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Total Intravenous anesthesia in Goat

A Graduation Project Submitted to the Department Council of the Internal and Preventive Medicine-College of Veterinary Medicine/ University of Al-Qadisiyah in a partial fulfillment of the requirements for the Degree of Bachelor of Science in Veterinary Medicine and Surgery.

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بسم الله الرحمن الرحيم

(قَالَ الَّذِي عِنْدَهُ عِلْمٌ مِنَ الْكِتَابِ أَنَا آتِيكَ بِهِ قَبْلَ أَنْ يَرْتَدَّ إِلَيْكَ طَرْفُكَ فَلَمَّا رَآهُ مُسْتَقِرًّا عِنْدَهُ قَالَ هَذَا مِنْ فَضْلِ رَبِّي لِيَبْلُوَنِي أَأَشْكُرُ أَمْ أَكْفُرُ وَمَنْ شَكَرَ فَإِنَّمَا يَشْكُرُ لِنَفْسِهِ وَمَنْ كَفَرَ فَإِنَّ رَبِّي غَنِيٌّ كَرِيمٌ)

صدق الله العظيم (النمل ٤٠)

بسم الله الرحمن الرحيم

الحمد لله الذي بيده كل الخير وبه تتم كل الصالحات، سبحانه لا إله إلا هو، نحمده كثيراً، ونشكر فضله في كل وقت وحين، ونشهد أن خاتم الرسل سيدنا محمد عليه افضل الصلوات واتم التسليم، أما بعد،،نقدم لكم اليوم هذا البحث الهام جدا في (الجراحة قسم التخدير)، وعنوان البحث (الحقن الوريدي الكلي في الماعز) ، ونحن نأمل ونطمع أن ينال إعجابكم جميعاً، ونتمنى من الله أن نكون قد وفقنا الله في تقديم وكتابة هذا البحث المتواضع، وهذا البحث يشمل كل المعلومات التي تطمح أن تجدها في أي بحث المختص بهذا العلم، ونرجو أن نكون حذنا على رضاكم عن هذا البحث،

Abstract

Injectable anesthesia is gradually becoming popular in veterinary practice. Traditionally, general anesthesia is induced with injectable drugs and then maintained with inhalation agents. Inhalation anesthetic agents cause more significant dose-dependent cardiorespiratory depression than in injectable anesthetic drugs, creating a need to use less of the inhalation anesthetic agents for maintenance of general anesthesia by supplementing with injectable anesthesia drugs. Better still, if anesthesia is maintained completely with injectable anesthetic drugs, autonomic functions remain more stable intra-operatively. Patient recovery from anesthesia is smoother and there is less pollution of this working environment than happens with inhalation anesthetic agents. Recently, a number of drugs with profiles (pharmacokinetic and pharmacodynamics) suitable for prolonged injectable anesthesia have been studied, mostly in humans and, to a certain extent, in dogs and hors es. There is currently very little scientific information on total injectable anesthesia in small ruminant, although, in the past few years, some scholarly scientific articles on drugs suitable for partial injectable anesthesia in sheep and goats have been published. This review article explored the information available on drugs that have been assessed for partial injectable anesthesia in small ruminant, with the aim of promoting incorporation of these drugs into total injectable anesthesia protocols in clinical practice. That way, balanced anesthesia, a technique in which drugs are included in anesthetic protocols for specific desired effects (hypnosis, analgesia, muscle relaxation, autonomic stabilization) may be utilized in improving the welfare of small ruminant undergoing general anesthesia

Introduction:

Total intravenous anaesthesia (TIVA) is becoming a vital technique for general anaesthesia and a well-established anaesthetic concept for some animal species, notably dogs and horses. Information on TIVA protocols for goats is very scarce at the moment; yet, there are situations (field anaesthesia, anaesthesia for MRI, research) when TIVA might be the only practically possible way to achieve general anaesthesia in goats (Carroll, Hartsfield & Hambleton 1997; Larenza et al. 2005). This review article highlights the latest developments in intravenous anaesthesia in goats, paying attention to outcomes of recent scientific articles on sedatives, analgesic and/or hypnotic drugs that can be used for TIVA in goats.

Ruminants in general can be anesthetized successfully by general anesthesia, but with special considerations that may affect anesthesia, like regurgitation, ruminal tympany, salivation, and cardiovascular and respiratory distress. Sheep is one species of ruminants frequently need to anesthetized with the surgical operations, and also frequently used as a model of anesthesia of ruminants. The inhalation anesthesia which is the best type of anesthesia, not always available in the field, and the use of the injectable anesthetics is mandatory. Not all the anesthetic or the analgesic drugs are effective in all species of animals. The economic considerations and limited number of anesthetics and analgesics used in small ruminants may direct the use of drug and technique (Galatos, 2011). There is no specific anesthetic or analgesic drug licensed for small ruminants (Taylor, 1991). Ketamine is frequently used as an injectable general anesthetic drug in most species of animals, but it has unpleasant adverse effects related to the rigidity, and absence of muscle relaxation. Many drugs are in combined with the ketamine as a part of balanced anesthesia to overcome these unwanted side effects and to enhance the quality of anesthesia. Tramadol is a potent non opioid analgesic long time used in human analgesics, and recently introduce to the veterinary medicine. The combination between tramadol and ketamine seen improve the anesthetic properties of ketamine (Ajadi, *et al*., 2009; Albdeery, 2009).

Pain:

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is a complex phenomenon based on pathophysiological and psychological components often difficult to recognize and interpret in the animals (Ott and short, 1998; Leonardi *et al.,* 2006). In recent years more attention has been paid to the issue of pain in animals, particularly in association with increasing awareness of animal welfare. It is therefore necessary for veterinarians to be able to recognize an confusingly whether an animal suffers from pain or not. In animals we have to recognise the signs of pain according to indirect markers which involve behavioral, physiological and finally clinical responses (Landa, 2012). Current approaches about animal welfare have increased the important of pain management in livestock. Even minor surgical procedures in livestock are now performed using a combination of regional, local, or general anesthesia combined with uninterrupted post-surgical analgesia (George, 2003).

Analgesia:

Analgesia is a relief of pain in response to stimulation which would normally be painful. Although the animal considered to be unconscious during general anesthesia and, therefore, incapable of gaining pain, there is now evidence that the use of analgesic drugs before and during general anesthesia assists in obtaining a smooth, pain-free recovery. All general anesthetics undoubtedly have an intrinsic analgesic action but further analgesia can be provided by four main methods:

1. Use of local analgesics. 2. Use of α_2-adrenoceptor agonists. 3. Use of non-steroidal anti-inflammatory drugs (NSAIDs) 4. Use of opioid drugs. With all of these drugs, there is now definite evidence that they are more effective if administered before pain becomes noticeable (Hall, *et al.* 2001).

The most popular non-steroidal anti-inflammatory agents are flunixin meglumine and phenylbutazone. The most popular opioid type drug is buprenorphine, followed by morphine. The most popular α_2-agonist drug is the xylazine. Analgesic premeditations are frequently administered, e.g. xylazine or ketamine, but no specific drug is administered for post-operative pain (Joubert, 2001). The detrimental effects of pain must be avoided by

analgesia (Galatos, 2011), which are mainly two treatment models such as pre-emptive (preventive) analgesia, and multimodal analgesia which have been favored during the past years in order to improve intra- and post-operative pain relief (MacKenzie, 2008) .

-**Preemptive Analgesia**:

Tissue injury can modify the responsiveness of the nervous system by peripheral sensitization as the reduction in nociceptor threshold and by central sensitization, defined as an activity-dependent increase in the excitability of spinal neurons. Both, peripheral and central sensitization contributes to postoperative pain. Therefore, it was concluded that analgesic intervention with a local anesthetic, nonsteroidal anti-inflammatory drug (NSAID) or opioid in advance of the development of pain (preemptively) rather than in reaction to it will be helpful in reducing the magnitude and duration of postoperative pain.

-**Multimodal Analgesia (balanced analgesia**)

The rational for a multimodal approach is the achievement of potent analgesia due to additive or synergistic effects between different classes of analgesic drugs, with concomitant reduction in side effects due to resulting lower doses of each analgesic and differences in their side-effect profiles. A combination of various analgesic drugs (e.g. local anesthetics, NSAID, and opioid) can suppress or interrupt the transmission of nociceptive impulses at numerous peripheral and central sites including the wound area, peripheral nerves, spinal cord and brain.

-**Endpoints of analgesic treatment**:

Analgesia is directed toward the restoration of the normal function of animal, such as normal breathing and moving, by blunting autonomic and somatic reflex responses to pain without excessive depression of the animal. The goal of peri-operative analgesic treatment is to make pain tolerable (MacKenzie, 2008), and thereby providing subjective comfort in addition to the suppression of the trauma-induced stress response that may cause catabolism. The goal of postoperative analgesia, therefore, is not the total suppression of pain which, in turn, could be associated with profound mental depression, recumbency and anorexia. Analgesia should enable the individual animal to return to its normal behavior at the earliest postoperative time point possible (Taylar, 1991; Galatos, 2011).

intravenous anaesthesia:

There are several advantages of TIVA, especially if the drugs are administered as continuous infusions. These advantages include rapid onset of action independent of ventilation status, reduction of adverse effects of other anaesthetic drugs if used in balanced anaesthesia protocols, allowing for provision of continuous analgesia if needed, smoother recovery from anaesthesia, low costs considering that the minimum requirement is a needle and a syringe, and reduction of the hazards of occupational health and atmospheric pollution (Dundee & McMurray 1984; Hasley 1991; Mani & Morton 2010; Waelbers et al. 2009). It must be noted that TIVA anaesthesia also contributes to decreased environmental pollution, to a largely unaccounted extent, through disposal of surplus drugs and excreted metabolites into the environment (Briggs 2003). In remote settings, TIVA would be a very useful method of restraint because it does not necessarily require bulky, sophisticated and expensive equipment such as the anaesthesia machine for inhalation anaesthesia (McKenzi 2008; Waelbers et al. 2009). There are some disadvantages to the use of TIVA that include the need for infusion pumps as the ideal modality of IVA delivery, difficulty of aligning infusion rates to depth of anaesthesia, tendency for the drug plasma concentrations to increase with duration of IVA time, and pain on injection of some drugs (Mani & Morton 2010; Waelbers et al. 2009). Even though the equipment required to deliver inhalation anaesthetic agent is expensive, the cost of IVA drugs used could prove more expensive, especially for very long anaesthetic procedures. Yet, in the author's opinion, when all is considered, the advantages of TIVA far outweigh the disadvantages, especially when patient comfort is considered.

Anesthesia in Goats:

Anaesthetic management in goats is usually uncomplicated, with the primary notable risk being regurgitation with potentially fatal pulmonary aspiration (Hall, Clarke & Trim 2001). Ruminants are classically considered farm animals and are often intended for the production of food, these species are used extensively in research and teaching and they are increasingly important as companion animals. goats is one of the most widely used

reproductive animals and for human's life also for biomedical research. Whatever their use may be, anesthetic and analgesic drugs and techniques should be used to ensure minimal stress and discomfort during the perioperative period (Taylor, 1991; Lee, 2006). Drugs available for prolonged intravenous anaesthesia in goats To avoid misunderstandings, prolonged intravenous anaesthesia is defined, in this review article, as an anaesthetic procedure lasting at least 60 min, or long enough to require a drug or drugs to be topped up more than once to maintain general anaesthesia at a desired level. For an anaesthetic drug to be deemed suitable for prolonged IVA it should, (1) be stable in solution, (2) water soluble, (3) lipid soluble and potent as an anaesthetic agent, (4) have a rapid onset of action, (5) have few adverse effects, (6) be rapidly cleared from body tissues and (7) cause short, smooth and predictable recovery from anaesthesia (Beths 2008; Dzikiti 2010; Joubert 2009; McKenzi 2008). Based on these criteria, drugs that can currently be used in prolonged IVA include general anaesthetics (propofol, ketamine, alfaxalone), opioids (fentanyl, remifentanil), benzodiazepines (diazepam, midazolam) and some anaesthetic adjuncts (lidocaine, glycerol guaicolate). In food animals such as goats, it is essential for administered drugs to have short half-lives to ensure short withdrawal times and that way restrict presence of excess drug residues in meat or milk to a very short period of time (Fajt 2011). General anaesthetic agents for intravenous anaesthesia in goats Goats are not amongst the commonly anaesthetised animals, which is partly why information on goat anaesthesia is scarce. General anaesthesia can be induced in goats using the same drugs commonly used in other species. These induction agents include thiopentone, propofol and ketamine, which can be administered with or without premedication at dosages of 5 mg/kg – 20 mg/kg, 3 mg/kg – 7 mg/kg and 4 mg/kg – 15 mg/kg, respectively (Dzikiti et al. 2010; Dzikiti et al. 2009; Galatos 2011; Prassinos, Galatos & Raptopoulos 2005; Taylor 1991). It is recommended to premedicate goats so that they are calm before administering these induction agents (Galatos 2011). Once induced, goats should have their tracheas intubated with a cuffed endotracheal tube to protect against aspiration of regurgitated ruminal contents (Dzikiti 2010; Galatos 2011; Reid et al. 1993; Taylor 1991). Of these induction agents,

propofol and possibly ketamine possess pharmacokinetic profiles that make them suitable for TIVA for maintenance of general anaesthesia in goats.

Techniques for intravenous anaesthesia:

Intravenous anaesthetic drugs are usually first administered as a large bolus to fill the volume of distribution of the central compartment, which is then followed by continuous lower dosages to maintain effective drug plasma concentrations for the duration of the anaesthetic procedure (Beths 2008; Waelbers et al. 2009). Administration of intravenous anaesthetic drugs for maintenance of anaesthesia can be achieved by multiple bolus injections or continuous infusion at a fixed or variable rate (Beths 2008; Waelbers et al. 2009). Intermittent multiple bolus injection of IVA drugs is very simple, but is characterised by inconsistent drug plasma concentrations, variable anaesthetic depth and may result in poor and/or prolonged recovery from anaesthesia (Beths 2008; Joubert 2009). Continuous administration of intravenous anaesthetic drugs can be achieved by using a drug-spiked intravenous fluid bag, buretrol or a syringe controlled by a basic volumetric pump (syringe driver) or computer-controlled pump (Beths 2008; Waelbers et al. 2009). If intravenous anaesthetic drugs are administered from a drug-spiked fluid bag or a buretrol, the rate of administration is calculated to drops per second and adjusted over time to achieve a desired anaesthetic effect (analgesia, hypnosis, surgical anaesthesia). However, administration of intravenous anaesthetic drugs can be undertaken in a more sophisticated manner by the constant rate infusion (CRI) technique using the conventional syringe driven by a pump, or by the target-controlled infusion (TCI) technique using a highly sophisticated computer-controlled pump that adjusts the rate of drug administration so as to maintain a user-defined target plasma or effect site drug concentration (Mani & Morton 2010; Waelbers et al. 2009). ruminal contents (Dzikiti 2010; Galatos 2011; Reid et al. 1993; Taylor 1991). Of these induction agents, propofol and possibly ketamine possess pharmacokinetic profiles that make them suitable for TIVA for maintenance of general anaesthesia in goats.

Balanced Anesthesia:

Balanced Anesthesia is the technique in which a number of different agents are combined to produce a desired effect. The combination of more than one drug in small doses is used to minimize the dose and subsequently the side-effects of each one of these drugs. It refers to the use of a mixture of these drugs in small amounts of each one to avoid the disadvantages of the large doses of any one. This technique requires a systematic clinical, and pharmacological understanding of the methods of administration, the interaction of these drugs, and the ability to manage the patient before, during, and after the administration of anesthesia. Thus, in a balanced anesthetic technique, anesthesia is produced by using several drugs, often administered by different routes, which can be detoxified and excreted in different ways. In veterinary practice, especially in small animal anesthesia, the inhalant drugs are usually administered alone to maintain anesthesia. Unfortunately, the cardiopulmonary function is reduced in dose-dependent manner by inhalant drugs and deepening the level of anesthesia in order to modify autonomic responses to noxious stimuli may increase morbidity and mortality. For that now the use of balanced anesthesia is increased to minimize the effect of these drugs on the cardiopulmonary systems. Both partial intravenous anesthesia technique (PIVA) (when use the injectable anesthetics and analgesics drugs with the inhalation anesthesia) (Duke, 2013), and total intravenous anesthesia techniques (TIVA) (when only the injectable drugs are used through the whole time of anesthesia) (Dzikiti, *et al.*, 2010) are used in balanced anesthesia. Drugs commonly used for PIVA include opioids, alpha-2 adrenergic agonists, injectable anesthetic agents, and lidocaine. Most are administered by intravenous infusion. Total intravenous anesthesia (TIVA) is commonly used for anesthesia where there are no facilities for inhalational anesthesia such as in the field. In equine balanced anesthetic techniques are commonly used and include the combination of a volatile anesthetic with at least one injectable anesthetic throughout the maintenance period. Injectable anesthetics used in balanced anesthesia include the α_2-agonists, lidocaine, ketamine, and opioids, and those with muscle-relaxant properties such as benzodiazepines and guaifenesin. Administration of these injectable anesthetics is best using

constant-rate infusions based on the pharmacokinetics of the drug, which allows steady-stat concentrations and predictable pharmacodynamic actions (Muir, and Yamashita, 2000; Doherty, and Valverde 2006; Valverde, 2013). Introducing computerized infusion pumps facilitates the maintenance of constant concentration of drugs in blood and solves the problems of repeated injection. Balanced anesthesia technique reduces the incidence of undesirable side-effects, like cardiopulmonary depression produced in a patient at surgical planes of anesthesia, provides superior quality of anesthesia and analgesia and improvement of recovery, post-operative analgesia and in some cases, a reduction in overall drug costs (Doherty and Valverde, 2006; Duke, 2013).

Total Intravenous Anaesthesia (TIVA):

Total intravenous anesthesia (TIVA) is becoming a vital technique for general anesthesia and a stable anesthetic model for some animal species, especially dogs and horses (Doherty and Valverde, 2006; Ortega and Cruz 2011; Valverde, 2013), also in sheep (Vesal and Oloumi, 1998), and recently in goats (Dzikiti, 2013) when the TIVA might be the only practically possible way to achieve general anesthesia. It is a technique that involves the use of only injectable anesthetics for induction and to maintain an adequate depth of anesthesia for a directed level of central nervous system depression, such as, hypnosis for diagnostic procedures or surgical anesthesia for painful interventions (Dzikiti, 2013). In veterinary practice, intravenous anesthetic drugs are commonly used as induction agents to facilitate endotracheal intubation, whilst inhalation anesthetic agents form the foundation for maintenance of general anesthesia. Inhalation anesthesia may not be applicable in all situations where anesthesia is required. General anesthesia can then be maintained by intravenous drugs in those situations. Intravenous anesthesia (IVA), instead of inhalation anesthesia, could soon become an conventional means of anesthetic provision for both induction and maintenance of anesthesia in veterinary practice.

In horses the injectable anesthetic drugs widely used before introducing the inhalant anesthetics in 1960s. Increasing the mortality rates with the inhalation anesthesia and development of new safest injectable compounds

encourage the reuse of TIVA, for achievement of low cardiopulmonary stress, reduce mortality rates, gain good analgesia, and improve recovery. Another advantage of TIVA is the decreased incidence of intraoperative hypotension. Many techniques are used to deliver the injectable anesthetic drugs such as intermittent injections, drip infusion, infusion pump, and computerized syringe pump. The most commonly used drug combination in TIVA in horses are the ketamine, α_2-agonists (xylazine, detomidine, medetomidine, and romifidine), guaiphenesin, benzodiazepines, and propofol (Doherty and Valverde, 2006). Anesthesia can be induced as described above, and the ketamine and an alpha-2agonist with guaiphenesin combination is the most used protocol. This mixture is also known as triple drip. The ketamine (1-1.5g) and xylazine (500mg) be added to 1L of a 5% solution of guaiphenesin and infused at the rate of 2-3mL/kg/hour. Because guaiphenesin is cleared slowly, it may contribute to weakness in recovery; thus, it is advisable to give the guaiphenesin only for the first hour of anesthesia. Beyond this time, anesthesia is maintained with ketamine and xylazine diluted in a balanced electrolyte solution (Doherty and Valverde, 2006).

In goats general anesthesia can be induced using the same drugs commonly used in other species. These induction agents include thiopentone, propofol and ketamine, which can be administered with or without premedication at dosages of 5mg/kg-20mg/kg, 3mg/kg-7mg/kg and 4mg/kg-15mg/kg respectively (Hall *et al*., 2001; Dzikiti, 2013). Of these induction agents, the propofol and possibly ketamine possess pharmacokinetic profiles that make them suitable for TIVA of maintenance of general anesthesia in goats (Dzikiti, 2013).

Ketamine:

Ketamine is a commonly used general anaesthetic agent in veterinary practice that has recently gained greater popularity because of its suitability for use as an analgesic agent to prevent development of chronic pain when administered at sub-anaesthetic doses by continuous infusion (Valverde & Gunkel 2005; White, Way & Trevor 1982). It is a dissociative anaesthetic agent which has major advantages in comparison with other general

anaesthetic agents because it mildly stimulates cardiovascular function via sympathomimetic effects and also provides analgesia as already stated (White et al. 1982). The major drawback with ketamine is inability to relax skeletal muscles, which has given rise to a need to always co-administer it with benzodiazepines to facilitate adequate muscle relaxation to enable intubation and minimise muscle excitation (Ghurashi et al. 2009; Prassinos et al. 2005). Ketamine causes less induction apnoea and respiratory depression in comparison with propofol in goats (Prassinos et al. 2005). Ketamine possesses most of the characteristics required for suitability for continuous IVA, lending itself well for field anaesthesia, but is longer acting and slightly more cumulative than propofol (Hodgkinson & Dawson 2007). Goats regain the swallowing reflex after more than 11 min following an intravenous bolus of ketamine (Prassinos et al. 2005), in comparison with less than 5 min anaesthesia with other anaesthetic drugs, usually inhalation anaesthetic agents (Taylor 1991).

Propofol:

Propofol provides a rapid and smooth onset of induction that easily facilitates intubation in the goat (Dzikiti et al. 2010; Dzikiti et al. 2009; Larenza et al. 2005; Prassinos et al. 2005; Reid et al. 1993). Propofol causes induction apnoea more frequently than other general anaesthetics (BettschartWolfensberger et al. 2000; Carroll et al. 1998; Langley & Heel 1988; Pablo, Bailey & Ko 1997), especially if administered too rapidly and at a high dose (Galatos 2011). Propofol causes dose-dependent cardiovascular and respiratory depression, implying a need to monitor these systems and take necessary corrective measures (intravenous fluid infusion, ventilation support) if required (Hodgkinson & Dawson 2007). Rapid metabolism and high body clearance make propofol suitable for IVA in goats either by intermittent incremental boluses or continuous infusion (Reid et al. 1993). In goats, propofol can be administered for TIVA on its own at a dose of 0.3 mg/kg/min – 0.6 mg/kg/min (12 mg/kg/h – 36 mg/kg/h), or in combination with other anaesthetic drugs at lower dosages adjusted to the effect required (Carroll et al. 1998; Dzikiti et al. 2010; Dzikiti, Stegmann, Cromarty, Dzikiti & Hellebrekers 2011; Larenza et al. 2005). Propofol

should be combined with analgesic drugs in anaesthesia protocols for noxious procedures because it is devoid of any substantial analgesic effects (Beths 2008; Langley & Heel 1988; Sneyd 2004). Alfaxalone (previously a component of saffan) Intravenous administration of alfaxalone is characterised by a rapid onset of action, rapid redistribution and a short terminal half-life (Ferré et al. 2006; Suarez et al. 2012). It fulfils most properties of an ideal intravenous infusion anaesthetic agent and has several advantages over other drugs, including a very high therapeutic index that is even greater than that of propofol (Muir et al. 2008). Alfaxalone has recently been used as an induction agent in sheep (Andaluz et al. 2012). In that study, alfaxalone administered as an intravenous bolus at 2 mg/kg produced minimal adverse effects and uneventful recovery from anaesthesia. The few publications leaning towards alfaxalone in goats (Amer et al. 1989, 1990; Camburn 1982; Gibbons 1986) are outdated, as they are based on saffan, which has since been discontinued because of the histamine release that was linked to its stabiliser (Child et al. 1971; Dodman 1980; Sear et al. 1983). Alfaxalone was first introduced in 1971 as althesin and saffan, which were composed of a mixture of the two neurosteroids, alfaxalone and alfadolone acetate (Child et al. 1971; Sear et al. 1983), solubilised in 20% polyethoxylated castor oil (CremophorEL). A new formulation has since been developed for use in dogs and cats from alfaxalone (without alfadolone) solubilised in 2-hydroxypropyl-beta cyclodextrin (HPCD) (Ferré et al. 2006; Suarez et al. 2012). In future, alfaxalone could become useful for prolonged IVA in goats as well, if more research-based data on its pharmacokinetic profile in this species become available and its cost decreases.

Alfaxalone

Alfaxalone is a synthetic, neuroactive steroid hypnotic agent (Ferré et al. 2006); several research teams have recently assessed the anaesthetic and cardiorespiratory effects of it. Its pharmacokinetic and pharmacodynamic profiles make it ideal for intravenous induction and maintenance of general anaesthesia in dogs (Ambrisko et al. 2011; Ambros et al. 2008; Ferré et al. 2006; Jiménez et al. 2012; Maddern et al. 2010; Michou et al. 2012; Muir et

al. 2008; Psatha et al. 2011; Rodriguez et al. 2012; Suarez et al. 2012). Alfaxalone has been reported to be a suitable anaesthetic-induction agent at a dose of 2.00 mg/kg in unsedated sheep (Andaluz et al. 2012, Torres et al. 2012), sedated dogs (Maddern et al. 2009; Suarez et al. 2012) and ponies (Klöppel & Leece 2011; Leece et al. 2010). Dosages of 3.47 mg/kg - 4.70 mg/kg have been reported for sedated cats (Martinez Taboada & Murison 2010; Mathis et al. 2012).

Intravenous administration of alfaxalone is characterised by a rapid onset of action, rapid redistribution and a short terminal half-life .It fulfils most properties of an ideal intravenous infusion anaesthetic agent and has several advantages over other drugs, (Ferre et al. 2006; Suarez et al. 2012).)including a very high therapeutic index that is even greater than that of propofol Alfaxalone has recently been used as an induction agent in sheep In that study, alfaxalone administered as an intravenous bolus at 2 mg/kg produced minimal adverse effects and uneventful recovery from anaesthesia. The few publications leaning towards alfaxalone in goats are outdated, as they are based on saffan, which has since been discontinued because of the histamine release that was linked to its stabiliser . Alfaxalone was first introduced in 1971 as althesin and saffan, which were composed of a mixture of the two neurosteroids, alfaxalone and alfadolone acetate solubilised in 20% polyethoxylated castor oil (Cremophor-EL). A new formulation has since been developed for use in dogs and cats from alfaxalone (without alfadolone) solubilised in 2-hydroxypropyl-beta cyclodextrin (HPCD) . In future, alfaxalone could become useful for prolonged IVA in goats as well, if more research-based data on its pharmacokinetic profile in this species become available and its cost decreases((Suarez et al. 2012; Waelbers, Vermoere & Polis 2009)

Thiopentone:

Thiopentone's pharmacokinetic profile makes it unsuitable for prolonged IVA. Maintaining general anaesthesia with thiopentone for any longer than 15 min progressively results in its accumulation in body tissues, which might result in delayed recovery from anaesthesia (Galatos 2011). For this reason, thiopentone should be used only for intravenous induction that

would be followed by maintenance of general anaesthesia with other anaesthetic drugs, usually inhalation anaesthetic agents (Taylor 1991).

Benzodiazepines: Midazolam and Valium:

Midazolam and diazepam are the most commonly used benzodiazepines (Galatos 2011; Posner 2007). Both benzodiazepines are fast-acting with short elimination half-lives (Lemke 2007; Posner 2007) making them suitable for prolonged IVA. Being water-soluble, midazolam can be administered by the intramuscular route as well as the intravenous route as it is non-irritant to tissues, unlike diazepam (Kanto 1985; Posner 2007). Diazepam, being insoluble in water, is delivered in propylene glycol, an organic solvent that causes pain with subcutaneous, intramuscular and intravenous injections and makes absorption after subcutaneous or intramuscular administration unpredictable (Posner 2007). Midazolam also has a shorter context-sensitive half-life than diazepam making it a better choice for prolonged IVA (Posner 2007). For premedication in goats, both midazolam and diazepam are usually administered at doses of 0.1 mg/kg – 0.5 mg/kg (Dzikiti et al. 2009; Ghurashi et al. 2009; Lemke 2007). Benzodiazepines cause mild and transient cardiovascular and respiratory effects and are commonly used as mild tranquillisers, potent muscle relaxants and anticonvulsants (Galatos 2011; Lemke 2007). The sedative and hypnotic effects of benzodiazepines are dose-dependent, with hypnosis attainable at intravenous doses of about 0.6 mg/kg following midazolam administration (Stegmann & Bester 2001). Midazolam has been administered intravenously as an adjunct to general anaesthetic drugs at doses of 0.1 mg/kg/h – 0.9 mg/kg/h in mechanically ventilated goats and at 0.3 mg/kg/h in spontaneously breathing goats, without adversely affecting vital physiological functions (Dzikiti et al. 2010; Dzikiti, Stegmann, Dzikiti & Hellebrekers 2011b).

Alpha-2 adrenergic agonists:

Use of α2 -adrenoceptor agonists in small ruminants is highly controversial at the moment. Development of profound hypoxaemia in goats, but especially in sheep, has been documented with anaesthetic protocols that

included α2 -adrenoceptor agonists such as xylazine, romifidine, detomidine and medetomidine (Celly et al. 1997; Kumar & Thurmon 1979; Mogoa, Stegmann & Guthrie 2000). For this reason, it is recommended to exercise caution when using these drugs in small ruminants (Carroll et al. 2005; Galatos 2011). Because the suitability of use of α2 -adrenoceptor agonists in goats is currently debatable, the author decided not to include literature on IVA with these drugs in goats in this review, Ruminant are very sensitive to the effect of xylazine (Valverde and Doherty, 2008). It is 10–20 times more potent in ruminants than in other species. Among the domestic animals, the cattle are the most sensitive, whereas the pig is quite resistant to xylazine (Hall et al., 2001). Xylazine in sheep, is potent and effective analgesic performances superior to opioid drugs. Whereas goats more sensitive to xylazine than sheep (Mogoa et al., 2000a,b; Galatos, 2011).

Sedative and analgesic agents for intravenous anaesthesia: in goats Opioids: Fentanyl:

Opioids are used extensively for premedication, for analgesic supplementation during regional and general anaesthesia, as primary anaesthetic agents and as analgesics for postoperative pain (Clutton 1998; Stanski 2000). Whilst many opioids of high analgesic potency are suitable for prolonged IVA, fentanyl is currently commonly preferred in veterinary practice as it offers clinically desirable effects over a wide dose range and has a wide therapeutic margin (Mama 2006). Fentanyl, a synthetic μ-opioid agonist, is commonly used for the treatment of moderate to severe pain (Carroll et al. 1999; Lamont & Mathews 2007; Plumb 2005). The onset of action of fentanyl is rapid following intravenous administration, with analgesia, sedation, ataxia, respiratory depression and hyperaesthesia developing in 3 min – 8 min (Carroll et al. 1999; Lamont & Mathews 2007). It has a short duration of action, with the peak effect lasting less than 30 min (Carroll et al. 1999; Lee, Papich & Hardie 2000). Fentanyl has been administered intravenously as an adjunct to general anaesthetic drugs at doses of 0.002 mg/kg/h – 0.030 mg/kg/h in mechanically ventilated goats and at 0.020 mg/kg/h in spontaneously breathing goats without severely affecting vital physiological functions, although some insignificant signs of

excitement (specifically tail-wagging) were observed at high dose rates (Andel et al. 2000; Dzikiti et al. 2010; Dzikiti, Stegmann, Dzikiti & Hellebrekers 2011a). Studies in humans and dogs have shown that fentanyl alone does not result in complete general anaesthesia, but can be combined with benzodiazepines or sub-anaesthetic doses of a general anaesthetic agent such as propofol to achieve satisfactory levels of general anaesthesia (Carroll et al. 1999; Stanski 2000). The plasma concentration of fentanyl declines mainly as a result of redistribution to a large volume following a single bolus or a brief intravenous infusion (Mani & Morton 2010; Roberts & Freshwater-Turner 2007). If fentanyl is administered at a constant rate for a period longer than 3 h in humans, it attains a steady state (elimination occurring at the same rate as administration), in which case redistribution becomes less important and a rise in context-sensitive halflife (plasma half-life after a specified period of time) ensues (Roberts & Freshwater-Turner 2007). It is therefore not recommended to administer fentanyl at a constant rate for periods longer than 3 h, but rather by the TCI technique to avoid fentanyl accumulation in tissues (Mani & Morton 2010; Roberts & Freshwater-Turner 2007). For opioids with small volumes of distribution, such as remifentanil, redistribution is very limited and the context-sensitive half-life changes very little even after very long periods of CRI (Roberts & Freshwater-Turner 2007; Sneyd 2004). Benzodiazepines: Midazolam and Valium Midazolam and diazepam are the most commonly used benzodiazepines (Galatos 2011; Posner 2007). Both. benzodiazepines are fast-acting with short elimination half-lives (Lemke 2007; Posner 2007) making them suitable for prolonged IVA. Being water-soluble, midazolam can be administered by the intramuscular route as well as the intravenous route as it is non-irritant to tissues, unlike diazepam (Kanto 1985; Posner 2007). Diazepam, being insoluble in water, is delivered in propylene glycol, an organic solvent that causes pain with subcutaneous, intramuscular and intravenous injections and makes absorption after subcutaneous or intramuscular administration unpredictable (Posner 2007). Midazolam also has a shorter context-sensitive half-life than diazepam making it a better choice for prolonged IVA (Posner 2007). For premedication in goats, both midazolam and diazepam are usually administered at doses of 0.1 mg/kg – 0.5 mg/kg (Dzikiti et al. 2009; Ghurashi et al. 2009; Lemke 2007).

Benzodiazepines cause mild and transient cardiovascular and respiratory effects and are commonly used as mild tranquillisers, potent muscle relaxants and anticonvulsants (Galatos 2011; Lemke 2007). The sedative and hypnotic effects of benzodiazepines are dose-dependent, with hypnosis attainable at intravenous doses of about 0.6 mg/kg following midazolam administration (Stegmann & Bester 2001). Midazolam has been administered intravenously as an adjunct to general anaesthetic drugs at doses of 0.1 mg/kg/h – 0.9 mg/kg/h in mechanically ventilated goats and at 0.3 mg/kg/h in spontaneously breathing goats, without adversely affecting vital physiological functions (Dzikiti et al. 2010; Dzikiti, Stegmann, Dzikiti & Hellebrekers 2011b). Alpha-2 adrenergic agonists Use of α2 -adrenoceptor agonists in small ruminants is highly controversial at the moment. Development of profound hypoxaemia in goats, but especially in sheep, has been documented with anaesthetic protocols that included α2 -adrenoceptor agonists such as xylazine, romifidine, detomidine and medetomidine (Celly et al. 1997; Kumar & Thurmon 1979; Mogoa, Stegmann & Guthrie 2000). For this reason, it is recommended to exercise caution when using these drugs in small ruminants (Carroll et al. 2005; Galatos 2011). Because the suitability of use of α2 -adrenoceptor agonists in goats is currently debatable, the author decided not to include literature on IVA with these drugs in goats in this review.

Drug combinations for total intravenous anaesthesia:

in goats In practical terms, the groups of drugs described above as suitable for IVA in goats can be used to achieve TIVA-based, balanced anaesthesia by utilising specific combinations to target individual components of the anaesthetic state (unconsciousness, analgesia, muscle relaxation) to achieve any desired purpose of anaesthesia in goats. Unconsciousness can be obtained from the propofol and ketamine, analgesia from fentanyl, ketamine and lidocaine, and muscle relaxation from benzodiazepines and possibly GGE. For TIVA in goats, propofol or ketamine can be combined with midazolam and fentanyl for both induction and maintenance of general anaesthesia. Table 1 summarises the dosages at which these drugs can be administered for the initial bolus and subsequent intermittent boluses or

continuous infusion. Monitoring the total intravenous anaesthesia - anaesthetised goat Anaesthetised goats should be carefully monitored to ensure an appropriate anaesthetic depth and assessment of associated peri-anaesthetic complications, mostly involving the digestive system (tympany, regurgitation, excessive salivation) and the cardiorespiratory system (choking, hypercarbia, hypotension, hypoxaemia) (Galatos 2011; Taylor 1991). An appropriately anaesthetised goat may display sluggish palpebral and pedal reflexes as well as stable autonomic responses (Galatos 2011; Garcia 2012). If a goat is too deeply anaesthetised, the palpebral reflex and even corneal reflex will be absent, the cornea will dry up and severe bradypnoea and even apnoea may be observed. On the other hand, a lightly anaesthetised goat might blink, lachrymate, vocalise, salivate excessively, breathe more rapidly, swallow or even move its extremities (Galatos 2011; Garcia 2012). The rate of administration of intravenous drugs for maintenance of general anaesthesia should be guided by the signs of anaesthetic depth displayed by individual patients and not necessarily by known theoretical infusion rates. Other basic parameters that can be monitored include heart rate, colour of the mucous membranes, capillary refill time, respiratory rate and body temperature (Galatos 2011; Garcia 2012; Taylor 1991). Symptomatic corrective therapy, which might include oxygen, fluids, electrolytes, specific drugs and patient therapy, should be instituted, where necessary, especially to ensure that circulation, respiration and body temperature stay within normal physiologic limits (Galatos 2011; Garcia 2012; Taylor 1991). During recovery from general anaesthesia, it is still essential to monitor the goat throughout, especially to avoid complications associated with the digestive and respiratory systems. The goat should be supported to sternal recumbency and the endotracheal tube only removed after the swallowing and coughing reflexes return (Galatos 2011; Garcia 2012; Taylor 1991).

Conclusion:

General anaesthesia is used to produce unconsciousness, analgesia and muscle relaxation, but might also suppress autonomic reflex activities and consequently lead to inadequate function of vital physiological systems such

as the cardiovascular and respiratory system (Antognini & Carstens 2002; Rees & Gray 1950). Use of inhalation anaesthetic agents to maintain general anaesthesia is associated with dose-dependent depression of the cardiopulmonary systems (Antognini & Eisele 1993; Hall et al. 2001; Hikasa et al. 2002). Balanced anaesthesia, a technique in which several drugs are combined at reduced dosages to decrease adverse effects of each drug, is used to limit cardiopulmonary depression associated with use of inhalation anaesthetic agents at high dosages to maintain general anaesthesia (Toner 2005). Incorporation of intravenous anaesthetic drugs in goat anaesthetic protocols would go a long way towards attaining balanced anaesthesia because the currently available inhalation anaesthetic agents do not have any significant muscle-relaxing or analgesic effects in goats. When applying balanced anaesthesia techniques, it is important to define the purpose of each drug used. Recent scientific papers have provided information on dosages of some drugs that can be successfully utilised for prolonged IVA in goats. It is envisaged that future scientific research will be conducted to provide more information on pharmacokinetic and pharmacodynamics profiles of currently suitable IVA drugs and other potential IVA drugs such as alfaxalone and remifentanil in goats.

Recommendations

1-We approve that future scientific research will be conducted to provide more information on pharmacokinetic and pharmacodynamics profiles of currently suitable IVA drugs and other potential IVA drugs such as alfaxalone and remifentanil in goats..

2-Need for further investigations to know the effect of each drug alone on the cardiovascular system in goats, using computerized monitors.

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