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Pass on the Gas: Understanding Total Intravenous Anesthesia (TIVA) Techniques and Indications

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General Anesthesia

The term "anesthesia" comes from the Greek word "anaisthesia" which means without feeling and can be further defined as a loss of sensation. Many associate the term anesthesia solely with general anesthesia. However, it is important to understand that there are various degrees of central nervous system depression with general anesthesia being the largest degree on this scale. Sedation can be defined as a drug induced state of *drowsiness* resulting from mild to moderate CNS depression. General anesthesia can be defined as controlled and reversible depression of the central nervous system in order to elicit *unconsciousness* and eliminate pain during periods of surgical stimulation. The most important distinction being; that when a patient is sedated, they can still respond to noxious stimuli but with general anesthesia, there is no response to noxious stimuli. Further, we can define and specify surgical anesthesia as a stage of general anesthesia where muscle relaxation and analgesia are sufficient to allow surgery without pain or movement. Inhalant anesthetics have become the primary modality of anesthetizing veterinary patients over the last several decades. While there are many options for inhalant anesthetics across academia and research, the most commonly used inhalant anesthetics in clinical practice are isoflurane and sevoflurane.

Isoflurane and Sevoflurane: The Basics

Both isoflurane and sevoflurane belong to a group of inhalant anesthetics known as halogenated ethers. The exact mechanism of action on the central nervous system by these drugs is not solidly understood. Both drugs are primarily metabolized by the lungs and enter the bloodstream via diffusion across the alveolar membranes when the patient inhales. They are eliminated in the same way when the patient exhales. Diffusion is controlled via a concentration gradient as well as lipid solubility. The cell membranes of the alveoli act as the concentration gradient. When inhalation of the agent begins, this concentration gradient favors the alveoli. This means more agent is present in the alveoli than in the bloodstream. During this period where the concentration gradient favors the alveoli, we see an increased rate of diffusion into the bloodstream. This slows as a balance in the concentration gradient is reached. Both isoflurane and sevoflurane are highly lipid soluble so they will rapidly enter the brain from systemic circulation to produce central nervous system depression and initiate unconsciousness or general anesthesia. When isoflurane or sevoflurane are discontinued, there becomes less and less of these agents available in the alveoli to diffuse into the bloodstream. Eventually, there is no agent remaining in the alveoli available for diffusion into the bloodstream. This in combination with the majority of the

inhalant in the bloodstream eliminated through exhalation, makes general anesthesia produced by these agents, quickly reversible. It is for this reason these agents became so highly utilized in veterinary anesthesia.

Isoflurane and sevoflurane: What do they do to our patients?

The attractive qualities of these agents come with a price. They require careful consideration with regards to their effects on the body. Isoflurane and sevoflurane have dose dependent adverse consequences on the cardiovascular and respiratory systems. Of all anesthetic agents, inhalants will cause the most profound effects on these systems. Isoflurane and sevoflurane are potent vasodilators and negative inotropes, meaning these agents cause significant myocardial depression leading to hypotension. Hypoventilation is a common occurrence with the use of isoflurane and sevoflurane. Hypoventilation leads to hypercarbia and respiratory acidosis. These effects trickle down to other body systems including the renal and cerebrovascular systems. Isoflurane and sevoflurane do not provide any analgesia to our patients. So, when used alone, they require higher doses to be administered to keep patients at an anesthetic depth appropriate for surgical stimulation. Potency of inhalants are defined by their minimum alveolar concentration or MAC. MAC is defined as the percentage of inhalant required to prevent movement and response to 50% of patients receiving surgical stimulation. MAC of isoflurane is 1.3% in the dog and 1.6% in the cat. MAC of sevoflurane is 2.3% in the dog and 2.6% in the cat. Across studies, the average dose of these two inhalants needed to keep patients at an appropriate depth of general anesthesia for surgical stimulation is 1.5-2 times MAC. This means that when used alone you likely need to have your patient on roughly 3% isoflurane or 4.5% sevoflurane to maintain adequate depth.

Why is this less than ideal in a patient with co-existing disease?

Cardiovascular disease: In the most basic terms, the primary function of the cardiovascular system is to deliver oxygen to tissues through the circulation of blood. Patients with cardiovascular disease already have a reduced ability to adequate deliver oxygen to the tissues and organs because of their co-existing disease. This includes reduced cardiac contractility, cardiac output, increased cardiac workload and increased myocardial oxygen consumption. Our goal with general anesthesia is to maintain homeostasis as much as possible. This becomes more difficult to achieve in patients with cardiovascular disease when considering the delicate balance of already present co-existing disease and the cardiovascular depression caused by inhalant anesthetics. Specifically, hypotension with subsequent decreased perfusion becomes a concern in patients with cardiovascular disease. Using higher concentrations of inhalant anesthetics in these patients can have a profound and certainly much more detrimental effect on these patients versus a patient with no co-existing cardiovascular disease. Additionally, cardiovascular disease can complicate how we approach treatment and blood pressure management in the face of hypotension. Large fluid boluses of crystalloids and colloids are contraindicated in these patients. Often times these patients are medically managed with beta blockers, ACE inhibitors, calcium channel blockers, sodium channel blockers, etcetera and these drugs will impact treatment and efficacy of vasopressors and positive inotropic agents used to manage hypotension.

Respiratory disease: The respiratory centers of the medulla in the central nervous system serve as the drive for breathing. Therefore, central nervous system depression and subsequent respiratory depression caused by inhalant anesthetics, can have significant consequences in a patient with respiratory disease. The respiratory system is responsible for gas exchange in the bloodstream including the uptake of oxygen and elimination of carbon dioxide. There are many complex factors that contribute to effective gas exchange that could serve as a stand-alone lecture. Many patients with co-existing respiratory disease, specifically lower respiratory disease already have decreased ability to ventilate adequately and this becomes much more profound when using inhalant anesthetics. Additionally, we know from what we discussed previously that adequate gas exchange becomes essential for inhalant anesthetics to enter the bloodstream and make their way to the brain to elicit general anesthesia. Patients with lung disease such as atelectatic lung tissue or a lung mass are going to have less alveoli to participate in gas exchange and it becomes increasingly difficult to maintain a steady anesthetic plane when using inhalant anesthetics.

Intracranial disease: Patients with neurologic disease such as head trauma or brain tumors are at significant risk if intracranial pressure and cerebral blood flow are increased. Inhalant anesthetics, as potent vasodilators, will contribute to an increase in intracranial pressure in these patients with already diminished cerebral autoregulation. These complications can be further exacerbated by respiratory depression related increases of carbon dioxide levels in the blood. Autoregulation of both intracranial pressure and cerebral blood flow occurs when PaCO2 is maintained between 30 and 40 mmHg. In patients with an increase in brain tissue mass such as, a tumor, hemorrhage or swelling, there is a pre-existing increase in cerebral blood flow exaggerated by co-existing disease. This compounded by vasodilation secondary to inhalant anesthetics, will predispose these patients to life threatening hypoxia.

Renal disease: Renal disease is a very common co-morbidity in veterinary patients presenting for general anesthesia. The profound effects on the cardiovascular and respiratory systems secondary to inhalant anesthetics can in turn increase complications in patients with underlying renal insufficiency. Cardiac output and blood pressure have significant impacts on renal blood flow and therefore renal perfusion. Careful monitoring to ensure that dangerous decreases in blood pressure are addressed immediately becomes an absolute necessity in the patient with renal disease. If allowed to persist, hypotension will result in irreversible damage to the kidneys. Even in a healthy patient with no renal disease, normotension and normovolemia are essential to maintain homeostasis. This becomes more difficult in a patient with renal disease because of the reduced ability to tolerate even the slightest insult.

Balanced anesthesia

Balanced anesthesia is the term applied to the concept of utilizing multiple agents to achieve general anesthesia. This enables us to use lower doses of each drug and therefore reduce harmful side effects. Balanced anesthesia is especially important in patients with co-existing disease specifically to reduce the concentration of inhalant anesthetics. While balanced anesthesia may seem like an elementary concept, it is significantly under-utilized in clinical practice across the board. Instead we see high doses of inhalant used

widely to anesthetize veterinary patients increasing peri-anesthetic complications. Taking the concept of a balanced anesthetic protocol one step further, we can evaluate drugs available to us to that allow for elimination of inhalant anesthetics completely in certain patients with co-existing disease.

Total intravenous anesthesia

Total intravenous anesthesia is defined as the maintenance of general anesthesia using solely injectable agents intravenously. Remember, the primary goals of general anesthesia are to produce unconsciousness, analgesia, muscle relaxation and amnesia while maintaining homeostasis of the body systems. Keeping balanced anesthesia in mind, this can be achieved using multiple injectable agents that have less of a deleterious effect on patients with co-existing disease. Using a TIVA protocol does not negate the necessity of appropriate premedication and induction protocols. TIVA becomes a part of the balanced anesthesia protocol and specifically represents the maintenance phase of general anesthesia. In short, TIVA is replacing the inhalant agent. The incorporation of local blocks whenever possible, also increases the effectiveness of a TIVA protocol and allows for the use of a lower effective dose of each agent to keep the patient at an appropriate depth of anesthesia. Administration of maropitant (Cerenia) should be considered in patients receiving TIVA from both an analgesic and anti-emetic standpoint to reduce nausea potentially associated with the use of injectable agents. Reasons TIVA is advantageous in specific patients presenting for general anesthesia include: improved hemodynamic stability (reduced cardiovascular depression, reduced respiratory depression and improved cerebral blood flow autoregulation), reduced post-operative nausea with certain protocols, adjustability and reversibility of the drugs, less dysphoric or rough recoveries, improved analgesia and improved stability of anesthetic depth during surgical stimulation. Additionally, TIVA eliminates veterinary staff exposure to waste anesthetic gases during procedures such as bronchoscopy or upper airway surgery. It is important to acknowledge that we are still producing general anesthesia in our patients when using a TIVA protocol. TIVA is not sedation. Meaning appropriate monitoring of patients on a TIVA protocol such as; heart rate and rhythm, ventilation and oxygenation, blood pressure, temperature and depth, must be at the highest standards and comparable to a patient on an inhalant anesthetic. Additionally, patients receiving a TIVA protocol should still be intubated and administered 100% oxygen supplementation if the procedure permits.

Total intravenous anesthesia: How do we do it?

Successful TIVA includes utilization of continuous rate infusions (CRIs) of multiple agents and specifically those agents with low potential for accumulation in the body. Continuous rate infusions are the use of low doses of the desired agent delivered to the patient at a constant (but adjustable) rate. Because doses used for CRIs are significantly lower than those used for pre-medication and induction, an initial bolus or “loading dose” is always required to achieve peak plasma concentrations. Often times these initial doses are achieved during the premedication and induction phases of anesthesia. Some of these agents, when used peri-anesthetically, absolutely require administration via CRI due to short half-life. This is necessary for the agent to remain therapeutic. CRIs maintain appropriate plasma concentrations of the agent avoiding “peaks and troughs” associated with intermittent bolusing. When multiple agents are used as a CRI, it allows for much lower doses

of each agent, again reducing undesired side effects. Intermittent boluses of these agents can be utilized to increase anesthetic depth if the patient is responding to surgical stimulation, similarly, to increasing the vaporizer dial with inhalant anesthetics. CRIs can be administered via a syringe pump or mixed with intravenous fluid therapy, although, there are special considerations for using agents mixed with crystalloid fluids. For example, in a patient with cardiovascular disease where fluid overload is of great concern. Additionally, CRIs mixed with fluids also require a second "clean bag" to be used for fluid boluses if indicated in the patient.

Total intravenous anesthesia: What drugs can we utilize?

Propofol and alfaxalone: When utilizing a TIVA protocol, it is essential to choose one primary anesthetic agent to elicit general anesthesia. The two most common agents used for TIVA are propofol and alfaxalone. Propofol is considered a non-barbiturate general anesthetic that binds to GABA receptors to produce CNS depression and induce general anesthesia. Propofol will lead to significant respiratory depression to the point of apnea when inducing general anesthesia. This most commonly occurs when propofol is administered too quickly. Like inhalants, propofol is a negative inotrope and vasodilator although much less significantly so. Because of this, propofol can lead to hypotension so it might not be the best choice for a patient with cardiovascular disease. Cats have a decreased ability to metabolize some of the compounds in propofol when used too frequently. Prolonged or repeat use of a propofol (specifically a CRI) is not recommended in cats and can lead to Heinz body anemia. Propofol is rapidly metabolized and eliminated from the body. Additionally, the clearance of propofol from the body occurs independent of hepatic blood flow indicating that other tissues likely contribute to metabolism as well. This makes propofol a good choice in patients with hepatic disease. Propofol will decrease cerebral blood flow, intracranial pressure and cerebral metabolic oxygen demands making it the ideal choice for a TIVA protocol in a patient with intracranial disease. Alfaxalone is a neurosteroid anesthetic that binds to GABA receptors to produce CNS depression and induce general anesthesia. When used at appropriate doses, alfaxalone causes significantly less cardiovascular depression and apnea than propofol. Alfaxalone is considered to have a "safe" cardiac profile and is also rapidly metabolized and cleared from the body. Because of the almost non-existent depression of the cardiovascular system, when compared to propofol, alfaxalone is almost certainly the first choice for a TIVA protocol in a patient with cardiovascular disease. Additionally, alfaxalone would be the first choice to use in a feline patient because of their reduced ability to metabolize propofol. Once it is decided which agent will be your primary anesthetic agent, it is important to select other agents to complete a balanced TIVA protocol.

Loading doses: ALWAYS to effect: propofol 4-6mg/kg, alfaxalone 1-5mg/kg

CRI doses: propofol 1-7mg/kg/hr, alfaxalone 4-8mg/kg/hr

Opioids: Opioids, specifically pure mu agonist opioids, are ideal agents to utilize in a TIVA protocol. Opioids are utilized primarily from an analgesic perspective but also provide mild to moderate sedation depending on the agent. Opioids act on the pain pathway at transduction, modulation and perception. While they do cause dose dependent CNS depression similarly to inhalant anesthetics, this is much less significant and therefore more desirable in a compromised patient. Common opioids used in clinical practice for CRIs include hydromorphone,

morphine, fentanyl and remifentanil. Short half-life, increased elimination, adjustability and low accumulation in the body, make fentanyl and remifentanil the most desirable agents of this list. Remifentanil especially is ideal when used in the patient with neurological disease due to an "ultra-short" duration of action. Butorphanol can be used as a CRI as well, however, butorphanol will only agonize the kappa receptor so it should only be used for non-painful procedures. Buprenorphine is not a reasonable choice for a CRI for several reasons. First, it has a very slow onset of action of 30-45 minutes IV. Secondly, it will only partially activate the mu receptor making it inferior to a pure mu opioid for effective analgesia. Most importantly, buprenorphine's duration of action is directly related to the dose. Meaning, higher doses will lead to longer duration of action. Lastly, buprenorphine has a "ceiling effect" which means that after repeated doses, efficacy will not improve. Any compromised patient including those with cardiovascular disease, renal disease, respiratory disease or neurological disease will benefit from an opioid used as part of their anesthetic protocol. There are no absolute contraindications with the use of opioids in patients with co-existing disease.

Loading doses: hydromorphone 0.1-0.2mg/kg, morphine: 0.3-0.5mg/kg, fentanyl/remifentanil 3-5mcg/kg,

CRI doses: hydromorphone 0.02-0.07mg/kg/hr, morphine 0.1-0.3mg/kg/hr, fentanyl/remifentanil 5-20mcg/kg/hr,

Midazolam: Midazolam is a benzodiazepine agent used to provide muscle relaxation and mild sedation. Midazolam inhibits GABA receptors to produce CNS depression. It is most effective in older and compromised patients. Half-life elimination is approximately 1-2 hours and midazolam does not tend to accumulate in the body. When used as a CRI, doses should be kept relatively low due to the potential for prolonged recovery and extubation times in patients receiving TIVA. To combat this, midazolam can be reversed with flumazenil once it is no longer needed. Administration of a midazolam CRI is generally not indicated post operatively because it does not provide analgesia, although, there may be certain situations where is could be of use. Midazolam should be used with caution in patients with hepatic disease and avoided completely in patients with severe hepatic dysfunction. This is because midazolam is highly protein bound and primarily metabolized by the liver.

Loading dose: 0.1-0.2 mg/kg

CRI dose: 0.2-0.4mg/kg/hr

Ketamine: Ketamine is a cyclohexamine anesthetic used to induce general anesthesia. It is also referred to as a dissociative agent. Ketamine will actually stimulate the CNS, so it is not a "true" anesthetic. Instead, it works by causing a "dissociation" between the thalamus and limbic system of the brain to produce a trance like state. Ketamine works on the pain pathway at modulation. Ketamine is known to reduce central neuronal hypersensitization also known as wind-up. Wind up occurs in the dorsal horn of the spinal cord when there is an overwhelming amount of noxious stimuli that activate the many NMDA receptors located there. This in turn amplifies the signal to the brain. Ketamine is an NMDA receptor antagonist effectively reducing wind-up. Ketamine will initially depress the cardiovascular system; however, ketamine will indirectly stimulate the sympathetic nervous system. This may lead to increased heart rate, cardiac output and therefore blood pressure. Ketamine should be avoided in patients with certain cardiac conditions such as hypertrophic

cardiomyopathy but can generally be used in patients with cardiovascular disease as long as the patient is not tachycardic. Ketamine causes an increase in cerebral blood flow, and intracranial pressure so it is not an appropriate choice for patient with intracranial disease. Ketamine at a moderate dose will have little impact on a patient with renal disease as it is primarily metabolized by the liver. However, ketamine is primarily excreted by the kidneys, sp caution should also be used in patients with moderate to severe renal disease due to increased elimination times

Loading dose: 0.5-1mg/kg

CRI dose: 0.12-1mg/kg/hr

Lidocaine

Lidocaine is a sodium channel blocker and is categorized as a class 1B antiarrhythmic. For these two reasons a lidocaine CRI may be helpful to use for certain patients in which there is concern for tachyarrhythmias. Lidocaine and other local anesthetics work on the pain pathway at transduction, transmission and modulation making them superior analgesics. Lidocaine can be of particular benefit in the patient with intracranial disease because it reduced cerebral metabolism and cerebral blood flow. One of the other benefits of lidocaine is that it is a prokinetic that can enhance gut motility helping to prevent ileus. A lidocaine CRI should never be used in a cat due to toxicity. When utilizing a local block as part of the TIVA protocol, it is important to consider total dosing to avoid toxicity.

Loading dose: 1-2mg/kg

CRI dose: 1-4mg/kg/hr

Careful Considerations with Total Intravenous Anesthesia

While TIVA has many attractive qualities for patients compromised by co-existing disease, there are important considerations when using a TIVA protocol. Because these agents are solutions, great care must be taken in the patient with cardiovascular disease to ensure that fluid overload does not become a concern. In these patients, agents should be administered via syringe pump versus mixed with intravenous fluids. The volume per hour of each of these agents must be factored into the total over all fluid volume per hour including crystalloid therapy. Rates must also be adjusted if additional blood pressure support is needed via the addition of a vasopressor or positive inotrope CRI. Although, the majority of agents discussed previously have short duration of action and elimination from the body, recovery with a TIVA protocol may be longer versus those patients who have been anesthetized with inhalant anesthetics. This become a particular concern in patients with hepatic disease.

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