TOTAL IV ANESTHESIA
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Animals can be anesthetized using injectable agents, inhalants or a combination of injectable and inhalant agents. Inhalant agents are commonly used to maintain anesthesia in veterinary practice for longer surgical procedures; however, injectable agents (IV or IM) have been used in shorter surgical procedures.

There are advantages and disadvantages associated with the use of injectable agents for the induction and maintenance of anesthesia. Induction of anesthesia using injectable agents is more easily accomplished compared with the use of inhalants. The induction time for injectable agents is shorter in most cases and this decreases patient stress. If the animal has an airway problem, the use of injectable agents results in a quicker way to control the airway and ensure a patent airway. Injectable agents do not pollute the atmosphere. There are disadvantages associated with the use of injectable agents. Prolonged recovery especially in agents that depend primarily on hepatic metabolism for inactivation will occur. Prolonged effects may also occur in very young and old patients. There is a possibility of hypoventilation and then hypoxemia especially in patients not supplemented with high concentration of oxygen. The depressant effects of the injectable agents cannot be reversed especially in agents without specific reversal agents. There will be a delay when attempting to lighten the depth of anesthesia if a problem arises.

Maintenance of anesthesia using injectable agents can be performed by either intermittent IV or IM injections or by constant rate infusion (CRI). In this presentation, total IV anesthesia (TIVA) pertains to the administration of IV agent(s) using CRI to provide an anesthetic state. Ideally, this technique involves the use of drugs that achieve the elements of the four components of general anesthesia: amnesia (anxiolysis), autonomic areflexia, analgesia, and muscle relaxation.

When performing TIVA, a CRI of drugs is preferred over the intermittent IV boluses. Using intermittent IV boluses, a constant plane of anesthesia is more difficult to achieve. The CRI of drugs results in fewer sudden hemodynamic changes, lower total amount of drug given, and more rapid recovery from anesthesia. More rapid recovery from anesthesia can be due to the ability to change the rate of infusion according to the anesthetic requirement of the patient. The major disadvantage when using an effective CRI is the cost of a precision infusion device. This device, which replaces the vaporizer in this technique, should accurately deliver the chosen dose.

Principles
TIVA is based on the principle that a plasma drug concentration needed to produce anesthesia has to be reached quickly and maintained over the period of time that anesthesia is planned. A loading dose is determined based on the volume of distribution and the initial plasma drug concentration. This is determined by pharmacokinetic studies in animals. With hypnotic agents like propofol, the loading dose is calculated and given to effect. Following initial administration, the drug is both redistributed to tissues and eliminated. Therefore, to maintain the desired plasma drug concentration, a CRI is initiated. The infusion rate is determined by the clearance of the drug and the plasma drug concentration in plasma (also based on pharmacokinetic studies). There will be individual variation as to the response of animals to the
CRI of the drug. Lightening of the anesthetic plane can be corrected by IV bolus of additional drug.

**Drugs**

When considering TIVA, one must examine the properties of the drugs to be used. Drugs used for TIVA should possess most if not all of the following properties: a) water-soluble to minimize toxicity associated with the solvent, b) stable in solution, c) no perivascular sloughing if extravasated, d) given in concentrated solution to avoid fluid overloading, e) not absorbed by plastics, f) does not promote bacterial growth, g) rapid onset of action, h) cleared rapidly from the body for a more rapid and predictable recovery, i) devoid of adverse side effects, j) potent and lipid-soluble, k) relatively cheap and l) chemically compatible with other drugs. There is no single agent that possesses all these properties. Propofol, thiopental, etomidate, ketamine, and methohexital can potentially be used for TIVA to provide unconsciousness. Propofol, a hypnotic agent, is the most commonly used agent for TIVA. It has a higher elimination clearance and a shorter elimination half-life compared with other injectable agents. The clearance rate of propofol is faster than the liver blood flow. The recoveries from propofol are judged to be good. The other injectable agents available commercially have some undesirable features making them less preferred for TIVA. Thiopental, a commonly used IV induction agent, is not suitable for TIVA because of prolonged recovery associated with longer infusions. Following a single dose of thiopental, recovery occurs rapidly due to redistribution; however once redistribution sites are saturated, metabolism (a slower process) takes over. Additionally, thiopental is not currently available commercially in the US. Methohexital is more rapidly metabolized compared to thiopental, however rough recoveries are commonly associated with methohexital. Ketamine, another commonly used injectable in practice can be added to the other agents for TIVA. By itself, some metabolites of ketamine are active and will accumulate, resulting in prolonged drug action. In addition, seizure activity and hypertonus during recovery may occur. In cats, a combination of propofol and ketamine for TIVA has been reported. Etomidate, which maintains good cardiopulmonary function, has been tried as a maintenance agent; however, it has several detrimental effects. It suppresses the production of cortisol. The high concentration of propylene glycol in etomidate preparation causes hemolysis resulting in hemoglobinuria. Other clinical signs reported in dogs given etomidate as infusion are bradycardia and obtundation. A new formulation of etomidate has been touted as non-hemolytic. However, this is not yet available in the United States. Etomidate is more expensive compared with other injectable agents.

The benzodiazepines (midazolam, diazepam) may be included in TIVA technique, especially with an opioid. The benzodiazepines produce minimal cardiopulmonary depression. It is important to remember that neither midazolam nor diazepam can be used alone because it does not produce an anesthetic state in small animals. The opioids used in TIVA include fentanyl, remifentanil, alfentanil, and sufentanil. In our clinical practice, we use mainly fentanyl or remifentanil. Fentanyl is approximately 50 times more potent than morphine. It is a pure agonist and produces analgesia necessary for painful surgical procedures. When given as an IV bolus injection, it is effective in 4-7 minutes. When used as a CRI at high dosages for a prolonged period, it can accumulate. Its context-sensitive half-life is longer than remifentanil, alfentanil, and sufentanil. It is cheaper than remifentanil and does not need reconstitution. It can also cause severe slowing of the heart rate and an anticholinergic (atropine or glycopyrrolate) is administered to treat the severe bradycardia. Alfentanil is less potent than fentanyl. The advantage of alfentanil over fentanyl is its more rapid onset of action (1-2 minutes) following an
IV injection. Alfentanil can be given as a bolus injection with a dose range of 5.0-10.0 ug/kg. To prevent apnea, the dose of alfentanil should not exceed 5 ug/kg. Sufentanil is more potent than fentanyl. It is not extensively used in veterinary medicine. Remifentanil is another fentanyl derivative. It is unique because it undergoes nonhepatic metabolism. It is acted upon by esterases in blood and tissues resulting in rapid clearance. After administration, it also has an immediate effect because the levels in the blood and brain equilibrate rapidly. The potency of remifentanil is somewhat between fentanyl and alfentanil; however, the author uses a similar initial IV dose and CRI rate for remifentanil and fentanyl.

**Table 1.** Drugs used for TIVA

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Initial IV dose</th>
<th>CRI dose (IV)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>0.1-0.25 mg/kg</td>
<td>0.2-0.5 mg/kg/hr</td>
<td>Given with an opioid</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.1-0.20 mg/kg</td>
<td>0.2-0.5 mg/kg/hr</td>
<td>Given with an opioid</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>5-10 ug/kg</td>
<td>0.2-2.0 ug/kg/min</td>
<td>For CRI, use lower dose rate first</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>5-10 ug/kg</td>
<td>0.2-2.0 ug/kg/min</td>
<td>For CRI, use lower dose rate first</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>2-5 ug/kg</td>
<td>0.1-0.2 ug/kg/min</td>
<td></td>
</tr>
<tr>
<td>Alfentanil</td>
<td>5 ug/kg</td>
<td>1.0 ug/kg/min</td>
<td>1/7-1/10th the potency of fentanyl</td>
</tr>
<tr>
<td>Propofol</td>
<td>1-4 mg/kg</td>
<td>0.2-0.5 mg/kg/min</td>
<td>Not suitable for prolonged infusion because of adrenal suppression and hemolytic effect of propylene glycol</td>
</tr>
<tr>
<td>Etomidate</td>
<td>1-2 mg/kg</td>
<td>0.02-0.3 mg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg IV</td>
<td>8.0 ug/kg/min</td>
<td>To complete induction, propofol may be needed</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>10 ug/kg</td>
<td>0.8-2.0 ug/kg/min</td>
<td></td>
</tr>
</tbody>
</table>

**Indications**

There are certain indications for the use of TIVA in small animals. This technique is suitable for surgical procedures that involved the upper airway when placement of an endotracheal tube will interfere with surgery. Bronchoscopic evaluation in smaller patients is facilitated by the use of TIVA. A bronchoscope can be inserted into the endotracheal tube; however, this procedure cannot be performed in very small patients since the bronchoscope cannot be inserted into the small endotracheal tubes. The use of IV agents as a form of general anesthesia for patients with intracranial hypertension such as an intracranial tumor is highly recommended, because inhalant agents increase blood flow to the brain while IV agents like propofol reduces the cerebral blood flow. Other uses of CRI using propofol include patients with postoperative seizures after portosystemic shunt ligation, anesthesia/sedation for patients that are mechanically ventilated in an intensive care setting, patients undergoing magnetic resonance imaging, radiation therapy and any general anesthesia when an anesthetic machine is not available.

**Clinical technique**

Preferably, an indwelling intravenous catheter should be placed prior to beginning the procedure. To perform TIVA, the use of a syringe pump is highly desirable. The syringe pump can accurately deliver the anesthetic dose over time and changes in delivery rate can be made more quickly. As an alternative, propofol can be infused using an IV administration set. For this technique, propofol is mixed with 5.0% dextrose in water. According to the manufacturer,
propofol should only be diluted with 5.0% dextrose in water and the final concentration of propofol should not be less than 2.0 mg/ml. The diluted form has 95% potency after 2 hours of running infusion in plastic. This technique is feasible, but takes more time to prepare, allows more chances for contamination during preparation, and is less accurate. The drip rate may be difficult to control because changes in the height of the fluid column and occlusion of the IV line changes the drip rate.

Premedication is highly recommended before TIVA. The quality of induction is vastly improved with the use of premedicants. The choice of premedicants will depend on the medical condition of the animal. If the animal is in pain or if the surgical procedure is painful, an analgesic (opioid preferably) should be incorporated in the premedicants. A tranquilizer or sedative (acepromazine, benzodiazepines, or alpha-2 agonist) should also be considered as part of premedication. The use of anticholinergic (atropine, glycopyrrolate) as preanesthetic is an option. Opioids stimulate the vagal tone and sinus bradycardia may occur following opioid administration. The author does not routinely administer an anticholinergic as premedicant. It is given when bradycardia occurs following and during opioid administration. Once sedation is achieved, anesthesia is induced using propofol. A calculated dose of 4.0 mg/kg is drawn up. Depending upon the degree of sedation, a typical initial dose is one-half of the calculated dose. This is given over 40-60 seconds. If the animal is still very light, the rest of propofol is given to effect. In procedures that will allow endotracheal intubation, an appropriately sized endotracheal tube is inserted and oxygen is supplied. Immediately after anesthetic induction, infusion of propofol at 0.4-0.5 mg/kg/min is started. The infusion rate should be adjusted based on the depth of anesthesia. It is important to remember that individual patients will vary in their anesthetic requirements. If the plane of anesthesia is getting too deep, characterized by lowering of blood pressure, decreased respiratory rate, and a central location eyeball without eye reflexes, the infusion rate can be reduced to as low as 0.2 mg/kg/min. In some instances, sudden application of surgical stimulus will lighten the plane of anesthesia resulting in patient’s movement. When that happens, a bolus dose of propofol should be given to rapidly increase the blood concentration of propofol. The guideline is to give 10.0-20.0% of the induction dose actually given to the patient. This can be repeated based on the response of the animal. Following the bolus injection, the infusion rate may have to be increased by 0.1 mg/kg/min to maintain a higher plasma level, which the patient requires to maintain anesthesia. Utmost attention should be made to monitor the depth of anesthesia when the infusion rate is increased. Regular adjustments to the rate of infusion are expected for the first 2-3 hours following the loading dose.

A modification of this technique is to add an opioid infusion to the propofol infusion. Propofol does not possess analgesic property. The author uses fentanyl or remifentanil for patients that undergo painful procedures. The infusion ranges from 0.5-2.0 ug/kg/min. In this situation, ventilatory support is required due to respiratory depression brought about by the propofol and the opioid. For patients with hepatic and/or renal insufficiency, remifentanil is preferred over fentanyl. Remifentanil results in rapid equilibration between the blood and the brain such that a bolus dose before the CRI is not necessary. With fentanyl, a bolus dose should be given slowly to minimize sudden changes in arterial blood pressure and heart rate.

In the author’s experience, the most common complication associated with a propofol CRI is respiratory depression. Hypoxemia can develop if the animal is inspiring room air. Administration of a higher concentration of oxygen via a facemask or endotracheal tube is advisable. Another possible complication associated with this technique is arterial hypotension. If the infusion rate is maintained at a higher level and the procedure being performed is not
painful, blood pressure will decrease. If the procedure is mildly painful or not painful at all, light anesthetic depth can be maintained characterized by the presence of weak palpebral reflex.

A further modification of TIVA is the inclusion of a neuromuscular blocking agent to the hypnotic and opioid. With this technique, all desired elements of the four components of general anesthesia are provided. The neuromuscular blocking agent (atracurium, pancuronium, vecuronium) provides muscle relaxation. Sedative-hypnotic drugs (propofol) produce unconsciousness and amnesia. Opioids provide analgesia and decrease or stop reflex response to surgery. In this technique, the ventilation should always be controlled because the neuromuscular blocking agent paralyzes the diaphragm. This technique requires more equipment (mechanical ventilator and nerve stimulator) and expertise. Its application in clinical practice is also quite limited.

TIVA is another anesthetic technique that can be utilized in veterinary practices. It has its advantages and disadvantages, which should be considered when choosing an anesthetic protocol for each case. There are cases that will benefit from TIVA, such as animals with intracranial hypertension. The procedure determines the appropriate TIVA protocol. Diagnostic imaging and non-painful procedures can be done by using a hypnotic (propofol) while painful surgical procedures will require a hypnotic, an opioid, and possibly ketamine. In very sick animals (e.g., septic patients), a combination of a benzodiazepine and an opioid for TIVA may be appropriate.

Case Examples
Example 1: An English bulldog that requires laryngeal saccullectomy and soft palate resection
Premedicans:

- Acepromazine - 0.03 mg/kg IM
- Butorphanol - 0.2 mg/kg IM

Induction:

- Propofol - calculated dose of 4.0 mg/kg IV; initial dose given over 40-60 seconds and the rest given to effect

Maintenance

- Propofol infusion - 0.2-0.5 mg/kg/min; boluses of propofol at 0.5 mg/kg as needed

Oxygen supplementation is highly recommended.

Example 2: Brain tumor removal in a boxer
Premedicans:

- Midazolam – 0.2 mg/kg IM
- Methadone – 0.3 mg/kg IM

Induction:

- Propofol – calculated dose of 4.0 mg/kg IV; 1.0 mg/kg IV given over 30 seconds
- Midazolam – 0.2 mg/kg IV follows the propofol administration
- Propofol – rest given to effect

Maintenance

- Propofol infusion – start at 0.4 mg/kg/min and adjust rate as needed
- Remifentanil infusion – start at 0.5 ug/kg/min

Provide intermittent positive pressure ventilation and ensure eucapnia (normal PaCO₂) and if needed, hyperventilate to reduce blood flow to the brain.