# REVERSAL OF DEPRESSANT EFFECTS OF XYLAZINE-KETAMINE ANESTHESIA IN RABBITS USING EITHER AN ALPHA-2 ANTAGONIST (YOHIMBINE) OR A MIXED ALPHA-1 AND ALPHA-2 ANTAGONIST (TOLAZOLINE)

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ABSTRACT

Nine rabbits were studied after injection intramuscularly with xylazine[1] (8mg/kg) and ketamine[2] (50mg/kg). Twenty minutes later, rabbits received intravenous injections of yohimbine[3] (0.5mg/kg), tolazoline[4] (6.6mg/kg), or physiological saline (0.5ml). Treatments were randomized according to Latin square design and at least seven days were allowed between treatment in each rabbit. Recordings were taken at ten-minute intervals for 80 minutes. Mean time to sternal recumbency (as measured from time of injection of reversal drugs or saline) was significantly shortened to $91 \pm 21$ minutes with yohimbine and $83 \pm 19$ minutes with tolazoline as compared to $117 \pm 13$ minutes with saline. Though not statistically significant ($p \leq .05$), mean time to standing ($128 \pm 40$ minutes for yohimbine, $114 \pm 23$ minutes for tolazoline, $134 \pm 17$ minutes for saline), mean time to walking ($128 \pm 44$ minutes for yohimbine, $111 \pm 27$ minutes for tolazoline, $142 \pm 11$ minutes for saline), and mean time to walking with full coordination ($150 \pm 37$ minutes for yohimbine, $142 \pm 23$ minutes for tolazoline, $187 \pm 60$ minutes for saline) were shortened with both drugs as compared to saline. Relapses to unconsciousness did not occur. Palpebral and withdrawal responses returned much more rapidly with yohimbine than with the other two drugs. These responses returned more quickly with tolazoline than with saline. Heart rates were highest after yohimbine. In all three groups, heart rates were significantly different from each other. Respiratory rates, though not significant, were higher with yohimbine and tolazoline than with saline. Though both yohimbine

and tolazoline were effective for reversing xylazine-ketamine anesthesia in rabbits at the dosages given, tolazoline provided the most desirable recovery. Both antagonists, however, would be useful for enhancing arousal in xylazine-ketamine depressed rabbits.

Key words: ketamine -- xylazine -- yohimbine -- tolazoline -- rabbits.

## INTRODUCTION

The combination of xylazine and ketamine has been shown to be a safe and effective intramuscular drug combination for anesthesia in rabbits (1). Xylazine-ketamine produces sufficient muscle relaxation and depth to provide a good plane of surgical anesthesia in rabbits for up to 60 minutes (1-3). Xylazine's stimulation of alpha-2 adrenergic receptors causes its central nervous system depression (4) while the specific receptor site or sites of ketamine action in the CNS remain unknown (5).

Yohimbine is believed to be an alpha-2 adrenergic blocking agent (6) and has been used to antagonize xylazine depression in many species (4-8). Though the mechanism is unknown, yohimbine shortens ketamine-induced anesthesia as well (4,5,9,10).

Tolazoline is a mixed alpha-1 and alpha-2 antagonist that has been shown to reverse xylazine-halothane anesthesia in dogs (11), xylazine-ketamine anesthesia in dogs, wolves, and elephants (12,13), xylazine depression in cattle, sheep, cats, mice, and chicks (4, 14-16), and the effects of clonidine (an alpha-2 adrenergic agent) in man (11,17).

The purpose of the present study was to determine if xylazine-ketamine anesthesia in rabbits could be safely, rapidly, and permanently reversed by yohimbine or tolazoline and to compare the responses to the two drugs.

## MATERIALS AND METHODS

Nine New Zealand white rabbits (5 males and 4 females) weighing 2.636±.034 kg were studied. They were housed in climate-controlled cages, fed a commercially prepared diet, and allowed water ad libitum for thirteen days prior to the initial testing. Prior to study, rabbits received a physical examination, and blood chemistry evaluations were performed.

The treatments and rabbits were randomized according to Latin square design. All rabbits were given xylazine (8mg/kg) followed immediately by ketamine (50mg/kg), both intramuscularly. Measurements of heart rate, respiratory rate, palpebral response, withdrawal reflex, and electrocardiogram were taken immediately before and at 10 and 20 minutes after injection of the anesthetics. At 20 minutes after the anesthetic injection, one of the experimental drugs was administered-- either yohimbine (0.5mg/kg), tolazoline (6.6mg/kg), or saline (0.5ml), all given intravenously. Measurements were taken at ten-minute intervals for an additional 60 minutes after reversal. Rectal temperatures were recorded at 10 and 80 minutes post-anesthesia.

Palpebral response was determined by tactile stimulation near the medial canthus, and withdrawal reflex was tested by clamping the third digit of the right rear foot with a hemostat. Palpebral responses were graded on the basis of the following scale: absent, very weak, weak, and strong. Withdrawal reflexes were graded on the basis of the following scale: no response, slight response, strong response, and full body response (complete movement of the head and all four limbs).

Time to sternal recumbency, time to standing, time to walking, and time to walking with full coordination, as measured from time of reversal, were recorded. Respiratory rate was also recorded, and heart rate and rhythm were determined by electrocardiographic observations.

Differences between the mean values of the three treatment groups were assessed by analysis of variance, and, where significance ($p \leq .05$) was found, paired t-tests were used to determine the location of the difference.

## RESULTS

All rabbits studied recovered completely from the anesthesia. Administration of xylazine-ketamine resulted in laterally recumbent animals with an almost total loss of palpebral and pedal responses. The eyes remained open with pupils dilated.

Recovery Rates: Data on recovery rates are presented in Table 1. The saline group took significantly longer (117±13 minutes) to reach sternal recumbency than either the yohimbine group (91±21 minutes) or the tolazoline group (83±19 minutes). Times to standing, walking, and walking with full coordination were slightly shorter with tolazoline (114±23, 111±27, and 142±23 minutes respectively) than with yohimbine (128±40, 128±44, and 150±37 minutes respectively) and considerably shorter than with saline (134±17, 142±11, and 187±60 minutes respectively). However, no significant statistical difference was noted for these values.

Chewing motions and voluntary head movements were seen as early as 10 minutes after yohimbine. One rabbit vocalized, and another showed reaction to being touched at 40 minutes. Tolazoline, upon injection, caused vocalization and a change in the facial expression, including increased opening of the eyes. Chewing and voluntary head movements were again seen as early as 10 minutes post-tolazoline and throughout the remainder of the study. Also noted as early as 10 minutes were voluntary blinking and reaction to touch. At 50 minutes, one rabbit voluntarily held its head up for over four minutes. Control rabbits exhibited no chewing motions or voluntary head movement until after 60 minutes post-saline.

Evaluation of Reflex Responses: Prior to anesthesia, all animals possessed strong palpebral and vigorous withdrawal responses. At 20 minutes post-anesthesia, 24 rabbits had no palpebral reflexes and 22 had no withdrawal responses. Those retaining response at this time had only very weak palpebral and only slight withdrawal reflexes, as illustrated in Table 2. Ten minutes after injection of yohimbine, five of the rabbits had regained strong palpebral responses, and after 20 minutes, seven had regained strong responses. All nine yohimbine rabbits regained vigorous (full body) withdrawal responses within 10 minutes. Seven of nine rabbits given tolazoline regained strong palpebral responses by 50 minutes post-tolazoline. Ten minutes after tolazoline, six of nine rabbits possessed vigorous (full body) withdrawal responses, and all nine had regained the full body response by 30 minutes. Sixty minutes post-saline, one rabbit had regained strong palpebral responses and seven had vigorous withdrawal responses.

Vital Statistics: Table 3 presents data on heart rates, respiratory rates, and temperatures. In all three groups, rectal temperature decreased over the period from 10 to 80 minutes after anesthetic induction with the mean value remaining above 38°C (100°F).

The heart rates, following administration of experimental drugs, were significantly different for the duration of the study. Upon injection of yohimbine, mean heart rate increased from 166±54 beats per minute (bpm) to 209±68 bpm. Following this initial increase, heart rates slowly decreased over the duration of the study to 152±27 bpm. Tolazoline decreased the mean heart rate from 150±21 bpm to a low of 118±14 bpm. Heart rates with saline decreased over the duration of the study.

Respiratory rates among groups were only significantly different at 10 and 20 minutes post-induction, before the reversals had been administered. Actual values did not appear variable enough to be of clinical importance. Yohimbine increased the mean respiratory rate from 50±15 respirations per minute (rpm) before administration to 71±17 rpm 10 minutes post-yohimbine. The respiratory rate fluctuated for the remainder of the study. Tolazoline increased the mean respiratory rate slightly from 48±15 rpm to 59±19 rpm 10 minutes post-tolazoline. Again, the respiratory rate fluctuated during the rest of the study. Saline allowed the respiratory rate to decrease until 40 minutes post-saline, at which time slight increases began.

Electrocardiograms: In one rabbit given saline, a premature ventricular contraction occurred at 60 minutes following induction of anesthesia. Electrical alternans was noted at 10 minutes following anesthetic induction and at 10 and 30 minutes following administration of yohimbine in one rabbit. Traces for all other rabbits appeared normal.

## DISCUSSION

Results of this study indicate that both yohimbine (0.5mg/kg) and tolazoline (6.6mg/kg) intravenously are effective at reversing xylazine-ketamine-induced depression in rabbits. Although yohimbine produces a more dramatic reversal as indicated by the marked increase in heart rate and more rapid return of palpebral and withdrawal responses, tolazoline provided a shorter overall recovery as shown by time to achievement of sternal recumbency, ability to stand, ability to walk, and ability to walk with full coordination.

Yohimbine arousal of xylazine-ketamine depressed rabbits is likely due to its competition with xylazine for alpha-2 adrenergic receptor sites and another effect with which yohimbine may reduce the effects of ketamine anesthesia (4,6). Tolazoline also competes with xylazine for the alpha-2 adrenergic receptors and has been recommended for clonidine antagonism ( an alpha-2 agonist structurally similar to xylazine) in man (11,13).

Though tolazoline produced a smoother emergence and more desirable antagonism than yohimbine at the doses used in this study, both yohimbine and tolazoline are capable of reducing anesthetic recovery time in xylazine-ketamine depressed rabbits, thereby potentially reducing undesirable anesthetic effects. Both drugs appear to be appropriate for theraputic intervention in cases where excessive depression develops in response to usual drug dosages or where inadvertent overdosage of xylazine occurs due to error.

REFERENCES

1. White GL, Holmes DD. A Comparison of Ketamine and the Combination Ketamine-Xylazine for Effective Surgical Anesthesia in the Rabbit. Lab Anim Sci 1976;26:804-806.

2. Mulder JR. Anesthesia in the Rabbit Using a Combination of Ketamine and Promazine. Lab Anim Sci 1978;28:321-322.

3. Kisloff B. Ketamine-Paraldehyde Anesthesia for Rabbits. Am J Vet Res 1974;36:1033-1034.

4. Hsu WH. Xylazine-Induced Depression and Its Antagonism by Alpha Adrenergic Blocking Agents. J Pharmaco Exp Ther 1981;218: 188-192.

5. Hatch RC, Booth NH, Kitzman JV, et al. Antagonism of Ketamine Anesthesia in Cats by 4-Aminopyridine and Yohimbine. Am J Vet Res 1983;44:417-423.

6. Hsu WH, Lu ZX. Effect of Yohimbine on Xylazine-Ketamine Anesthesia in Cats. J Am Vet Med Assoc 1984;185:886-888.

7. Kitzman JV,Wilson RC,Hatch RC, et al. Antagonism of Xylazine and Ketamine Anesthesia by 4-Aminopyridine and Yohimbine in Geldings. Am J Vet Res 1984;45:875-877.

8. Kitzman JV, Booth NH, Hatch RC, et al. Antagonism of Xylazine Sedation by 4-Aminopyridine and Yohimbine in Cattle. Am J Vet Res 1982;43:2165-2169.

9. Hatch RC, Ruch T. Experiments on Antagonism of Ketamine Anesthesia in Cats Given Adrenergic, Serotonergic, and Cholinergic Stimulants Alone or in Combination. Am J Vet Res 1974;35:35-39.

10. Lipman NS, Phillips PA, Newcomer CE. Reversal of Ketamine/ Xylazine Anesthesia in the Rabbit with Yohimbine. Lab Anim Sci 1985;35:548.

11. Tranquilli WJ, Thurmon JC, Corbin JE. Halothane Sparing Effect of Xylazine in Dogs and Subsequent Reversal with Tolazoline. J Vet Pharmacol Ther 1984;7:23-28.

12. Fagella AM, Seal US, Kreager TJ. Cardiovascular Effects and Antagonism by Tolazoline of Xylazine-Ketamine Anesthesia in Dogs and Wolves. Abstracts Presented at Second Annual Veterinary Midwest Anesthesia Conference. University of Illinois 1986;1.

13. Allen JL. Use of Tolazoline as an Antagonist to Xylazine-Ketamine-Induced Immobilization of African Elephants. Am J Vet Res 1986;47:781-783.

14. Hartsfield SM, Thurmon JC, Benson GJ. Comparison of the Effects of Tolazoline, Yohimbine, and 4-Aminopyridine in Cats Medicated with Xylazine. Abstracts Presented at Second Annual Veterinary Midwest Anesthesia Conference, University of Illinois 1986;2.

15. Rooming LGP. Tolazoline as Xylazine Antagonist in Cattle. DTW 1984;91:154-157.

16. Zingoni MR, Garcia-Villar R, et al. La Tolazoline Comme Antagoniste de la Sedation par la Xylazine chez le Mouton. Rev Med Vet 1982;133:335-339.

17. Houston MC. Clonidine Hydrochloride: Review of Pharmacologica and Clinical Aspects. Prog Cardiovasc Dis 1981;23:337-350.

FOOTNOTES

[1]Rompun[R], Bayvet Division, Miles Laboratories, Shawnee, KA

[2]Ketaset[R], Bristol Laboratories, Syracuse, NY

[3]Yohimbine, Sigma Chemical Company, St. Louis, MO

[4]Priscoline[R], CIBA Pharmaceutical Company, Summit, NJ

Table 1 Recovery rates in minutes of xylazine-ketamine anesthetized rabbits following an intravenous injection of saline, yohimbine, and tolazoline*.

| | Saline | Yohimbine | Tolazoline |
|---|---|---|---|
| Sternal Recumbency° | $117 \pm 13_a$ | $91 \pm 21_b$ | $83 \pm 19_b$ |
| Standing | $134 \pm 17$ | $128 \pm 40$ | $114 \pm 23$ |
| Walking Without Coordination | $142 \pm 11$ | $128 \pm 44$ | $111 \pm 27$ |
| Walking With Full Coordination | $187 \pm 60$ | $150 \pm 37$ | $142 \pm 23$ |

*Rabbits received 8mg/kg xylazine at time 01 minutes and 50mg/kg ketamine at time 01 minutes, both IM, and either 0.5ml saline, 0.5mg/kg yohimbine, or 6.6mg/kg tolazoline IV at time 21 minutes. Rates are recorded in minutes (mean$\pm$standard deviation) as measured from the time of injection of the experimental drug or saline.

°Rates indicated showed statistically significant difference among groups (at $p \leq .05$). Values designated by the same letter are not significantly different from each other.

Table 2 Responses of xylazine-ketamine anesthetized rabbits before and after an intravenous injection of saline, yohimbine, and tolazoline*.

| | 00 min | | | | 10 min | | | | 20 min | | | | 30 min | | | | 40 min | | | | 50 min | | | | 60 min | | | | 70 min | | | | 80 min | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EVALUATION OF PALPEBRAL RESPONSE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | S | W | VW | A | S | W | VW | A | S | W | VW | A | S | W | VW | A | S | W | VW | A | S | W | VW | A | S | W | VW | A | S | W | VW | A | S | W | VW | A |
| Yohimbine | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 1 | 8 | 5 | 2 | 2 | 0 | 7 | 1 | 1 | 0 | 7 | 2 | 0 | 0 | 7 | 2 | 0 | 0 | 7 | 2 | 0 | 0 | 7 | 2 | 0 | 0 |
| Tolazoline | 9 | 0 | 0 | 0 | 0 | 1 | 0 | 8 | 0 | 0 | 2 | 7 | 0 | 3 | 6 | 0 | 1 | 6 | 2 | 0 | 2 | 6 | 1 | 0 | 6 | 3 | 0 | 0 | 7 | 2 | 0 | 0 | 7 | 2 | 0 | 0 |
| Saline | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 2 | 7 | 0 | 0 | 6 | 3 | 0 | 1 | 7 | 1 | 0 | 6 | 3 | 0 | 1 | 6 | 2 | 0 |
| EVALUATION OF WITHDRAWAL OF THE HIND LIMB | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | F | S | Sl | N | F | S | Sl | N | F | S | Sl | N | F | S | Sl | N | F | S | Sl | N | F | S | Sl | N | F | S | Sl | N | F | S | Sl | N | F | S | Sl | N |
| Yohimbine | 9 | 0 | 0 | 0 | 0 | 0 | 3 | 6 | 0 | 0 | 2 | 7 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 0 |
| Tolazoline | 9 | 0 | 0 | 0 | 0 | 0 | 2 | 7 | 0 | 0 | 3 | 6 | 6 | 2 | 1 | 0 | 8 | 1 | 0 | 0 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 9 | 0 | 0 | 0 |
| Saline | 9 | 0 | 0 | 0 | 0 | 0 | 2 | 7 | 0 | 0 | 0 | 9 | 0 | 0 | 2 | 7 | 0 | 0 | 4 | 5 | 0 | 0 | 7 | 2 | 0 | 1 | 8 | 0 | 0 | 6 | 3 | 0 | 7 | 2 | 0 | 0 |

*Rabbits received 8mg/kg xylazine at time 01 minutes and 50mg/kg ketamine at time 01 minutes, both IM, and either 0.5mg/kg yohimbine, 6.6mg/kg tolazoline, or 0.5ml saline IV at time 21 minutes. Numbers in the columns indicate the number of animals out of nine that showed the level of response described.

S= strong response; W= weak response; VW= very weak response; A= absence of response; F= full body response; Sl= slight response; N= no response

Table 3 Vital statistics of xylazine-ketamine anesthetized rabbits before and after an intravenous injection of saline, yohimbine, and tolazoline*.

| | SALINE | | | YOHIMBINE | | | TOLAZOLINE | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | RPM | Tp | HR | RPM | Tp | HR | RPM | Tp |
| 00 min | 172±40 | 108±38 | | 194±35 | 113±46 | | 165±33 | 107±32 | |
| 10 min[o] | 173±28 | 65±30$_a$ | 103±01 | 187±54 | 58±24$_b$ | 104±01 | 160±23 | 54±21$_b$ | 103±01 |
| 20 min[o] | 157±24 | 57±20$_a$ | | 166±54 | 50±15$_b$ | | 150±21 | 48±15$_b$ | |
| 30 min[v] | 144±16$_a$ | 56±21 | | 209±68$_b$ | 71±17 | | 123±13$_c$ | 59±19 | |
| 40 min[v] | 139±14$_a$ | 56±19 | | 194±66$_b$ | 72±20 | | 119±14$_c$ | 59±17 | |
| 50 min[v] | 135±11$_a$ | 53±17 | | 171±61$_b$ | 68±29 | | 120±19$_c$ | 63±17 | |
| 60 min[v] | 135±10$_a$ | 58±17 | | 170±46$_b$ | 64±28 | | 118±14$_c$ | 75±31 | |
| 70 min[v] | 135±13$_a$ | 62±19 | | 158±26$_b$ | 79±52 | | 123±23$_a$ | 85±35 | |
| 80 min[v] | 134±17$_a$ | 68±18 | 102±01 | 152±27$_b$ | 75±46 | 102±02 | 123±21$_a$ | 68±22 | 101±01 |

*Rabbits received 8mg/kg xylazine at time 01 minutes and 50mg/kg ketamine at time 01 minutes, both IM, and either 0.5ml saline, 0.5mg/kg yohimbine, or 6.6mg/kg tolazoline IV at time 21 minutes.

[o]Values indicated show statistically significant difference in respirations per minute between groups (at $p \leq .05$). Values designated by the same letter are not significantly different from each other.

[v]Values indicated show statistically significant difference in heart rates among groups (at $p \leq .05$). Values designated by the same letter are not significantly different from each other.

HR= heart rate; RPM= respirations per minute; Tp= temperature($^{o}$F).