Commissioned paper

Current anaesthetic considerations and techniques in rabbits

Part I: Pre-anaesthetic considerations and commonly used analgesics and anaesthetics

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SUMMARY

Rabbit anaesthesia is perceived by many as a difficult, high-risk procedure. Many veterinarians therefore do not feel comfortable when having to sedate or anaesthetize a rabbit. Fortunately, the arrival of newer, safer anaesthetic agents, development of specialized anaesthetic equipment, and increased knowledge about veterinary anaesthesia has greatly reduced the risks of anaesthesia-related morbidity and mortality. In particular the use of endotracheal tubes or supraglottic airway devices, administration of intra-operative fluids and provision of adequate thermal support, combined with adequate and continued monitoring of the patient are important to prevent potentially fatal conditions such as hypoxia, hypovolaemia and/or hypo- or hyperthermia. Vigilant monitoring of the patient should, however, not only be limited to the anaesthetic procedure, but also extend to the pre- and post-anaesthetic period, in which a thorough evaluation of the patient may help to detect pre-existing conditions or post-anaesthetic complications that need to be dealt with in order to maximize chances of success. Various injectable and inhalant anaesthetics, premedicants and analgesics may be combined to achieve a balanced anaesthesia which minimizes the chances of adverse events. The first part of this review discusses the various aspects that need to be taken into consideration during the pre-anaesthetic evaluation as well as the most commonly used analgesics and anaesthetics in rabbit medicine.

Keywords: Rabbit; *Oryctolagus cuniculi*; Anaesthesia; Analgesia; Sedation; Premedication

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Introduction

Pet rabbits may easily be stressed when handled. A period of prolonged, repetitive and/or forceful handling may therefore quickly lead to a deterioration of the rabbit's clinical condition, especially if it already was sick or debilitated prior to the restraint. In addition, incorrect handling and/or vigorous kicking or struggling by the rabbit in an attempt to escape may result in serious injuries such as vertebral fractures, (sub)luxations and (permanent) damage to the spinal cord [1,2]. Correct handling is therefore essential for the wellbeing of the rabbit. To facilitate the safe performance of medical procedures such as blood collection, IV catheter placement, radiography and dental inspections, the use of sedatives and/or anaesthetic agents may be beneficial.

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Sedatives may furthermore be useful to reduce anxiety or stress related to medical conditions. For example, the use of the sedative midazolam may be beneficial in dyspnoeic rabbits as the drug will help the animal relax, thereby allowing it to breathe more easily and with less effort and increasing the efficacy of oxygen delivery into the deeper airways [3]. For diagnostic procedures, such as ultrasound, radiographs or computed tomography, a deeper type of sedation is possible by adding other sedatives such as butorphanol and combining this with inhalant drugs such as isoflurane. For more invasive procedures, such as orthopaedic or soft tissue surgeries, general anaesthesia is required with more analgesic properties. This can be achieved using (a combination of) injectable and/or inhalant drugs.

In particular anaesthesia for exotic species carries substantial risks and both peri- and postoperative complications commonly occur. Rabbits in particular prove difficult to safely sedate or anaesthetise, especially because of their relative sensitivity to the respiratory depressant effects of many anaesthetics and the required experience needed for proper intubation [4,5]. A study by Brodbelt (2008) among veterinarians across the UK revealed a significantly higher risk for peri- or post-anaesthetic death for rabbits (1.39%) compared to dogs or cats (0.17 and 0.24%, respectively), with more than one-third (36%) of patients dying during the procedure [6,7]. In addition, the study revealed that that the risk of mortality is approximately ten times higher for a sick rabbit compared to a healthy individual (7.37 versus 0.73%)[6,7]. Factors which may contribute to the rabbit's overall higher susceptibility to anaesthesia-related morbidity and mortality include a) the increased susceptibility to stress from loud noises; the unfamiliar surroundings; and sight, smell or sound of predators, which may predispose to development of cardiac arrhythmias; b) the increased susceptibility to effects of pain after surgery, which may result in reduced appetite and gastric stasis; c) quick development of hypoxia due to breath holding, respiratory depression and the relative small lung capacity in combination with the increased difficulty to intubate; d) relative difficulty to gain intravenous access, particularly in smaller breeds, which limits the ability to correct fluid and/or electrolyte imbalances during anaesthesia; and e) the presence of pre-existing (subclinical) disease (e.g. dental disease, pneumonia, gastric stasis) [8,9].

To reduce the risk of anaesthesia-related morbidity and mortality, preventive measures may be taken. These include: a) performing a preoperative clinical assessment of the health status of the patient and optimizing the patient's clinical condition prior to the procedure; b) use of an anaesthetic protocol tailored to the individual patient, with a particular emphasis on provision of sufficient analgesia; c) [endotracheal] intubation to guarantee oxygen suppletion and enable assisted breathing if needed; d) placement of an intravenous or intraosseous catheter for the administration of fluids and drugs; and e) continued monitoring of vital signs, both during the intervention and follow-up period [8]. The first part of this review will focus on the various precautions and considerations that should be taken into account during the pre-anaesthetic evaluation and induction of anaesthesia.

Pre-Anaesthetic Considerations

Prior to performing a procedure involving anaesthesia, a thorough history and physical examination should be performed to assess the animal's overall health (Figure 1a – d). Particularly in prey species such as rabbits, it may be difficult to identify presence of (subclinical) disease as the animal often tries to hide that it is sick and may not show any signs of disease unless it is severely debilitated. Particularly diseases involving the respiratory tract, which may manifest itself by coughing, sneezing, nasal discharge (which can also be found at the medial side of the front paws), increased respiratory sounds and/or changes in breathing pattern or frequency, may pose an increased anaesthetic risk [8,10]. Other diseases or conditions that affect the animal's ability to withstand anaesthesia include diseases of the digestive tract (e.g. anorexia, dental disease, gastric stasis and/or diarrhoea) and cardiovascular system (e.g. dehydration and/or shock) as well as obesity or cachexia [8,10,11]. Based on the findings during the clinical and diagnostic work-up, patients may be classified as ASA-I to ASA-V according to their fitness prior to surgery (Table 1). Whenever possible, the patient's clinical condition should be stabilized prior to commencing anaesthesia, e.g. by providing subcutaneous, intravenous or intraosseous fluid therapy to dehydrated or hypotensive patients, oxygen to dyspnoeic patients and/or nutritional support to anorectic rabbits.

During the physical exam, care should also be taken to obtain an accurate weight, which is required to calculate the dosages of fluids and/or drugs that are used during the procedure. In the waiting period prior to the anaesthesia, and in the post-anaesthetic period, prey species such as rabbits should be hospitalized in a quiet environment, away from potential predators (e.g. dogs, cats, ferrets).

Figure 1a. The pulse in rabbits can be taken at the central ear artery (A. auricularis). This artery is located on the outer surface of the pinna.

Figure 1c. The conjunctival mucous membranes can be examined by everting the upper and lower eyelids.

Figure 1d. Auscultation of the lung and heart is an essential part of the preanaesthetic exam.

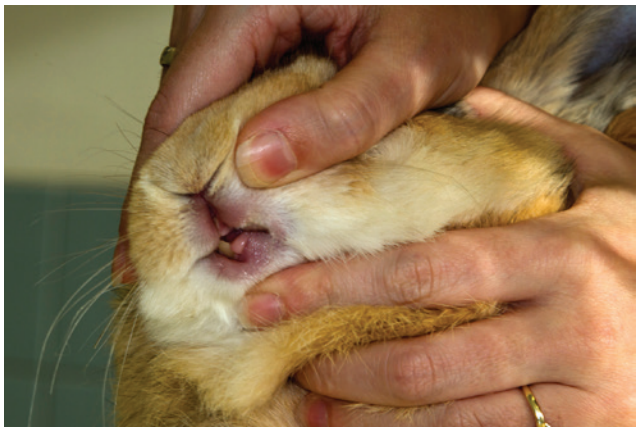

Figure 1b. The oral mucous membranes can be inspected by slightly raising the upper lip. Care must be taken not to occlude the nostril, as this compromises breathing and may therefore be stressful to the rabbit.

Table 1. ASA physical status classification system[12]

ASA class	Description
I	Normal, healthy patient
II	Patient with mild systemic disease, without functional limitations
III	Patient with moderate systemic disease, with functional limitations
IV	Patient with severe systemic disease that poses a constant threat to life
V	A moribund patient who is, with or without intervention, not expected to survive anaesthesia and will most likely die within 24 hrs

Provision of hiding boxes, bedding and nesting materials, or social housing may provide additional security. Since rabbits are not able to vomit, pre-anaesthetic fasting is not required. Withholding food for periods of 1-2 hours is, however, recommended to ensure that the oral cavity is empty [8,9]. Water should be provided at all times. Pre-oxygenation may be considered prior to induction of anaesthesia as this will help to improve oxygen saturation, which is particularly useful in animals with cardiac or respiratory disease and/or when using drugs that induce (temporary) apnoea, such as alphaxalone or propofol.

Sedation and premedication

Administration of sedatives may be beneficial in patients that need to undergo procedures such as radiography, IV catheter placement or blood collection. Sedatives may furthermore alleviate anxiety and reduce stress, thereby facilitating facemask induction and avoiding breath holding in response to the smell of inhalant anaesthetics, while at the same time also allowing reduction of the amount of administered anaesthetic drugs helping to minimize the risk of detrimental side effects to the anaesthesia and allowing smooth recovery from anaesthesia. Before administering the drugs, the calculated dosages should always be checked carefully and adjusted to the patient's clinical condition. For example, sick, debilitated rabbits may need lower doses of the same drug compared to healthy, young rabbits presenting for an elective procedure.

Midazolam, a short-acting benzodiazepine, is commonly used to facilitate diagnostic procedures (e.g. radiography,

Table 2. Commonly used drugs for premedication in rabbits [9,16]

Drug	Dose	Effects
Acepromazine	0.25-1 mg/kg IM	Phenothiazine derivative, tranquilizer, moderate sedation, no analgesia, hypotension, hypothermia
Atropine	0.1-0.5 mg/kg SC, IM	Parasympathicolytic drug, reduces salivary bronchial secretions, protects the heart from vagal stimulation. Note: some rabbits possess atropinesterase which deactivates the above described activities. Glycopyrrolate is therefore preferred over atropine in rabbits
Butorphanol	0.1-1 mg/kg SC, IM, IV q4-6h	κ-agonist, sedation, analgesia, dose-dependent respiratory depression
Butorphanol / midazolam	0.3-0.5 mg/kg (B) + 0.1-0.5 mg/kg (M) SC, IM	Commonly used combination for sedation and/or premedication in rabbits
Chlorpromazine	1-10 mg/kg IM, IV	Phenothiazine derivative, tranquilizer, moderate sedation, no analgesia, hypotension, hypothermia
Dexmedetomidine	0.20-0.35 mg/kg SC, IM, IV	α2-receptor agonist, sedation, some analgesia, respiratory depression, peripheral vasoconstriction, bradycardia, cardiac arrhythmias
Diazepam	1-2 mg/kg IM, IV	Benzodiazepine, tranquilizer, sedation and muscle relaxation, no analgesia
Glycopyrrolate	0.01-0.1 mg/kg SC, IM	Parasympathicolytic drug, reduces salivary and bronchial secretions, protects heart from vagal stimulation
Medetomidine	0.20-0.35 mg/kg SC, IM, IV	α2-receptor agonist, sedation, some analgesia, respiratory depression, peripheral vasoconstriction, bradycardia, cardiac arrhythmias
Midazolam	1-2 mg/kg SC, IM, IV, IP	Benzodiazepine, tranquilizer, sedation and muscle relaxation, no analgesia
Morphine	2-5 mg/kg SC, IM	μ-agonist, sedation, analgesia, dose-dependent respiratory depression
Xylazine	1-5 mg/kg SC, IM	α2-receptor agonist, sedation, some analgesia, respiratory depression, bradycardia, cardiac arrhythmias

IM = intramuscular; IP = intraperitoneal; IV = intravenous; SC = subcutaneous

ultrasonography) and will provide effective sedation for approximately one hour [13]. As midazolam and other benzodiazepine tranquilizers (diazepam, zolazepam) have minimal cardiorespiratory side effects, these drugs are considered relatively safe, even in critically ill patients. Midazolam may also be combined with a variety of other drugs, including ketamine, medetomidine and opioids such as buprenorphine, butorphanol and fentanyl [14-16]. A commonly used combination of sedatives that is used for premedication in rabbits includes midazolam (0.1-0.5 mg/kg SC, IM) and butorphanol (0.3-0.5 mg/kg SC, IM), which provides both muscle relaxation and analgesia (Table 2). Other tranquilizers that may be used as premedicants for anaesthesia or as a single drug for sedation to perform non-invasive procedures such as venepuncture include phenothiazine derivatives (e.g. acepromazine, chlorpromazine) and α2-adrenergic agonists (xylazine, medetomidine, dexmedetomidine; Table 2). Phenothiazine derivatives have excellent sedative and muscle relaxing properties, but also result in marked peripheral vasodilation due to their alpha-adrenergic blockage, which can lead to hypotension and hypothermia, particularly in smaller-sized rabbits [17]. Due to these effects, the authors do not recommend the use of these agents in smaller exotic patients. Should they be used, careful monitoring of the rabbit's body temperature is warranted. Alpha-2-adrenergic agonists, in particularly medetomidine, are commonly employed as premedicants due to their sedative, muscle relaxing and analgesic properties and may be used alone or in combination with other drugs (e.g. ketamine, propofol, midazolam) to provide surgical anaesthesia [17]. Following administration, a marked peripheral vasoconstriction and bradycardia may be noted, as well as a respiratory depression and increased risk of developing cardiac arrhythmias (particularly in higher dosages). To reverse the effects of the α2-agonist, the α2-antagonist

Table 3. Commonly used analgesics in rabbits

Drug	Dose	Effects
Acetylsalicylic acid	10-100 mg/kg q8-24h PO	Salicylate drug, anti-inflammatory, antipyretic, analgesic
Bupivacaine	1 mg/kg	Local anaesthetic for infiltrative, epidural, nerve block and intrathecal administration
Buprenorphine	0.01-0.05 mg/kg q6-12h SC, IM, IV, IP	Partial μ-agonist; properties with regard to κ-receptor (agonist/antagonist) less well-defined; post-anaesthetic analgesia
Butorphanol	0.1-1 mg/kg SC, IM, IV q4-6h	κ-opioid receptor agonist, sedation, analgesia, dose-dependent respiratory depression
Carprofen	2-4 mg/kg q12h PO	NSAID, anti-inflammatory, antipyretic, analgesic
Fentanyl	30-100 μg/kg/min CRI	μ-receptor agonist, analgesia, dose-dependent respiratory depression
Ketamine	2-20 μg/kg/min CRI	NMDA-receptor antagonist, mediation of sensitization of pain
Ketoprofen	1-3 mg/kg q12-24h SC, IM	NSAID, anti-inflammatory, antipyretic, analgesic
Lidocaine	2-4 mg/kg	Local anaesthetic for infiltrative, epidural, nerve block and intrathecal administration
Meloxicam	0.3-1.0 mg/kg q24h PO	NSAID, anti-inflammatory, antipyretic, analgesic A recent study showed doses of 1 mg/kg q24h PO did not result in detrimental effects when given for a period of 30 days.
Morphine	2-5 mg/kg q2-4h SC, IM	μ-receptor agonist, analgesia, dose-dependent respiratory depression
Piroxicam	0.2 mg/kg q8h PO	NSAID, anti-inflammatory, antipyretic, analgesic
Tramadol	11 mg/kg q12h PO	μ-opioid receptor agonist, mainly used in the treatment of chronic pain Note: dose did not result in adequate plasma concentrations based on human data

CRI = constant rate infusion; IM = intramuscular; IV = intravenous; IP = intraperitoneal; PO = per os; SC = subcutaneous;

atipamezole may be administered in doses varying from 1-5 times the medetomidine/dexmedetomidine dose [18]. Anticholinergic drugs, including atropine and glycopyrrolate, are not routinely used as premedicant in rabbits but may be used in patients that develop bradycardia due to vagal stimulation. In addition, they may help to reduce salivary and bronchial secretions that can occlude the airway, although it should be taken into account that the viscosity of these secretions may increase following administration of these drugs [19]. As many rabbits possess atropinesterase, which degrades atropine into inactive products [20,21], glycopyrrolate is usually the anticholinergic drug of choice.

Analgesia

One of the main goals of anaesthesia is to prevent the animal from sensing pain. In addition analgesics may be used to provide pain relief post operatively and/or given pre-emptively, prior to the procedure, which may result in more effective pain management and helps to lower the amount of anaesthetics required during the procedure [22]. For these reasons, pre-emptive analgesia should be considered an important part of the anaesthetic regimen for any animal undergoing a procedure that may result in pain. Analgesic drugs can be divided into different groups, each exerting their own action on the peripheral and central nervous systems. The most commonly used analgesics include local anaesthetics, non-steroidal anti-inflammatory drugs (NSAIDs) and opioid drugs (Table 3).

Local anaesthetics

Local anaesthetics such as lidocaine and bupivacaine provide regional anaesthesia by reversibly blocking the transmission of nociceptive signals from nerve endings to the central nervous system [23,24]. They can be used topically, via direct infiltration into soft tissue containing nerve endings, intra-articularly, intravenously, or epidurally [25]. EMLA cream, a topical preparation containing 2.5% lidocaine and 2.5% prilocaine, is particularly useful for application to the ear and provides sufficient anaesthesia to prevent the rabbit from shaking its head in response to venepuncture or catheter placement in the marginal ear vein. The cream may, however, take up to 60 minutes to take effect [26]. When administering local anaesthetics, care should always be taken to prevent administration of toxic dosages, particularly in small animals, because of potential cardiovascular side effects.

NSAIDs

NSAIDs are a class of drugs that have analgesic, antipyretic and anti-inflammatory effects. Within the veterinary field, they are the most frequently used drugs for pain relief as they are effective for both acute and chronic pain [22,23]. They exert their mode of action through inhibition of cyclooxygenase (COX), thereby reducing the production of pro-inflammatory cytokines and increasing the threshold for activation of peripheral nociceptors [27]. Over the years, many different NSAIDs have been used for analgesia in rabbits, including ketoprofen, meloxicam and carprofen. Meloxicam, a COX-2 selective inhibitor, is among the most commonly used NSAIDs of this era, primarily because of its ease of use, overall good palatability and relative safety with fewer side effects. Based on clinical experience, meloxicam appears safe for short-term administration. Long-term administration of NSAIDs, however, may lead to renal papillary necrosis, gastrointestinal ulcerations and/or toxicity [27]. As to date no studies have been performed on the efficacy and safety of long-term treatment with NSAIDs (>30 days), it is advisable to periodically collect blood and monitor plasma liver enzymes, urea and creatinine levels in patients that are in need of prolonged treatment with NSAIDs [22,23].

Opioids

Opioids or narcotic analgesics are psychoactive chemicals that resemble morphine and interact with opioid receptors, which can be found in the central, and peripheral nervous system and the gastrointestinal tract. Opioids produce a variety of effects dependent on the type of receptor that is stimulated. Their analgesic effects are mainly the resultant of stimulation of the μ-receptors, which are primarily responsible for supraspinal analgesia, or stimulation of the κ-receptors, which are mainly responsible for spinal analgesia [22,23,28]. Opioids do not only provide a decreased perception of and reaction to pain, but also prevent sensitization that may develop from continued nociceptive stimulation [28]. They can thus be employed both in the pre-, intra- and post-anaesthetic phase. Opioids may, however, also produce less desirable side effects such as respiratory depression, constipation, sedation, euphoria or dysphoria, hallucinations, and physical dependence. These effects may be antagonized by administration of a μ-antagonist such as naloxone [28].

The affinity for the different receptors varies among the different opioids. Based on their affinity to the different receptors they may be classified as mixed agonist-antagonists, partial agonists, pure agonists, and pure

antagonists. For example, morphine is a full μ-agonist, whereas butorphanol and buprenorphine, the most commonly used analgesics in rabbits, are mixed agonist/antagonist. Butorphanol is classified as a μ-agonist, with primary affinity to the κ-receptor; buprenorphine, in contrast, is classified as a partial μ-agonist with less well-defined characteristics with regard to the κ-receptor. As a result, both may be used for mild to moderate pain. Because of its longer half-life, buprenorphine is mostly used in the post-anaesthetic phase, whereas butorphanol also has some sedative properties and is therefore mainly used in the pre-anaesthetic phase [22,23,28-30].

Ketamine

Ketamine is a dissociative drug that is primarily used for the induction and maintenance of general anaesthesia. It has, however, also been shown to act as an analgesic due to its antagonist effect on the excitatory N-methyl-D-aspartate receptors in the CNS, which mediate sensitization to pain [31]. It may thus be of use on patients with chronic pain syndromes, and also appears useful to augment intra- and post-operative analgesia when administered as a constant rate infusion (CRI) [21,22,32].

Tramadol

Tramadol is a weak μ-opioid receptor agonist, a serotonin releaser and a reuptake inhibitor of norepinephrine, which is metabolized by the liver into O-desmethyltramadol, a significantly more potent μ-opioid agonist [32]. Tramadol has become increasingly popular in veterinary medicine to use as an analgesic agent for treatment of mild to severe chronic pain. Studies on the pharmacokinetics of tramadol in rabbits after both oral and intravenous administration have shown that dosages up to 11 mg/kg orally resulted in plasma levels below those that are considered analgesic in people [33]. Therapeutic plasma levels in the rabbit are, however, currently not known and although tramadol anecdotally has been used in the management of chronic pain, further studies are needed to determine the effective dose and dosing interval. Furthermore the drug appears to be extremely unpalatable when compounded, thereby necessitating the use of strong flavouring agents to increase palatability and acceptance of the drug [22,23].

Injectable Anaesthetics

A great variety of different injectable anaesthetics are available for use in rabbits, which can be administered via the subcutaneous (SC), intramuscular (IM), intravenous (IV) or intraosseous (IO) route (Figure 2a – e; Table 4). A variety of factors have contributed to the overall popularity of these agents, including their ease of use, overall reasonable to good predictability and efficacy, and avoidance of the more expensive and technically-demanding inhalant anaesthesia. Compared to these inhalant anaesthetics, however, they allow less control over depth and duration of the anaesthesia, necessitating redosing and/or higher doses to accomplish anaesthesia of longer duration on the one hand, but offering little to no opportunity to shorten or reverse the anaesthesia because of the limited availability of antidotes. Because of this, use of injectable anaesthetics will more quickly lead to development of undesired physiologic side-effects (especially in animals with impaired liver or kidney function) and/or longer recovery times compared to inhalant anaesthetics. Thus, in general it is advisable to reserve the use of injectable anaesthetics for procedures that will maximally last 30-60 minutes.

Alphaxalone-alphadolone

Alphaxalone-alphadolone is a neurosteroid anaesthetic agent that is registered for use in dogs and cats, but has also been used in rabbits [34]. It is found to produce a light to medium depth anaesthesia over a short period of time, and can be given repeatedly and/or slowly to effect to obtain the desired plane and duration of anaesthesia. A dose of 2-3 mg/kg IV appears suitable to induce anaesthesia and perform endotracheal intubation in rabbits [35]. Alphaxalone/alphadolone in general provides good muscle relaxation, but has poor analgesic properties. The use of an additional analgesic is thus required. In higher doses, the drug may cause respiratory depression, apnoea and cardiac arrest, and is therefore not recommended for use in rabbits if intubating the rabbit is not possible [36].

Barbiturates

Although barbiturates have been used as anaesthetic agents in laboratory rabbits, their use is relatively uncommon in pet rabbits, mainly due to their small margin of safety [37]. Pentobarbitone in particular is known to cause respiratory depression and apnoea at levels that are extremely close to the levels that are needed to induce surgical anaesthesia [38]. Of the different barbiturates, the short-acting barbiturate thiopentone (also referred to as sodium thiopental) is occasionally used during the induction phase to facilitate endotracheal intubation [8,17].

Table 4. Commonly used drugs for induction and maintenance of anaesthesia in rabbits

Drug	Dose	Effects
Alphaxalone / alphadolone	12 mg/kg IV	Neurosteroid anaesthetic; light to medium anaesthesia for 8-10 min duration, muscle relaxation, no analgesia, dose-dependent respiratory depression; doses of 2-3 mg/kg may be sufficient to enable endotracheal intubation in rabbits
Fentanyl-droperidol (Innovar-vet®)	1 mg/kg 0.02-0.05 mg/kg (F) + 1-2.5 mg/kg (D) SC, IM (0.2-0.4 ml/kg)	Commonly used combination for neuroleptanalgesia, provides anaesthesia of 30-60 min duration; give incremental doses of 0.1 ml/kg every 30-40 min to prolong anaesthesia; may cause respiratory depression and/or bradycardia
Fentanyl-fluanisone (Hypnorm®)	2-4 mg/kg q12h PO 0.075-0.16 mg/kg (Fe) + 2-5 mg/kg (Fl) SC, IM (0.2-0.5 ml/kg)	Commonly used combination for neuroleptanalgesia, provides anaesthesia of 30-60 min duration; may cause respiratory depression and/or bradycardia
Halothane	To effect;l 3-4% induction, 1-2% maintenance; MAC = 1.39%	Inhalant anaesthetic; narrower margin of safety than isoflurane or sevoflurane; cardiovascular depression
Isoflurane	To effect; 3-5% induction, 1.5-3% maintenance; MAC = 2.05%	Inhalant anaesthetic; dose-dependent respiratory depression, less risk of cardiovascular side-effects than halothane
Ketamine	20-60 mg/kg IM, SC or 10-20 mg/kg IV	Dissociative agent, muscle rigidity, dose-dependent respiratory depression, tachycardia, hypotension; provides mild to moderate anaesthesia for approx. 20 min
Ketamine / medetomidine	5-15 mg/kg (K) + 0.15-0.35 mg/kg (M) SC, IM	Commonly used combination for injectable anaesthesia, provides surgical plane of anaesthesia for duration of 45-60 min. To prolong anaesthesia 1/3 of the original dose may be repeated
Ketamine / medetomidine / butorphanol	5-10 mg/kg (K) + 0.2-0.25 mg/kg (M) + 1 mg/kg (B) SC, IM	Commonly used combination for injectable anaesthesia; provides sufficient anaesthetic depth to intubate the rabbit; continue with isoflurane or sevoflurane to effect
Ketamine / xylazine	20-50 mg/kg (K) + 2.5-10 mg/kg (X) SC, IM	Combination that was used commonly in the past for injectable anaesthesia, provides surgical plane of aneasthesia for duration of 45-60 min
Propofol	2-15 mg/kg IV, slowly to effect	Short-acting hypnotic/amnestic agent used for induction of anaesthesia (5 min) to allow endotracheal intubation; dose-dependent respiratory depression and hypotension
Sevoflurane	To effect; MAC=3.7%	Inhalant anaesthetic; wide margin of safety
Thiopentone	15-30 mg/kg IV, give slowly to effect	Short-acting barbiturate, used for induction of anaesthesia (5-10 min) to allow endotracheal intubation; dose-dependent respiratory depression and hypotension

IM = intramuscular; IV = intravenous; MAC = minimal alveolar concentration; SC = subcutaneous

Neuroleptanalgesic combinations

Of the different neuroleptanalgesic combinations, fentanyl-droperidol (Innovar-vet®, Janssen, Pharmaceuticals Inc, Beerse, Belgium) and fentanyl-fluanisone (Hypnorm®, VetaPharma Ltd, Leeds, UK) are the two most commonly used ones in rabbits [39,40]. The combination of fentanyl-fluanisone in particular appears useful in rabbits as it provides good analgesia (up to 3 hrs after administration) and can be used as premedicant or sedative.

In combination with a muscle-relaxing benzodiazepine (midazolam, diazepam) surgical anaesthesia of moderate duration can also be achieved [41]. Respiratory depression and bradycardia may occur, which are mainly attributed to the highly potent fentanyl present in the combination [42]. To reverse the respiratory depression, doxapram (a respiratory stimulant), naloxone (an opioid antagonist) and/or mixed agonist/antagonist opioids may be used [43].

Figure 2a. By lifting the skin over the thorax a subcutaneous (SC) injection can be given. A 22-gauge needle is used as smaller needles tend to bend when inserting these through the thick skin of rabbits.

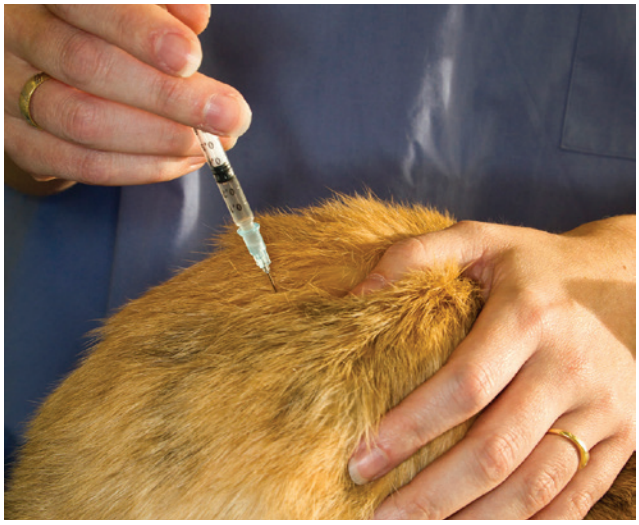

Figure 2b. An intramuscular (IM) injection can best be given in the M. longissimus dorsi.

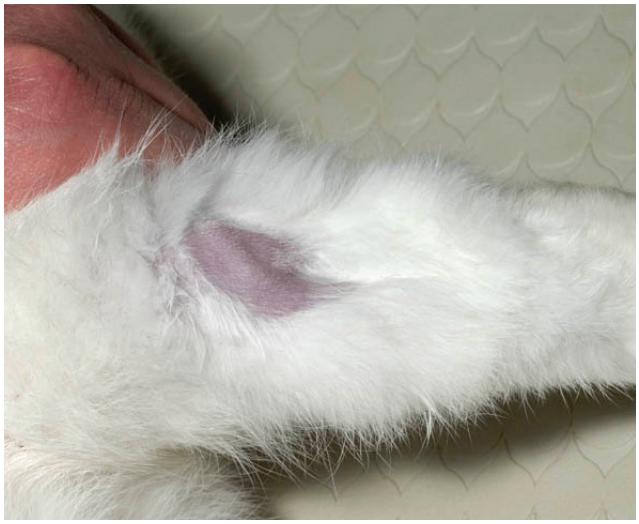

Figure 2c. An intravenous (IV) injection can be given in the saphenous vein or in the marginal ear vein. In this figure the saphenous vein is shown.

Figure 2d. An intravenous (IV) injection can be given in the saphenous vein or in the marginal ear vein. In this figure the marginal ear vein is shown.

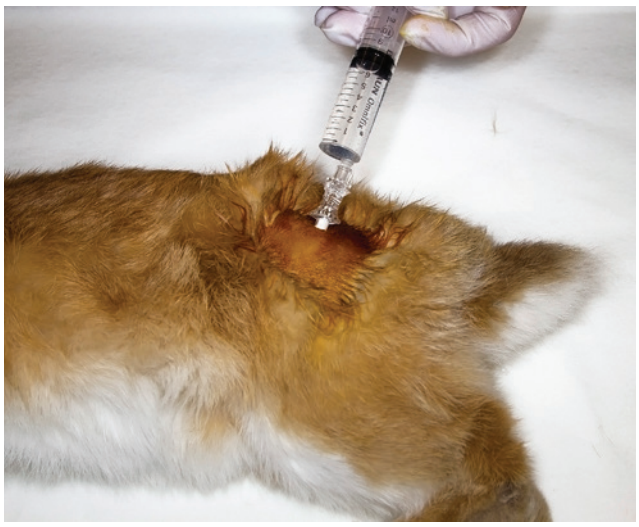

Figure 2e. An intraosseous (IO) catheter can be placed in the proximal femur. This will not affect movement of the leg and does not pose a risk of entering the joint. Strict hygiene must be employed when placing the catheter. Providing fluids through an IO catheter is just as effective as through an IV catheter.

Ketamine

Ketamine is the most widely used dissociative agent in rabbit anaesthesia. Although it may be used as a sole agent for induction and/or minimally invasive procedures, it is typically used in combination with other agents (e.g. xylazine, medetomidine) for induction and maintenance as it only provides limited muscle relaxation and analgesia [44]. Using these combinations, it provides a surgical plane of anaesthesia lasting for approximately 45-60 minutes. When administered as a single drug, ketamine has a sympathomimetic effect, resulting in an increase in heart rate, cardiac output and blood pressure [45].

Propofol

Propofol, an alkyl phenol agent, which is licensed for use in dogs and cats can also be used in rabbits to produce a deep sedation of rapid onset and short duration. Due to its short-lived effect (~5 min), recovery after propofol sedation is usually smooth and rapid. A dose of 5-14 mg/kg IV usually provides sufficient sedation to intubate the rabbit [46]. As the drug does not accumulate in the body, repeated administration and/or continuous rate infusion is possible [47,48]. Long-term administration may, however, induce hypoxia, hypotension and/or prolonged recovery; it is therefore mainly recommended for induction and/or use during short-term, minimally invasive procedures [47]. When administered in higher doses, transient apnoea and/or respiratory arrest may occur.

Constant Rate Infusion

Constant rate infusion (CRI) is a technique with which opioids or ketamine are intravenously administered in a constant low dose [49]. The effects of lidocaine administration via CRI on reduction of the Minimum Alveolar Concentration (MAC) have also been studied. Unfortunately, results of this study have not been published yet [50].

To reach effective plasma concentrations of the drugs, an initial loading dose needs to be given. After that, very low dosages can be given while still achieving a sparing effect on the inhalant anaesthetics needed. Slight changes in the dose rate can quickly result in changes in anaesthetic depth. The only potential disadvantage is that an intravenous (or intraosseous) access is needed in combination with an infusion pump to allow for a constant flow of administration. The great benefit of this multimodal approach is that side effects of each drug are so low that no clinical effect of the potential side effects is seen [49].

Inhalant anaesthetics

Although the use of inhalant anaesthetics requires more training and specific equipment, it generally does provide a more reliable and efficacious anaesthesia with excellent control over its depth and duration. In addition, induction and recovery are usually rapid. These features make inhalant anaesthetics particularly useful in exotic animal practice. The two most common agents currently used in practice include isoflurane and sevoflurane (Table 4).

In the past, nitrous oxide (also known as laughing gas), was used as an adjunct to anaesthesia with other volatile agents (e.g., halothane), but the arrival of newer, safer inhalant anaesthetics has limited its use in current practice. Nitrous oxide generally has good analgesic properties with minimal effects on the cardiovascular and respiratory system, and is particularly useful to reduce the amount of other inhalant anaesthetics in rabbits [8]. Long-term administration may, however, predispose to hypoxia and gastric and/or caecal dilation as the nitrous oxide may diffuse into the stomach and/or caecum [51]. Thus, it is recommended to limit its use to the induction phase of anaesthesia (in a 50/50 combination with 100% oxygen) and switch off the nitrous oxide as soon as a satisfactory plane of anaesthesia is reached.

Halothane is another volatile agent that was frequently used in the past, but has become more or less obsolete with the arrival of safer inhalant anaesthetics such as isoflurane and sevoflurane. All three allow good and rapid control over anaesthetic depth, but induction and recovery times are shorter with the latter two because of the relative low blood solubility. In addition, the latter two do not sensitize the heart to catecholamines, thereby posing less risk of development of hypotension or cardiac arrhythmias compared to halothane [52]. Isoflurane and sevoflurane are furthermore minimally metabolized in the liver, which renders them the preferable agents to use in rabbits with impaired liver and/or renal function [52]. In humans, the non-irritating properties of sevoflurane have rendered it particularly useful for facemask induction in children [53]. In rabbits, however, it was not found to prevent a breath holding response compared to isoflurane [54]. In addition, the high cost and need for special vaporizers have further prohibited its widespread use, still rendering isoflurane as the most commonly used inhalant anaesthetic in practice.

Conclusions

Anaesthesia consists of 4 distinct but equally important periods, i.e. the pre-anaesthetic evaluation and premedication phase, induction, maintenance and recovery. Many veterinarians often tend to consider the first and latter phase to be less important, yet these contribute just as much to a successful anaesthesia as do the induction and maintenance phase. A proper patient preparation and evaluation allows veterinarians to take appropriate measures and select the most suitable anaesthetic protocol for the patient to minimize the risks of complications throughout the anaesthetic procedure. A multi-modal approach, in which a combination of anaesthetic and analgesic agents are combined, is

generally recommended as this helps to maximize the desired effects while minimizing side effects that may occur when using a single drug. Tranquilizers or sedatives are often included in such a protocol as these will help to prevent stress while also allowing a reduction in the dose of both induction and maintenance drugs. In addition, the provision of analgesics needs to be considered in any patient. Regardless of the choice of analgesics, three basic rules need to be taken into consideration: 1) analgesics preferably need to be administered prior to the painful stimulus (pre-emptive analgesia) thereby lowering the overall amount of anaesthetics required, ensuring that pain is controlled despite the anaesthesia wearing off, and preventing sensitisation of pain mechanisms; 2) preferably a combination of analgesics is used (multimodal analgesia); and 3) analgesia should be continued for as long as pain affects the quality of life of the patient.

During the induction, maintenance and recovery period, several other measures may also be taken to minimize risks involved with anaesthesia in rabbits. These aspects will be discussed in part II of this review.

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