

Use of supplemental intravenous anaesthesia/analgesia in horses



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General anaesthesia in horses is associated with a significant risk of both morbidity and mortality. One major factor contributing to this is the marked cardiopulmonary depression that occurs in this species in association with the use of volatile anaesthetic agents. Attempts to minimise the required volatile concentration for the maintenance of unconsciousness by administering additional injectable agents may have beneficial effects on the outcome for the animal. This article describes the characteristics of the agents commonly used for supplemental intravenous anaesthesia/analgesia (SIVA), and highlights the key points that must be taken into consideration when undertaking the concurrent administration of these drugs.

Anaesthetic risk

The Confidential Enquiry into Perioperative Equine Fatalities (CEPEF) reported a mortality of approximately 0.9 per cent for non-colic surgical cases rising to 7.9 per cent in surgical colics (Johnston and others 2002). The most common causes of death in both groups were cardiac arrest (33 per cent), fractures (26 per cent) and myopathy (7 per cent), with the last two normally manifesting during anaesthetic recovery.



Fig 1: Myopathy affecting the right gluteal muscles of a horse following general anaesthesia in dorsal recumbency. Note the marked muscle swelling. (Picture, Dr K. Hughes)

Maintenance of anaesthesia with volatile agents (most commonly halothane at the time CEPEF was undertaken) resulted in significantly greater mortality (0.99 per cent) when compared with a total intravenous anaesthetic (TIVA) technique (0.31 per cent). However, there were substantially fewer procedures performed under TIVA (1926) versus volatile anaesthesia (30,920) in the study, and the duration of the TIVA cases also tended to be shorter, which would be likely to result in an improved safety profile. When the short duration TIVA cases were compared with short cases maintained with volatile anaesthesia, there was still significantly reduced mortality following TIVA. Consequently, it would appear that maintenance of anaesthesia with TIVA may be genuinely 'safer' in horses than maintenance with volatile agents.

There are several reasons why this may be the case. Many instances of equine anaesthetic-related morbidity/mortality can be attributed to the marked cardiopulmonary depression commonly seen with volatile anaesthetic maintenance in this species. Reduced cardiac output, with resultant hypotension, is considered one of the major risk factors for myopathy (Fig 1), which may manifest in recovery as an inability to rise or may contribute to limb fracture during multiple uncoordinated attempts to stand. It has been demonstrated that TIVA may cause less cardiovascular depression than volatile agents in horses, with potentially better maintenance of cardiac output and arterial blood pressure (Luna and others 1996, McMurphy and others 2002). Consequently, muscle perfusion may be superior and the risk of myopathy reduced, when TIVA is compared with volatile anaesthetic maintenance. In addition, horses tend to ventilate more effectively during TIVA than with inhalational techniques, resulting in lower arterial partial pressure of carbon dioxide and higher partial pressure of oxygen, assuming an equivalent inspired oxygen concentration in both groups.

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Agents used for TIVA

Given the beneficial effects of TIVA on equine cardio-pulmonary performance when compared with that achieved during volatile maintenance, it would seem logical to choose TIVA for every case. However, most of the drugs used in TIVA techniques in horses (eg, ketamine, alpha-2 agonists, guaifenesin) either accumulate with prolonged infusion or have active metabolites that accumulate. This can lead to poor recovery if the TIVA infusion is used for periods in excess of about 60 to 90 minutes. Despite being extensively used in the UK, combinations of ketamine, guaifenesin and alpha-2 agonists are not licensed for maintenance of anaesthesia in horses.

Due to rapid clearance from the body, propofol is relatively non-cumulative in most species, and is the drug most commonly used for TIVA in both humans and dogs. However, in horses, although experimental studies have suggested that recovery from propofol-based anaesthetic techniques may be smoother than from inhalational anaesthesia, induction with propofol is often problematic, with horses commonly undergoing periods of 'paddling' after becoming recumbent. In addition, the large volumes of propofol required to maintain anaesthesia in horses, along with its cost, generally limits its clinical usefulness.

Based on the previously outlined potential benefits of TIVA in horses over maintenance with inhalational agents, and taking into account the possible drawbacks that limit its use, the logical conclusion might be to use a combination of both intravenous and inhalational agents for maintenance of anaesthesia. In this way, it should be possible to reduce the concentration of both the inhalational agent (decreasing its cardiopulmonary depressant effects) and the TIVA drugs (reducing the potential for adverse effects due to accumulation etc). In addition, since there is less reliance on one or the other to be the sole means of maintaining anaesthesia, the use of a low concentration of volatile anaesthetic agent offsets some of the muscle twitching and increased muscle tone that may be seen when TIVA is used alone for maintaining anaesthesia in horses, particularly when ketamine is part of the combination. There is also the suggestion that anaesthesia is more stable, with less intraoperative movement, when a combined intravenous-inhalational anaesthetic technique is used. Given the expense of some of the newer inhalational anaesthetic agents, such as sevoflurane (not currently licensed in the UK for equine use, but widely employed), any reduction in the concentration required during maintenance of anaesthesia may have financial benefits.

Terminology

Various terms have been used to describe this combined intravenous-inhalational technique. Doherty and Valverde (2006) suggested the term partial intravenous anaesthesia (PIVA), but since some of the intravenous agents currently used as part of the system are analgesic rather than anaesthetic, this is perhaps inappropriate. In addition, the use of the word 'partial' may imply – at least to some people – that the animal is not 'fully' anaesthetised. Other authors have referred



Fig 2: Volumetric infusion pump delivering a continuous rate infusion of lidocaine. A syringe driver is delivering a continuous rate infusion of medetomidine

to the technique as 'balanced anaesthesia' (Bettschart-Wolfensberger and Larenza 2007), but this is a slight variance on the classical definition of this technique in human anaesthesia.

The authors feel that the term supplemental intravenous anaesthesia/analgesia (SIVA) may be a more appropriate description, as it infers that the intravenous agent(s) are in addition ('supplemental') to an inhalational agent and that they may be either anaesthetic or analgesic drugs. SIVA is therefore used throughout this article.

Equipment

Although SIVA can be accomplished by intermittent bolus injection of drugs, this results in large variations in plasma concentration, and produces peaks and troughs in clinical effect. Greater control can be achieved by administering a constant rate infusion (CRI), using either a volumetric infusion pump or syringe driver (Fig 2). Alternatively, drugs can be added to a dedicated bag of intravenous fluids and delivered by gravity infusion, but this is much less accurate, with greater potential for drug overdose.

Drugs used for SIVA

The characteristics of an ideal injectable drug for use as part of SIVA in horses are listed in Box 1. However, to date, no drug is able to meet all these criteria, and the various injectable drugs used are all selected principally to decrease the requirement for the volatile anaesthetic agent. The term minimum alveolar concentration (MAC) describes the pharmacological potency of different inhaled anaesthetics, and represents the alveolar concentration of the particular agent that prevents gross movement in response to a noxious stimulus in 50 per cent of patients (ie, MAC is inversely related to potency). It is important to recognise that the anaesthetic concentration defined here is alveolar, and although this has some correlation with the concentration set on the vaporiser, the two values may be markedly different during equine anaesthesia due to the large volume of the equine lung and the capacity of the breathing system used. In addition, the requirement during clinical anaesthesia is to achieve immobility in 100 per cent of patients, and MAC only defines that concentration required for 50 per cent of

Box 1: Desirable characteristics of injectable agents used for SIVA

- No/minimal cardiopulmonary depressant effects
- Muscle relaxation/no increase in muscle tone
- Analgesic effect
- Lack of accumulation
- No active metabolites
- No central nervous stimulatory effects
- Facilitates a smooth recovery

animals. Consequently, although MAC determination has some clinical use (in that it allows you to appreciate that agent A will require a higher vapouriser setting than agent B if agent A's MAC value is greater than agent B's), it is of most use in research studies for quantifying the precise effect of various interventions on the requirements for inhaled anaesthetic agents. A research-based MAC-reducing effect is the basis by which most of the injectable agents discussed below are selected for SIVA.

Alpha-2 agonists

Alpha-2 agonists are a group of drugs with profound sedative, muscle relaxant and analgesic effects, and are used extensively for chemical restraint within equine practice. It has long been recognised that the administration of these agents for premedication results in a significant reduction in both induction and maintenance requirements for subsequently administered anaesthetic drugs. However, it is only relatively recently that the alpha-2 agonists have begun to be infused as part of a SIVA technique alongside volatile agents. In the UK, although xylazine, detomidine and romifidine are the alpha-2 agonists licensed for equine use, most of the research concerning equine SIVA has focused on medetomidine due to its favourable pharmacokinetics (a high clearance rate and short half-life, when administered to horses as a CRI), and greater receptor specificity (Bettschart-Wolfensberger and others 1999).

Significant reductions in inhaled anaesthetic requirements have been demonstrated in horses receiving medetomidine CRIs. In addition, maintenance of a stable plane of anaesthesia appears easier to achieve, with horses requiring fewer intravenous 'top-ups' of anaesthetic agents, when compared with maintenance using a volatile agent alone. The infusion of medetomidine to horses in this way has been used for procedures of up to 420 minutes without showing adverse effects, thus highlighting its clinical value. Horses maintained with medetomidine SIVA techniques should have a more vigorous palpebral reflex (Fig 3) than those maintained solely with inhalational agents; attempts to suppress ocular reflexes to the same degree as normally expected with 'traditional' volatile anaesthetic maintenance is likely to result in anaesthetic overdose.

Although alpha-2 agonists classically have fairly profound cardiovascular effects, including marked reductions in cardiac output, the infusion rate

described for medetomidine as part of an equine SIVA protocol is well tolerated, and cardiovascular function in horses receiving medetomidine CRI during isoflurane anaesthesia, for instance, appears to be well maintained (Ringer and others 2007).

Medetomidine is a racemic (50:50) mixture of the active isomer, dexmedetomidine, and the inactive isomer, levomedetomidine. There is some evidence that administration of dexmedetomidine may potentially offer pharmacokinetic and pharmacodynamic advantages compared with the racemate (Uilenreef and others 2008). Although there have been only limited studies of dexmedetomidine in horses compared with medetomidine, some evidence suggests that the cardiopulmonary side effects of dexmedetomidine in this species are very short lived due to rapid redistribution (Bettschart-Wolfensberger and others 2005), and its pharmacokinetics favour its administration as a CRI. The drug therefore appears to be suitable as part of a SIVA technique in horses, although further work is required before it can be recommended for routine practice use.

Motility of the gastrointestinal tract in the perioperative period is disrupted by the administration of a number of anaesthetic and analgesic drugs. Although the most notorious of these are the opioids, alpha-2 agonists can produce a profound reduction in gastrointestinal motility; however, the effects of a medetomidine CRI in clinical cases remains unclear.

It is strongly advised that a urinary catheter (Fig 4) is placed in anaesthetised horses receiving alpha-2 agonist infusions, as these drugs are diuretic and will significantly increase urine production. Facilitating an empty bladder will help to promote a smoother and less agitated recovery.

The dose of medetomidine commonly used for SIVA in horses is detailed in Table 1, but it is important to emphasise that this drug is not licensed for administration to horses in the UK.

Lidocaine

Despite having a relatively narrow therapeutic index, there has been increasing interest in the administration of intravenous lidocaine to animals over the past few years. The drug is widely administered via CRI in horses to reduce the incidence of postoperative intestinal ileus following colic surgery, but it also offers systemic analgesic effects and reduces inhalational anaesthetic agent requirements. MAC reductions of up



Fig 3: Monitoring the palpebral response in an anaesthetised horse, which is more vigorous in horses receiving medetomidine infusions as part of the anaesthetic technique



Fig 4: Gelding with bladder catheterised during anaesthesia to facilitate a smooth recovery period. Bladder catheterisation is recommended in horses receiving alpha-2 agonist infusions

Table 1: Suggested doses for drugs used for SIVA in horses

	Loading dose	Infusion rate	Comments
Medetomidine*	7 µg/kg intravenously before induction of anaesthesia (ie, replaces any alternative alpha-2 agonist as part of the induction protocol)	3.5 µg/kg/hour intravenously	Studies demonstrate superior recovery quality following medetomidine SIVA compared with lidocaine SIVA Diuretic effects necessitate urinary bladder catheterisation
Ketamine†	Probably unnecessary if infusion commenced shortly after induction of anaesthesia with ketamine. Alternatively, ~0.2 mg/kg intravenously	1 to 3 mg/kg/hour intravenously (higher infusion rate more likely to lead to accumulation, so probably better to restrict to 1 mg/kg/hour)	Possibly best to restrict infusion to durations of less than two hours to prevent accumulation Stop infusion at least 20 minutes before the end of volatile anaesthesia Provide sedation (eg, alpha-2 agonist) for recovery
Lidocaine†	1.3 mg/kg intravenously administered over 15 minutes	30 to 50 µg/kg/minute intravenously	Stop infusion 30 minutes before terminating volatile anaesthesia
Morphine*	~0.12 mg/kg intramuscularly or intravenously	0.05 mg/kg/hour intravenously	Rapid intravenous injection may result in histamine release, so administer bolus slowly over 10 minutes
Fentanyl*	1 µg/kg slowly intravenously	0.01 to 0.1 µg/kg/minute intravenously	Intermittent positive pressure ventilation required. Stop infusion 30 minutes before the end of anaesthesia. Further work required

*Drug not licensed for administration to horses, †Drug licensed for equine use, but not in the manner/route described

to 50 per cent have been reported but, at the infusion rates used clinically (Table 1), a reduction of about 25 per cent may be attained in volatile anaesthetic requirements. Plasma levels achieved with lidocaine CRI can vary widely from horse to horse and, consequently, the effects on the requirements for inhaled anaesthetics may differ between animals as MAC reduction is dose (plasma concentration) dependent.

Lidocaine undergoes rapid and extensive hepatic metabolism and, therefore, stable plasma concentrations can only be achieved by administering the drug as a CRI. Clearance may be reduced in horses with hepatic failure or cardiovascular disease (as a result of reduced hepatic blood flow), so appropriate dose reduction (or avoiding the use of this drug as a CRI) should be considered in these animals, or else toxicity may result (see below). The administration of intravenous lidocaine to anaesthetised horses should be carried out cautiously. The disposition of lidocaine may be altered during anaesthesia compared with conscious animals, and therefore higher than expected plasma levels may be achieved. This alteration may, in part, be due to changes in cardiovascular function and, therefore, hepatic blood flow, in anaesthetised horses (Feary and others 2005).

CRI of lidocaine should be given using a syringe driver or fluid infusion pump so that accuracy can be guaranteed. This ensures that the risk of toxicity developing through overdosing can be minimised, although vigilance must be maintained. Neurological and cardiovascular toxic effects can be seen if plasma levels become elevated, with neurological effects becoming evident first. In the conscious animal, these include the development of ataxia, muscle weakness and collapse followed by seizures, although the speed of onset of side effects is very dependent on how quickly the toxic dose is administered. For example, if a loading dose of lidocaine is given too quickly, a plasma concentration capable of inducing seizures can be reached without the manifestation of any other clinical signs. Compared to the central nervous system, the cardiovascular system is relatively resistant to lidocaine toxicity, but animals may exhibit arrhythmias and hypotension if sufficiently high plasma levels are reached. Toxic side effects generally disappear rapidly once the infusion is terminated due to the short half-life of lidocaine.

It must be borne in mind that the neurological effects of lidocaine overdose will be masked in horses under general anaesthesia and, as a result, the progression to cardiovascular toxicity may occur without obvious prior warning. At therapeutic plasma concentrations, however, the cardiovascular effects of a lidocaine CRI administered as an anaesthetic adjunct to horses are mild, and cardiac output and arterial blood pressure, generally well maintained.

Although lidocaine CRI can be used beneficially in most equine cases, it is particularly useful in the management of surgical colic or other high-risk patients where profound cardiovascular depression from even low concentrations of volatile anaesthetic may be especially problematic. A loading dose of the drug should be administered over about 15 minutes before commencing the CRI (Table 1).

Lidocaine has been shown to affect the degree of ataxia in horses during the recovery period and may reduce quality of recovery. To avoid this, it is recommended that CRI is stopped 30 minutes before the horse is transferred to the recovery room (Valverde and others 2005).

Although extensively used, the administration of lidocaine via the intravenous route to horses is unlicensed in the UK.

Ketamine

Ketamine is a phencyclidine derivative that is commonly administered to horses to induce and maintain dissociative anaesthesia. More recently, it has been used as part of a SIVA technique (Table 1) as it provides a MAC-sparing effect and is a potent analgesic agent at doses far below those required for anaesthesia. These characteristics facilitate a reduction in the requirement for volatile anaesthetics and can, therefore, offset the cardiovascular depressant effects of these inhalational drugs.

Ketamine has a dual effect on cardiovascular function: it directly depresses myocardial contractility *in vitro* but this is usually offset *in vivo* by a stimulatory effect on the sympathetic nervous system. This results in increased circulating levels of epinephrine and norepinephrine and, consequently, maintenance (in the healthy individual, at least) of heart rate, cardiac output and arterial blood pressure. However, in horses that may be effectively 'sympathetically

exhausted', such as those presenting with a large bowel torsion in extremis (where sympathetic tone is generally near maximal in an attempt to maintain cardiovascular function), the myocardial depressant effects of ketamine may be 'unmasked' without a concomitant increase in sympathetic tone. This may then lead to deterioration in cardiac output and arterial blood pressure. Therefore, although the use of ketamine as part of a SIVA technique will allow a reduction in volatile anaesthetic requirements, it is important to recognise that its administration, particularly in horses with pre-existing elevated sympathetic tone, may actually have cardiac depressant effects. As the studies performed to date have mainly examined the effects of MAC reduction in healthy horses, it is not certain whether these cardiac depressant effects are actually any worse than those seen following the use of volatile agents, or how great the magnitude of these effects actually is at the relatively low ketamine doses used as part of SIVA. It should be noted that ketamine administered as part of a SIVA technique to horses is not licensed in the UK.

Ketamine is presented as a racemic mixture of the S(+) and R(-) enantiomers, with the S(+) enantiomer being two to three times more potent. An enantiopure S(+) formulation has recently become available for human use and there is much interest in its administration to horses, as it may offer potential benefits over racemic ketamine because its enantioselective pharmacokinetics potentially result in faster metabolism (Larenza and others 2009a) and improved recovery characteristics (Larenza and others 2009b). In addition, the S(+) enantiomer exhibits a much reduced direct depressant effect on the cardiovascular system.

Ketamine is metabolised in the liver and produces an active metabolite, norketamine, which has 30 per cent of the potency of the parent drug and has the potential to accumulate after intravenous infusion. Emergence phenomena are a potential cause for concern in recovering horses, and central nervous system excitement and delirium could potentially lead to violent recoveries. Therefore, it is recommended that ketamine infusions are terminated at least 20 minutes before animals are transferred to the recovery room, although infusions of long duration should be terminated sooner. It is essential that sedation is administered to recovering horses that have received ketamine as an adjunct to inhalational anaesthesia to prevent emergence excitement.

Although the intravenous infusion of ketamine is generally accepted as a useful adjunct to inhalational anaesthesia in the horse, there is little published information on its effects. However, an early study on the use of ketamine infusion during halothane anaesthesia in the horse showed that the MAC of halothane was significantly reduced and, due to ketamine's sympathetic effects and a reduction in volatile concentration, that cardiac output also improved significantly (Muir and Sams 1992).

Opioids

In most species, opioids have a definite role as an adjunct to inhalational anaesthesia and consistently reduce MAC values of volatile agents in a dose-dependent manner. This reduction helps to maintain a degree of cardiovascular stability during general anaes-

thesia. MAC studies in horses, however, have reported variable effects of opioids on the requirement for inhalational anaesthetics. Some studies have shown that the administration of opioids during general anaesthesia has, in fact, increased the requirement for volatile anaesthetic agents (Steffey and others 2003), which is counterintuitive if data and experience is extrapolated from other species. Later work has documented a MAC-reducing effect of the potent short-acting opioid fentanyl in horses (Thomasy and others 2006), although data from clinical case studies is currently lacking.

It is important to realise that results from MAC evaluation studies may produce different results from those obtained in clinical cases. In particular, MAC studies involve the animal being mask induced with the inhalational agent with no other drugs in situ, and this is very different from the manner in which anaesthesia is performed in a clinical setting. Given that horses are more sensitive to excitatory effects of opioids than most other species, it has been suggested that the results obtained from studies evaluating the effect of opioids on MAC may have limited relevance in clinical cases. The administration of multiple additional drugs (eg, acepromazine, alpha-2 agonists) as part of premedication may mask the central nervous stimulatory effect of opioids and, therefore, the effects on inhaled anaesthetic requirements may be very different from those obtained during laboratory-based MAC studies. That is, it is potentially more likely that anaesthetic requirements will be reduced by opioids in a clinical setting.

Although opioids may decrease the concentration of volatile agent required to maintain unconsciousness, thereby promoting cardiostability, they may have cardiovascular side effects of their own. These include bradycardia due to a vagomimetic action and, potentially, an increase in both heart rate and arterial blood pressure, probably due to a sympathomimetic effect. While any cardiovascular perturbations associated with this group of drugs are likely to be minimal, the administration of opioids – either to conscious or anaesthetised horses – remains a contentious issue among equine clinicians. Arguably, from an anthropomorphic standpoint, the use of opioids in horses either demonstrating pain or likely to undergo a noxious event (surgery) can only be beneficial to the animal. However, potential side effects, such as central nervous system stimulation resulting in behavioural and locomotor changes, gastrointestinal motility effects and ileus, and respiratory depression (especially during inhalational anaesthesia), following the administration of opioids are of particular concern in equine species. While some experimental studies evaluating the effects of opioids on MAC have reported evidence of possible opioid-induced excitation during recovery from general anaesthesia (Thomasy and others 2006), clinically-based studies have suggested an improvement in recovery quality following intraoperative opioid administration (Clark and others 2008). The authors routinely administer opioid drugs (commonly morphine) to horses undergoing general anaesthesia without noting any adverse effects (Table 1). There is no doubt that further work needs to be undertaken in horses to precisely determine the value of opioids as part of a SIVA technique, particularly those resulting in potent short-duration effects such as fentanyl.

Propofol

Although propofol could be used as part of a SIVA technique in horses – as its administration would allow a reduction in requirements for the volatile anaesthetic agent – its lack of analgesic action and the cardiopulmonary depression it produces, would negate any potential benefit from the volatile reduction.

Drug combinations

Given that alpha-2 agonists, lidocaine and ketamine have all been shown individually to reduce the requirements for volatile anaesthetic agents, combinations of two or more of these drugs will have greater anaesthetic-sparing effects than any one drug alone (Table 1). However, care must be taken with this approach, as the potential for drug interaction and possible increased plasma concentrations due to altered clearance may be increased.

Summary

SIVA using a combination of injectable analgesic/anaesthetic drugs concurrently with volatile anaesthetic agents tends to provide better cardiopulmonary function in anaesthetised horses than volatile anaesthetic techniques alone. Given that many of the complications of anaesthesia in this species are related to reduced cardiac output and hypotension and based on the lower mortality shown with TIVA techniques in the CEPEF study, there are valid reasons for using SIVA in horses during general anaesthesia.

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Self-assessment test: Use of supplemental intravenous anaesthesia/analgesia in horses

- In the CEPEF study, of horses that died, what percentage died as a result of myopathy?
 - 1%
 - 3%
 - 7%
 - 25%
- Which of the following drugs is licensed for infusion during inhalational anaesthesia in horses in the UK?
 - Lidocaine
 - Ketamine
 - Medetomidine
 - None of the above
- Why is medetomidine suitable for SIVA infusions in horses?
 - It has a short half-life
 - It has a high clearance
 - It reduces MAC
 - All of the above
- SIVA infusions of lidocaine at clinical doses can reduce the MAC of an inhalational agent by how much?
 - 10%
 - 25%
 - 40%
 - 75%
- During inhalational anaesthesia in horses, how long before the end of anaesthesia should lidocaine infusions be terminated?
 - 0 minutes (run the infusion until the end of anaesthesia)
 - 10 minutes
 - 30 minutes
 - 60 minutes
- What is the effect of opioids on MAC in the horse?
 - No effect
 - Increases MAC
 - Reduces MAC
 - May increase or decrease MAC

Answers

1. c, 2. d, 3. d, 4. b, 5. c, 6. d



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