Pharmacology- Intravenous Anesthetic Agents & Dissociatives

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Introduction

- The term intravenous anesthetic agents implies inducing anesthesia by drugs administered intravenously.
- Advantages of IV anesthesia include rapid and smooth induction of anesthesia, little equipment requirement (syringes, needles, catheters), and easy administration of drugs.
- Disadvantages include difficult retrieval of drug once administered, less control of depth and duration of anesthesia, lack of ventilatory support, and poor tolerability in debilitated, dehydrated or toxicated animals.
- Details of pharmacokinetics and uptake and metabolism of these agents are beyond the scope of this lecture, but more pharmacokinetic knowledge is essential for safe use of these agents.
- Ideal characteristics of IV anesthetics are
  - high therapeutic index
  - no toxic metabolites
  - non-cummulative
  - potent, so small volume is required for anesthetic induction/maintenance
  - long shelf life and resistance to microbial contamination
  - compatible with other dugs
  - quick and smooth induction and recovery
  - reversible with specific antagonist
  - non-allergenic
  - no cardiopulmonary depression
  - independent of liver and kidneys for metabolism and excretion
  - no effect on cerebral blood flow
  - no endocrinologic effect
  - no pain on injection
  - inexpensive
- Response to administration of IV anesthetic induction agents depends on
  - Dose, concentration and speed of administration
  - Blood volume between injection site and brain
  - Ionization
  - Protein binding
  - Redistribution to non nervous tissue
  - Metabolism and excretion of the drug and metabolites
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- Major clinical properties include good hypnosis, poor to moderate analgesia and doserelated respiratory and cardiovascular depression.
- However, at light levels of anesthesia, cardiovascular depression is minimal unless the patient is hypovolemic.
- There can be marked recovery excitement, but this is reduced or removed by premedication.
- Barbiturates will cross the placenta, and will affect the fetus
- Adult ruminants metabolize barbiturates faster than do cats and dogs. Thus they may be shorter acting and less cumulative in ruminants. Neonates do not have the necessary enzymes, and prolonged effect may be seen. Although theoretically the horse also has the ability to metabolize barbiturates faster than the dog, this is not so in the clinical circumstances, and recovery from cumulative doses of barbiturates may be prolonged and violent.
- Treatment of overdose of barbiturates is IPPV to remove respiratory depression (NB, analeptics do not last as long as the barbiturate) and fluid therapy to increase renal excretion.
- In small animals, general anesthesia is induced by administering part of pre calculated dose until the desired anesthetic depth (usually just deep enough for endotracheal intubation) is reached – referred to as "titrating to effect".
- All barbiturates are controlled substances and therefore require good record keeping and security as required by the DEA.

Pentobarbital (Saggital®, Nembutal®)

- Controlled substance (Schedule II)
- Anesthetic concentration is 60 mg/ml. (NB euthanasia solutions contain a higher concentration, and various stabilizing agents sometimes cause cardiac arrest).
- No longer used routinely for anesthetic induction due to its prolonged rough recovery
- Pentobarbital is mainly used for seizure control in the animal.
- Intravenous dose of healthy unpremedicated dogs and cats is 30 mg/kg, given to effect. It has a slower onset of action than thiopental (minutes).
- Pentobarbital is metabolized by the liver.
- Administered IV (slow response, give very slowly) or IP (laboratory rodents).
- Intratesticular injection is still used for castrating pigs (the depot of drug is then removed with castration).
- In single stomached animals, full anesthetic doses produce about 1 hour surgical anesthesia, but recovery takes up to 24 hours. Recovery is violent (dogs howl and paddle) unless premedication is used.
- Small animals become very hypothermic.
- Ruminants, however, recover quietly and very much faster, and the drug still has a place to play in farm animal anesthesia.
- Contraindicated in neonates and animals with liver failure, respiratory disease, porphyria, requiring cesarean section, hypovolemia and emaciation

Ultra-short acting barbiturates: Thiopental, Thiamylal, Methohexital

- Ultra-short acting barbiturates are often used in the clinic for inducing general anesthesia in both small and large animals.
- Advantages of ultra-short-acting barbiturates for induction of anesthesia:
  - They are the least expensive of the injectable anesthetics.
  - Need no specialized equipment for administration (vs. inhalation anesthetics).
  - These drugs have a rapid onset of action, provide a predictable response, and rapid recovery following single-dose administration.
- Patients that benefit from thiobarbiturates induction:
  - Patients with raised intracranial pressure - thiobarbiturates decrease intracranial pressure.
  - Patients with seizure history - thiobarbiturates decrease seizure activity.
  - Patients with corneal lacerations or glaucoma - thiobarbiturates decrease intraocular pressure.
  - Patients for examination of laryngeal function - thiobarbiturates does not depress laryngeal reflexes at the light dose.
  - Patients with hyperthyroidism - thiobarbiturates have antithyroid effect.
  - In large animals, ultra-short acting barbiturates are usually used in combination with glyceryl guaiacolate (also called guaifenesin). When compared to using ultra-short acting barbiturates alone, the total dose of ultra-short acting barbiturates is decreased when it is given with guaifenesin. This results in less cardiovascular depression and smoother inductions and recoveries from anesthesia.
- Precautions when using ultra-short acting barbiturates for induction of anesthesia:
  - The drug must be given intravenously because of its highly alkaline pH (= 11); perivascular injection will cause tissue necrosis. The drug must not be used when venous access is not possible or questionable.
  - Small margin of safety between an effective dose and a lethal dose especially in debilitated patients.
  - Apnea and profound respiratory depression following ultra-short

Thiopental (Thiopentone) (Pentothal®)

- The most widely used barbiturate.
- Presented as powder and dissolved in water to required concentration. Limited shelf life of solution. Only for IV use.

- Propofol is, in general, non cumulative. Thus it can be used for prolonged anesthesia by intermittent injection or by continuous infusion (NB, in neonatal children problems occurred when it was used by continuous infusion for several days to obtain sedation in intensive care. It is probable that the toxicity was due to accumulation of the carrier in patients whose enzymes were sufficiently undeveloped to cope. It can be used safely for anesthesia in neonates).
- Propofol has extensive protein binding (over 90 %).
- Propofol should be administered slowly ("titrate to effect") for endotracheal intubation.
- Single induction dose of propofol in healthy non-sighthound dogs makes no clinically significant difference in terms of awakening time from induction to recovery compared to thiobarbiturates anesthesia.
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Imiazole anesthesia: Etomidate/Metomidate

Etomidate (Amidate®; Hypnomidate®)

- Etomidate is a carboxylated imidazole derivative
- Etomidate is an intravenous, ultra-short-acting, nonbarbiturate hypnotic drug.
- Etomidate is quite widely used in man as an induction agent and by continuous infusion. In man, the IV induction dose is 0.3mg/kg, but higher dose is needed in dogs and cats (2-4 mg/kg).
- Prolonged infusion suppresses adrenocortical function.
- A single IV dose also suppresses adrenal steroidogenesis in dogs and cats for several hours, but clinical significance of this is unknown.
- Initial recovery is by redistribution, and the half life is moderate (about 1 hour in man), so there is some cumulative effect.
- Etomidate, then, undergoes rapid hepatic metabolism resulting in rapid recovery and does not accumulate when repeated boluses or infusion is given.
- Major advantages are minimal cardiopulmonary depression, it produces minimal change in heart rate, mean arterial blood pressure, or myocardial performance.
- The respiratory effects of etomidate are similar to thiopental and propofol in it will induce respiratory depression and apnea in animals.
- Etomidate has not gained popularity as a regular anesthetic induction agent in veterinary medicine because:
  - It is the most expensive (vs propofol and thiopental)
  - Sneezing, retching, and myoclonic twitching are often observed during induction (these side effects can be minimized with a premedication)
  - Etomidate inhibits adrenocortical function
  - Hemolysis and hematuria also have been reported in dogs and cats following either induction or infusion of etomidate
  - It is painful upon injection due to its propylene glycol preparation
- Perivascular injection of etomidate does not cause tissue irritation.

Metomidate (Hypnodil®)

- Metomidate has been used over two decades as a hypnotic agent in the pig
- Given IV (irritant), its advantages are minimal respiratory or cardiovascular depression with good quality hypnosis.
- Analgesia is very poor.
- Recovery time is of moderate length (about 1 hour).
- It has been withdrawn and is currently not available.

Dissociatives(Phencycline derivatives): Ketamine and Tiletamine

- Dissociative anesthesia implies dissociation from the surrounding with only superficial sleep mediated by interruption of neuronal transmission from unconscious to conscious parts of the brain.
  - During dissociative anesthesia, the animal maintains its pharyngeal, laryngeal, corneal, palpebral, and swallowing reflexes. The eyes also remain open.
  - Dissociative anesthetic agents increase muscle tone, spontaneous involuntary muscle movement (occasionally seizures are seen in some species)
  - Salivation, lacrimation are also increased.
  - Somatic analgesia is good.
- Ketamine and tiletamine (combined with zolazepam in Telazol®) are the two dissociative anesthetics currently available in veterinary practice.
- Cardiovascular effects of dissociatives are dose dependent. At clinical doses, ketamine (and tiletamine) centrally stimulate the sympathetic system resulting in tachycardia, increased blood pressure and increased cardiac output. Large doses of ketamine depress the myocardium directly and may produce hypotension.
- Ketamine and Telazol® produce less respiratory depression than other intravenous anesthetic agents (propofol, midazolam, barbiturates); however, clinically effective dose of ketamine or Telazol® may induce apnea in some susceptible animals.
- In most species, ketamine and Telazol® are metabolized by the liver. In cats, a significant amount (50%) of ketamine is excreted unchanged by the kidney. This difference may account for differing responses seen in dogs and cats receiving dissociatives. Dogs tend to have slow and stormy recoveries (head shaking, salivating, muscle rigidity, vocalization, defecation) from ketamine and Telazol®, while cats tend to have faster and smoother recoveries.
- Both ketamine and Telazol® are control substances (schedule III) and require for accurate documentation and security. ketamine is currently widely abused.
- Ketamine and Telazol® reliably produce anesthesia following either IM or IV administration
- The effectiveness of these drugs following IM administration is an important reason for the popularity of these agents in cats, many exotic species, and intractible patients.

Ketamine

- Ketamine is congener of phencyclidine. It was first used in human anesthesia in 1965 and in veterinary anesthesia in 1970.
- The ketamine molena 2(ne)4(a)4(nd)]TJ -0.004 Tc 0.004 Tw 3.17 0 Td [(T)-3(el)-6([(n(he)

- Ketamine appears to selectively depress the thalamocortical system, an

Steroid anesthesia

- Historically,

Opioid/Benzodiazepine combination as neuroleptanalgesia induction technique

- In man, high dose potent opioids may be used in combination with sedatives (usually midazolam) to produce anesthesia induction or total intravenous anesthesia (neuroleptanalgesia)
- The combination is popular for anesthesia induction or intra