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Ketamine, Telazol®, Xylazine and Detomidine

A Comparative Anesthetic Drug Combinations Study in Ponies

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Lin, H. C., K. R. Branson. J. C. Thurmon, G. J. Benson, W. J. Tranquilli W. A. Olson, and A. T. Vähä-Vahe: Ketamine, Telazol®, Xylazine and Detomidine: A comparative anesthetic drug combinations study in ponies. Acta vet. scand. 1992, 33, 109-115. – This study was designed to assess the effects of 5 anesthetic drug combinations in ponies: (1) ketamine 2.75 mg/kg, xylazine 1.0 mg/kg (KX), (2) Telazol® 1.65 mg/kg, xylazine 1.0 mg/kg (TX), (3) Telazol® 2 mg/kg, detomidine 20 μg/kg (TD-20), (4) Telazol® 2 mg/kg, detomidine 40 μg/kg (TD-40), (5) Telazol® 3 mg/kg, detomidine 60 μg/kg (TD-60). All drugs were given iv with xylazine or detomidine preceding ketamine or Telazol® by 5 min. Heart rate was decreased significantly from 5 min to arousal after TD-20 but only at 60 and 90 min after TD-40 and TD-60 respectively. Respiratory rate was decreased significantly for all ponies. Induction time did not differ between treatments. Duration of analgesia was 10 min for KX, 22.2 min for TX, 27.5 min for TD-20, 32.5 min for TD-40, and 70 min for TD-60. Arousal time was significantly longer with detomidine and Telazol®. Smoothness of recovery was judged best in ponies receiving KX and TD-40. All ponies stood unassisted 30 min after signs of arousal.

Introduction

In horses, short-term general anesthesia can be safely induced and maintained with injectable anesthetic drugs and combinations there of. The drug combinations should be selected on their ability to induce balanced anesthesia characterized by narcosis, analgesia and muscle relaxation *(Thurmon et al. 1985).* Guaifenesin, a central muscle relaxant, when combined with an ultra-short acting barbiturate (thiopental sodium or thiamylal sodium) has been used successfully as a general anesthetic for over 2 decades for short elective surgical procedures. Of major concern with this drug combination is relatively poor analgesia and prolonged, rough recovery after large doses ie. after continuous infusion maintenance *(Thurmon et al. 1985).* In 1970, xylazine-ketamine became a fashionable drug combination for induction of anesthesia and is still used today for induction and short elective surgical and diagnostic procedures. While safe and relatively effective, muscle relaxation is generally poor. More recently, guaifenesin has been combined with xylazine and ketamine for its contribution to balanced

anesthesia. The combination is referred as "Triple Drip". After 1 to 2 h of "Triple Drip" anesthesia recovery is rapid and smooth *(Greene et al. 1986).*

Of importance to the equine practitioner is the availability of drug combination that can be given in a single or perhaps 2 sequential injections that will provide a reasonable length of anesthetic time, under field conditions.

Telazol®[a] is a proprietary combination of tiletamine and zolazepam. Tiletamine is a dissociative closely related to ketamine but more potent. Zolazepam is similar to diazepam, acting centrally to induce muscle relaxation. In "Triple Drip" guaifenesin supplies this component of balanced anesthesia. Telazol®[a] anesthesia has been studied extensively in a wide variety of exotic and domestic animals, though it is only approved for use in dogs and cats.

Recently a combination of Telazol®[a] and xylazine was studied for its anesthetic effect in horses. When xylazine (1.1 mg/kg IV) was followed by Telazol®[a] (1.65 mg/kg IV) or (2.2 mg/kg IV), favorable anesthesia of 10-20 min duration occurred *(Hubbell et al. 1989).* But occasionally, recovery were considered rougher than desirable. It is reasonable to speculate that this occurred because of the short plasma half-lives (t½)of xylazine and tiletamine as compared to zolazepam's central muscle relaxing action.

Detomidine induces strong sedation, analgesia and muscle relaxation *Jöchle & Hamm 1986, Ricketts 1986).* Its action is of longer duration than that of xylazine. Thus, we chose to compare the anesthetic responses of ponies receiving ketamine-xylazine or Telazol®-xylazine to those of ponies given Telazol®-detomidine at 3 different doses.

[a]Telazol®, A. H. Robins Co., Richmond, VA.

Materials and Methods

Eighteen mixed breed ponies (b.wt. 114.5-262.2 kg) were used in this study to assess the effects of 5 anesthetic drug regimens: (1) Ketamine (2.75 mg/kg) + Xylazine (1.1 mg/kg) (KX); (2) Telazol® (1.65 mg/kg) + Xylazine (1.1 mg/kg) (TX); (3) Telazol® (2 mg/kg) + Detomidine (20 µg/kg) (TD-20); (4) Telazol® (2 mg/kg) + Detomidine (40 µg/kg) (TD-40); (5) Telazol® (3 mg/kg) + Detomidine (60 µg/kg) (TD-60). Ponies were randomly assigned to 3 groups of 6 each. KX and TX were given to ponies of group 1, TD-40 and TD-60 to group 2 and TD-20 to group 3. A 1 week interval was allowed between studies for ponies receiving 2 drug regimens. The ponies were fasted for 12 h before each study. All drugs were injected through a 16 G-calibre, 3 inch-catheter into the left jugular vein. Xylazine or detomidine always preceded ketamine or Telazol® by 5 min. In addition to the foregoing studies, 4 randomly selected ponies were given a 2nd dose of either KX, TX, TD-40 and TD-60 equal to half of the original dose. Both drugs were combined in the same syringe and given at the 1st signs of arousal. This permitted us to assess the response to repeat injection for extend anesthesia time as might be required under field conditions.

Before any drug was administered, baseline values (Time-0) were recorded for heart rate (HR) and respiration rate (RR). At 5 min and at each 15 min interval thereafter, values for HR and RR were recorded and the level of analgesia was evaluated based on the ponies' response to pressure from a standard hoof tester applying pressure at the coronary band and across the hoof. The response was graded accordingly: 10 = good (no response), 5 = fair (minimal response but detectable attempt to withdraw limb) and 0 = poor (active limb withdrawal). Time of recum-

bency (TR), duration of analgesia (DA), time of 1st sign of arousal (TA), time from arousal to standing unassisted (AS), and smoothness of recovery was evaluated and recorded. Criteria used to evaluate AS are presented in Table 1. These criteria were assigned numerical values of 15, 10, 5, and 0 for excellent, good, fair and poor respectively according to the number of attempts required for a pony to stand unassisted. Heart rate and RR were analyzed using ANOVA. Student's t-test was used to determine differences in TR, DA, TA, and AS between drug regimens. A probability of less than 5% ($P < 0.05$) was considered significant.

Table 1. Criteria used to assess smoothness of recovery of ponies.

Smoothness of recovery	No. of attempts
Excellent (15)	1
Good(10)	2
Fair(5)	3-5
Poor(0)	>5

Results

The first sign of sedation (ie. lowering of the head) occurred 1-3 min after administration of xylazine or detomidine. Following injection of ketamine or Telazol®, all ponies became recumbent within 25 to 60 sec and were easily intubated. There was no significant difference between TR of ponies given any of the 5 drug regimens. All appeared to be equally effective (Table 2). Heart rate decreased significantly after injection of either xylazine or detomidine and persisted for all drug regimens until TA (Table 3). Respiration rate decreased below baseline after TX, TD-20, TD-40 and TD-60 but only in ponies receiving TD-20 did HR remain below baseline until the end of study. Respiration rate did not change significantly after administration of KX (Table 4). Table 2 summarizes the time required for TR, DA, AS and SR. Analgesia was of longer duration with TX, TD-20, TD-40 and TD-60 than with KX. Likewise, AS occurred significantly sooner with KX than with all the other regimens. Ponies receiving TX and TD-40

Table 2. Values for time of recumbency (TR), duration of analgesia (DA), time of arousal (TA), time from arousal to standing (AS), and smoothness of recovery (SR) for ponies anesthetized with 5 drug regimens. Mean ± SD.

Drug Regimens	TR(sec)	DA(min)	TA(min)	AS(min)	SR
KX	46.5±15.6	10±5.8	18±5.6	16.5±5.1	15
TX	33.8±4.0	22.5±8.2[a]	32.8±2.8[a]	7.3±4.7[a]	10.8
TD-20	22.5±9.4	27.5±11.3[a]	38.5±9.0[a]	16.5±12.8	9.2
TD-40	60.3±30.4	32.5±14.7[a]	66.5±10.3[a]	20.3±6.2	15
TD-60	44.2±6.9	70±12.2[a]	91.5±18.0[a]	32.2±15.8[a]	7.5

KX: Ketamine (2.5 mg/kg IV) + Xylazine (1.1 mg/kg IV).
TX: Telazol® (1.65 mg/kg IV) + Xylazine (1.1 mg/kg IV).
TD-20: Telazol® (2 mg/kg IV) + Detomidine (20 µg/kg IV).
TD-40: Telazol® (2 mg/kg IV) + Detomidine (40 µg/kg IV).
TD-60: Telazol® (3 mg/kg IV) + Detomidine (60 µg/kg IV).

[a]Significantly different from KX ($P < 0.05$).

Table 3. Values for heart rate (beats/min) for ponies anesthetized with 5 drug regimens. Mean ± SD.

Time(min)	KX	TX	TD-20	TD-40	TD-60
0	54±3	53±3	60±5	56±7	53±4
1[b]	42±2[a]	42±6[a]	38±3[a]	32±5[a]	32±2[a]
5	46±2[a]	46±3[a]	47±2[a]	39±4[a]	39±2[a]
15	45±2[a]	43±3[a]	47±3[a]	35±1[a]	37±3[a]
30	–	47±4[a]	44±2[a]	37±3[a]	37±4[a]
45	–	–	45±3[a]	36±2[a]	35±2[a]
60	–	–	–	39±2[a]	36±2[a]
75	–	–	–	–	40±3[a]
90	–	–	–	–	36±0[a]
105	–	–	–	–	42±6[a]

KX: Ketamine (2.5 mg/kg IV) + Xylazine (1.1 mg/kg IV).
TX: Telazol® (1.65 mg/kg IV) + Xylazine (1.1 mg/kg IV).
TD-20: Telazol® (2 mg/kg IV) + Detomidine (20 µg/kg IV).
TD-40: Telazol® (2 mg/kg IV) + Detomidine (40 µg/kg IV).
TD-60: Telazol® (3 mg/kg IV) + Detomidine (60 µg/kg IV).
[a]Significantly different from that of KX ($P < 0.05$).
[b]Time after xylazine or detomidine injection and before Telazol® or ketamine injection.

Table 4. Values for respiration rate (breaths/min) for ponies anesthetized with 5 drug regimens. Mean ± SD.

Time(min)	KX	TX	TD-20	TD-40	TD-60
0	26±8	36±8	38±8	38±5	41±5
1[b]	19±5	22±2[a]	28±5[a]	21±3[a]	18±0[a]
5	27±2	36±6	28±6[a]	36±4	39±3
15	35±10	28±6	25±5[a]	32±2	41±4
30	–	28±6	24±5[a]	33±4	40±5
45	–	–	23±7[a]	35±4	38±3
60	–	–	–	31±3[a]	38±4
75	–	–	–	–	41±6
90	–	–	–	–	33±5[a]
105	–	–	–	–	33±3[a]

KX: Ketamine (2.5 mg/kg IV) + Xylazine (1.1 mg/kg IV).
TX: Telazol® (1.65 mg/kg IV) + Xylazine (1.1 mg/kg IV).
TD-20: Telazol® (2 mg/kg IV) + Detomidine (20 µg/kg IV).
TD-40: Telazol® (2 mg/kg IV) + Detomidine (40 µg/kg IV).
TD-60: Telazol® (3 mg/kg IV) + Detomidine (60 µg/kg IV).
[a]Significantly different from that of KX ($P < 0.05$).
[b]Time after xylazine or detomidine injection and before Telazol® or ketamine injection.

Table 5. Values for time of recumbency (TR), duration of analgesia (DA), time of arousal (TA), time from arousal to standing (AS), and smoothness of recovery (SR) for 4 ponies anesthetized with repeat dosing of 4 drug regimens.[a].

Drug Regimens	TR(sec)	DA(min)	TA(min)	AS(min)	SR
KX	44	15	31	17	15
TX	27	60	69	11	0
TD-40	43	75	88	8	10
TD-60	50	180	224	73	0

KX: Ketamine (2.5 mg/kg IV) + Xylazine (1.1 mg/kg IV).
TX: Telazol® (1.65 mg/kg IV) + Xylazine (1.1 mg/kg IV).
TD-40: Telazol® (2 mg/kg IV) + Detomidine (40 µg/kg IV).
TD-60: Telazol® (3 mg/kg IV) + Detomidine (60 µg/kg IV).
[a]Repeat dosing was given at the first sign of arousal with half of the original dose of each drug.
The repeat dosing trial was not conducted with TD-20.

required the least amount time to stand unassisted. As would be expected, ponies receiving TD-60 required the greatest amount of time. Smoothness of recovery was rated excellent in ponies receiving KX and TD-40. Repeat dosing of KX did not significantly extend DA although DA was significantly prolonged with repeat dosing of TX, TD-40 and TD-60. Repeat dosing also increased roughness of recovery. It was judged greatest in ponies given TX and TD-60 (Table 5). Repeat dosing trials were not conducted with TD-20. All ponies made full recoveries without any lasting side effects.

Discussion

Both xylazine and detomidine induce profound sedation and analgesia though detomidine is the more potent. But with either xylaxine or detomidine, recumbency and anesthesia occurred rapidly and smoothly after injection of ketamine or Telazol®. Regimens including Telazol® were judged to induce the greatest degree of muscle relaxation. This appears to be due, in large part, to the central muscle relaxing actions of zolazepam. Likewise, the level and duration of analgesia was increased with the Telazol® regimens and further enhanced when regimens contained detomidine. The mean peak serum concentration and elimination t½ are 15 and 50 min and 30 and 79 min respectively for xylazine and detomidine *Salonen et al. 1989, Garcia-Villar et al. 1981)* Detomidine, 20 µg/kg IV is thought to induce maximal sedation. Increasing the dose only serves to increase detomidine's duration of action *(Hamm & Jöchle 1984).* This seemed to be true in the present study in as much as increasing the dose of detomidine only increase the TA. There was no significant difference in TR between TD-20, TD-40 and TD-60.

Xylazine and detomidine, characteristically, decreased HR in all regimens. Heart rate decreased below baseline after ketamine or Telazol® injection and remained so until TA. Stimulation of α_2-adrenoceptors causes bradycardia and sometimes 2nd degree AV node blockade in horses *(Garner et al. 1971, Sarazan 1989).* The mechanism is attributed to a decrease in CNS sympathetic activity and early increases in vagal nerve tone in response to an increase in arterial blood

pressure *(Antonaccio et al. 1973)*. In the present study, sinus dysrhythmia was detected in 1 pony after injection of detomidine (TD-60) and persisted until the end of study. Detomidine (doses from 20-160 μg/kg IV) reportedly causes a significant decrease in HR similar to that seen with xylazine (1.1 mg/kg IV) *(Short et al. 1984)*. While increasing the dose of detomidine prolonged the duration of analgesia, in the present study, sinus dysrhythmia did not appear to be dose-dependent. Although ketamine and tiletamine reportedly increase HR via direct CNS stimulation, resulting in an increase in sympathetic outflow (*White et al. 1982, Chen & Ensor 1986),* neither reversed the bradycardia induced by xylazine or detomidine.

Respiration rate decreased significantly after injection of xylazine or detomidine in all drug regimens. With KX and TX, RR had returned to baseline within 5 min while TD-20, TD-40 and TD-60 tended to depress RR somewhat longer. However, only with TD-20 did RR remain significantly below baseline until TA. We have no sound explanation for TD-20's RR depressing actions. However, one expects to see a decrease in RR after xylazine injection *(Hoffman 1974)*. The decrease in RR after detomidine alone is generally followed by an increase in both RR and tidal volume *(Short et al. 1984)*. Cyclohexamines derivatives (eg. ketamine and tiletamine) induce dose-dependent respiratory depression. The respiratory pattern also changes taking on a peculiar apneustic characteristic (ie. rapid and irregular breathing intermixed with breath holding) *(Wright 1982)*. While some of the decreases in RR were statistically significant, the RR always remained within clinically safe limits for anesthetized ponies. We further speculate that surgical stimulation would have actively restored RR to baseline for this has been our clinical experience with these drug combinations.

For the most part, recovery was rated as smooth with KX, TX, TD-20 and TD-40 although, for some unexplained reason, recovery was not as smooth with TD-20 as with TD-40. At this time, we can only attribute this unexpected response to individual pony variation. Ponies receiving TD-60 required 3-5 attempts to stand unassisted. This suggests that the duration of detomidine is shorter than that of Telazol® when both drugs are given at high doses. However, this assumption conflicts somewhat with the fact that increasing the dose of detomidine prolongs its actions *(Hamm & Jöchle 1984)* We believe that the higher dose of Telazol® (3 mg/kg IV) had a major influence on the roughness of recovery in the TD-60 group. It also seems that this can be attributed largely to the zolazepam component of Telazol®. In the repeat dosing trials, all Telazol® treated ponies experienced an increase in roughness of recovery. The pony receiving the repeat dose of TD-60 had the roughest recovery. The inability to stand was characterized by muscular weakness reflecting the central muscle relaxing actions of zolazepam.

Conclusion

From the results of the present study, we conclude that xylazine-ketamine, xylazine-Telazol® or detomidine-Telazol® can be safely used to anesthetize ponies. Further, that the detomidine-Telazol® drug combination will extend analgesia and thus should provide more surgical time. However, as the dose of detomidine and Telazol® is increased, smoothness of recovery will be adversely affected. On the basis of these limited trials, supplemental dosing of Telazol® drug regimens can not be recommended because the smoothness of recovery will be adversely affected.

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Sammanfattning

Ketamin, Telazol, Xylazin och Detomidine: Ett jämförande försök mellan fem olika anestetikakombinationer hos ponnyn.

Detta Försök utfördes för att jämföra effekten av fem anestetikakombinationer hos ponnyn: (1) ketamin 2,75 mg/kg, xylazin 1,0 mg/kg (KX), (2) Telazol 1,65 mg/kg, zylazin 1,0 mg/kg (TX), (3) Telazol 2 mg/kg, detomidin 20 µg/kg (TD-20), (4) Telazol 2 mg/kg, detomidin 40 µg/kg (TD-40), (5) Telazol 3 mg/kg, detomidin 60 µg/kg (TD-60). Alla läkemedel gavs intravenöst; xylazin eller detomidin 5 min efter ketamin eller Telazol. Hjärtfrekvensen sjönk signifikant från 5 min till uppvaknandet efter TD-20 men endast vid 60 och 90 min respektivt. Andningsfrekvensen sjönk signifikant för alla ponnyn. Induktionstiden för de olika behandlingarna visade ingen skillnad. Analgesins duration var 10 min för KX, 22,2 min för TD-20, 32,5 min för TD-40 och 70 min för TD-60. Uppvakningstiden var signifikant längre med detomidin än med Telazol. Återhämtningen ansågs vara lugnast hos ponnyn som fått KX och TD-40. Alla ponnyn stod upprätta utan hjälp 30 min efter tecken på uppvakning.

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