceration repair, dental extraction, and ear canal ablation among others).

ANESTHETIC INDUCTION DRUGS

Propofol is a short acting hypnotic that is unrelated to other general anesthetic drugs. Propofol’s onset of action is within seconds and the duration of effect of a single bolus is 2 to 5 minutes. Induction is usually smooth; however muscle twitching can occur. The incidence of muscle twitching can be reduced if midazolam or diazepam are administered IV prior to propofol induction. Propofol is rapidly metabolized and has NO analgesic properties. Some adverse effects of propofol include apnea, especially with rapid administration, hypotension, bradycardia or tachycardia, and decreased cardiac output by as much as 50%. Repeated administration may cause Heinz body production in cats. Propofol should be used with caution in patients with decreased cardiac reserve. Propofol’s cardiopulmonary effects are similar to those of thiopental (Pentothal).

The combination of diazepam or midazolam and ketamine will induce anesthesia within 30 to 60 seconds. The duration of a single bolus is approximately 2 to 5 minutes. Intubation is slightly different because laryngeal reflexes are maintained. Patients may also exhibit salivation, apnea, and muscle stiffness, especially with a 1:1 volume ratio of diazepam:ketamine. The author prefers a 2:1 volume ratio of diazepam:ketamine dosed at 0.5 to 1 ml/10 kg (diazepam 0.165 to 0.33 mg/kg and ketamine 1.65 to 3.3 mg/kg) to reduce muscle stiffness. Ketamine causes a central release of catecholamines resulting in tachycardia, increased cardiac output, and increased blood pressure. In catecholamine depleted patients, ketamine will act as a direct myocardial depressant and decrease cardiac output.

Etomidate (Amidate®) is an imidazole derivative whose mechanism of action is not fully understood. Etomidate has no analgesic properties. Analgesia must be provided for invasive procedures. Etomidate has little to no effect upon myocardial metabolism, cardiac output, peripheral circulation, or pulmonary circulation, but it may depress ventilation slightly. It is supplied in a propylene glycol base therefore rapid IV injection may cause hemolysis. Reduced plasma cortisol and aldosterone levels have been reported for up to six hours after etomidate administration, but the clinical importance of this has not been decided. Etomidate has been shown to be embryocidal in rats, caution is advised in pregnant patients.

Alfaxalone (Alfaxan®, Jurox Pty Limited; Rutherford NSW, AU) is a newly FDA approved anesthetic induction drug approved for use in dogs and cats. It is classified as
a neuroactive steroid and exerts its mechanism of action by modulating neuronal cell membrane chloride ion transport by binding to GABA<sub>A</sub> cell surface receptors. Alfaxalone is administered slow and steady to effect over about 60 seconds. Induction doses are between 1 and 2 mg/kg IV in dogs and between 3 and 4 mg/kg IV in cats. Alfaxalone can be administered as intermittent boluses or a CRI for maintenance of anesthesia. Alfaxalone can depress cardiorespiratory function in a dose dependent manner. It has also been administered IM in combination with other sedatives and analgesics to successfully sedate fractious patients. Alfaxan<sup>®</sup> is supplied in 10 ml vials containing alfaxalone 10 mg/ml. Alfaxan will likely be assigned by the FDA to a Controlled Substance Classification Schedule.

**INHALANT ANESTHETICS: ISOFLURANE AND SEVOFLURANE**

- Increased anesthetic depth results in increased desynchronization of electrical activity of the cerebral cortex
- Bronchodilation
- Decreased ventilation (Sevoflurane considerably less than isoflurane)
- Increased PaCO<sub>2</sub>
- Increased acidemia
- Decreased sympathoadrenal function
- Myocardial depression
- Vasodilation
- Decreased cardiac output
- Decreased blood pressure
- Decreased renal perfusion
- Decreased liver blood flow

**REFERENCES**