Evaluation of anesthesia recovery quality after low-dose racemic or S-ketamine infusions during anesthesia with isoflurane in horses

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Objective—To compare anesthesia recovery quality after racemic (R-/S-) or S-ketamine infusions during isoflurane anesthesia in horses.

Animals—10 horses undergoing arthroscopy.

Procedures—After administration of xylazine for sedation, horses (n = 5/group) received R-/S-ketamine (2.2 mg/kg) or S-ketamine (1.1 mg/kg), IV, for anesthesia induction. Anesthesia was maintained with isoflurane in oxygen and R-/S-ketamine (1 mg/kg/h) or S-ketamine (0.5 mg/kg/h). Heart rate, invasive mean arterial pressure, and end-tidal isoflurane concentration were recorded before and during surgical stimulation. Arterial blood gases were evaluated every 30 minutes. Arterial ketamine and norketamine enantiomer plasma concentrations were quantified at 60 and 120 minutes. After surgery, horses were kept in a padded recovery box, sedated with xylazine, and video-recorded for evaluation of recovery quality by use of a visual analogue scale (VAS) and a numeric rating scale.

Results—Horses in the S-ketamine group had better numeric rating scale and VAS values than those in the R-/S-ketamine group. In the R-/S-ketamine group, duration of infusion was positively correlated with VAS value. Both groups had significant increases in heart rate and mean arterial pressure during surgical stimulation; values in the R-/S-ketamine group were significantly higher than those of the S-ketamine group. Horses in the R-/S-ketamine group required slightly higher end-tidal isoflurane concentration to maintain a surgical plane of anesthesia. Moderate respiratory acidosis and reduced oxygenation were evident. The R-norketamine concentrations were significantly lower than S-norketamine concentrations in the R-/S-ketamine group.

Conclusions and Clinical Relevance—Compared with R-/S-ketamine, anesthesia recovery was better with S-ketamine infusions in horses. (Am J Vet Res 2009;70:710–718)

Horses are among the species with the highest number of perianesthetic fatalities, with recovery from anesthesia accounting for an overall mortality rate as high as 1.9%. Moreover, the risk of perianesthetic death increases with the duration of anesthesia and surgery time. With the permanent implementation of modern and sophisticated surgical techniques, the indications for anesthesia and the anesthesia times have been increasing during the past few years, highlighting the need for investigating new anesthetic agents for prolonged surgical procedures in horses.

Received May 16, 2008.
Accepted August 26, 2008.

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Supported in part by the Swiss National Science Foundation and Dr. E. Gräub Laboratories.

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ABBREVIATIONS

| CRI | Constant rate infusion |
| FEISO | End-tidal concentration of isoflurane |
| FISO2 | Inspired O2 concentration |
| MAP | Mean arterial pressure |
| NRS | Numeric rating scale |
| P(A-a)O2 | Alveolar to arterial O2 partial pressure difference |
| Pb | Barometric pressure |
| PECO2 | End-tidal carbon dioxide partial pressure |
| PHO2 | Partial pressure of water at 37°C |
| RIP | Peak inspiratory pressure |
| R | Respiratory rate |
| VAS | Visual analogue scale |
| VDAlv/VT | Alveolar dead space ventilation |
Racemic (R-/S-) ketamine infusions have been widely used in equine anesthesia as part of the balanced anesthesia concept aiming to improve analgesia, reduce the amount of inhaled agents, and preserve cardiac function, thus reducing the anesthetic fatalities in such species. Despite many attractive features, R-/S-ketamine can induce reactions during the anesthetic recovery period characterized by muscular tremor and rigidity, involuntary limb movements, excitation, and ataxia, which can precipitate a negative outcome. These phenomena are related to ketamine and norketamine (an active metabolite of ketamine) plasma concentrations and the length of drug infusion, making the use of R/S-ketamine limited to the use of low doses and for procedures lasting < 2 hours.

In humans, the frequency of psychotomimetic phenomena appeared to be lower after administration of S-ketamine, in comparison to R-/S-ketamine. For this reason, R-/S-ketamine is now being replaced by S-ketamine for human use in many European countries. Recently, the S-enantiomer has been introduced into the European veterinary market as well. In equidae, short-term anesthesia with single or repetitive bolus of S-ketamine proved to be superior to R-/S-ketamine on the basis of faster recovery and better recovery outcome.

Thus, we hypothesized that it would be possible to diminish adverse effects of ketamine infusions in horses by administering S-ketamine instead of R-/S-ketamine. In this way, the S-isomer of ketamine could offer advantages in clinical practice by enabling the use of equipotent doses, potentially resulting in fewer adverse effects during the anesthesia recovery phase than the racemate. The purpose of the study reported here was to compare anesthesia recovery quality after R-/S-ketamine or S-ketamine infusions during isoflurane anesthesia in horses.

Materials and Methods

Study design and test animals—The experimental trial was performed with permission from the local committee for animal experimentation and was designed as a blinded randomized prospective clinical study. Ten adult horses (6 geldings, 3 mares, and 1 stallion), with a mean ± SD weight of 553 ± 80.8 kg and a median age of 8 years (range, 1 to 20 years), undergoing elective arthroscopy were included. They were conventionally housed individually at the stables of the Equine Clinic of the Vetsuisse-Faculty in Zürich. The horses were housed in individual stalls, and access to water was allowed until 30 minutes prior to anesthesia induction. A 14-gauge over-the-needle catheter was placed into a jugular vein of the horses after preparing the overlying skin by clipping, aseptically scrubbing, and desensitizing with mepivacaine 2%. Thirty minutes before anesthesia induction, IM administration of acepromazine (0.03 mg/kg) and IV administration of flunixin meglumine (1 mg/kg) were performed. The horses were transferred to the surgical wards, and xylazine (1.1 mg/kg) was administered IV over 2 minutes for sedation. Horses were placed into an anesthetic induction stock and kept in place with a head halter and a breast rope. When signs of sedation were seen (head drop, ataxia, and indifference to environment), the horses were gently leaned toward a lateral wall and restrained from the contralateral side with a swinging door. Five minutes after xylazine administration, anesthesia was induced with midazolam (0.03 mg/kg, IV) followed by a rapid IV bolus of either R-/S-ketamine (2.2 mg/kg) or S-ketamine (1.1 mg/kg) diluted to a final volume of 20 mL with physiologic saline (0.9% NaCl) solution to preserve masking of the study groups. Two animal care persons assisted the procedure by holding the head of the horses and the swinging door. Quality of anesthesia induction was evaluated by the anesthesiologist by use of a modified NRS (Appendix) and a VAS (0 mm = best possible induction; 100 mm = worst possible induction). Once the horses were in lateral recumbency, a 30-mm–inner-diameter tube was introduced into the trachea and connected to a large animal anesthesia machine via a large animal circle system that had been primed with 3% isoflurane in O2. The horses were then positioned on the surgical table in lateral or dorsal recumbency, depending on the surgical approach. Anesthesia was maintained with isoflurane in O2 (3 to 5 L/min) and a CRI of R-/S-ketamine (1 mg/kg/h) or S-ketamine (0.5 mg/kg/h). For each group, isoflurane delivery was adjusted by the anesthesiologist to the minimum FiCO2 that prevented the horse from moving or having muscle rigidity and nystagmus and preserved the corneal or blinking reflexes. If sudden movement or nystagmus occurred during anesthesia, thiopental was injected IV until cessation of the undesired event; the total amount of thiopental administered was recorded. The horses’ lungs were mechanically ventilated to maintain the PEtCO2 < 55 mm Hg by adjusting the inspiratory pressure, expiratory time, and flow rate of a pneumatically driven ventilator with a bag-in-the-barrel system. Values for FiO2 were obtained from a manometer placed within the ventilator. A 20-gauge cannula was inserted into a facial artery and connected via a nondistensible extension filled with heparinized saline solution to an electronic pressure transducer, which was placed and zered at the level of the shoulder joint for horses in dorsal recumbency or at the sternal manubrium for horses in lateral recumbency, and MAP was obtained. The accuracy of the transducer had been checked with a mercury column. A lead II ECG was displayed, and HR was calculated. A side-stream gas sampler was connected to a port placed at the bifurcation of the Y-piece of the breathing system; FiO2, FiCO2, capnogram, and PEtCO2 were obtained, and RF was calculated. All data were continuously monitored and recorded every 5 minutes with an anesthesia monitor. The monitor was calibrated with a
standardized calibration gas to according to the manufacturers' instructions before each anesthetic episode.

An infusion (5 mL/kg/h) of lactated Ringer's solution was delivered during the entire anesthetic procedure through the jugular catheter. The lactated Ringer's solution line was connected to 3-way stopcock valves connected in parallel to allow for dobutamine, R/S- or S-ketamine CRI, and thiopental administration, in that order. The last 3-way valve was connected to the hub of the jugular catheter. To avoid retrograde administration of solutions or drugs, unidirectional flow valves were placed between the 3-way valves. Dobutamine was diluted to a final concentration of 1 mg/mL, and to preserve treatment identity, S-ketamine was diluted to a final concentration of 50 mg/mL. All drugs for CRI were handed to the anesthesiologist in syringes containing 60 mL of solution. Dobutamine and ketamine CRIs were administered with an infusion pump with places for 2 syringes, which were connected to their respective 3-way valves via 2×2-cm-long (total volume, 4 mL) nondisposable extension tubes. To ensure accuracy in calculating the infused volumes, the extension tubes of both CRIs were filled with 4 mL of drug solution and the initial volume contained in the syringe was recorded. At the end of the procedure, the infused volume of drug was calculated from the initial volume minus the volume that remained in the syringe. For R/S-ketamine and S-ketamine, the total CRI time was calculated from the start to the end of CRI delivery, and actual CRIs were calculated by dividing the total administered dose by the corresponding CRI time for each compound. Dobutamine was initially infused at a dosage rate of 0.01 mg/kg/h and subsequently adjusted to a target MAP from 70 to 100 mm Hg. If MAP was < 70 mm Hg, the infusion rate was increased by 0.01 mg/kg/h every 5 minutes until target MAP was reached. Conversely, if MAP was > 100 mm Hg, the infusion rate was reduced by 0.01 mg/kg/h every 5 minutes (or discontinued if the rate was already 0.01 mg/kg/h) until target MAP was reached. At the end of the procedures, the total dose rate delivered was calculated.

Arterial blood samples were anaerobically collected, and arterial blood pH, PaO₂, PaCO₂, HCO₃⁻ concentration, andSaO₂ were assessed by use of a portable blood gas analyzer validated for horses. The P[A-a]O₂ was calculated as follows:

\[
P[A-a]O_2 = (F' O_2 [Pb - PH2O] - 1.2 [Paco2]) - PaO_2
\]

and VD̅o̅2V̅1 was calculated by use of the Bohr equation as follows:

\[
VD̅o̅2V̅1 = ([Paco2 - PeCO2]/Paco2)
\]

If intraoperative PaO₂ decreased to < 70 mm Hg, salbutamol was delivered through the endotracheal tube via a 3-way valve connector placed between the gas sampling port at the Y-piece of the breathing system and the gas sampling line at a dose of 2 sprays/100 kg (approx 2 µg/kg) every 15 minutes until PaO₂ ≥ 70 mm Hg was achieved.

Blood sample collection and plasma ketamine analysis—Five milliliters of blood was collected manually into heparinized tubes from the jugular catheter before anesthesia induction or from the arterial catheter at 60 and 120 minutes after anesthesia induction. After the samples were obtained, the arterial catheter was flushed with 10 mL of heparinized physiologic saline solution. To avoid contamination with the arterial flushing solution, 5 mL of blood was collected and discharged before every sampling event. Immediately after collection, the samples were placed on ice until centrifugation was performed. Plasma was separated and frozen at –80°C until the assay was performed.

The samples were analyzed via enantioselective capillary electrophoresis according to the technique originally described by Theurillat et al. The latter approach was adapted to lower concentrations by Petrbauer et al and used with small modifications in the present study. Briefly, this technique is based on liquid-liquid extraction of ketamine and norketamine at alkaline pH from 0.5 mL of plasma by use of pseudephedrine instead of lamotrigine as internal standard, followed by analysis of the reconstituted extract by use of capillary electrophoresis with a Tris-phosphate buffer (pH, 2.5) containing 10 mg of sulphated β-cyclohex dextrin/mL as chiral selector. Analyses were performed on a capillary electrophoresis analyzer by use of a 50-μm-inner-diameter fused-silica capillary of 45 cm total length, an applied voltage of ~20 kV, and a cartridge temperature of 20°C. The detection wavelength was 195 nm. The quantification limit for all enantiomers was 2.5 ng/mL. The calibration range for each enantiomer was from 12.5 to 1,000 ng/mL, and the sample injection was 7.5 seconds at 1.5 lb/inches². The intraday precision (3 measurements) was < 6.9%.

Anesthesia recovery—Twenty minutes before the end of surgery, the horses were administered morphine IM (0.1 mg/kg). At the end of surgical procedures, CRIs and isoflurane were discontinued and total anesthesia time was calculated from induction time until cessation of isoflurane delivery. The horses were fitted with a protective helmet, transferred to a quiet padded recovery box, and positioned in lateral recumbency, and 5 mL of phenylephrine (0.15%) was instilled into each nostril to decrease nasal mucosal swelling. Oxygen was insufflated (10 L/min) through the endotracheal tube, and at the signs of nystagmus, swallowing, or spontaneous movements, 0.4 mg of xylazine/kg was injected IV, the endotracheal tube was removed, and O₂ was insufflated through the nose. Horses were permitted to recover without assistance, and the times required to achieve the sternal and standing positions were recorded. In addition, the whole recovery phase was videographically recorded, and 4 independent observers experienced in equine anesthesia and unaware of the treatment identity assessed the anesthesia recovery quality from the observation of the videographic films by means of an NRS (Appendix) and a VAS (0 mm = best possible recovery; 100 mm = worst possible recovery).

Statistical analysis—For all tests, a software package was used and a value of P < 0.05 was considered to be significant. All data were analyzed for their Gaussian distribution. Parametric and nonparametric independent data with 2 levels were compared between groups by use of 2-sample Student t tests and Mann-Whitney
U tests, respectively. Parametric independent variables with more than 2 levels were analyzed with a 1-way ANOVA test. Categoric data were analyzed with χ² tests.

Variables recorded for intra-anesthetic HR, MAP, and FE′iso were divided into 2 subgroups: 1 before surgical stimulation, which consisted of the data collected between 10 and 30 minutes after induction, and the other during surgical stimulation, which contained the data collected during 90 minutes after surgical incision. Differences between values obtained before and after surgical incision and between groups were assessed with Kruskal-Wallis 1-way ANOVA on ranks, corrected for ties. All other data collected for HR, MAP, and FE′iso were excluded from statistical analysis. For each group, recovery VAS value was associated with the length of the CRIs by use of the Pearson correlation coefficient (r) and linear regression analysis, and significance was tested by use of the Student t test.

Parametric data are reported as mean ± SD. Nonparametric or categoric data are reported as median, range, or interquartile ranges (box plots) or by use of descriptive statistics.

**Results**

Test horses—There were no significant differences between groups with regard to median age (R-/S-ketamine, 8 years [range, 1 to 20 years]; S-ketamine, 10 years [range, 3 to 10 years]), mean weight (R-/S-ketamine, 590 kg [range, 470 to 650 kg]; S-ketamine, 520 kg [range, 400 to 640 kg]), sex distribution (R-/S-ketamine, 3 geldings, 1 stallion, and 1 mare; S-ketamine, 3 geldings and 2 mares), baseline HR (R-/S-ketamine, 38 beats/min [range, 28 to 54 beats/min]; S-ketamine, 38 beats/min [range, 36 to 40 beats/min]), RF (12 breaths/min [range, 8 to 18 breaths/min for both groups]), PCV (R-/S-ketamine, 29% [range, 22% to 36%]; S-ketamine, 34% [range, 25% to 36%]), and total protein concentration (R-/S-ketamine, 61 g/L [range, 55 to 70 g/L]; S-ketamine, 65 g/L [range, 61 to 67 g/L]). During anesthesia, all horses were positioned in dorsal recumbency except 3 (R-/S-ketamine, n = 1; S-ketamine, 2) that were positioned in lateral recumbency.

Anesthesia—Overall, the anesthetic episodes were without adverse events in all 10 horses. Values obtained for induction NRS were not significantly (P = 1.0) different between groups (median, 1 [range, 1 to 2 for both groups]). Similarly, there were no significant (P = 0.91) differences for the values obtained for induction of VAS (R-/S-ketamine, 12 mm [range, 4 to 12 mm]; S-ketamine, 9 mm [range, 6 to 16 mm]).
Differences in anesthesia time intervals (R/S-ketamine, 152 minutes [range, 109 to 182 minutes]; S-ketamine, 148 minutes [range, 100 to 266 minutes]) were not significant (P = 0.84) between groups. The CRI of R/S-ketamine administered was 0.96, with a range of 0.93 to 0.98 mg/kg/h, and the CRI of S-ketamine administered was 0.5, with a range of 0.41 to 0.58 mg/kg/h. The total dose (induction plus CRI) of R/S-ketamine administered to the horses allocated to this group was 4.5, with a range of 3.7 to 5.1 mg/kg (total dose for R-ketamine and S-ketamine each, 2.2 mg/kg [range, 1.8 to 2.5 mg/kg]) and total dose of S-ketamine administered to horses in this group was 2.5 mg/kg, with a range of 1.8 to 2.9 mg/kg. There were no significant differences for S-ketamine administration between groups (P = 0.42). Four of 5 horses in each group required intraoperative administration of thiopental (P = 0.39; R/S-ketamine, 0.21 mg/kg [range, 0 to 1.6 mg/kg]; S-ketamine, 0.39 mg/kg [range, 0 to 2 mg/kg]).

Values for HR, MAP, and FE'iso, and their comparisons between groups and within groups before and during surgical stimulation were determined (Figure 1). Both groups had significantly increased HR and MAP values after surgical stimulation. Although HR values before surgical stimulation were not significantly different between groups, horses allocated to the R/S-ketamine group had significantly higher HRs during surgical stimulation, compared with those allocated to the ketamine group. Values for MAP were not significantly different between groups before and during surgical stimulation before surgical stimulation, values for FE'iso were not significantly different between groups. Horses in the R/S-ketamine group required significantly higher FE'iso concentrations during surgical stimulation, compared with values obtained before surgical stimulation and also values for horses in the S-ketamine group during surgical stimulation. Values for FE'iso were not significantly different in the S-ketamine group before and during surgical stimulation. The dobutamine dose rates necessary for maintaining the targeted MAP (R/S-ketamine, 0.34 μg/kg/min [range, 0.17 to 0.35 μg/kg/min]; S-ketamine, 0.37 μg/kg/min [range, 0.18 to 0.74 μg/kg/min]) during the whole anesthetic episode were not significantly (P = 0.84) different between groups. Blood gases, P[A-a]O2, and VD·Vt were determined (Table 1). Horses in both groups had respiratory acidosis and decreased oxygenation values. Even though the values for PacO2 and VD·Vt were comparable between groups, significantly lower PaO2 values and increased P[A-a]O2 values were found for the

Table 1—Mean ± SD values for arterial blood gas variables obtained at 30, 60, 90, and 120 minutes after anesthesia induction in horses (n = 5/group) anesthetized with isoflurane in oxygen receiving a CRI of racemic (S-(R)-)ketamine (loading dose, 2.2 mg/kg; CRI, 1 mg/kg/h) or S-ketamine (loading dose, 1.1 mg/kg; CRI, 0.5 mg/kg/h).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time (min)</th>
<th>No. of samples</th>
<th>pH</th>
<th>PaO2 (mm Hg)</th>
<th>PaCO2 (mm Hg)</th>
<th>SaO2 (%)</th>
<th>HCO3⁻ (mmol/L)</th>
<th>PA-aO2 (VdVt) (%)</th>
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</thead>
<tbody>
<tr>
<td>R/S-ketamine</td>
<td>30</td>
<td>5</td>
<td>7.39 ± 0.03</td>
<td>58.5 ± 4.4</td>
<td>208 ± 151</td>
<td>96.2 ± 5.1</td>
<td>31.4 ± 2.9</td>
<td>346 ± 193</td>
</tr>
<tr>
<td>S-ketamine</td>
<td>30</td>
<td>5</td>
<td>7.36 ± 0.08</td>
<td>53.6 ± 9.7</td>
<td>326 ± 115</td>
<td>99.4 ± 1.3</td>
<td>32.2 ± 3.9</td>
<td>252 ± 146</td>
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<td>R/S-ketamine</td>
<td>60</td>
<td>5</td>
<td>7.31 ± 0.03</td>
<td>62.7 ± 4.3</td>
<td>229 ± 138</td>
<td>98.6 ± 1.5</td>
<td>32.6 ± 2.3</td>
<td>343 ± 149</td>
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<tr>
<td>S-ketamine</td>
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<td>7.35 ± 0.07</td>
<td>58.9 ± 9.2</td>
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<td>99.6 ± 0.8</td>
<td>32.7 ± 2.2</td>
<td>224 ± 185</td>
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<td>65.6 ± 3.8</td>
<td>182 ± 115</td>
<td>96.8 ± 0.5</td>
<td>34.2 ± 1.9</td>
<td>392 ± 127</td>
</tr>
<tr>
<td>S-ketamine</td>
<td>90</td>
<td>5</td>
<td>7.36 ± 0.06</td>
<td>57.7 ± 6.8</td>
<td>369 ± 189</td>
<td>99.8 ± 0.4</td>
<td>32.8 ± 2.0</td>
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<td>7.32 ± 0.03</td>
<td>64.2 ± 5.9</td>
<td>176 ± 114</td>
<td>97 ± 3.9</td>
<td>33.9 ± 2.4</td>
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<td>S-ketamine</td>
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<td>4</td>
<td>7.32 ± 0.08</td>
<td>68.8 ± 11.8</td>
<td>311 ± 227</td>
<td>99.7 ± 0.5</td>
<td>34.1 ± 1.6</td>
<td>300 ± 216</td>
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<tr>
<td>R/S-ketamine</td>
<td>All</td>
<td>19</td>
<td>7.32 ± 0.03</td>
<td>63.1 ± 5.1</td>
<td>198 ± 120*</td>
<td>97.2 ± 3.8*</td>
<td>31.5 ± 7.7</td>
<td>376 ± 140*</td>
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<tr>
<td>S-ketamine</td>
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<td>19</td>
<td>7.34 ± 0.02</td>
<td>58.9 ± 9.7</td>
<td>350 ± 154*</td>
<td>99.0 ± 0.8*</td>
<td>32.9 ± 2.5</td>
<td>264 ± 159*</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05) difference between groups.

Figure 2—Histograms of NRS values (1 = excellent to 5 = poor) obtained from 4 observers who evaluated the anesthesia recovery quality of horses anesthetized with isoflurane in oxygen that received an infusion of R/S-ketamine (n = 5; white bars; loading dose, 2.2 mg/kg; CRI, 1 mg/kg/h) or S-ketamine (n = 5; shaded bars; loading dose, 1.1 mg/kg; CRI, 0.5 mg/kg/h).
R-/S-ketamine group, compared with the S-ketamine group. Only 1 horse in the R-/S-ketamine group that was positioned in dorsal recumbency had PaO\textsubscript{2} values < 70 mm Hg at 90 and 120 minutes after anesthesia induction (61.5 and 68.2 mm Hg, respectively) and required salbutamol administration. Subsequently, the PaO\textsubscript{2} values for that horse at 150 and 180 minutes were 116 and 196 mm Hg, respectively, and no further salbutamol was administered. To maintain PaO\textsubscript{2} > 55 mm Hg, both groups were ventilated at equal R\textsubscript{t} (7 breaths/min [range, 4 to 9 breaths/min]) and PIP (15 mm Hg [range, 13 to 17 mm Hg]).

Recovery from anesthesia—There were no significant differences regarding the time to achieve the sternal position (P = 0.6; R-/S-ketamine, 32 minutes [range, 15 to 45 minutes]; S-ketamine, 25 minutes [range, 24 to 60 minutes]) or the time to achieve the standing position (P = 0.6; R-/S-ketamine, 47 minutes [range, 25 to 78 minutes]; S-ketamine, 35 minutes [range, 31 to 77 minutes]).

Values for recovery NRS were significantly lower (P = 0.002) for the S-ketamine group (2 [range, 1 to 3]) than for the R-/S-ketamine group (3 [range, 1 to 4]). Distributions of recovery NRS values for each group were determined (Figure 2). Values for recovery VAS were significantly (P = 0.044) lower for the S-ketamine group (29.2 ± 17.7 mm) than for those in the R-/S-ketamine group (44.8 ± 29.2 mm). Results of linear regression analysis and correlation of recovery VAS values with CRI times were determined (Figure 3). The horse in the R-/S-ketamine group with transient hypoxemia had a median recovery NRS value of 4 and a median recovery VAS value of 64 mm.

**Discussion**

In accordance with results of other studies\textsuperscript{6,8–10,18} performed in humans, mice, and horses, administration of S-ketamine as a CRI provided better recovery qualities than did administration of R-/S-ketamine as a CRI, suggesting that S-ketamine can be administered at the doses reported here for long-term balanced anesthesia. Despite the fact that longer infusion times of R-/S-ketamine were associated with poor recoveries (Figure 3), the duration of S-ketamine infusions was associated with poor recoveries, suggesting that the use of this enantiomer alone might be preferred for prolonged ketamine infusions in horses.

Similar to a previous study\textsuperscript{9} with Shetland ponies sedated with xylazine, 1.1 mg of S-ketamine/kg provided good conditions for a smooth anesthesia induction, compared with those of 2.2 mg of R-/S-ketamine/kg. The anesthetic potency of S-ketamine is twice that of R-ketamine. Plasma concentrations of ketamine enantiomers were not significantly different between treatment groups at any evaluated time point. No significant differences were found in the R-/S-ketamine group for plasma concentrations of S-ketamine and CRI, suggesting that S-ketamine can be administered at the doses reported here for long-term balanced anesthesia, despite the fact that longer infusion times of R-/S-ketamine were associated with poor recoveries (Figure 3).

Table 2—Mean ± SD arterial plasma concentrations of ketamine and norketamine enantiomers obtained from horses (n = 5 for each group) anesthetized with isoflurane in oxygen during an infusion of R/S-ketamine (loading dose, 2.2 mg/kg; CRI, 1 mg/kg/h) or S-ketamine (loading dose, 1.1 mg/kg; CRI, 1 mg/kg/h).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group</th>
<th>S-ketamine (μg/mL)</th>
<th>R-ketamine (μg/mL)</th>
<th>S-norketamine (μg/mL)</th>
<th>R-norketamine (μg/mL)</th>
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</thead>
<tbody>
<tr>
<td>60</td>
<td>S-ketamine</td>
<td>0.329 ± 0.073</td>
<td>—</td>
<td>0.378 ± 0.114</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>R-/S-ketamine</td>
<td>0.311 ± 0.056</td>
<td>0.319 ± 0.051</td>
<td>0.355 ± 0.098*</td>
<td>0.109 ± 0.046*</td>
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<td>120</td>
<td>S-ketamine</td>
<td>0.354 ± 0.076</td>
<td>0.411 ± 0.034</td>
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<td></td>
<td>R-/S-ketamine</td>
<td>0.381 ± 0.07</td>
<td>—</td>
<td>0.346 ± 0.111*</td>
<td>0.097 ± 0.038*</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05) difference within the R-/S-ketamine group. — = Not applicable.
its effects with those of R/S-ketamine at equivalent amounts of S-enantiomers. The lack of a negative control group might have been a disadvantage when trying to elucidate whether ketamine infusions are better than none with regard to recovery quality in horses. However, because the study was designed to compare 2 ketamine formulations, the inclusion of a negative control group was considered unnecessary. Another potential drawback of the study was the low number of horses. Although none of the horses was harmed in the present study, a larger number was discouraged because of the potential risk of self-injuries during the anesthesia recovery phase for horses that received prolonged R/S-ketamine CRIs. Nevertheless, even with this low number of subjects, significant differences were detected between groups with regard to the quality of the recovery phase.

Horses in the S-ketamine group had better recovery NRS and VAS scores, probably because those horses had fewer attempts to achieve the sternal and standing positions with no signs of excitement. These results were consistent with studies performed in human volunteers in which a faster recovery of psychomotor function was observed after S-ketamine injection, compared with R/S-ketamine at an equivalent enantiomer dose. Although S-ketamine has 3 to 4 times the anesthetic potency of R-ketamine, studies performed in mice revealed that S-ketamine induces less spontaneous movement than does R-ketamine in comparable anesthetic doses. Thus, the presence of a pharmacologically active R-enantiomer, although weaker, could explain the difficulties that horses in the R/S-ketamine group encountered when attempting to achieve the sternal and standing positions. In addition, the faster elimination of S-ketamine when this enantiomer is given separately from the racemate is also associated with better or faster recoveries, compared with R/S-ketamine. Accordingly, in vitro studies performed in human and equine liver microsomes revealed that S-ketamine N-demethylation is delayed in the presence of R-ketamine, suggesting that R-ketamine might inhibit S-ketamine elimination, probably as the result of an enzyme-substrate competition. Interestingly, this phenomenon seems to be inhibited when the volatile agent isoflurane is concomitantly given. In the present study, comparable S-ketamine plasma concentrations were found for either group at 60 and 120 minutes during CRI, supporting the theory that isoflurane might interfere with ketamine enantioselective N-demethylation. Unfortunately, plasma samples for ketamine analysis could not be collected after discontinuing the infusions to test the hypothesis that S-ketamine is eliminated faster when given separately from the racemate and in the absence of isoflurane.

Similar to results in previous studies performed in isoflurane-anesthetized ponies, higher plasma concentrations for S-norketamine were found at every time point in the R/S-ketamine group, compared with R-norketamine, confirming the enantioselective elimination of norketamine. Because norketamine has one-third of the anesthetic potency of its parent compound, the rate at which this metabolite is eliminated might play an important role in overall recovery from anesthesia. Interestingly, Ryder et al detected R-norketamine concentrations 3 times those of S-norketamine in brain tissue of mice, probably accounting for the higher prevalence of spontaneous movements seen in that species after application of equal R-ketamine or S-ketamine doses.

In agreement with a previous study in nonstimulated ponies sedated with xylazine, administration of equivalent enantiomeric doses of S-ketamine or R/S-ketamine led to comparable HR values 10 to 30 minutes after anesthesia induction. However, horses allocated to the R/S-ketamine group had significantly higher HR values during the first 90 minutes after surgical incision. It has been proposed that S-ketamine’s analgesic effects are stronger than those of the racemate. Unfortunately, Peterbauer et al failed to prove this hypothesis. Contrary to the results reported here, Larenza et al detected higher HR and lower MAP values in isoflurane-anesthetized ponies receiving S-ketamine concentrations, compared with R/S-ketamine, that were not surgically stimulated or administered adrenergic agents. Even though both groups required similar rescue doses of thiopental, horses in the R/S-ketamine group required slightly higher but still significantly different concentrations of isoflurane to achieve an adequate surgical anesthetic plane. It remains unclear whether these increases in HR and the different isoflurane requirements are the consequence of direct sympathomimetic or analgesic effects of the tested drugs or whether other factors such as surgical approach and preexisting medical conditions confounded these results. Both groups required similar dobutamine doses to achieve the targeted MAP. These results probably reflect the pattern of dobutamine administration used to obtain a predetermined MAP. Increases in MAP during surgical stimulation might reflect sympathetic stimulation from ketamine, intraoperative noceception, or both.

In anesthetized horses, hypoxemia frequently occurs as a result of impaired pulmonary gas exchange and increases in venous admixture are often expected. The P[A-a]O₂ is a widely used variable for assessing the magnitude of the intrapulmonary shunt, an extreme of the ventilation-perfusion mismatch. Both groups had an increased P[A-a]O₂ (expected value, < 100 mm Hg with FIO₂ = 1) which was significantly higher in the R/S-ketamine group, compared with the S-ketamine group. However, these differences could have been biased by other factors not considered in the statistical analysis, such as body position and body shape. In addition, because mean SaO₂ values remained > 95% in both groups, the differences in Pao₂, SaO₂, and P[A-a]O₂ were not considered to be clinically relevant. Only 1 horse in the R/S-ketamine group had Pao₂ from 60 to 70 mm Hg for < 1 hour and required salbutamol administration in the inspiratory gases. It has been debated whether intraoperative hypoxemia might induce poor recoveries in horses; however, Taylor could not detect such an association. In both groups, additional arterial blood gases values (VD/VT, R/L, and PIP) remained in the reference range for mechanically ventilated horses.

In horses anesthetized with isoflurane in oxygen, administration of a CRI of S-ketamine provided better anesthesia recovery than equivalent enantiomeric R/S-
ketamine CRIs. Although analysis of the effects of S-ketamine CRIs on the evaluated physiologic variables detected a beneficial effect, the specific cardiopulmonary effects of S-ketamine require further investigation.

References


**Appendix**

Scoring system of responses associated with anesthetic induction and recovery, modified from a scoring system in another report.11

<table>
<thead>
<tr>
<th>Score</th>
<th>Induction</th>
<th>Recovery</th>
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</thead>
<tbody>
<tr>
<td>1—Excellent</td>
<td>Smooth induction, no muscle twitching, no forward or backward movements.</td>
<td>Quiet, coordinated efforts (1–2) to sternal or standing positions. No or light ataxia once standing. Calm.</td>
</tr>
<tr>
<td>2—Good</td>
<td>Smooth induction with no risk of self-injury, but with slight head or limb twitching or tendency to walk forward or backward.</td>
<td>Quiet, slightly uncoordinated efforts (1–2) to sternal or standing positions. Mild ataxia once standing. Calm.</td>
</tr>
<tr>
<td>3—Fair</td>
<td>Recumbency achieved but without relaxation of limbs or with a strong forward or backward movement. Possible risk of self-injury.</td>
<td>Multiple (=3) quiet attempts to sternal and standing positions. Mild to considerable ataxia once standing. Calm.</td>
</tr>
<tr>
<td>4—Moderate</td>
<td>Induction with considerable movement or excitement with subsequent attempts to stand or any other dangerous movement that resulted in a self-injury.</td>
<td>Multiple (=3) uncoordinated attempts to sternal and standing positions. Moderate excitement.</td>
</tr>
<tr>
<td>5—Poor</td>
<td>Failure to achieve recumbency.</td>
<td>Unable to stand 2 hours after endotracheal extubation. Required additional sedation because of severe excitement.</td>
</tr>
</tbody>
</table>