Derailing the Pain Train: Analgesia in the ER

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Veterinarians are faced with clinical challenges every day with the goal of solving diagnostic dilemmas, reducing morbidity and mortality, and ultimately restoring patient health. One of the most challenging issues we face is determining the best sedation and/or anesthesia protocol for the sick, small animal patient. The objective of this lecture is to provide a clinical tool for understanding common sedation and/or anesthesia options for veterinary patients.

Regardless of the presenting complaint, an important concept to remember when approaching any emergency patient is a rapid primary survey, keeping in mind the ABCDs of evaluation and resuscitation. Briefly, "**A**" refers to **A**irway or **A**rterial Bleeding. "**B**", **B**reathing is equally important assessing the character of the patient's respirations. "**C**" refers to **C**irculation and the overall perfusion status of the patient. Finally, "**D**" refers to **D**isability notably the patients mental status.

What can we control?

The importance of oxygenation and perfusion can not be over emphasized. Supplemental oxygen either on presentation or pre-oxygenation prior to anesthesia are important concepts to remember in the sick, small animal patient.

Oxygen supplementation techniques

Supplementation technique	Required flow rate	Maximum inspired oxygen concentration achieved
Flow-by	3-15 l/min	40%
Oxygen cage	15 l/min	45-60%
Oxygen hood (unsealed bag)	5-15 l/min	85-95%
Oxygen collar	1 l/10 kg bodyweight/min	<80%
Nasal cannula	50-100 ml/kg/min	40%
Nasal catheters	50-100 ml/kg/min	40-50%
Nasopharyngeal catheter	50-100 ml/kg/min	60-70%
Nasotracheal catheter	25-50 ml/kg/min	80-90%

Aside from oxygenation, perfusion is an essential part of health to assess and address. Perfusion is defined as the flow of blood through arteries and capillaries delivering nutrients and oxygen to cells (hence the importance of oxygen supplementation as listed above) and removing cellular waste products.

Aside from oxygen, what else can we control?

Blood products

Oxygen delivery to the issues is more than just administration of oxygen. Oxygen is carried in the blood in two forms: (1) dissolved in plasma and RBC water (about 2% of the total) and (2) reversibly bound to hemoglobin (about 98% of the total). It is therefore easy to see how oxygen molecules need a carrier to transport to the vital organs, hemoglobin. Patients that are anemic (PCV <20%) may require supplementation of red blood cells to improve their oxygen carrying capacity prior to sedation or anesthesia. This can be achieved with red blood cell products such as packed red blood cells or hemoglobin based oxygen carrying solutions (i.e. Oxyglobin®).

Volume

Aside from oxygen and a carrier molecule (hemoglobin within red blood cells), hypovolemic patients require volume replacement to improve perfusion and therefore oxygenation. Volume replacement is commonly achieved with crystalloid and/or colloid solutions.

Once the patient is deemed to be stable for sedation / analgesia / anesthesia, the clinician must critically evaluate which medication or medications would be most suitable.

Anesthesia / analgesia drug review

Alpha-2 agonists (medetomidine, dexmedetomidine, xylazine)

Alpha-2 agonist dexmedetomidine (Dexdomitor®) is a very specific drug affecting the alpha-2 receptor. More specifically, alpha-2 agonists work in the CNS via pre-synaptic receptors to decrease norepinephrine release, resulting in enhanced parasympathetic tone. Following administration, sedation lasts approximately 2 to 4 hours with analgesia lasting for a shorter period of time. Dexmedetomidine is reversible with atipamezole (Antisedan®).

Side effects of alpha -2 agonists include stimulation of peripheral alpha-1 and alpha-2 receptors in the vasculature causing peripheral vasoconstriction (increased systemic vascular resistance). Clinicians commonly note hypertension with a reflex bradycardia, often with heart rates of 50 beats per minute or less! Additional clinical findings include an appearance of pale mucous membranes and peripheral vasoconstriction with cold extremities.

The combination of the dissociative tiletamine and benzodiazepine, zolazepam (Telazol®), is also commonly in small animal medicine, notably as a feline premedication. Telazol® provides mild analgesia and should not be used alone for procedures in which moderate to severe pain is expected, including castration, ovariohysterectomy, and dental extraction.

Xylazine, another alpha-2 agonist is less potent as compared to dexmedetomidine but induces a longer duration of hypertension through vasoconstriction. Xylazine is reported to induce a bi-phasic blood pressure with initial hypertension followed by prolonged hypotension. Anticholinergic agents such as atropine or glycopyrrolate are often used in combination with xylazine. Conversely, the use of anticholinergic agents with dexmedetomidine is discouraged due to the risk of hypertension and arrhythmias. The sedation and analgesia induced by xylazine can be reversed with yohimbine.

Benzodiazepines (diazepam, midazolam)

The benzodiazepines, diazepam (Valium®) and midazolam (Versed®), are tranquilizers, specifically enhancing the activity of the central nervous system inhibitory neurotransmitter, gamma-aminobutyric acid, as well as, combining with benzodiazepine receptors in the central nervous system. These medications induce mild sedation, muscle-relaxation, and acts as an anticonvulsant.

Importantly, the benzodiazepine class of drugs does not have analgesic activity. They are reversible with flumazenil (Romazicon®).

Diazepam is supplied in a propylene glycol base, not a water based preparation, and therefore it is recommended to administer this intravenously as uptake from IM or SQ injection may be slow, unpredictable, and painful. Moreover, IV administration of propylene glycol based solutions have the risk of hemolysis, thrombophlebitis and cardiotoxicity. Conversely, midazolam is water-soluble and can be administered IV, SQ or IM with predictable uptake.

Dissociatives (ketamine)

Ketamine, a NMDA Receptor Agonist, provides both analgesic and sedative effects and cause dose-dependent depression of the central nervous system. Although the patient is dissociated from the environment, pharyngeal, laryngeal, corneal, and pedal reflexes persist and the eyes remain open. Tiletamine, which is chemically similar to ketamine, is more potent and has a longer duration of effect than ketamine.

These dissociative medications have minimal cardiovascular or respiratory depression. Ketamine should be used with caution in patients with cardiac disease such as hypertrophic cardiomyopathy, ischemic heart disease and renal insufficiency as it increases sympathetic tone and thus can increase blood pressure, heart rate and cardiac output. Ketamine also increases intra-cranial and intraocular pressure so should be used with caution with head trauma or seizure history.

Etomidate

Etomidate is a non-barbiturate anesthetic. Unlike other medications used for sedation or anesthesia, it does not affect cardiovascular function, notably having no effect on blood pressure, heart rate, or cardiac output. Concerns with this medication include its high osmolality (>4000 mOsm) which has the potential for hemolysis. It also interferes with cortisol production following induction.

Opioids (hydromorphone, methadone, morphine, oxymorphone, buprenorphine, butorphanol)

Opioids are considered to have three notable receptors, but clinically the mu and the kappa receptors are the ones most often considered when planning for sedation and analgesia.

Opioids commonly used in practice include hydromorphone, methadone, oxymorphone, morphine, butorphanol, and buprenorphine. Hydromorphone, methadone, oxymorphone and morphine are μ receptor agonists and are good choices for patients expected to experience moderate-to-severe pain. These opioids provide excellent analgesia as well as good sedative properties. Common clinical side effects include hypersalivation, vomiting, nausea, and panting. Morphine is also known to cause histamine release following IV administration.

Butorphanol is a not a pure agonist, rather considered an μ agonist/ K antagonist, meaning that it will reverse some μ opioid effects. These provide less potent analgesia as compared to the primary μ agonists and should be used only for mild pain or short-term pain.

Buprenorphine is considered a partial μ agonist with four-to-six-hour duration of effect. Clinically, the author uses this more in cats than dogs.

Phenothiazines (acepromazine)

Acepromazine is the most common drug used in the class of drugs known as the phenothiazines. Acepromazine provides sedation via anti-dopaminergic (D2) effects and suppression of the sympathetic nervous system. It causes an alpha-adrenergic blockade which results in vasodilation and often hypotension. It has a relatively long duration of action, considered to be 6-12 hours and is not recommended for patients with liver disease as decreased hepatic metabolism may result in a prolonged recovery. Acepromazine does not result in analgesia and therefore should not be used as a pain medication. It should also be avoided in patients with hypotension, hypovolemia, shock, significant heart disease, or coagulopathy/ platelet disease.

While previously it was believed that acepromazine may result in seizures in dogs with a history of seizures, A recent retrospective study has shown that acepromazine does not cause seizures in dogs with a history of seizures of various origins.

Propofol

Propofol is a non-barbiturate anesthetic and a popular medication in veterinarian medicine. Propofol undergoes hepatic metabolism as well as extra-hepatic metabolism. This dug has significant cardiovascular effects, deceasing cardiac output and causing vasodilation without a reflex tachycardia. Propofol should be used with caution in animals with hypotension, hypovolemia or cardiovascular dysfunction.

Alfaxalone

Alfaxalone is another drug that is becoming more popular in veterinary medicine and reported to have less cardiopulmonary depression than other intravenous induction agents such as thiopental or propofol. Alfaxalone, a progesterone analogue, is a neurosteroid which interacts with the gamma aminobutyric acid $(GABA)_A$receptor and produces anesthesia and muscle relaxation.

Opioid drug potency chart

Drug	Other names	Potency*
Morphine	Generic	1
Codeine	Generic	1/10
Hydrocodone	Vicodin, generic with acetaminophen	6x
Oxycodone	Percocet, OxyContin	3–6x
Oxymorphone	Numorphan	10x
Hydromorphone	Dilaudid, generic	8x
Meperidine	Demerol	1/6
Propoxyphene	Darvon	1/3–1/6
Buprenorphine	Buprenex	25x
Fentanyl	Sublimaze	100x
Butorphanol	Torbugesic, Stadol	5x

Common drug doses

	Dogs	Cats
Acepromazine mg/kg	0.01–0.02 S/C 0.005–0.01 IV	Acp is not an effective sedative
Alfaxalone mg/kg	Premedicated: 2mg/kg IV Not premedicated 3mg/kg IV	Premedicated: 2mg/kg IV Not premedicated 3mg/kg IV
Buprenorphine mg/kg	0.01–0.02 mg/ kg SQ, IM, IV	0.01–0.02 mg/ kg SQ, IM, IV
Butorphanol mg/kg	0.2–0.4mg/kg SQ, IM, IV	0.2–0.4mg/kg SQ, IM, IV

Dexmedetomidine micrograms/m^2	375 IV; 500 IM micrograms/m^2	40 micrograms/kg IM micrograms/m^2
Etomidate mg/kg	1–2 mg/kg	1–2 mg/kg
Fentanyl µg/kg	CRI: 0.1–0.7 µg/kg/min	CRI: 0.1–0.7 µg/kg/min
Hydromorphone mg/kg	0.05–0.2mg/kg SQ, IM, IV	0.05–0.2mg/kg SQ, IM, IV
Methadone mg/kg	0.1–1.0 mg/kg SQ, IM, IV	0.05–0.5 mg/kg SQ, IM, IV
Midazolam mg/kg	0.1–0.5 SQ, IM, IV	0.1–0.5 S/C, IV
Morphine mg/kg	0.1–1.0 mg/kg SQ, IM, IV	0.1–1.0 mg/kg SQ, IM, IV
Propofol mg/kg	1-6mg/kg IV	1-6mg/kg IV

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