



Total Intravenous Anesthesia - TIVA

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Definitions:

Anesthesia: Loss of consciousness, analgesia, immobility, and muscle relaxation

Tranquilizer: any of a group of compounds that calm or quiet an anxious patient. There are two types: the *major tranquilizers* called also neuroleptics¹ or antipsychotic agents, such as acepromazine, and the *minor tranquilizers* called also antianxiety agents, such as diazepam (Valium).

Dissociative Anesthesia: A form of general anesthesia characterized by catalepsy, catatonia, and amnesia, but not necessarily involving complete unconsciousness, as that produced by ketamine.

Catalepsy: A condition that occurs in a variety of physical and psychological disorders and is characterized by lack of response to external stimuli and by muscular rigidity, so that the limbs remain in whatever position they are placed.

Catatonia: a motor abnormality involving under activity. A patient's arms often retain any position in which they are placed.

Amnesia: short-term memory loss without other neurological impairment.

Analgesia: absence of sensibility to pain, particularly the relief of pain without loss of consciousness; absence of pain or noxious stimulation.

Benzodiazepine: any of a group of drugs having similar molecular structure. A drug in this group that has significant use in veterinary medicine is diazepam (Valium).

Opioid:

1. Any synthetic narcotic that has opiate-like activities but is not derived from opium.
2. Any of a group of naturally occurring peptides, e.g., enkephalins that bind at or otherwise influence opiate receptors, either with opiate-like or opiate antagonist effects.

CRI: Constant rate infusion is delivered intravenously at a constant rate, frequently over a long period of time.

Central Sensitization: an increased magnitude and duration of neuron firing caused by intense or chronic noxious input leading to an amplification of the pain response.

Hyperalgesia: an excessive response to a painful stimulus.

Allodynia: pain caused by a stimulus that does not normally result in pain – a component of maladaptive pain

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Comparing TIVA and Combined Anesthesia

For many years it has been accepted that the “best” anesthetic protocols involved use of injectable drugs to induce anesthesia, followed by intubation and maintenance of anesthesia with volatile, inhaled anesthetic drugs (combined anesthesia)^{2,3,4}. Total intravenous anesthesia (TIVA) is now commonly used in veterinary institutions as an alternative to the use of inhalation anesthetics^{2,4}. I will discuss today some of the advantages of TIVA as well as discussing some of the techniques and protocols which may be used.

One of the main reasons that TIVA is being used in veterinary institutions is that the intravenous agents cause less cardiovascular and respiratory depression than the inhalation anesthetics². In the field TIVA is a useful method of anesthesia because it does not require specialized equipment or an oxygen delivery system.

Drugs used for TIVA have analgesic properties and thus contribute to pre-emptive analgesia thereby reducing reflex responses to noxious stimuli. Volatile anesthetics have no analgesic properties and only prevent pain perception by rendering the animal unconscious².

The volatile anesthetics which are predominantly in use today are: halothane, isoflurane and sevoflurane. The use of these inhalants requires special anesthetic delivery equipment which is complex, costly and bulky. It requires regular maintenance in order to work properly. In contrast TIVA can be done with just a needle and a syringe, although as will be discussed later, IV pumps, syringe drivers and burettes are available and not overly expensive but allow for more accurate and reliable administration of these drugs. In the human field it has been shown that there is less risk for organ toxicity with IV drugs than with inhalant drugs but this has not been reported in animals². This has serious implications for the veterinarian and staff.

One of the advantages of inhalation anesthesia is that the plane of anesthesia can be changed relatively rapidly and the animal recovers from anesthesia quite quickly. Newer injectable anesthetic drugs allow for more rapid recovery than previous injectable anesthetic agents and thus the plane of anesthesia can be altered in a more timely fashion. IV anesthetics do not cause atmospheric pollution so there is much less risk to veterinarians and nursing staff involved in the administration of these drugs. Human exposure to inhalation anesthetics results from poor scavenging systems, accidental disconnections from the anesthetic machine during procedures, the use of ‘leaky’ breathing systems and proximity to animals that are recovering from anesthetics. All practices that use inhalant anesthetics should be monitoring the levels of anesthetic gases in the operating room annually².

Drugs Used for Intravenous Anesthesia / Analgesia

An ideal drug would possess the following properties:

- water soluble,
- stable in solution,
- non- tissue toxic (in case of peri-vascular injection),
- can be given in a concentrated form,
- not absorbed by plastics (tubing etc.),

- does not promote bacterial growth,
- rapid onset of action,
- cleared rapidly from the body for rapid predictable recovery,
- few adverse side effects,
- potent and lipid soluble,
- relatively cheap,
- chemically compatible with other drugs.

There is no single agent that possesses all of these properties³.

Table 1: Common drugs and doses used for anesthesia and / or analgesia^{5,6,7,8,9}

Name	Class	Loading Dose	CRI Dose
Fentanyl	Opioid (full agonist)	Pain - 4 - 10 mcg/kg	0.1 – 0.7 mcg / kg / min or 4 - 10 mcg / kg / hr
Hydromorphone	Opioid (full agonist)	0.05 – 0.2 mg / kg IV or IM	0.01 – 0.07 mg / kg
Morphine	Opioid (full agonist)	0.1 - 0.3mg / kg IV (slowly)	2 – 6 mcg / kg / min
Butorphanol	Opioid (agonist-antagonist)	0.1 to 0.4 mg / kg	0.1 – 0.2 mg / kg / hr
Oxymorphone	Opioid (full agonist)	0.02 – 0.2 mg / kg IM or IV every 2 – 6 hours	Not used for CRI – long duration
Buprenorphine	Opioid (partial mu agonist)	0.01 – 0.04 mg / kg IM or IV every 4 – 8 hours	Not used for CRI – long duration
Ketamine (pain)	NMDA* receptor antagonist / dissociative	0.15 – 0.5 mg / kg	2 - 20 mcg / kg / min or 0.12 – 2 mg / kg / hour
Anesthesia		2.2 – 4.4 mg / kg IV Us. mixed with valium	
Medetomidine(pain)	Alpha 2 agonist	1 mcg / kg	1 - 3 mcg / kg / hr
Propofol	Hypnotic agent	3 – 8 mg / kg IV to effect	0.05 – 08 mg / kg / min
Diazepam	Benzodiazepine	0.2 – 0.5 mg / kg IV	0.1 – 0.5 mg / kg / hr
Midazolam	Benzodiazepine	0.1 – 0.25 mg / kg IV or IM	0.1 – 0.4 mg / kg / hr
Lidocaine	Local Anesthetic Agent	1 – 4 mg / kg Up to 8 mg/kg over 10”	10 - 100 mcg / kg / min

*N-methyl D-aspartate antagonist

Propofol is the most commonly used single agent for intravenous anesthesia but other drugs can be combined and used for TIVA. TIVA with Propofol is not recommended for patients with or suspected of having bleeding disorders¹⁰. Thiopental is not recommended as a choice for total intravenous anesthesia because recovery is prolonged with longer infusion. Following a single dose of thiopental recovery occurs rapidly because of redistribution, however once the redistribution sites are saturated, metabolism takes over and this is a slow process.

Sample protocols using the above drugs:

1.)

Premedicants:

- Acepromazine -- 0.05 mg / kg IM
- Morphine -- 0.5 mg / kg IM

Induction:

- Propofol -- calculated dose of 4.0 mg/kg IV; initial dose given over 40-60 seconds

Maintenance: kg

- Propofol infusion -- 0.2 - 0.5 mg/min⁴

2.)

Premedicants:

- Medetomidine – 5 mcg / kg IM (up to 20 mcg / kg in very aggressive dogs but then decrease the induction dose of ketamine /valium)
- Butorphanol - .2 mg / kg

Induction:

- Ketamine & Valium: 1:2 mix - 0.1 cc / kg is drawn up but administered only to effect. Once intubation is possible administer more anesthetic only as needed

Equipment

For TIVA all that is really needed is a needle and a syringe but for more exact and careful and thus safer administration of the anesthetic drugs it is advisable to:

1. Place an IV catheter,
2. Use a syringe pump or IV pump,
3. Consider constant rate infusion.

The merits and recommendations of these will be discussed.

The placement of an intravenous catheter is becoming routine for all general anesthesia in veterinary medicine. A catheter allows for appropriate intravenous fluid administration and thus allows greater control over blood pressure. With a catheter in place there is immediate intravenous access in the event that emergency drugs are needed. When administering TIVA a catheter is essential to provide intravenous access for additional anesthetic drug as needed.

Syringe pumps are available and allow for slow and controlled administration of minute amounts of drug. Intravenous pumps can administer as little as 1 cc / hour and are invaluable when setting up a constant rate infusion system.

Before syringe pumps and IV pumps became commonplace we used the micro-drip system and when closely monitored that system can be accurate. If the micro-drip system is not watched closely or if the patient positioning changes it does allow for greater errors. By combining a micro-drip system with a buretrol (burette) one can increase the accuracy of dosing and administration and prevent inadvertent over administration of anesthetic drugs however this system is not fail safe and must be watched closely.

Human medicine is now using a computer controlled system for intravenous anesthesia called Target Controlled Infusion. Using the pharmacokinetic parameters of drugs and inputting patient data these systems can be much more specific and careful when delivering anesthesia. The anesthesiologist can titrate the target concentration in a similar manner to the way we adjust the dial on an Isoflurane vaporizer⁴.

Constant Rate Infusion:

An ideal drug for use in CRI has a rapid onset of action and a short half life. The veterinarian can then provide a continuous, steady-state concentration of the drug and titrate it to the desired effect. The CRI method is also an excellent way to deliver analgesic agents because it eliminates the peak and trough effects that occur with intermittent dosing^{6,11}.

There are several advantages to CRI's. They allow the drug(s) to be titrated to effect resulting in a reduction in the total amount of drug used, frequently resulting in fewer side effects, less "rollercoaster" anesthesia or analgesia, fewer hemodynamic effects and more cost-effectiveness. While TIVA is a type of CRI, not all CRI's produce full anesthesia

Some of the reasons why a veterinarian might avoid CRI are: the mathematics can be intimidating, unfamiliarity of the drugs or little experience with their use and lack of specialized equipment needed for their use⁶.

There are many formulas and combinations available for CRI. Several web sites provide assistance with the calculations (www.vin.com, www.vasg.org). Karol Mathews Emergency and Critical Care Manual¹² is replete with CRI charts for various single agents. It is advised that one become familiar with one or two types of CRI and get used to using them and then apply this knowledge to further use.

CRI Dosing Information for Morphine, Lidocaine and Ketamine Combination⁸:

Morphine Lidocaine Ketamine CRI is used for intense or severe pain – as an adjunct to general anesthesia but this is NOT full general anesthesia. This is used for dogs only as Lidocaine is not recommended for use in cats. Protect from light as morphine and Lidocaine are light sensitive.

Morphine (15 mg / ml) – 2 to 6 mcg / kg / minute = (0.12 to 0.36 mg / kg / hour).
Loading dose is 0.5 mg / kg IM or very slowly IV.

Lidocaine (20 mg / ml) – 10 to 50 mcg / kg / minute = (0.6 to 3.0 mg / kg / hour).
Loading dose is 1 mg / kg IV.

Ketamine (100mg / ml) – 2 to 20 mcg / kg / minute = (0.12 to 1.2 mg / kg / hour).
Loading dose is 0.25 to 0.50 mg / kg IV.

1. Remove 29.5 cc's from a 500 ml bag of fluids (D5W, LRS or Saline)
2. Then add to the bag:

- a. Ketamine (100 mg / ml) – 0.6ml
 - b. Morphine (15 mg / ml) – 4 ml
 - c. Lidocaine (20 mg / ml) – 25 ml
3. Preload with:
- a. Ketamine (0.25 to 0.50 mg / kg IV)
 - b. Morphine (0.5 mg / kg IM or very slow IV,)
 - c. Lidocaine (1mg / kg IV bolus)
4. Deliver the solution at 1 ml / kg / hour. The rate can be increased up to 3 ml / kg / hour without exceeding the dosing guidelines for any of the drugs in the dog.

Dosing Information for Fentanyl CRI:

Fentanyl at this dosage could be used to combat moderate to severe pain and also as an adjunct to general anesthesia.

Fentanyl (50 mcg / ml)

1. Remove 15 ml of fluid from a 250 ml bag of Sodium Chloride or Plasmalyte^R
2. Add 15 ml of Fentanyl (50 mcg / cc)

This is administered at 1 – 2 cc's / kg / hour and will deliver 3 – 6 mcg / kg / hour.

Avoiding or Preventing Complications

As with any anesthetic protocol it is very important to make careful calculation of drug doses and infusion rates. A familiarity with the drugs being used and their properties and associated potential problems is also essential.

Each patient must be assessed as an individual and then an anesthetic protocol should be chosen based on the assessment. As part of the assessment the level of pain for the procedure should be estimated and then an appropriate preemptive analgesia protocol should be chosen¹³.

ASA classification for patients undergoing anesthesia:

(ASA = American Society of Anesthesiologists)

- ASA 1 – Normal healthy patient – elective procedure
- ASA 2 – A patient with MILD systemic disease
 - Compensated cardiac disease, mild fever
- ASA 3 – A patient with severe systemic disease
 - Moderate dehydration, anemia, cachexia, hypovolemia
- ASA 4 – A patient with severe systemic disease that is life-threatening
- ASA 5 – A patient not expected to live

By making an ASA assessment and where possible correcting or compensating for systemic disease we will improve the anesthetic outcome. Examples of this would be correcting dehydration prior to anesthesia, blood, plasma or colloid transfusion where indicated. It may also be prudent to delay surgery if possible until the ASA status can be improved.

Optimally, postoperative complications can be minimized or alleviated by thorough preoperative assessment and stabilization and appropriate intraoperative management and support. Regardless of pre-operative or intra-operative techniques, attentive monitoring and continued support well into the recovery period is imperative for a successful anesthetic outcome.

- All patients should be left intubated until they are swallowing vigorously and patients with suspected upper airway dysfunction should remain intubated until they will no longer tolerate the endotracheal tube. Patients should not be excessively stimulated so that the tube may be removed.
- Since we know that most anesthetic drugs cause hypotension, we should strive to make blood pressure monitoring routine in all phases of anesthesia. Note that it is not enough to simply monitor blood pressure but we should be prepared to adequately treat hypotension with fluids and if necessary positive inotropic agents (dopamine or dobutamine).
- Pain causes stress and excitement during the post-anesthetic period. Untreated pain can become pathology in itself causing tachycardia, hypertension, tachypnea, gastric ulcerations, ileus, decreased renal function, catabolism and altered homeostasis, impaired wound healing etc. Appropriate medication for pain will also decrease excitement as the patient regains consciousness resulting in a smoother recovery. When necessary drugs that provide sedation as well as analgesia should be considered. Appropriate use of analgesic drugs in the preemptive and intraoperative period will decrease the amount of pain that the patient experiences in recovery but patient pain must be continually reassessed and treated during the post-operative period.
- Hypothermia causes a variety of complications including clotting dysfunction, increased risk of infection, tissue hypoxia, acidosis, abnormal electrical condition in the heart, myocardial ischemia etc. Because hypothermia has cerebral effects that decrease the patient's anesthetic needs. This might lead to a deeper than planned anesthesia when a patient's temperature is allowed to drop. In the recovery phase shivering increases the consumption of oxygen by up to 200%. It also increases the discomfort of the patient. Prevention of hypothermia should be the goal for all anesthesia patients and active re-warming should begin immediately once hypothermia has occurred^{13,14}.

Pain Management

It used to be thought that animals either did not feel pain or that their perception of pain was different than humans. However, because cats and dogs have neural pathways and neurotransmitters that are similar or identical to humans it is highly likely that animals

experience pain similarly. Untreated pain decreases quality of life in all patients; ad prolongs recovery from surgery, injury or illness. Preventing and managing pain is a fundamental part of good patient care. The veterinary team must recognize, prevent and treat pain. It is recommended that pain should be thought of as the fourth vital sign (temperature, pulse, respiration and pain assessment). When integrated into all patient evaluations we would be more likely to routinely treat for pain. This would lead to improved quality of life and reduced complications for all patients¹.

The categorization of pain as adaptive or maladaptive is recommended by the AAFP and AAHA⁵. This is a change from the traditional categories of acute and chronic pain. Adaptive pain is a normal response to tissue damage. This includes inflammatory pain which includes the acute pain following surgery or trauma. Some chronic pain states such as osteoarthritis. If adaptive pain is not appropriately managed physical changes occur in the spinal cord and brain leading to pain that is termed maladaptive. The pain-induced changes in the nervous system cause it to become more sensitive rather than less sensitive. Wind-up pain is a heightened sensitivity that results in altered pain thresholds, both peripherally and centrally such that pain is experienced in areas unrelated to the original source. Hyperalgesia is a component of this and is an excessive response to a painful stimulus. Allodynia is pain caused by a stimulus that does not normally result in pain and can be a component of maladaptive pain⁵.

To optimize pain management and improve the safety of anesthesia, use a perioperative approach to pain management. For example, giving an opioid prior to a surgical procedure is much more beneficial than administering the same dose afterward and will also decrease the dose of anesthetic required for induction and maintenance¹⁵. Adequate analgesia during the intraoperative and postoperative period increases patient comfort and facilitates a smoother recovery from anesthesia. It may also prevent the development of maladaptive pain⁵.

Techniques for Providing Analgesia:

Local Anesthetic: Local anesthesia provides pre-emptive analgesia because it is usually administered prior to surgery. By applying analgesia directly to the nerve endings excellent pain control is achieved while reducing the need for systemic drugs. Local anesthetics disrupt neural transmission of information by axons at the treatment site and provide 'true' analgesia. The most common local anesthetic is Lidocaine – this takes effect 3 to 5 minutes after injection and the effect lasts for 60 to 90 minutes. The duration of effect can be prolonged by adding epinephrine. Bupivacaine takes 15 to 20 minutes to take effect but lasts for 3 to 6 hours. Sometimes the two types of local anesthesia are combined to give a quick onset of action but longer duration. Local anesthesia can be used for local infiltration, dental nerve blocks, intra-articular or joint space blocks, pleural space, regional anesthesia (brachial plexus block or intercostal block), IV regional anesthesia (Bier block)⁷ and epidural nerve blocks^{8,11,15}.

Opioid Analgesia: Opioid are the most commonly used analgesics in hospitalized critical patients due to their efficacy, rapid onset of action and safety. These are classified as agonists, antagonists and mixed agonist / antagonist opioids. The availability

of antagonists makes the use of opioids safer because their drug effects can be rapidly removed. The pure agonists are the most potent. Morphine, hydromorphone, Oxycodone and Fentanyl are pure agonists. Buprenorphine is a partial agonist and has longer duration than morphine. This drug is becoming popular in the feline species and allows for buccal mucosal administration providing analgesia for up to 8 hours from a single dose. Butorphanol is a mixed agonist / antagonist. It is used for mild to moderate pain and has a 1 to 2 hour duration of action. Naloxone is a pure antagonist and is used to reverse the effect of the pure agonist. Tramadol is an oral synthetic opioid which is being used more frequently in animals to combat chronic pain which is moderate to severe^{8,11,15}.

Transdermal Fentanyl: Patches come in 25, 50 and 100 mcg patches. Appropriate size patches or combinations of patches should be applied to shaved and gently washed skin. For cats that are 2.5 kg or smaller only part of the patch should be exposed (i.e. the backing should be left attached). Therapeutic levels of drug are achieved in 12 to 24 hours so prior to this other methods of analgesia must be used.

Alpha₂ Agonists: α_2 -agonists inhibit the release of the excitatory neurotransmitter norepinephrine and thus produce analgesia and sedation. They have a short duration of action and also have the benefit that they can be quickly reversed with an α_2 -antagonist. They have profound effects on the cardiovascular and nervous systems but adverse side effects can be minimized by using low dosages. Bradycardia and vomiting are the most common side effects with α_2 -agonists. Medetomidine is a dose-dependent sedative and analgesic commonly used as a pre-anesthetic in healthy animals. It can be given IM or IV and will take effect in 5 to 15 minutes depending on the route used. The effect last for up to 90 minutes. When combined with a narcotic such as butorphanol, medetomidine can be used for short term minor procedures such as suturing lacerations, biopsies and lump removals. Animals seems sensitive to light and sound and precautions should be taken to minimize these effects^{1,11,15}.

NMDA Receptor Antagonists: Ketamine is the most commonly used n-methyl-d-aspartate antagonist. Ketamine can reverse central hypersensitivity due to prevention of the exaggerated response or wind-up activity that occurs with intense or chronic noxious stimuli. At lower doses the ketamine provides analgesia without the anesthesia or profound sedation that is seen at higher doses. Ketamine is also often used in CRI to provide analgesia in combination with other drugs.

Non-steroidal Anti-Inflammatory Drugs (NSAIDs): These drugs are among the most widely used analgesics in the treatment of chronic pain. They are also effective in reducing acute pain in the peri-operative period. Pretreatment with NSAIDs greatly reduces intraoperative and postoperative pain. NSAIDs have also been shown to have a synergistic effect when combined with other classes of drugs such as opioids. Since there is potential for compromise of renal function, candidates for NSAID therapy should be chosen carefully. There has also been some concern in the past that the use of NSAIDs can prolong bleeding time but with most of the newer COX-2 selective NSAIDs this is not a problem^{11,15}.

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