Block the Box: Getting away from mask and box induction techniques

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There are literally thousands of combinations of sedatives/tranquilizers, muscle relaxers, neurosteroids, opioids, dissociative agents, paralytics and so on to choose from. Selecting what is safe, practical and even cost efficient is necessary for our patients, keeping in mind the specific signalment and health status of our individual patient. Anesthetic induction techniques in veterinary medicine are one area we continue to fall short on. While larger mammalian patients tend to suffer less by the induction box or forced masking techniques, with pre-medication and easier IV access for injectable forms of induction agents, we continue to practice outdated and unsupported methods of anesthesia induction for our rodent and other small animal patients.

Isoflurane is the predominate gas anesthetic used in the veterinary clinic setting. Isoflurane has a lower blood solubility compared to halothane, but greater solubility compared to sevoflurane. While the definite mechanism of actions is still not fully understood, we do suspect isoflurane binds tightly to GABA centers and inhibits NMDA subtypes. Regardless of the type of gas anesthetics we are using, halogenated anesthetics are going to be one of our most cardio-respiratory depressive agents. To alleviate these depressive effects, we strive to use mean alveolar concentration (MAC) sparing drugs in combination or to fully replace gas anesthetics. MAC is understood as the minimum alveolar concentration of the gas anesthetic in the alveoli needed to keep a majority of a species population at a surgical plane of anesthesia. Isoflurane, along with its close relatives halothane and sevoflurane, have some pretty significant side effects especially at higher concentrations (>2% on the vaporizer), or with repeated chronic use.

Post- operative cognitive (long-term cognitive impairment) and muscle dysfunction are two common side effects described in the literature for both humans and animals. This is a disorder that is temporary but can last hours to weeks depending on the health status of the patient, including age and the duration of use. It is characterized in animals as a general depression or blunted natural behaviors. In studies evaluating post-isoflurane exposure, animal models have failed previously taught behaviors, had significantly slower responses, or poorer scores. General weakness is described in humans with post-operative muscle dysfunction and is suspected to be the same in animals.

Isoflurane has been shown to be genotoxic in rats, but not mutagenic in male wild-type flies at lower levels, (<2%). This is damage to DNA structure, usually temporary, but may have lasting effects not currently understood. In healthy animals this damage is typically auto-repaired. Damage to DNA integrity can represent a critical variable in studies using transgenic mice or gene therapy directed goals. Along with some genotoxic effects, researchers have appreciated isoflurane triggered neurodegeneration in the developing mouse pup brain with repeated exposure to concentrations >1% on the vaporizer for certain periods of time.

Anesthetic inhalants can also cause persistent nausea in several animal species, along with ileus. Ileus is a concern in every species when exposed to anesthetic inhalants, most prominently rabbits.

Finally, we must consider the ethical and animal welfare concerns when utilizing anesthetic gas induction. Stress hormone surges, such as cortisol, are well described in the literature for gas induction. High levels of cortisol are immunosuppressive and can delay wound or surgical site healing, not to mention the changes in behavior or social status in groupings of animals. Continued efforts in reducing stress hormone release fails to find non-pharmacologic means.

We must also consider human safety and exposure to waste anesthetic gas (WAG). Chronic exposure to WAG is well described in human literature. While most gases have a certain odor additive, staff can become desensitized to it and risk further health risks, especially for pregnant females. The cost for large animal models and using higher concentrations of gas and oxygen is relevant from an economic point of view and should also be factored in when considering best practices.

Ehrenwerth and Eisenkraft give the formula: 3 x Fresh gas flow (FGF) (L/min) x volume % = mL liquid used per hour

Behaviors such as circling, pacing, digging and jumping have also been described with inhalant anesthesia induction. This is likely due to the strong odor of isoflurane and its irritating effects to the airway and eyes. These signs illustrate a state of distress to the animal. This distress is similar to the ongoing debate and concerns with euthanizing with carbon dioxide.

Solutions to these concerns are varied. With the medications available to us today we have options to do either completely injectable protocols that can offer sedation times from 10-30 minutes with a single injection, or total intravenous anesthesia (TIVA) techniques for animals that have IV access. We also have mixed protocols which would eliminate gas induction altogether and minimize vaporizer percentages having the injectable induction agent(s) on board. Any of the anesthetic options we have available will need to be chosen based on the aim of the study, variables the agents can contribute to, and the level of invasiveness or pain expected from the procedure. The other benefit of injectable anesthesia protocols is the ability of some of the agents to be fully reversible (dexmedetomidine) or be short acting, such as fentanyl, remifentanil or sufentanil. Many of the combinations with injectable anesthetics are likely to contain one that provides analgesia during and after the procedure, addressing welfare concerns.

Anesthetic Agent	Dose	Effects	Reversible	Analgesic
Dexmedetomidine	0.25-15mcg/kg IV, IM, SQ, TM	Moderate to profound sedation, dose dependent	Yes	Yes
Alfaxalone	1-30mg/kg IV, IM	Moderate to profound sedation, dose dependent	No	No
Ketamine	1-35mg/kg IV, IM, SQ, TM	Moderate sedation when used alone	No	Yes
Telazol	mg/kg	Moderate to profound sedation, dose dependent	Partially	Yes
Midazolam	0.1-0.5mg/kg IV, IM, TM	Slight sedation when used alone	Yes	No

Fentanyl (F), Remifentanil (R), Sufentanil (S, Alfentanil (A)	F = 5-25mcg/kg IV R= S= 1-7.5mcg/kg IV A= 2-15mcg/kg IV	Moderate to profound sedation, dose dependent	Yes, fast acting	Yes
Butorphanol		Slight to moderate sedation when used alone	Yes	Yes, limited to 30-40 minutes in mammals
Buprenorphine	Mammals 0.015-0.05mg/kg IM, SQ, IV, TM	Slight to moderate sedation when used alone	Partially	Yes

Benzodiazepines are reported to enhance the positive subjective effects of opioids (euphoria) but it is unclear whether the reinforcing effects are additive or synergistic. Either way we see a great MAC sparing effect with the combination of the two medications. However, unfavorable behavioral effects are noticed when used in both cats and dogs as a solo agent.

When creating a multimodal anesthetic plan utilizing volatile anesthetic to avoid gas induction, or TIVA, we should always consider this formula.

Analgesia + Muscle relaxation + Sedation

Often one of these medication on the equation will have anxiolytic effects as well.

Alfaxalone has been the most recent drug to alleviate the need for gas induction as it can be given IV or IM; some even use it SQ- although the author is less inclined to use the SQ method. Alfaxalone offers a great alternative to combinations of drugs, particularly for fractious cats. The author does encourage using alfaxalone in combination with a benzo or opioid for additive effects.

Dexmedetomine is another drug good for sedation of generally healthy animals. It also has analgesic effects and often smaller procedures can be done with an animal under deeper sedation dexmedetomidine offers. The author does encourage using dexmedetomidine in combination with an opioid or even ketamine for additive effects.

OPIOID CONTINUOUS RATE INFUSIONS

Premedication with a mu opioid agonist will provide an effective loading dose for any mu opioid CRI

Fentanyl (50mcg/mL or 0.05mg/mL)

- Commonly used in a CRI as the sole agent or can be combined with ketamine +/- lidocaine.
- A single IV bolus will only last approximately 20-30 minutes.
- Fentanyl has a context sensitive half-life. When used as a CRI for greater than 2 hours the drug will start to accumulate in the tissues. Once accumulation has occurred the plasma concentration does not decrease rapidly once the CRI is discontinued. To prevent a prolonged recovery, it may be beneficial to decrease the fentanyl CRI rate and/or make adjustments to the

vaporizer about 30-40 minutes prior to the end of surgery. The effects tend to last much longer in cats compared to dogs.
- Extremely high dosages may depress ventilation and cause bradycardia.
- Fentanyl does not require dilution when used in a syringe pump
- An IV bolus (loading dosage) of 1-5mcg/kg should be given prior to the start of the CRI if no other mu agonist opioid has been administered.
- CRI rate (intra-op): 0.1-0.7mcg/kg/min (6-42mcg/kg/hr) **It is recommended to start with 0.1mcg/kg/min and adjust the dosage up as needed depending on patient response to surgical stimulus. If the patient responds to surgical stimulation, then it is recommended that a bolus (1-3mcg/kg) be administered and the CRI rate increased in 0.1 increments until no further surgical stimulation occurs.
- CRI rate (post-op): 0.03-0.05mcg/kg/min (2-3mcg/kg/hr)

Remifentanil (1mg powder)
- Commonly used alone in a CRI or can be combined with ketamine +/- lidocaine.
- Metabolized by nonspecific plasma esterases to inactive metabolites. This makes remifentanil superior to fentanyl for patients with renal or hepatic dysfunction.
- Rapid onset of action and short duration of action. It must be administered as a CRI because the short duration of action limits use as a bolus injection.
- It has non-cumulative effects within the body, so recovery is rapid after CRI is discontinued.
- Extremely high dosages may cause profound sedation, respiratory depression and bradycardia.
- Supplied as a 1mg powder that must be reconstituted with sterile saline prior to use.
  Dilution: mix 1mg powder in 20mL NaCl $\rightarrow$ 50mcg/mL or mix 1mg powder in 10mL NaCl $\rightarrow$ 100mcg/mL
- Loading dosage: 1-5mcg/kg IV should be given prior to the start of the CRI if no other mu agonist opioid has been administered.
- CRI rate: 0.1-0.7 mcg/kg/min

Hydromorphone (2mg/mL)
- Can be used alone or in combination with ketamine +/- lidocaine.
- Does not cause histamine release.
- Dilution: add 2mg (1mL) to 9mL NaCl $\rightarrow$ 0.2mg/mL
- Loading dosage: 0.03-0.05mg/kg IV prior to starting the CRI if no other mu agonist opioid has been administered.
- CRI rate: 0.3-0.8mcg/kg/min (0.02-0.05mg/kg/hr)

Morphine (15mg/mL)
- Commonly used alone or in combination with ketamine +/- lidocaine.
- Caution with use in cats. Morphine CRIs are not commonly administered alone to cats when awake due to the likelihood of causing excitation.
- Morphine is light sensitive. The syringe or fluid bag should be covered when using a morphine CRI long term.
- Dilution: add 15mg (1mL) to 9mL NaCl $\rightarrow$ 1.5mg/mL or add 30mg (2mL) to 8mL NaCl $\rightarrow$ 3mg/mL
- Loading dosage: 0.1-0.2mg/kg IV (very slowly) should be given prior to the start of the CRI if no other mu agonist opioid has been administered.
- CRI rate: 2-6mcg/kg/min (0.1-0.3mg/kg/hr)

Methadone (10mg/mL)

- Can be used alone or in combination with ketamine +/- lidocaine.
- Also acts as an NMDA receptor antagonist to help treat and prevent central sensitization.
- Dilution: add 10mg (1mL) to 9mL NaCl $\rightarrow$ 1mg/mL
- Loading dosage: 0.1-0.5mg/kg IV prior to starting the CRI if no other mu agonist opioid has been administered.
- CRI rate: 0.05-2mg/kg/hr

ADJUNCT CRIs FOR ADDITIONAL PAIN MANAGEMENT

Ketamine (100mg/mL)

- Classified as an NMDA receptor antagonist that effectively blocks central sensitization from occurring in the dorsal horn of the spinal cord and helps prevent hyperalgesia and allodynia.
- Ketamine does not have any direct analgesic effects, but it is used as an adjunct to other analgesic drugs such as opioids. It may help improve opioid receptor sensitivity. DO NOT use ketamine as the sole analgesic agent.
- Dosages used for the CRI are given at sub-anesthetic levels so none of the dissociative effects are seen during CRI administration.
- Starting a ketamine CRI prior to a painful stimulus will provide the best means of preventing CNS sensitization but it is still effective in patient's that present with established pain.
- Loading dosage: 0.5mg/kg IV of ketamine should be given prior to starting the CRI in order to achieve initial therapeutic blood levels. Induction with ketamine/diazepam or Telazol® will provide an effective loading dose.
- CRI rate (intra-op): 10-20mcg/kg/min
- CRI rate (post-op): 2-10mcg/kg/min for at least 24 hours

Lidocaine (20mg/mL)

- MAC sparing and analgesic effects when administered as a CRI intra-op.
- Classified as a sodium channel blocker and a class IB antiarrhythmic.
- Displays free radial scavenging effects which may be helpful at preventing reperfusion injury.
- Acts as an inflammatory modulator by decreasing neutrophil chemotaxis and platelet aggregation.
- Acts as a prokinetic that enhances gut motility and helps prevent ileus.
- NOT recommended for use in cats due to its potential for toxicity. If used, do not exceed a dosage of 10mcg/kg/min and monitor closely for seizure activity and bradycardia.
- Commonly used as a first line treatment for ventricular premature complexes (VPC) or ventricular tachycardia.
- Some brands of lidocaine are sensitive to light. If lidocaine comes in a brown bottle the syringe or fluid bag containing the lidocaine should be covered when used as a CRI long term.
- Loading dosage: 1-2mg/kg IV of lidocaine should be given prior to starting the CRI in order to achieve an appropriate therapeutic level.
- CRI rate: 25-75mcg/kg/min

Dexmedetomidine (500mcg/mL or 100mcg/mL)

- Generally combined with an opioid CRI to enhance analgesia and sedation when an opioid CRI alone is not enough.
- Will greatly reduce MAC of inhalants when used intra-operatively.
- Commonly used during the post-operative period as a treatment for emergence delirium or when the patient would benefit from long term sedation during the post-operative period.
- Can be given in combination with ketamine, lidocaine and opioids
- Cardiovascular effects (significant bradycardia, biphasic effects on blood pressure) will likely be seen during CRI administration. Vital signs should be monitored closely. It is best to avoid a dexmedetomidine CRI if the patient has cardiovascular disease.
- Inhibits antidiuretic hormone (ADH), so an increase in urine production may be seen. The bladder should be expressed prior to recovery if used as an intra-operative CRI.
- Inhibits insulin release so a transitory hyperglycemia may be seen. Avoid a dexmedetomidine CRI if serial glucose values need to be obtained.
- Loading dosage: 0.5-1mcg/kg IV should be given prior to starting the CRI in order to achieve an appropriate therapeutic level.
- CRI rate: 0.5-3mcg/kg/hr

Medetomidine

- Used in the same manner as dexmedetomidine.
- Loading dosage: 1-2mcg/kg IV prior to starting the CRI.
- CRI rate: 1-2mcg/kg/hr

* Used with permission from Palmer, D. (2013). Information originally published in the VSPN Notebook®, 4th ed. Veterinary Support Personnel Network/Veterinary Information Network (www.vin.com). Davis, CA.

TABLE 1: Dosages for constant rate infusions (CRIs) used in *CATS.*

Drug	Loading Dose	CRI dose	Quick Calculation	Comments
Morphine (M)*	0.10 mg/kg IM	0.03 mg/kg/hr (0.5 mic/kg/min)	Add 15 mg to 500 ml fluid & run at 1 ml/kg/hr	Cat may need light sedation; can be combined with K &/or L
Hydromorphone (H)	0.025 mg/kg IV	0.01 mg/kg/hr	Add 5 mg to 500 ml fluid & run at 1 ml/kg/hr	May cause hyperthermia; can be combined with K &/or L
Fentanyl (F)	0.001-0.003 mg/kg IM or IV (1-3 mic/kg IV)	2-5 mic/kg/h (0.03-0.08 mic/ kg/min) post-op 5-20 mic/kg/h (0.08-0.3 mic/ kg/min intra-op	For 5 mic/kg/h, add 2.5 mg to 500 ml fluid & run at 1 ml/kg/hr	2.5 mg=50 ml F, remove 50 ml LRS before adding F; can be combined with K &/or L.
Methadone	0.1-0.2 mg/kg IV	0.12 mg/kg/hr	Add 60 mg to 500 ml fluid & run at 1 ml/kg/hr	MAY cause sedation; can be combined with K &/or L.

Butorphanol	0.1 mg/kg IV	0.1-0.2 mg/kg/hr	Add 50 mg to 500 ml fluid & run at 1 ml/kg/hr for 0.1 mg/kg/hr	Only moderately potent & has ceiling effect - use as part of multimodal protocol
Ketamine (K)*	0.25 mg/kg IV	0.12-0.6 mg/kg/hr (2 -10 mic/kg/ min)	Add 60 mg to 500 ml fluid & run at 1 ml/kg/hr for 0.12 mg/kg/hr	Generally combined with opioids; may cause dysphoria
Lidocaine (L)	0.25 mg/kg IV	1.5 mg/kg/hr (25 mic/kg/min) Some sources recommend no more than 10 mic/kg/min in cats	Add 750 mg to 500 ml fluid & run at 1 ml/kg/hr 10 mic/kg/min would be 300 mg lidocaine in 500 ml fluid with a rate of 1 ml/kg/hr	750 mg=37.5 ml, remove 37.5 ml LRS before adding L; can be combined with opioid &/or K; **Lidocaine MAY be contraindicated in the cat due to cardiovascular effects.**
Medetomidine (Med) or Dexmedetomidine (D)	1-5 mic/kg Med 1-2 mic/kg D Can be IV or IM May not be necessary	0.001-0.004 mg/kg/hr Med (1-4 mic/kg/hr) 0.0005-0.002 mg/kg/hr D	Add 500 mic Med or 250 mic D (0.5 ml of either) to 500 ml fluid and run 1-4 ml/kg/ hr	Provides analgesia and light sedation. Excellent addition to opioid CRI, or can be administered as solo drug CRI.
Morphine* / Ketamine*	M: 0.10 mg/kg IM K: 0.25 mg/kg IV	0.03 mg/kg/hr M & 0.12 mg/kg/hr K	Add 15 mg M & 60mg K to 500 ml fluid & run at 1 ml/kg/hr	Can be administered up to 3 ml/kg/hr but dysphoria MAY occur. Can substitute, F, or methadone for M.
Morphine / Ketamine / Lidocaine (MLK)	M: 0.10 mg/kg IM K: 0.25 mg/kg IV L: 0.25 mg/kg IV	0.03 mg/kg/hr M, 0.12 mg/kg/hr K; 1.5 mg/kg/hr L	Add 15 mg of M, 60 mg K and 750 mg (or 300 mg) L to 500 ml fluid & run at 1 ml/kg/hr	Can substitute H, F or methadone for M.

* Any of the drug amounts in the bag of fluids can be decreased and the fluids administered at a higher rate if necessary. For example, for morphine, ketamine and morphine/ketamine infusions, 7.5 mg of morphine & 30 mg of ketamine can be used and the CRI administered at 2 ml/kg/hr if more fluids are needed.

TABLE 2: Dosages for constant rate infusions (CRIs) used in *DOGS.*

Drug	Loading Dose	CRI dose	Quick Calculation	Comments
Morphine (M)*	0.5 mg/kg IM (or 0.25 mg/kg SLOWLY IV)	0.12-0.3 mg/kg/hr (2.0 mic/kg/min-3.3mic/kg/min	Add 60 mg to 500 ml fluid & run at 1 ml/kg/hr for 0.12 mg/kg/hr	MAY cause sedation; can be combined with K &/or L.
Hydromorphone (H)	0.05-0.1 mg/kg IV	0.01-0.05 mg/kg/hr	Add 5-24 mg to 500 ml fluid & run at 1 ml/kg/hr	MAY cause sedation; can be combined with K &/or L.

Fentanyl (F)	0.001-0.003 mg/kg IM or IV (1-3 mic/kg IV)	2-10 mic/kg/h (0.03-0.2 mic/ kg/m) post-op 3-40 mic/kg/h (0.05-0.7 mic/ kg/min intra-op	For 5 mic/kg/h, add 2.5 mg to 500 ml fluid & run at 1 ml/kg/hr	2.5 mg=50 ml F, remove 50 ml LRS before adding F; can be combined with K &/or L; Intra-op dose can be up to 20-40 mic/kg/h
Methadone	0.1-0.2 mg/kg IV	0.12 mg/kg/hr	Add 60 mg to 500 ml fluid & run at 1 ml/kg/hr	MAY cause sedation; can be combined with K &/or L.
Butorphanol	0.1 mg/kg IV	0.1-0.2 mg/kg/hr	Add 50 mg to 500 ml fluid & run at 1 ml/kg/hr for 0.1 mg/kg/hr	Only moderately potent & has ceiling effect - use as part of multimodal protocol
Ketamine (K)*	0.25 mg/kg IV	0.12-0.6 mg/kg/hr (2 -10 mic/kg/ min)	Add 60 mg to 500 ml fluid & run at 1 ml/kg/hr for 0.12 mg/kg/hr	Generally combined with opioids; may cause dysphoria; post-op dose may be higher
Lidocaine (L)	0.5 – 1.0 mg/kg IV	1.5-3.0 mg/kg/hr (25-50 mic/kg/min)	Add 750 mg to 500 ml fluid & run at 1 ml/kg/hr for 25 mic/ kg/min	750 mg=37.5 ml, remove 37.5 ml LRS before adding L; can be combined with opioid &/or K.
Morphine / Ketamine / Lidocaine (MLK)	M: 0.5 mg/kg IM K: 0.25 mg/kg IV L: 0.5 mg/kg IV	0.12 mg/kg/hr M, 0.12 mg/kg/hr K; 1.5 mg/kg/hr L	Add 60 mg of M, 60 mg K and 750 mg of L to 500 ml fluid & run at 1 ml/kg/hr	Can substitute H, F or methadone for M. Dr. Muir's dose is 3.3 mic/kg/min M, 50 mic/kg/min L; 10 mic/kg/min K.

*Any of the drug amounts in the bag of fluids can be decreased and the fluids administered at a higher rate if necessary. For example, for morphine, ketamine and morphine/ketamine infusions, 30 mg of morphine & 30 mg of ketamine can be used and the CRI administered at 2 ml/kg/hr if more fluids are needed.