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Balancing Total Intravenous Anesthesia and Inhalant Anesthesia in Horses

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1. Introduction

Intravenous drugs such as chloral hydrate, pentobarbital, and thiamylal were once commonly used for general anesthesia of horses but were often associated with prolonged or violent recoveries. When inhalant anesthetics such as halothane were introduced in the 1960s, the use of IV drugs for maintenance of anesthesia became less common. In recent years, interest in IV anesthetic techniques has been renewed, both by recognition of the relatively high risk of morbidity or mortality with inhalant techniques and by the development of injectable drugs with fewer undesirable side effects and potentially improved recovery characteristics.

In 2002, a large, multi-center prospective study reported peri-anesthetic mortality for horses to be 0.9% (1 death per 111 anesthetized horses). Subsequently, one individual equine hospital reported a much lower mortality rate of 0.12–0.24% (1 death per 417–833 cases). In the multi-center study, anesthesia induced and maintained using only IV drugs (total intravenous anesthesia [TIVA]) was reported to be associated with a lower risk of death (0.3%, or 1 death per 321 cases) than anesthesia induced with IV drugs and maintained with inhalant anesthesia. Recoveries from short-term IV anesthesia are often smoother and more controlled than recoveries from inhalant anesthesia. Other advantages of TIVA include the minimal equipment required compared with inhalant anesthesia and potentially reduced stress. The development of reversible or shorter-acting drugs such as α2 agonists, ketamine, and propofol has facilitated the use of TIVA for longer procedures than previously considered safe.

This article will review the current state of TIVA in horses, as well as how certain IV sedatives, anesthetics, and analgesics are being used to supplement and improve inhalant anesthesia.

2. Short-Term IV Anesthesia (≤ 20 min)

In the United States, the most common technique used for short-term IV anesthesia is xylazine sedation followed by ketamine induction, with or without diazepam for improved muscle relaxation. Xylazine-ketamine or xylazine-diazepam-ketamine provides an average of 16 min of surgical anesthesia, with recovery to standing in ~25–32 min. It has been suggested that duration of surgical anesthesia is longest in grade horses and shorter in Thoroughbreds. Most equine practitioners find both induction and recovery with this drug regimen to be satisfactory and reasonably safe. For good quality

NOTES
of surgical anesthesia, it is important to ensure that sedation and muscle relaxation are adequate; therefore, in general, a higher dose of xylazine (1.1 mg/kg or ~500 mg per 450-kg horse) than would typically be used for standing sedation is recommended. Additional methods for improving muscle relaxation and quality of IV anesthesia are listed in Table 1.

Although xylazine is the most common pre-medication in the United States, other α2 agonists may be used and may afford a slightly longer anesthesia time. For example, detomidine (0.02 mg/kg, IV) followed by ketamine (2.2 mg/kg, IV) produced recumbency of slightly longer duration (average, 27 min) than xylazine (1.1 mg/kg, IV) and ketamine (2.2 mg/kg, IV) (average, 23 min). However, muscle relaxation during anesthesia and recovery quality were both slightly less satisfactory with detomidine-ketamine than with xylazine-ketamine.11

Romifidine is a newer α2 agonist associated with a longer duration and purportedly less ataxia than xylazine. Both of these characteristics could be beneficial for short-term IV anesthesia. A comparison of romifidine (0.1 mg/kg, IV) to xylazine (1.1 mg/kg, IV), in combination with diazepam and ketamine, showed that both regimens produced excellent quality anesthesia, with good induction and recovery quality, and good muscle relaxation. The romifidine combination produced about 5 additional min of surgical anesthesia (21 min) compared with the xylazine combination (16 min). Recovery required about 44 min for the romifidine group compared with 32 min for the xylazine group.8

Butorphanol has been used as an adjunct for IV anesthesia. A comparison of xylazine-ketamine or detomidine-ketamine, with and without the addition of butorphanol (0.04 mg/kg, IV, or 18 mg per 450-kg horse), suggested that butorphanol may improve muscle relaxation and surgical conditions and prolong recumbency time slightly.11

Thiopental, once the “gold standard” of anesthetic induction agents, is no longer commonly used for short-term anesthesia in horses. Although with appropriate premedication such as xylazine, thiopental inductions are quite predictable and smooth, recoveries from short-term thiopental anesthesia tend to be somewhat uncoordinated.10 In addition, thiopental can be very irritating if accidentally injected perivascularly, and the volume typically required to anesthetize a 450-kg horse (~27 ml of 10% solution) makes perivascular injection a considerable risk, unless an IV catheter is in place.

Interestingly, results of a controlled study suggested that thiopental produced better-quality inductions than did ketamine and that combining either ketamine or thiopental in various proportions with propofol improved both induction and recovery quality.10 Propofol is an induction agent that has become extremely popular both in humans and in small animals, with generally smooth inductions and particularly rapid and smooth recoveries, with none of the residual “hangover” often associated with other anesthetics. In the equine study, combinations of ¼ induction dose of propofol with ¼ induction dose of ketamine or thiopental produced the smoothest inductions. However, the best-quality recoveries were achieved by combining ¼ dose of propofol with ¼ dose of ketamine or thiopental. One might then think that combining ½ dose of propofol with ½ dose of the others would result in both excellent inductions and excellent recoveries, and indeed, the “½-½” combinations did result in both induction and recovery quality that appeared to be slightly better than either ketamine or thiopental alone.10

Unfortunately, there are issues related to propofol administration in horses that detract from its usefulness as a sole induction agent. Inductions by propofol alone may be quite violent, with paddling of
the limbs and uncoordinated muscle activity.\textsuperscript{12} Premedication with either xylazine or detomidine does not prevent excitatory behavior and muscle activity.\textsuperscript{13, 14} With the currently available propofol concentr ation of 10 mg/ml, the required induction dose (2 mg/kg) for a typical horse is nearly 100 ml, making it inconvenient and time consuming to administer. Respiratory depression may be profound and may necessitate assisted ventilation.\textsuperscript{12, 13} Despite its reputation for rapid recoveries in most species, a single induction dose of propofol in horses (after xylazine premedication) is associated with slightly longer times to standing (~33 min) than a single dose of ketamine (~25 min).\textsuperscript{10, 15}

The use of tiletamine-zolazepam, another option for induction of anesthesia of horses, was first described 20 yr ago.\textsuperscript{14} Tiletamine is a dissociative anesthetic similar to ketamine, and zolazepam is a benzodiazepine similar to diazepam. Tiletamine and zolazepam are marketed in the United States as the 50:50 combination Telazol,\textsuperscript{4} formulated as a powder that must be reconstituted before use. A 500-mg vial contains 250 mg of tiletamine and 250 mg of zolazepam, and the recommended doses are given as milligram per kilogram of both drugs combined. After sedation with xylazine, anesthesia induced with tiletamine-zolazepam, at doses of 1.1, 1.65, or 2.2 mg/kg, IV, resulted in surgical anesthesia of ~20 min, lateral recumbency of 30- to 39-min duration, and recovery to standing in 32–46 min; thus, tiletamine-zolazepam produces longer duration of anesthesia than does ketamine. Quality of anesthesia was judged to be best with tiletamine-zolazepam doses of 1.65 or 2.2 mg/kg, IV. However, PaO$_2$ decreased more than with xylazine-ketamine anesthesia.\textsuperscript{14} In addition, recoveries from short-term xylazine-tiletamine-zolazepam anesthesia tend to be less satisfactory than recoveries from xylazine-ketamine anesthesia.\textsuperscript{11} In the United States, tiletamine-zolazepam is usually more expensive than ketamine-diazepam. Potential advantages of tiletamine-zolazepam include the slightly longer duration of anesthesia and the very small volume required for injection, which may be advantageous for certain situations, such as darting feral horses.

A combination of tiletamine-zolazepam-ketamine-detomidine (TZKD) has been used for induction of anesthesia in horses.\textsuperscript{15} The combination was prepared by adding 4 ml of ketamine (100 mg/ml) and 1 ml of detomidine (10 mg/ml) to reconstitute a 5-ml bottle of tiletamine-zolazepam. Horses were first sedated with xylazine 0.44 mg/kg, IV (~200 mg for a 450-kg horse), and the combination TZKD was administered at 3 ml/450 kg, IV. This volume resulted in individual drug doses of tiletamine-zolazepam at 0.67 mg/kg, ketamine at 0.53 mg/kg, and detomidine 0.013 mg/kg. The authors reported that advantages of this combination included the small volume of drug to administer, predictable and rapid induction, good muscle relaxation and analgesia that lasted longer than that associated with xylazine-ketamine, and acceptable cardiorespiratory values. All horses stood satisfactorily in two or fewer attempts within 40 min after induction.\textsuperscript{15}

### 3. TIVA (>20 min)

When a procedure requires >15–20 min, surgical anesthesia can be prolonged by administering additional IV anesthetics, either as intermittent boluses or constant rate infusions (CRIs) (Table 2). To gain an extra 3–5 min of surgical anesthesia, additional $\alpha_2$ agonist and ketamine can be administered at approximately one third the original induction doses. These boluses can be repeated several times as needed.

When a procedure is anticipated to take >30 min, it is advisable to use a CRI to maintain anesthesia to provide a more stable plane of anesthesia. Since the early 1980s, the most common technique used for this purpose has been “triple drip” or “GKX,” a combination of guaifenesin (50 mg/ml), ketamine (1–2 mg/ml), and xylazine (0.5 mg/ml).\textsuperscript{16} For more painful or noxious procedures, the higher concentration of ketamine (2 mg/ml) is recommended, whereas for restraint involving minimal stimulus, the lower ketamine concentration (1 mg/ml) may suffice. Although GKX can be used for induction of anesthesia, this induction involves a relatively prolonged period of ataxia, and most practitioners prefer to induce with xylazine-ketamine or xylazine-diazepam-ketamine and then use GKX for maintenance. Typical infusion rates vary from 1.5 to 2.2 ml/kg/h, depending on the procedure and the individual’s response, as well as the concentration of ketamine in the GKX.

Guaifenesin-ketamine-detomidine (GKD) is another combination used for TIVA. After sedation

<table>
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<tr>
<th>Table 2. Simplified Continuous Rate Infusions</th>
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<td>A simple way to deliver CRIs without a fluid pump is to add 1 h worth of the appropriate drug(s), based on the individual patient’s weight, to a 250-ml bag of IV fluid. At 1 drop/s (assuming an IV set that delivers 15 drops/ml), the contents of the bag will be delivered in ~1 h.</td>
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<td>For example, to achieve a xylazine-ketamine (XK) infusion in a 450-kg horse:</td>
</tr>
<tr>
<td>X: 450 kg $\times$ 2.1 mg/kg/h = 945 mg/h = 9.5 ml/h</td>
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<tr>
<td>K: 450 kg $\times$ 7.2 mg/kg/h = 3240 mg/h = 32.4 ml/h</td>
</tr>
<tr>
<td>Therefore, remove ~40–46 ml from a 250-ml bag of IV fluid; replace with 950 mg (9.5 ml) xylazine and 3240 mg (32.4 ml) ketamine; and deliver at 1 drop/s (assuming 15 drops/ml).</td>
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with detomidine (0.02 mg/kg, IV) and induction with ketamine (2 mg/kg, IV), anesthesia was maintained in ponies for 90 min with GKX (guaifenesin 100 mg/ml, ketamine 4 mg/ml, and detomidine 0.04 mg/ml; note these concentrations of guaifenesin and ketamine are about twice the usual concentrations used in GKX), at an infusion rate of 0.8 ml/kg/h for the first 60 min and 0.6 ml/kg/h for the final 30 min.17 The ponies took longer to stand (average, 46 min) compared with ponies anesthetized with halothane (35 min), but recovery quality was generally good to excellent. Oxygen was supplemented during anesthesia.17

An alternative to guaifenesin-based combinations is a CRI of xylazine and ketamine. After a standard induction, an infusion of xylazine at 35 μg/kg/min (2.1 mg/kg/h) and ketamine at 120 μg/kg/min (7.2 mg/kg/h) can be administered to maintain anesthesia for up to 70 min.18

Xylazine-ketamine CRIs are associated with smooth recoveries, but after 70 min of anesthesia, the time required for the horse to recover to standing is generally longer (50–55 min) compared with recoveries from inhalation anesthesia (15–40 min, depending on the specific Inhalant used).18

Other alternatives for TIVA include various combinations of α2 agonists with propofol. Detomidine (0.015 mg/kg, IV) and propofol (2 mg/kg, IV) were used to induce anesthesia in horses for experimental abdominal surgery, with anesthesia maintained by propofol infusion at an average of 0.18 mg/kg/min. However, the combination was not recommended for clinical use, because inductions were associated with some excitement, and respiratory depression and hypoxemia occurred.19

Medetomidine, an α2 agonist developed for use in small animals, has also been combined with propofol for TIVA in horses. In a clinical study of horses, medetomidine (7 μg/kg, IV) was given for sedation, and because of poor inductions with propofol, anesthesia was induced using ketamine (2 mg/kg, IV) and diazepam (0.02 mg/kg, IV); anesthesia was maintained by CRIs of medetomidine (3.5 μg/kg/h, IV) and propofol (0.1 mg/kg/min). Duration of anesthesia averaged just under 2 h, but the longest was nearly 4 h. About one half of the horses were apneic and needed mechanical ventilation. Horses were given an additional dose of medetomidine (2 μg/kg, IV) 10 min after terminating the CRIs and stood in an average of 42 min.20 In another study, horses were sedated with medetomidine (5 μg/kg, IV), induced with midazolam (0.04 mg/kg, IV) and ketamine (2.5 μg/kg, IV), given a loading dose of propofol (0.5 mg/kg, IV), and maintained on either propofol (0.22 mg/kg/min) or a combination of ketamine (1 mg/kg/h), medetomidine (1.25 μg/kg/h), and propofol (0.14 mg/kg/min). Most horses became apneic and hypoxemic and were therefore mechanically ventilated. After just under 2 h of anesthesia, recoveries were actually better quality and faster (average, 62 min) in the horses receiving the combination compared with propofol only (average, 87 min), leading the authors to suggest that propofol was the drug most responsible for prolonging recoveries.21

The time limit for safely maintaining anesthesia using TIVA is uncertain. Ponies maintained with GKX for 120 min were able to stand without help within 30 min after terminating the infusion, “and postanesthetic problems were not encountered.” However, these ponies weighed only 150–275 kg, they were endotracheally intubated, and they received supplemental oxygen.16 Some of the other CRI techniques described here have been used to maintain anesthesia for >2 h in full-size horses, but again, the horses were intubated, breathing high inspired oxygen, often mechanically ventilated, and positioned on padded surgery tables. Without supplemental oxygen, an anesthetized, recumbent horse is likely to be hypoxemic (arterial PO2 in the range of 40–60 mm Hg), which increases the risk of damage to muscles and other vital organs from inadequate oxygen delivery (Table 3). Because TIVA is often performed under field conditions, without supplemental oxygen or a well-padded surface, a common recommendation is to limit anesthesia time to ∼60 min.22

### 4. Intravenous Adjuncts During Inhalant Anesthesia

Partly because inhaled anesthetics are associated with several disadvantages—including cardiovascular depression, an increased stress response, and variable recovery quality—and partly because of increasing interest in improving pain management, a number of anesthetic or analgesic adjuncts are being used to augment inhalation anesthesia in

<table>
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<th>Table 3. When to Supplement Oxygen During Anesthesia</th>
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<td>During general anesthesia, supplementation of oxygen is recommended, although rarely used in field situations. Anesthesia and recumbency cause ventilation-perfusion mismatch in the lungs that lowers PaO2 considerably. Even if you do not normally supplement oxygen, consider doing it when:</td>
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<tr>
<td>Anesthesia and recumbency will be prolonged &gt; 30 min</td>
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<tr>
<td>The horse has respiratory abnormalities such as COPD</td>
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<tr>
<td>The horse has cardiac abnormalities such as a murmur</td>
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<tr>
<td>The horse is very young (neonate) or very old</td>
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Although typically oxygen may be delivered by nasal insufflation (10–15 l/min), intubation and manual or mechanical ventilation may be necessary for some TIVA procedures, especially those involving propofol.
horses. The use of multiple agents in this manner is termed “balanced anesthesia” or “partial intravenous anesthesia” (PIVA). The usual goals of adding these adjuncts are to decrease the requirement for the inhalant (therefore minimizing cardiovascular depressant effects), provide analgesia, and improve recoveries.

Intravenous lidocaine has been shown to decrease the maximum alveolar concentration (MAC) for inhalant anesthetics in a dose-dependent fashion. After a loading dose of 2.5 or 5 mg/kg, IV, lidocaine infusions of either 50 or 100 μg/kg/min decreased halothane MAC by 30–70%.28 Because of the purported benefit of lidocaine infusions on gastrointestinal motility, lidocaine CRIs are frequently administered to horses anesthetized for colic surgery but are also used during other surgeries. For routine clinical use as an anesthetic adjunct, a loading dose is probably not necessary, because a lidocaine CRI reaches steady state in ~20 min.24 Because of concerns about potential residual ataxia in recovery after IV lidocaine,25 it is recommended that lidocaine CRI be terminated ~15 min before the end of anesthesia.

Ketamine CRIs are also used to supplement inhalant anesthesia. A plasma ketamine concentration of ~11 μg/ml was associated with halothane MAC reduction of ~37% and corresponding improvement in cardiac output.26 Approximately 30% MAC reduction might be achieved by administration of 50 μg/kg/min (3 mg/kg/h).27 Because ketamine has antagonist properties at spinal cord n-methyl-d-aspartate (NMDA) receptors associated with the pain “wind-up” phenomenon, even infusion rates <50 μg/kg/min may be associated with improved pain management, although evidence of this benefit specific to horses is not available. Ketamine infusion rates of 10–50 μg/kg/min (0.6–3 mg/kg/h) are typically used clinically.

Medetomidine CRIs have gained some popularity as an adjunct to inhalant anesthesia in horses. Infusion rates of 3.5–5 μg/kg/h (∼1.6–2.3 mg/h for a 450-kg horse) reduce MAC by ∼25%.27 An added benefit of medetomidine CRI as a supplement to isoflurane anesthesia is reported to be improved recovery quality.28

In dogs, opioids are a mainstay of anesthesia and perioperative pain management, but use of opioids in horses is much more controversial, not only because of undesirable side effects such as central nervous system excitation and impaired gastrointestinal function, but also because of inconsistent results from studies of various opioids’ effect on MAC for inhalants. Butorphanol (0.05 mg/kg or ∼22.5 mg per 450-kg horse) had no reliable effect: it increased halothane MAC in three of six ponies tested, decreased it in one pony, and did not change it in two others.29 Alfentanil and morphine likewise had no predictable beneficial effect on the MAC for isoflurane in horses.30,31 A more recent study reported that a high dose of fentanyl reduced isoflurane MAC but that the effect was less than that of fentanyl in humans or dogs.32

Some investigators have used multiple IV drugs combined with inhalant anesthesia in a true “PIVA” technique. One protocol supplemented halothane anesthesia with a CRI of ketamine and guaifenesin that was gradually decreased over time (mean infusion rates varied from 39 μg/kg/min and 1 mg/kg/min at 20 min, respectively, to 13 μg/kg/min and 0.3 mg/kg/min at 120 min). This protocol was associated with a 50% reduction in halothane requirement, fewer “top-up” doses of ketamine, and less need for dobutamine to support blood pressure. Recovery times and quality were “acceptable” and similar to horses recovering from halothane only.33

Another example of PIVA is infusion of guaifenesin, ketamine, and medetomidine in combination with sevoflurane. A solution of guaifenesin (∼50 g/l), ketamine (∼2 g/l), and medetomidine (∼2.4 g/l) was administered at 0.5 ml/kg/h. Horses receiving this combination during sevoflurane anesthesia maintained excellent quality of anesthesia, did not require dobutamine for blood pressure support, and required fewer attempts to stand in recovery compared with horses maintained with sevoflurane only.34

5. Intravenous Anesthetics at the End of Inhalant Anesthesia

Because inhalant anesthesia is often associated with less-than-ideal recovery quality, a variety of techniques have been used in an attempt to improve recoveries. The most common involve administration of an α2 agonist at the end of anesthesia or on the horse’s arrival at the recovery stall. The use of xylazine (0.1 mg/kg, IV), detomidine (2 μg/kg, IV), or romifidine (8 μg/kg, IV) after isoflurane anesthesia improved recovery and reduced ataxia compared with isoflurane alone, with each of the drugs being similarly effective.35 Clinically, a slightly higher dose of xylazine (0.22 mg/kg, IV or ∼100 mg per 450-kg horse) is often used to improve recovery.

Acepromazine is also used to modify recovery, although there is no documented proof of its benefit. Clinical experience suggests that a very small dose of acepromazine (0.007 mg/kg, IV, or ∼3 mg per 450-kg horse), given about 20 min before the end of anesthesia (to allow enough time for onset of effect), may result in calmer, more controlled recoveries. However, even after administration of acepromazine, many horses still benefit from additional sedation with xylazine in recovery.

Part of the recent interest in TIVA is attributable to the good-to-excellent recovery quality typically associated with TIVA; however, as previously mentioned, there is still concern about maintaining anesthesia >1–1.25 h using TIVA. A compromise might be to use inhalant anesthesia for maintenance during the majority of a long procedure and then terminate delivery of the inhalant and continue anesthesia using IV drugs for the last 30 min or so, the goal being to allow the horse to eliminate the inhalant completely before awakening from the IV anesthetics. A recent experi-
mental study of seven horses used CRIs of xylazine (20 μg/kg/min) and ketamine (60 μg/kg/min) to continue anesthesia for 30 min after 90 min of isoflurane anesthesia. Although no statistically significant improvement in recovery quality was shown, the average scores for quality of standing and overall quality of recovery suggested the technique might have benefit. The authors have continued to use this technique for specific clinical cases, such as horses that have undergone orthopedic procedures in which a smooth recovery is especially important.

6. Summary

To date, there are numerous drug combinations that can be used to produce general anesthesia in horses. Currently, there is no single perfect method that is uniformly reliable and safe, particularly for long-term anesthesia. However, the development of newer injectable drugs and continuing studies into their use for TIVA or PIVA promise further improvements in the near future.

References and Footnote


"Telazol®, Fort Dodge Animal Health, Overland Park, KS 66210."