REVIEW ARTICLE

Partial intravenous anaesthesia in the horse: a review of intravenous agents used to supplement equine inhalation anaesthesia. Part 1: lidocaine and ketamine

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Abstract

Objective To review the literature with regard to the use of different intravenous agents as supplements to inhalational anaesthesia in horses. These drugs include lidocaine, ketamine, opioids and α2-agonists. The Part 1 of this review will focus in the use of lidocaine and ketamine.

Databases used Pubmed & Web of Science. Search terms: horse, inhalant anaesthesia, balanced anaesthesia, partial intravenous anaesthesia, lidocaine, ketamine.

Conclusions Different drugs and their combinations can be administered systemically in anaesthetized horses, with the aim of reducing the amount of the volatile agent whilst improving the recovery qualities and providing a multimodal analgesic approach. However, full studies as to whether these techniques improve cardiopulmonary status are not always available and potential disadvantages should also be considered.

Keywords equine, inhalation anaesthesia, intravenous drugs, ketamine, lidocaine.

Introduction

During inhalation anaesthesia, reduction of concentration of volatile anaesthetic is one of the general principles to prevent and treat cardiopulmonary depression. Modern volatile anaesthetics have poor analgesic properties (Tomi et al. 1993; Petersen-Felix et al. 1995) and consequently, it may not be practicable to reduce their concentration for maintenance of anaesthesia, especially during painful surgical procedures. Lack of intra-operative analgesia also may lead pain after the anaesthetic period, which in turn may influence the recovery negatively. The use of systemically administered supplementary anaesthetics/analgesics can reduce the need for volatile anaesthetics while improving the recovery qualities in the so-called ‘balanced anaesthetic protocols’.

The concept of balanced anaesthesia can be defined as the use of a combination of pharmacological agents that will act together to provide the desired effects for the procedure, most usually some or all of hypnosis, analgesia and muscle relaxation, whilst resulting in reduced side-effects compared with the use of higher doses of one agent alone (Gray & Halton 1946; Tonner 2005). In horses, balanced anaesthesia for prolonged surgery usually is based on a combination of volatile anaesthetics with either locoregional anaesthetic techniques or supplementary intravenous (IV) anaesthetics/analgesics, the technique also being called partial IV anaesthesia (PIVA). The aim is to maintain adequate conditions for surgery whilst maintaining good intraoperative cardiopulmonary function, this then being followed by a calm, smooth and coordinated recovery (Betts-chart-Wolfensberger & Larenza 2007). The concept
of PIVA has been used frequently in equine anaesthesia (Doherty & Valverde 2006; Bettscchart-Wolfensberger & Larenza 2007) and has been defined as ‘a form of balanced anaesthesia that implies the use of low concentrations of inhalation anaesthetics in combination with injectable agents in order to reduce the cardiorespiratory depressant effects of the inhalants and to improve analgesia and anaesthetic stability’ (Nannarone & Spadavecchia 2012).

The following sections will review the current literature with regard to the different drugs that can be used for these purposes. The focus will be placed on the local anaesthetic agent lidocaine, the dissociative anaesthetic agent ketamine, the analgesic opioids and the sedative/analgesic α2-agonists.

To assess the effects of anaesthetic methods cardiovascular function it is necessary to know not only blood pressures and heart rate (HR), but also cardiac output (CO). In the equine anaesthetic literature, measurement of this vital parameter often is not performed, and the term ‘cardiovascular depression’ taken to refer only to arterial blood pressures, neglecting the important features of cardiac performance and resultant blood flow. Since the introduction of lithium dilution measurement for CO, more equine studies have included this parameter. Unfortunately recent work has demonstrated that the lithium sensor is influenced by clinically relevant blood concentrations of, in particular xylazine (Ambrisko et al. 2013; Ambrisko & Moens 2014; Hopster et al. 2014a), in general resulting in an overestimation of CO. Thus the potential for error has to be taken into consideration for all research in this field that used this method of CO measurement.

**Lidocaine**

In human medicine, the IV use of the local anaesthetic, lidocaine, for anaesthetic and analgesic purposes was first reported over 60 years ago (Gilbert et al. 1951; De Clive-Lowe et al. 1958). Its use decreased for thirty years mainly due to toxicity matters and the development of other drugs and analgesic/anaesthetic techniques. However, as local anaesthetics were shown to be efficient at blood concentrations lower than those causing toxicity (Rimbäck et al. 1986, 1990), a renewed interest of IV lidocaine was created in the 1980s for applications such as the treatment of neuropathic pain (Kastrup et al. 1987; Ferrante et al. 1996) and the reduction of the duration of colonic stasis (Rimbäck et al. 1990). Additionally, IV lidocaine was reported to decrease postoperative pain (Koppert et al. 2004), to have antihyperalgesic (Koppert et al. 1998) and anti-inflammatory properties (Hollmann & Durieux 2000), to improve gastrointestinal function postoperatively (Groudine et al. 1998), to facilitate rehabilitation (Kaba et al. 2007) and also to reduce the minimum alveolar concentration (MAC) of volatile agents (Himes et al. 1977). However, its negative inotropic effects limit its use in human anaesthesia (Wilson et al. 1993).

With regard to antinociception, the mechanism whereby systemic lidocaine exerts an analgesic action has not been completely elucidated. Tanelian & MacIver (1991) suggested that the analgesia produced by lidocaine is the result of the suppression of tonic neural discharges in injured peripheral A-δ and C fibre nociceptors, although a direct action on spinal transmission in the spinal cord has also been proposed (Woolf & Wiesenfeld-Hallin 1985; Nagy & Woolf 1996; Koppert et al. 2000). It is also possible that both peripheral and central actions contribute to the analgesic action of systemic lidocaine and that the predominant mechanism varies according to the nature of pain (Wallace et al. 1996). Low doses of systemic lidocaine have been used with good results for the treatment of severe cases of laminitis in equine patients (Malone & Graham 2002). Furthermore, electroencephalographic findings have demonstrated that lidocaine provides antinociception contributing to additional analgesia during castration in ponies (Murrell et al. 2005). However, much less is understood about the action of lidocaine on visceral pain. Indeed, lidocaine failed to have a significant effect on the response to colorectal or duodenal distension in horses (Robertson et al. 2005), although it did inhibit, in a dose dependent manner, the cardiovascular responses to colorectal distension in rats (Ness 2000). Furthermore, lidocaine significantly increased the thermal threshold in horses (Robertson et al. 2005), which was in clear contrast with the findings in human volunteers, where systemic lidocaine had no effect on thermal thresholds (Wallace et al. 1997).

Systemically administered lidocaine has recently gained popularity for use in equine anaesthetized patients as it produces anaesthetic-sparing (Doherty & Frazier 1998; Dakiti et al. 2003), analgesic (Murrell et al. 2005; Robertson et al. 2005) and anti-inflammatory effects (Nellgard et al. 1996; Cook et al. 2009). The mechanism by which lidocaine reduces the MAC of volatile anaesthetics may involve different receptor types, such as sodium,
calcium and potassium channels, and NMDA, GABA,
acetylcholine, glycine and vanilloid receptors (Zhang et al. 2007; Doherty & Seddighi 2010). Lidocaine dose
dependently reduced the MAC of halothane in six experimental ponies (Doherty & Frazier 1998) receiving a loading
dose (2.5 or 5 mg kg⁻¹) over 5 minutes followed by a CRI (50 or 100 μg kg⁻¹ minute⁻¹) for 1 hour. In a clinical
study performed in 12 horses, Dzikiti et al. (2003) reported that IV administration of lidocaine at 2.5 mg kg⁻¹ over 10
minutes (15 minutes after induction) followed by a CRI of 50 μg kg⁻¹ minute⁻¹ during 75 minutes resulted in a 25% reduct-
ion in isoflurane requirement, without negative effects on the cardiovascular system. Administration of IV lidocaine in
horses with colic (1.5 mg kg⁻¹ bolus before surgery followed by a CRI 30 μg kg⁻¹ minute⁻¹) produced analgesia and dose
dependent MAC sparing effects ranging from 20 to 25% without significant cardiovascular or other side
effects (Driessen 2005). More recently, the administration of a bolus of lidocaine (1.3 mg kg⁻¹) over 15 minutes followed by a 50 μg kg⁻¹ minute⁻¹ CRI in eight experimental adult horses was shown to reduce the MAC of sevoflurane by 27% (Rezende et al. 2011). However, at equi-anæsthetic depth there were no differences in cardiopulmonary parameters (including CO) between isoflurane alone and the lower concentration of isoflurane with lidocaine infusion (Wagner et al. 2011). Also, under clinical circumstances, management of anaesthesia in horses receiving lidocaine (2 mg kg⁻¹ over 15 minutes plus CRI of 50 μg kg⁻¹ minute⁻¹) was more difficult and a higher expired fraction of isoflurane (Fe/ISO) was required to maintain an appropriate, stable surgical plane of anaesthesia compared with horses receiving medetomidine (7 μg kg⁻¹ followed by a CRI of 3.5 μg kg⁻¹ hour⁻¹) (Ringer et al. 2007).

Recovery from general anaesthesia is the most critical phase when anaesthetizing horses. No negative
effects were noted by Dzikiti et al. (2003) during the recovery period in horses receiving a CRI of lidocaine throughout anaesthesia (for at least 90 minutes) compared with a saline group. When a bolus of 1.5 mg kg⁻¹ of lidocaine was adminis-
tered just before surgery and the infusion of 30 μg kg⁻¹ minute⁻¹ stopped when the surgeon started to close the abdomen, horses with lidocaine had similar recoveries than those of the control group (Driessen 2005). In contrast, Valverde et al. (2005) described in a clinical study involving 54 horses (2 mg kg⁻¹ over fifteen minutes followed by 50 μg kg⁻¹ minute⁻¹) higher degrees of ataxia and lower recovery qualities in horses receiving lidocaine until the end of the surgery. These authors recom-
mended to discontinue the CRI 30 minutes before the end of the anaesthesia. Ringer et al. (2007) reported significantly better recoveries after the continuous infusion of medetomidine (3.5 μg kg⁻¹ hour⁻¹) compared with lidocaine where both CRIs were stopped at the end of surgery and sedation was given prior to recovery. Furthermore, in a clinical study performed in 12 horses undergoing elective surgery, the addition of a medetomidine infusion (5 μg kg⁻¹ hour⁻¹) to an infusion of lidocaine (2 mg kg⁻¹ plus infusion at a rate of 50 μg kg⁻¹ minute⁻¹) improved the quality of recovery compared with lidocaine alone (Valverde et al. 2010). In horses undergoing field castration, a bolus of lido-
caine (3 mg kg⁻¹ IV) did not affect the recovery quality, although the overall recovery period was longer. Its use also did not reduce the needs for additional injectable anaesthesia during surgery (Sinclair & Valverde 2009).

In equine animals, lidocaine is metabolized via the hepatic cytochrome P450 (CYP450) system into the active metabolites monoethylglycinexilidide and glycineylxilidide, both lidocaine and the metabolites being excreted in the urine (Doherty & Frazier 1998). Although it has not been elucidated whether the metabolites of lidocaine play a role during recovery from anaesthesia, it seems possible that they contribute to the low quality of recovery that has been reported. In contrast, the cardiovascular system has been shown to be more resistant to the effects of IV lidocaine in horses (Meyer et al. 2001; Sinclair & Valverde 2009). As lidocaine is highly metabolized by the liver and has a very short half-life (Engelking et al. 1987), it should be used intraoperatively as a bolus followed by a CRI. Lidocaine clearance is highly dependent on hepatic blood flow (Engelking et al. 1987) and general anaesthesia has a profound effect on serum lidocaine concentrations in horses, mainly due to a decrease in the volume of distribution and clearance of lidocaine (Feary et al. 2005). Moreover, other anaesthetic drugs metabolized via the CYP450 system may compete for binding sites and delay clearance (Doherty & Seddighi 2010). Importantly, factors such as different body mass composition, age, sex and weight may influence lidocaine disposition (Feary et al. 2005). This is of special importance in patients where liver function might be impaired (neonates, the elderly or
compromised patients) and which should be taken into account, as these patients may more easily show signs of lidocaine toxicity.

Toxicosis should be considered when lidocaine is included in balanced anaesthetic protocols, especially because its neurological signs (weakness or ataxia) may be masked by anaesthesia. In the last decade, efforts have been made to determine the toxic blood levels for lidocaine in the horse. Meyer et al. (2001) demonstrated that lidocaine produced muscle fasciculations, tremors and ataxia in healthy awake horses at plasma levels between 1.85 and 4.53 $\mu$g mL$^{-1}$, substantially different from humans (1.56 ± 0.61 $\mu$g mL$^{-1}$) (Wallace et al. 1997) and dogs (8.21 ± 1.69 $\mu$g mL$^{-1}$) (Wilcke et al. 1983). Serum lidocaine concentrations ranged from 1 to 2 $\mu$g mL$^{-1}$ in awake horses after abdominal surgery, receiving a loading dose of 1.3 mg kg$^{-1}$, followed by a CRI of 50 $\mu$g kg$^{-1}$ minute$^{-1}$. This resulted in a reduction in the volume of gastric reflux in horses with proximal enteritis and postoperative ileus, while clinical signs of toxicosis were not observed (Malone et al. 1999). In patients undergoing elective procedures, Feary et al. (2005) showed that general anaesthesia using sevoflurane has a profound effect on lidocaine disposition in horses, and that lidocaine plasma levels were higher during anaesthesia than in awake horses (3.35 ± 0.60 and 1.85 ± 0.39 $\mu$g mL$^{-1}$ respectively) after a loading dose of 1.3 mg kg$^{-1}$ following by a CRI of 50 $\mu$g kg$^{-1}$ minute$^{-1}$. Although no clinical signs of toxicosis were observed, the authors speculated that general anaesthesia may mask neurologic manifestations of toxicosis. Lower doses compared to previous studies were recommended by Brianceau et al. (2002), who used a loading dose of 0.65 mg kg$^{-1}$ during the first 30 minutes of general anaesthesia followed by a maintenance rate of 25 $\mu$g kg$^{-1}$ minute$^{-1}$ in colic horses. Lidocaine had also favourable effects on jejunal distension and peritoneal fluid accumulation after abdominal surgery. The mean intraoperative lidocaine concentration was 1.06 ± 0.6 $\mu$g mL$^{-1}$, although in one horse intraoperative concentrations of 2.72 $\mu$g mL$^{-1}$ were found. The authors attributed this variability mainly to individual differences in CO. Indeed, horses experiencing pain may have a higher CO, higher clearance of the drug and lower lidocaine serum concentrations. More compromised patients, with impaired cardiovascular function, will have a reduced liver blood flow and metabolism and higher lidocaine plasma levels.

In conclusion, lidocaine can be included in balanced anaesthetic protocols at different doses, providing intraoperative analgesia and reducing (dose dependently) the MAC of the volatile agent. However, potential side effects such as toxicosis should be taken into account, especially in cardiovascularly impaired patients. Furthermore, the infusion should be stopped at least thirty minutes before the end of anaesthesia to reduce the incidence of ataxia, improving the quality of the recoveries. An overview of the literature on the use of lidocaine in equine anaesthesia is provided in Table 1.

**Ketamine**

The use of the dissociative anaesthetic ketamine, at subanaesthetic doses, has been accepted in human medicine in order to provide multimodal analgesia in patients with pain related to opioid tolerance but also for the treatment of acute severe, neuropathic, ischaemic, peripheral somatic, visceral, cancer or chronic post surgical pain (Menigaux et al. 2001; Petrenko et al. 2003; Correll et al. 2004; Visser & Schug 2006). Ketamine is a non-competitive antagonist of the NMDA receptor, a ligand gated calcium channel with glutamate as its major endogenous agonist (Kohrs & Durieux 1998). Blockade of NMDA receptors enhances analgesia, but when exaggerated may result in memory impairment, excitation, dementia, ataxia and motor incoordination (Muir 2010). The interaction with NMDA receptors was proposed to be responsible for the general anaesthetic effects and analgesia (Visser & Schug 2006). However, although most of its effects are mediated via NMDA receptors (Kohrs & Durieux 1998; Chang et al. 2002), ketamine also interacts with non-NMDA glutamate, opioid, nicotinic, muscarinic and GABA$_A$ receptors (Kohrs & Durieux 1998; Knobloch et al. 2006). The clinical use of NMDA antagonists at routine doses can be restricted mainly because of the psychomimetic side effects, ataxia and uncoordinated motor activity (Petrenko et al. 2003). These side effects are dose dependent and less common when using small, subanaesthetic doses (Himmelseher & Durieux 2005).

In contrast to the other drugs used for induction of anaesthesia, ketamine produces an indirect cardiovascular stimulation with significant increases in blood pressure and HR (Zielmann et al. 1997). Additionally, it induces only a minimal respiratory depression with mild hypercapnia (Werner et al. 1997) and has been shown to antagonize the
hypoventilation induced by alfentanil in humans (Persson et al. 1999). In horses, IV doses of 2.2 mg kg\(^{-1}\) combined with xylazine provided excellent short term anaesthesia with stable cardiorespiratory function (Muir et al. 1977). Heart rate and mean arterial blood pressure did not change when plasma ketamine concentration increased but CO did significantly increase during ketamine infusion (Muir et al. 1997; Hubbell et al. 2000). Nowadays, ketamine is also administered in horses in combination with other drugs to achieve multimodal analgesia for acute and chronic pain (Muir 2010). Moreover, it produces effective epidural analgesia (Gómez de Segura et al. 1998) and has clear local anaesthetic effects (López-Sanromán et al. 2003a,b).

In equine practice, ketamine has been used routinely for induction and maintenance of general anaesthesia for many years and has become a popular drug, especially when combined with an \(\alpha_2\)-agonist or centrally acting muscle relaxants (Muir et al. 1977; Butera et al. 1978; Luna et al. 1997; Hubbell et al. 2000). Nowadays, ketamine is also administered in horses in combination with other drugs to achieve multimodal analgesia for acute and chronic pain (Muir 2010). Moreover, it produces effective epidural analgesia (Gómez de Segura et al. 1998) and has clear local anaesthetic effects (López-Sanromán et al. 2003a,b).

When administered IV in horses, ketamine produces antinociceptive (Johnson et al. 1999; Knobloch et al. 2006; Peterbauer et al. 2008; Leignonnois et al. 2010a) and anaesthetic effects (Bettschart-Wolfensberger et al. 1996; Mama et al. 2005). To date, the possible role of ketamine in the treatment of equine endotoxaemia, remains controversial (Lankveld et al. 2005; Alcott et al. 2011). A 1.5 mg kg\(^{-1}\) hour\(^{-1}\) CRI of ketamine in healthy conscious horses showed that an infusion of ketamine can be safely administered for at least 6 hours (Lankveld et al. 2006). In contrast, Fielding et al.

### Table 1 Different loading doses and infusion rates reported for the use of IV lidocaine in equine balanced anaesthesia

<table>
<thead>
<tr>
<th>Animals</th>
<th>Loading dose (mg kg(^{-1}))</th>
<th>CRI ((\mu g) kg(^{-1}) minute(^{-1}))</th>
<th>Main findings</th>
<th>References</th>
<th>CO measured?</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 experimental ponies</td>
<td>2.5–5 over 5 minutes</td>
<td>50–100</td>
<td>↓ MAC(_{HALO}) dose dependently</td>
<td>Doherty &amp; Frazier (1998)</td>
<td>/</td>
</tr>
<tr>
<td>28 colic horses</td>
<td>0.65 over 30 minutes</td>
<td>25</td>
<td>Desirable intestinal effects</td>
<td>Brianceau et al. (2002)</td>
<td>/</td>
</tr>
<tr>
<td>12 healthy clinical horses</td>
<td>2.5 over 10 minutes</td>
<td>50</td>
<td>↓ MAC(_{ISO}) by 25%</td>
<td>Dzikiti et al. (2003)</td>
<td>/</td>
</tr>
<tr>
<td>50 colic horses</td>
<td>1.5 before start of surgery</td>
<td>30</td>
<td>No influence on recovery quality</td>
<td>Driessen (2005)</td>
<td>/</td>
</tr>
<tr>
<td>54 healthy clinical horses</td>
<td>2 over 15 minutes</td>
<td>50</td>
<td>Affects degree of ataxia Stop CRI 30 minutes before end of surgery</td>
<td>Valverde et al. (2005)</td>
<td>/</td>
</tr>
<tr>
<td>16 experimental horses</td>
<td>1.3 over 15 minutes</td>
<td>50</td>
<td>Anaesthesia influences</td>
<td>Feary et al. (2005)</td>
<td>/</td>
</tr>
<tr>
<td>89 healthy clinical horses</td>
<td>2 over 15 minutes</td>
<td>50</td>
<td>lidocaine disposition Maintenance easier and lower F(_{\text{r}})/ISO with medetomidine</td>
<td>Ringer et al. (2007)</td>
<td>CO-L</td>
</tr>
<tr>
<td>8 experimental horses</td>
<td>1.3 over 15 minutes</td>
<td>50</td>
<td>↓ MAC(_{SEVO}) by 27%</td>
<td>Rezende et al. (2011)</td>
<td>/</td>
</tr>
<tr>
<td>8 experimental horses</td>
<td>1.3 over 15 minutes</td>
<td>50</td>
<td>At a comparable anaesthetic depth, Lidocaine CRI did not improve cardiopulmonary variables compared to sevoflurane anaesthesia alone</td>
<td>Wagner et al. (2011)</td>
<td>CO-TD</td>
</tr>
</tbody>
</table>

CRI, constant rate infusion; MAC, minimum alveolar concentration; HALO, halothane; ISO, isoflurane; SEVO, sevoflurane; F\(_{\text{r}}\), expired fraction; CO, cardiac output; CO-L, cardiac output measured by lithium dilution technique; CO-TD, cardiac output measured by thermodilution technique.
Ketamine is used in equine anaesthesia to induce immobility and analgesia, but its metabolism and pharmacokinetics differ from those in humans. Studies have shown that ketamine is metabolized more rapidly in horses, with a higher clearance rate compared to racemic ketamine. This is due to the faster elimination of the S-enantiomer, which has a higher clearance rate than the R-enantiomer. The elimination of S-ketamine is also faster in plasma, leading to lower plasma concentrations and a reduced risk of overdose.

Ketamine is often used in combination with other drugs, such as xylazine, to achieve immobility and analgesia. These drugs have different pharmacodynamic properties and can complement each other in providing a balanced anaesthetic effect. For example, ketamine has a rapid onset of action and induces immobility, whereas xylazine has a slower onset and can provide analgesia.

The use of ketamine in equine anaesthesia has been studied extensively, and it is often preferred for its ability to provide rapid induction and immobility. However, it is important to monitor the effects of ketamine closely, as its metabolites can accumulate and cause toxicity if administered for extended periods. The use of ketamine in equine anaesthesia is subject to specific guidelines and protocols, with careful consideration of the patient's condition and the planned surgical procedure.

In conclusion, ketamine is a valuable drug in equine anaesthesia, but its use should be carefully managed to ensure patient safety and optimal outcomes. Further research is needed to explore the full potential of ketamine in equine anaesthesia and to develop better strategies for its use in combination with other drugs.
Ketamine and its metabolites may produce excitatory side effects that can result in fatal consequences in the recovery period in horses (Schatzmann & Girard 1984; Bettschart-Wolfensberger & Larenza 2007). These excitatory effects are claimed to be associated mainly with the R-enantiomer (White et al. 1985; Filzak et al. 2003). When given at low doses in standing ponies, S-ketamine produced more ataxia and disorientation compared to the racemate, but these effects were of short duration (Peterbauer et al. 2008). Side effects in the recovery such as excitement or ataxia may occur when using ketamine as the sole agent for induction and maintenance of general anaesthesia (Bettschart-Wolfensberger et al. 1996). Furthermore, when infused in combination with other anaesthetics/analgesics, its adverse effects during the recovery phase may be prevented by reducing ketamine administration early enough before recovery (Knobloch et al. 2006). Prolonged infusions may lead to excessive norketamine formation and accumulation in fat and muscle (Knobloch et al. 2006), causing undesirable side effects. Consequently, it has been recommended that IV boluses higher than 2 mg kg\(^{-1}\) or CRIs exceeding 1 mg kg\(^{-1}\) hour\(^{-1}\) should not be used in anaesthetic procedures longer than 1.5–2 hours while ketamine CRIs should be reduced in long procedures and/or stopped fifteen to twenty minutes before the recovery (Bettschart-Wolfensberger & Larenza 2007). Undesired recoveries may also occur after prolonged infusions of rates lower than 1 mg kg\(^{-1}\) hour\(^{-1}\), possibly due to effects of norketamine, which has been shown to possess a longer half-life than ketamine (Lankveld et al. 2006). It has been recommended that an \(\alpha_2\)-agonist should be administered to reduce the incidence of complications during the recovery phase (Santos et al. 2003). Furthermore, it is worth mentioning that ketamine infusions may produce increases in gastrointestinal transit time and decreases in fecal output (Ellenbein et al. 2011).

In summary, low doses of IV racemic or S-ketamine may be useful in equine balanced anaesthetic protocols because of the demonstrated analgesic effects, the reduction of the anaesthetic requirements and the improvements of the cardiovascular haemodynamics. However, caution should be taken to prevent its undesirable excitatory side effects that may worsen the quality of the recoveries, mainly by avoiding high doses/rates and infusion times longer than 1.5–2 hours.

**Multiple drug combinations**

Combinations of several different IV agents are now used commonly for PIVA in horses. Of specific relevance to this part of the review is the combination of lidocaine and ketamine. Co-administration of IV lidocaine and ketamine in horses was reported to produce an additive effect on the inhalant anaesthetic-sparing effects. This was first suggested by Enderle et al. (2008) from a clinical study on the basis of reduced isoflurane requirements, but was confirmed in an experimental study by Villalba et al. (2011), who demonstrated MAC reductions of 40% and 49% respectively at different doses and rates. In a recent ‘blinded’ clinical trial, the mean Fi/ISO in anaesthetized horses undergoing elective surgery when receiving lidocaine and ketamine infusions was 1% (0.62–1.2%) and was further reduced to 0.65% (0.4–1.0%) when a medetomidine CRI was added (Kempchen et al. 2012). Other multiple combinations of IV agents are reviewed in Part 2 (Gozalo-Marcilla et al. 2014) of this review.

**References**


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Meyer GA, Lin HC, Hanson RR et al. (2001) Effects of 


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