Comparison of four drug combinations for total intravenous anesthesia of horses undergoing surgical removal of an abdominal testis

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Objective—To evaluate anesthetic effects of 4 drug combinations used for total intravenous anesthesia of horses undergoing surgical removal of an abdominal testis.

Design—Clinical trial.

Animals—32 healthy cryptorchid horses.

Procedure—Horses were sedated with xylazine and butorphanol and were randomly assigned to 1 of 4 groups: induction of anesthesia with ketamine and diazepam and maintenance with bolus administration of ketamine and xylazine (KD/KX); induction and maintenance of anesthesia with bolus administration of tiletamine-zolazepam, ketamine, and detomidine (TKD); induction and maintenance of anesthesia with continuous infusion of xylazine, guaifenesin, and ketamine; and induction and maintenance of anesthesia with continuous infusion of guaifenesin and thiopental. Horses that moved 3 consecutive times in response to surgical stimulation or for which surgery time was >60 minutes were administered an inhalant anesthetic, and data from these horses were excluded from analysis.

Results—Quality of induction was not significantly different among groups. Muscle relaxation and analgesia scores were lowest for horses given KD/KX, but significant differences among groups were not detected. Horses anesthetized with TKD had a significantly greater number of attempts to stand, compared with the other groups, and mean quality of recovery from anesthesia for horses in the TKD group was significantly worse than for the other groups. Anesthesia, surgery, and recovery times were not significantly different among groups.

Conclusions and Clinical Relevance—Results suggest that all 4 drug combinations can be used to induce short-term anesthesia for abdominal cryptorchidectomy in horses. However, horses receiving TKD had a poorer recovery from anesthesia, often requiring assistance to stand. (/Am Vet Med Assoc 2000;217:869-873)

Several groups of investigators have reported the cardiorespiratory, analgesic, and anesthetic effects associated with use of various combinations of sedative-analgesic (xylazine, detomidine, and romifidine), muscle relaxing (guaifenesin, diazepam, zolazepam, temazepam, and climaizolam), and dissociative anesthetic (ketamine, tiletamine) drugs for total intravenous anesthesia (TIVA) in horses.1-15 These drug combinations have been administered as single or multiple intravenous boluses or by infusion to induce anesthesia for short periods (usually <60 minutes), and most investigators have concluded that cardiovascular function is well-preserved, muscle relaxation and analgesia are adequate, and the quality of induction of, maintenance of, and recovery from anesthesia are good to excellent.1,2,4,6,9,11,15 Only respiratory function has consistently been reported to be negatively affected, with most drug combinations causing transient (5 to 15 minutes) periods of respiratory depression resulting in hypoxemia (PaO2 < 60 mm Hg) and hypercapnia (PaCO2 > 50 mm Hg).6,9,11,15 Additionally, some drug combinations have occasionally resulted in prolonged recovery, multiple attempts to stand, and ataxia once standing.1,4,9,11,15

Importantly, most previous studies have involved healthy experimental horses or ponies that were not subjected to surgery. In the few clinical studies involving TIVA of horses undergoing elective surgery, few, if any, details of the quality of induction of, maintenance of, and recovery from anesthesia were reported.1,2,4,6,9,13,15 We recently reported the cardiovascular, analgesic, and anesthetic effects of a combination of tiletamine-zolazepam, ketamine, and detomidine (TKD) for TIVA in horses.15 Although quantitative methods were used to determine the quality of analgesia, surgery was not performed. The purpose of the study reported here was to evaluate the anesthetic and analgesic effects of 4 drug combinations used for TIVA of horses undergoing surgical removal of an abdominal testis.

Materials and Methods

Patient selection—Thirty-two cryptorchid horses between 2 and 4 years old and weighing between 410 and 532 kg (902 and 1,170 lb; mean, 432 kg [950 lb]) were used in the study. There were 14 Quarter Horses, 7 Standardbreds, 4 Thoroughbreds, 3 Appaloosas, 2 Tennessee Walking Horses, 1 Trakehner, and 1 Hallinger. All horses were confirmed at surgery to have 1 testis within the abdominal cavity. Horses were considered to be healthy otherwise on the basis of results of a physical examination, ECG (base-apex lead), hematologic testing, and measurement of serum fibrinogen concentration.

Drug combinations—Four drug combinations were used for TIVA. Combination 1 (KD/KX) consisted of administration of ketamine hydrochloride and diazepam (KD; 2.2 mg/kg [1.0 mg/lb] of body weight), IV, and 0.06 mg/kg [0.027 mg/lb] of body weight, IV, and 0.06 mg/kg [0.027 mg/lb] of body weight, IV.
mg/lb), IV, respectively) for induction of anesthesia followed by repeated IV administration of boluses of ketamine and xylazine (XK; 0.25 mg/kg [0.11 mg/lb] and 0.25 mg/kg [0.11 mg/lb], respectively) as needed to maintain anesthesia. Combination 2 (TKD) consisted of IV administration of tiletamine-zolazepam (0.67 mg/kg [0.30 mg/lb]), ketamine (0.53 mg/kg [0.24 mg/lb]), and detomidine (0.013 mg/kg [0.006 mg/lb]). The combination was prepared by adding 4 ml of ketamine (100 mg/ml) and 1 ml of detomidine (10 mg/ml) to an unreconstituted 5-ml bottle of tiletamine-zolazepam. This combination was administered at a dose of 0.007 ml/kg (0.003 ml/lb) for induction of anesthesia; additional boluses (0.002 ml/kg [0.001 ml/lb]) were administered IV as needed to maintain anesthesia. Combination 3 (XGK) consisted of IV administration of xylazine, guaifenesin, and ketamine (XGK; 0.5 mg/ml, 50 mg/ml [5%], and 1 mg/ml, respectively) to effect at an approximate rate of 1.5 ml/kg/h (0.68 ml/lb/h). Combination 4 (GT) consisted of IV administration of guaifenesin and thiopental (GT; 50 mg/ml [5%] and 2 mg/ml, respectively) to effect at an approximate rate of 1.5 ml/kg/h (0.68 ml/lb/h). Drugs and doses were selected on the basis of results of experimental and clinical studies conducted in horses. Numbers of additional boluses or temporary increases in the infusion rate required to maintain adequate surgical anesthesia were recorded.

Experimental protocol—Horses were randomly assigned to receive 1 of the 4 anesthetic drug combinations. Food, but not water, was withheld the morning of surgery. Thirty minutes before surgery, horses were groomed, their mouths were rinsed with water, their feet were picked clean of debris, and a 14-gauge 14-cm polytetrafluoroethylene catheter was placed percutaneously in the left jugular vein for IV administration of all drugs. Horses were moved to a padded stall and sedated with xylazine hydrochloride (1.1 mg/kg [0.5 mg/lb], IV) and butorphanol tartrate (0.02 mg/kg [0.01 mg/lb], IV). Ten to 15 minutes later, TIVA was performed. Once horses were recumbent, a cuffed endotracheal tube was placed, and horses were placed in dorsal recumbency. The endotracheal tube was connected to an anesthetic machine with the vaporizer turned off, and horses were allowed to spontaneously breath 100% oxygen (5 L/min). The endotracheal tube was connected to an anesthetic machine with the vaporizer turned off, and horses were allowed to spontaneously breath 100% oxygen (5 L/min). Arterial blood pressure was considered to be the point of the shoulder after attempts to attain a sternal position. Arterial blood pressure was monitored during the anesthetic drug combination (approx 10 to 15 minutes after administration of xylazine and butorphanol), and at 15-minute intervals until the horse was in recovery and began attempts to attain a sternal position. Arterial blood pressure was recorded every 15 minutes after induction of anesthesia (recumbency) until the end of the surgical procedure. Arterial blood samples were obtained approximately 15 minutes after induction of anesthesia.

Quality of sedation, quality of induction, degree of muscle relaxation, quality of analgesia, and recovery from anesthesia were scored by 2 independent observers, and the mean value of the 2 observers’ scores was recorded as the score for each time period. Quality of sedation was scored as 1 (calm, relaxed, no restraint required, minimally responsive to environmental stimuli, reluctant to move), 2 (no restraint required, relaxed, infrequent responses to environmental stimuli, easily walked without problems), 3 (minimal restraint required, interested in environmental stimuli, reactive to noise and sudden movements), or 4 (unsatisfactory, minimal or no signs of sedation, nervousness or apprehension requiring additional sedative administration). Quality of induction was scored as 1 (minimal or no muscle twitching, no movement, relaxed limbs), 2 (brief muscle rigidity followed by relaxation and minimal movement), 3 (marked muscle rigidity, movement, struggling), or 4 (fails to attain lateral recumbency). Degree of muscle relaxation was scored as 1 (no trunk or limb twitching or movement, no resistance to flexion of limbs), 2 (slight trunk or limb muscle twitching, minimal resistance to flexion of limbs), 3 (strong trunk or limb muscle twitching, resistance to flexion of limbs), or 4 (muscle rigidity and strong resistance to flexion of limbs). Quality of analgesia (ie, response to surgical stimulation) was scored as 1 (no response to surgical stimulation), 2 (brief contraction of abdominal or limb muscles, temporary twitching or spasms), 3 (movement of a forelimb or hind limb), or 4 (repeated movement of a forelimb or hind limb requiring additional drug administration). Recovery from anesthesia was scored as 1 (unassisted, uneventful, 1 attempt to stand), 2 (unassisted, 2 or 3 attempts to stand), 3 (minimal assistance requiring 1 attendant because of > 3 attempts to stand), or 4 (assistance to stand requiring 2 attendants to provide head and tail support because of moderate or severe ataxia).

Quality of anesthesia (ie, degree of muscle relaxation and quality of analgesia) was scored 6 times: when towel clamps were placed in the skin, at the initial skin incision, during retraction of each testicle, and during emasculation of each testicle. These 6 scores were averaged to produce a single score for degree of muscle relaxation and a single score for quality of analgesia for each horse. Horses that moved (score of ≥ 3 for degree of muscle relaxation or quality of analgesia) 3 consecutive times in response to surgical stimulation despite administration of additional anesthetic drug or for which surgery time was > 60 minutes were administered an inhalant anesthetic to complete the procedure, and data from these horses were excluded from further analysis.

Induction time (ie, time from initial anesthetic drug administration until lateral recumbency), anesthesia time (ie, time from anesthetic induction to the end of anesthetic drug administration), surgery time (ie, time from the initial skin incision to placement of the last suture), recovery time (time from the end of anesthetic drug administration to standing), and number of attempts to stand were recorded. Two attendants assisted horses that required > 3 attempts to stand.

Data analysis—Eight of the 32 horses required the use of inhalational anesthesia and were excluded from analyses of the data; for the remaining 24 horses, only TIVA was required, and values for these horses (6/anesthetic drug combination) are reported. Data are reported as mean ± SD. An ANOVA for repeated measures was used to compare cardiovascular and respiratory data within and among groups. The Dunnett test was used where indicated to compare changes over time within each anesthetic drug combination; differences among drug combinations were examined by use of Student t-tests. Categorical data were compared by use of the Mann-Whitney U test. For all analyses, a value of P < 0.05 was considered significant.

Results—Heart rate and respiratory rate significantly decreased after administration of xylazine and butor-
tion score of 3) in all horses and was not significantly
judged to be good (sedation score of 2) or fair (seda-

The administration of xylazine and butorphanol was
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Three horses in the KD/KX group and 1 horse in each
differences among groups were again not detected.

Horses anesthetized with KD/KX

and analgesia scores were lowest for horses given

Table 1—Cardiorespiratory effects of 4 drug combinations used for total intravenous anesthesia (TIVA)
in horses (n = 6/group) undergoing surgical removal of an abdominal
dicting TIVA, using 4 drug combinations

Table 2—Quality of sedation, induction and maintenance of anesthesia, and recovery for horses under-

Table 1 for key.

Values are given as mean ± SD.

Ten to 15 minutes after administration of xylazine and butorphanol.

Significantly (P < 0.05) different from baseline value.

Significantly (P < 0.05) different from values for other groups. KD/KX = Induction of anesthesia with ketamine and diazepam
and maintenance with bolus administration of xylazine and butorphanol. HR = Heart rate. RR = Respiratory rate. SABP = Systolic arterial blood pressure. DABP = Diastolic arterial blood pressure. MABP = Mean arterial blood pressure. TKD = Induction and maintenance of anesthesia with bolus administration of tiletamine-zolazepam, ketamine, and detomi-
diene. XGK = Induction and maintenance of anesthesia with continuous infusion of xylazine, guaifenesin, and ketamine.
GT = Induction and maintenance of anesthesia with continuous infusion of guaifenesin and thiopental. NA = Not deter-
mained. ND = Not applicable (surgical procedure had been completed in all horses).

Table 2—Quality of sedation, induction and maintenance of anesthesia, and recovery for horses under-

ging TIVA, using 4 drug combinations

Phenol. Heart rate and respiratory rate were not signifi-
cantly different among groups before or 10 minutes
after administration of xylazine and butorphanol (Table 1). In addition, quality of sedation induced by
administration of xylazine and butorphanol was judged to be good (sedation score of 2) or fair (sedation score of 3) in all horses and was not significantly
different among groups (Table 2).

Mean quality of induction was not significantly
different among groups (Table 2). Muscle relaxation
and analgesia scores were lowest for horses given
KD/KX, but significant differences among groups
were not detected. Horses anesthetized with KD/KX
required a higher number of additional boluses, com-
pared with horses in the other groups, but significant
differences among groups were again not detected. Three horses in the KD/KX group and 1 horse in each
pressure was significantly greater in horses that received TKD than in horses in the other groups (Table 1). Arterial blood gas partial pressures did not indicate any substantial respiratory (maximum P_{CO2}, 52 mm Hg) or nonrespiratory acidosis (minimum pH, 7.36).

The precise initial rate of infusion for horses in the XGK and GT groups was not determined; therefore, induction times could not be accurately determined for horses in these groups. All horses in these groups became laterally recumbent in less than 5 minutes, but each required 3 to 5 minutes, which was longer than the induction times for horses in the KD/KX and TKD groups. Anesthesia, surgery, and recovery times were not significantly different among groups (Table 3).

### Discussion

Total intravenous anesthesia has been advocated on the basis of cardiorespiratory, endocrine, and economic data as a potentially superior alternative to inhalant anesthesia in horses. In the present study, we compared the cardiorespiratory and anesthetic qualities of 4 drug combinations for TIVA in horses undergoing removal of an abdominal testis. Two of these combinations were administered as boluses; the other 2 were administered as infusions. Results of the present study suggest that all 4 anesthetic drug combinations can be used to induce short-term anesthesia for abdominal cryptorchidectomy in horses, although a few differences in effects of the combinations were detected. Three horses given KD/KX had to be removed from the study because of movement in response to surgical stimulation. Also, horses in this group generally had a poorer quality of anesthesia (ie, higher muscle relaxation and quality of analgesia scores), compared with horses in the other 3 groups, even though significant differences among groups were not detected. Horses receiving TKD had significantly higher blood pressures throughout the anesthetic period, compared with horses in the other 3 groups, and a poorer recovery from anesthesia, often requiring assistance to stand.

Studies investigating the anesthetic potential of combinations of α2-adrenoceptor agonists (eg, xylazine, detomidine, and romifidine), dissociative anesthetic drugs (eg, ketamine and tiletamine), and muscle relaxing drugs (eg, guaifenesin, diazepam, zolazepam, and temazepam) for TIVA in horses have generally demonstrated minimal cardiovascular depression, with infrequent transient periods of systemic hypertension. We did not measure arterial blood pressure before anesthesia in the present study and, therefore, do not know whether arterial blood pressure was different from baseline values or values after administration of xylazine and butorphanol. We suspect that arterial blood pressure increased transiently following the administration of xylazine and butorphanol, because previous studies from our laboratory and others have documented this effect. Increases in arterial blood pressure have been attributed to α2-adrenoceptor agonist activation of peripheral α1- and α2-adrenoceptors and dissociative anesthetic-induced increases in centrally mediated sympathetic tone, release of catecholamines from peripheral storage sites, inhibition of neuronal and extraneuronal uptake of catecholamines, inhibition of baroreceptor reflex activity, and increases in intracellular calcium concentration. Blood pressure was higher for horses in the KD/KX and TKD groups, compared with horses in the XGK and GT groups, although a significant difference was detected only for horses in the TKD group. We believe that the most probable cause for this difference was a higher plasma concentration of the α2-adrenoceptor agonist (xylazine, detomidine), ketamine, or ketamine and tiletamine associated with bolus drug administration, although we did not determine the plasma concentrations of these drugs.

In the present study, respiratory rate decreased after administration of xylazine and butorphanol, similar to results of previous studies of the effects of α2-adrenoceptor agonists in horses. The decrease in respiratory rate was attributed to sedation, and decreases in respiratory rate following administration of α2-adrenoceptor agonists has been reported to produce no change or only a minimal increase in Pa_{CO2}, suggesting that there is no change or only a minimal decrease in alveolar ventilation. In the present study, Pa_{CO2} was slightly increased, compared with values for clinically normal horses, but values were not significantly different among groups and were not high enough that they would be expected to cause clinically significant changes in arterial blood pH. This varies from results of other studies that investigated the cardiorespiratory effects of α2-adrenoceptor agonist and dissociative anesthetic drug combinations in horses in which surgery was not performed, and suggests that surgical stimulation can minimize or prevent respiratory depression.

We intentionally used 4 drug combinations and 2 drug administration techniques for TIVA in the present study. We selected these 4 drug combinations and dosages on the basis of published reports and suggestions by equine veterinary surgeons in private practice. Although most of the changes that we observed may be attributed to the drugs, drug dosages, and surgical procedure, some of the differences may be attributable to the anesthetic technique (bolus vs infusion). Bolus induction times for horses in the KD/KX and TKD groups. Anesthesia, surgery, and recovery times were not determined; therefore, induc

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1. Increases in arterial blood pressure have been attributed to α2-adrenoceptor agonist activation of peripheral α1- and α2-adrenoceptors and dissociative anesthetic-induced increases in centrally mediated sympathetic tone, release of catecholamines from peripheral storage sites, inhibition of neuronal and extraneuronal uptake of catecholamines, inhibition of baroreceptor reflex activity, and increases in intracellular calcium concentration. Blood pressure was higher for horses in the KD/KX and TKD groups, compared with horses in the XGK and GT groups, although a significant difference was detected only for horses in the TKD group. We believe that the most probable cause for this difference was a higher plasma concentration of the α2-adrenoceptor agonist (xylazine, detomidine), ketamine, or ketamine and tiletamine associated with bolus drug administration, although we did not determine the plasma concentrations of these drugs.

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drug administration would be expected to produce a rapid increase in plasma concentration followed by a decrease determined by the drugs' plasma half-lives, clearance rates, and volumes of distribution. This technique produces peak and trough plasma concentrations that are primarily determined by the drugs' pharmacokinetics, the initial drug dosages, and the frequency of drug administration. In the present study, we did not administer boluses of KD/KX or TKD at predetermined times but on an as-needed basis, as subjectively determined by the horses' anesthetic depth (heart rate, respiratory rate, and response to palpebral and corneal stimulation) and response to surgical stimulation. This approach may have biased evaluations of the quality of anesthesia, because additional doses were not administered until the horse demonstrated signs indicative of a light plane of anesthesia or moved. In contrast, horses in the XGK and GB groups received an initial loading dose followed by a continuous infusion that would be expected to result in relatively steady plasma drug concentrations exceeding the trough concentrations associated with bolus administration and, hypothetically, greater than the minimal drug concentrations required to prevent movement during all but the most painful surgical manipulations.

An important practical consideration is the time required to complete the surgical castration procedure. Although surgery time averaged approximately 21 minutes (range, 18 to 23 minutes), shorter surgery times would have decreased the total number of additional drug boluses required by horses in the KD/KX and TKX groups and decreased the total amount of drug administered in all groups. Furthermore, because the initial doses of anesthetic drugs required to produce anesthesia were larger than subsequent dosages, therefore producing higher plasma concentrations and deeper anesthesia early during the course of anesthesia, a short and uneventful surgery would be expected to produce more favorable categorical data.

References