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Comparison of Three α_2-antagonists, Yohimbine, Tolazoline, or Atipamezole for Reversing the Anesthetic Effects of Medetomidine and Ketamine in Dairy Calves

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Abstract

Six healthy, Holstein calves, weighing 345 to 530 lb (156.8 to 241.1 kg), were used to evaluate the anesthetic effects of medetomidine and ketamine combination and to compare the effectiveness of three α_2 antagonists, yohimbine, tolazoline, and atipamezole. Four different anesthetic treatments were included in this study: Treatment 1 (MK): medetomidine (20 µg/kg, IV) and ketamine (2.2 mg/kg, IV); Treatment 2 (MKY): medetomidine (20 µg/kg, IV) and ketamine (2.2 mg/kg, IV) followed by yohimbine (0.25 mg/kg, IV); Treatment 3 (MKT): medetomidine (20 µg/kg, IV) and ketamine (2.2 mg/kg, IV) followed by tolazoline (2.2 mg/kg, IV); Treatment 4 (MKA): medetomidine (20 µg/kg, IV) and ketamine (2.2 mg/kg, IV) followed by atipamezole (60 µg/kg, IV). Calves were randomly assigned to one of the treatments with a one-week interval between each treatment. Yohimbine, tolazoline, and atipamezole were administered 30 minutes after the induction of MK anesthesia. Heart and respiratory rates, indirect arterial blood pressures (systolic [SAP], mean [MAP], diastolic [DAP]), and arterial blood gases variables were recorded.

Quality of induction and recovery, duration of recumbency, and time from injection of antagonists to standing were also monitored. Calves became sternally recumbent in 23±14 seconds for a duration of 94±25 minutes after administration of MK. Significant increases in respiratory rate, $PaCO_2$ and arterial blood pressure and decreases in PaO_2, pHa, and SaO_2 were observed during anesthesia. The values for most of the blood gas variables returned to baseline values after administration of tolazoline and atipamezole. The duration of recumbency following administration of yohimbine, tolazoline, or atipamezole was 80±22, 46±9, and 34±3 minutes, respectively. Calves stood in 48±20, 16±9, and 4±3 minutes, respectively, after the injection of yohimbine, tolazoline, and atipamezole. In conclusion, medetomidine and ketamine combination can be used effectively to induce anesthesia in dairy calves. Either tolazoline or atipamezole can be administered to antagonize the anesthetic effects and induce a rapid recovery.

Introduction

Medetomidine[a] (4-[1-(2,3-dimethylphenyl)ethyl-1H]-imidazole), a newly manufactured α_2-adrenoceptor agonist, produces sedation, analgesia, and central muscle relaxation in animals. Compared to other α_2-adrenoceptor agonists such as xylazine and detomidine, medetomidine is more lipophilic, efficacious, and potent with an α_2/α_1 selectivity ratio which is approximately 8 times that of detomidine and 10 times that of xylazine.[10,44,45] Medetomidine is approved by the Food and Drug Administration (FDA) for use as a sedative/analgesic and anesthetic adjunct only in dogs.[6] Its use in food animals is not FDA approved, therefore its use in calves is extra-label. Studies have shown that it is also capable of producing sedation, analgesia and sometimes immobilization in large animals and a wide variety of zoo animal species.[b,2,18,21,23,24,27,32] As with xylazine and detomidine, medetomidine can be used in combination with ketamine to produce short duration of anesthesia for minor surgical procedures.[6,18,27]

An advantage of using an anesthetic drug that acts on one specific type of receptor is that its pharmacological actions are easier to antagonize by administration of a competitive antagonist. Yohimbine[c] (17-hydroxyyohimban-16-carboxylic acid methylester) and tolazoline[d] (2-benzyl-2-imidazoline) are the α_2-adrenoceptor antagonists most used in veterinary medicine.[13] Atipamezole[e] (4-[2-ethyl-2,3-dihydro-1H-inden-2-yl]-1H-imidazole) is an α_2-adrenoceptor antagonist recently developed specifically for medetomidine. Atipamezole also can be used effectively in antagonizing xylazine-induced sedation, bradycardia, and ruminal atony in calves.[37] The order of α_2/α_1 selectivity ratio of these three antagonists is as following: atipamezole > yohimbine > tolazoline. Tolazoline appears to have more α_1-adrenoceptor antagonistic activity than yohimbine or atipamezole.[9,46] Theoretically, drugs with greater α_2-adrenoceptor selectivity are the more effective antagonists. Clinically, tolazoline, with its low α_2-adrenoceptor selectivity, has been reported to be more effective in antagonizing xylazine's effects in cats, calves and ewes than yohimbine.[f,15,16]

The objectives of this study were to evaluate the anesthetic effects of medetomidine and ketamine and to compare the effectiveness of three α_2 antagonists, yohimbine, tolazoline, and atipamezole, in dairy calves.

Materials and Methods

Six Holstein calves (2 male, 4 female), weighing 345-530 lb (156.8 to 241.1 kg, mean, 195.8 ± 21.0 kg), were used in this study, which was approved by the Institutional Animal Care and Use Committee of Auburn University. Prior to each experiment, food was withheld for 48 hours and water for 24 hours to minimize regurgitation and bloating during anesthesia. An intravenous (IV) catheter (14-gauge, 5 -inch)[g] was placed in the jugular vein for drug administration. Four treatments were evaluated: Treatment 1 (MK): medetomidine (20 µg/kg, IV) and ketamine[h] (2.2 mg/kg, IV) anesthesia; Treatment 2 (MKY): medetomidine (20 µg/kg, IV) and ketamine (2.2 mg/kg, IV) anesthesia followed by yohimbine (0.25 mg/kg, IV); Treatment 3 (MKT): medetomidine (20 µg/kg, IV) and ketamine (2.2 mg/kg, IV) anesthesia followed by tolazoline (2.2 mg/kg, IV); and Treatment 4 (MKA): medetomidine (20 µg/kg, IV) and ketamine (2.2 mg/kg, IV) anesthesia followed by atipamezole (60 µg/kg, IV). Medetomidine and ketamine (MK) were mixed in the same syringe and given as a bolus injection. Yohimbine, tolazoline, and atipamezole were administered 30 minutes after the administration of MK. Calves received all four treatments and were randomly assigned to one of the four treatments with a one-week interval between each treatment. After induction of anesthesia endotracheal intubation was performed and the calves were placed in sternal recumbency and allowed to breath spontaneously.

Heart rate, respiratory rate, and indirect arterial blood pressure were recorded before (time-0) and 5 and 15 minutes after drug administration and then every 15 minutes thereafter until the calf recovered from anesthesia and returned to standing position. Heart rate was measured directly by auscultation using a stethoscope. Respiratory rate was measured by the movement of the chest wall. Indirect arterial blood pressure (systolic [SAP], mean [MAP], and diastolic [DAP]) was measured by an oscillometric blood pressure machine[i] with an inflatable pressure cuff placed over the coccygeal artery of the tail. An 18-gauge, 2-inch catheter[j] was placed in the auricular artery for arterial blood sample collection. Blood samples were collected for determination of acid-base status (pHa and base excess) and blood gas analysis (PaO_2, $PaCO_2$, and SaO_2) at time-0 and every 30 minutes after the administration of MK and 15 minutes after the administration of yohimbine, tolazoline, or atipamezole. No painful stimuli, such as surgical incision, needle pin prick, or electrical stimulation, was applied to assess analgesia during anesthesia. The quality of induction and recovery were monitored. Cardiac rhythm was also monitored by a standard limb lead-II electrocardiogram[k]. Time from administration of MK to sternal recumbency, duration of recumbency, and time to standing were recorded.

Treatment effects were evaluated using repeated-measures ANOVA[l]. Values of $p \leq 0.05$ were considered to be significant.

Results

The results of this study are summarized in Tables 1, 2, 3, and 4 and the values are presented as mean values ± SD. Values for heart rate, respiratory rate, SAP, MAP, and DAP recorded at 45 minutes in MK calves were compared to those recorded at 15 minutes after the administration of an antagonist and there was no significant difference between treatments. No cardiac arrhythmias were observed either by induction of MK anesthesia or by administration of an antagonist in this study.

Following IV administration of MK, all calves in all groups assumed sternal recumbency smoothly within 5 to 75 seconds with an overall mean of 23 ± 14 seconds. The duration of recumbency for Treatment 1 (MK) was 94 ± 25 minutes. Recovery from anesthesia was smooth and uneventful in all calves. Heart rate decreased transiently at 60 minutes, whereas respiratory rate increased from 5 to 30 minutes after

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Table 1. Mean values (± SD) for time to sternal recumbency (TSR), duration of recumbency (DR), and time to standing (TS) in calves anesthetized with medetomidine (20 µg/kg, IV) and ketamine (2.2 mg/kg, IV) (MK), comparing to those receiving yohimbine (MKY; 0.25 mg/kg, IV), tolazoline (MKT; 2.2 mg/kg, IV), and atipamezole (MKA; 60 µg/kg, IV) at 30 minutes following medetomidine and ketamine administration.

Treatment	TSR (seconds)	DR (minutes)	TS (minutes)*
MK	21 ± 27	94 ± 25	94±25
MKY	23 ± 3	80 ± 22	48 ± 20
MKT	23 ± 10	46 ± 9 *,¶,£	16 ± 9¶,£
MKA	26 ± 10	34 ± 3 *,¶,#	4 ± 3¶,#
Overall mean	23 ± 14	-----	-----

* TS: time to standing in calves receiving one of the antagonists (e.g., yohimbine, tolazoline, or atipamezole) 30 minutes during medetomidine and ketamine anesthesia.
*Significant difference from MK.
¶Significant difference from MKY.
£Significant difference from MKA.
#Significant difference from MKT.

MK administration. Arterial blood pressures (SAP, MAP, and DAP) increased significantly throughout the experiment. Decreases in pHa, PaO_2, and SaO_2 and increases in $PaCO_2$ and base excess were observed during MK anesthesia.

In MKY calves, heart rate increased transiently at 5 minutes after MK administration and was not affected by yohimbine administration. Respiratory rate increased significantly during MK anesthesia and had returned to baseline values after yohimbine administration. Arterial blood pressure (SAP, MAP, and DAP) tended to increase during MK anesthesia, but the values were statistically significant only at 15 minutes for MAP and 30 minutes for DAP. However, arterial blood pressures were decreased significantly by yohimbine administration when compared to the value recorded prior to its injection. Administration of MK resulted in an increase in $PaCO_2$ and decreases in PaO_2 and SaO_2. The value for PaO_2 remained decreased from baseline values after yohimbine administration. Values for pHa and base excess were not changed either by MK or yohimbine administration. The duration of recumbency in MKY calves was 80 ± 22 minutes, which was similar to those receiving MK only. Calves stood within 48 ± 20 minutes after yohimbine administration.

In MKT calves, heart rate increased briefly immediately after administration of MK and after administration of tolazoline. Respiratory rate increased significantly throughout the experiment. Systolic arterial blood pressure increased at 30 minutes following MK administration and at 5 minutes after administration of tolazoline. The values of MAP and DAP increased during MK anesthesia and they remained increased following administration of tolazoline. Arterial pH, PaO_2, and SaO_2 decreased 30 minutes after the induction of anesthesia, but they returned to baseline values after administration of tolazoline. Administration of MK caused an increase in $PaCO_2$ at 30 minutes which decreased significantly after administration of tolazoline, but the values remained higher than those at time-0. No changes in base excess were observed. The duration of recumbency in MKT calves was 46 ± 9 minutes with calves standing at 16 ± 9 minutes after administration of tolazoline, which was significantly shorter than MKY but longer than MKA.

For calves receiving Treatment 4 (MKA), heart rate was elevated only at 5 minutes following administration of MK and did not change after the administration of atipamezole. Respiratory rate

Table 2. Mean values (± SD) for heart rate (HR), respiratory rate (RR), arterial blood pressure (systolic [SAP], mean [MAP], and diastolic [DAP]), acid-base status (pHa and base excess [BE]), and arterial blood gases ($PaCO_2$, PaO_2, and SaO_2) in calves anesthetized with medetomidine (20 µg/kg, IV) and ketamine (2.2 mg/kg, IV).

Time(min)	HR	RR	SAP	MAP	DAP	pHa	BE	$PaCO_2$	PaO_2	SaO_2
0	79±16	36±10	122±17	83±9	63±10	7.41±0.02	-0.68±1.35	37±2	91±11	97±1
5	72±11	55±7‡	152±20‡	122±22‡	102±22‡					
15	63±9	59±15‡	151±25‡	123±23‡	106±20‡					
30	65±8	57±14‡	166±19‡	128±23‡	109±20‡	7.35±0.03§	-0.5±2.0	47±3‡	70±8§	92±3§
45	64±9	46±18	149±21‡	108±21‡	95±20‡					
60	62±8§	34±14	123±49	105±16‡	88±18‡	7.40±0.02	1.34±1.92‡	43±5‡	77±10§	95±2§
75	63±9	37±15	147±17‡	110±22‡	95±28‡					
90*	70±9	22±3§	134±17	99±34‡	84±41‡					

§Significant decrease from baseline (time-0) values.
‡Significant increase from baseline (time-0) values.
*Values represent data collected from 2 calves that remained recumbant after 75 minutes.

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Table 3. Mean values (± SD) for heart rate (HR), respiratory rate (RR), and arterial blood pressure (systolic [SAP], mean [MAP], and diastolic [DAP]) in calves receiving yohimbine (MKY; 0.25 mg/kg, IV), tolazoline (MKT; 2.2 mg/kg, IV) or atipamezole (MKA; 60 μg/kg, IV) 30 minutes following medetomidine (20 μg/kg, IV) and ketamine (2.2 mg/kg, IV) anesthesia.

Time(min)	HR	RR	SAP	MAP	DAP
0	59±10	27±10	119±29	86±28	69±23
5	72±9‡	62±13‡	124±22	92±19	71±14
15	56±11	61±16‡	148±20	115±7‡	90±8
30	59±7	52±12‡	146±15	111±14	96±15‡
MKY-5	59±3	33±12#	109±17#	77±17#	60±16#
MKY-15	55±6	27±9#	127±15#	89±23#	69±16#
0	61±7	29±3	120±15	78±13	59±6
5	71±6‡	61±16‡	124±30	94±20‡	74±17‡
15	64±13	61±23‡	129±45	111±18‡	95±18‡
30	57±8	50±23‡	149±22‡	113±25‡	95±21‡
MKT-5	75±14‡,#	45±22‡	138±45‡	109±41‡	90±39‡
MKT-15	61±9	34±13‡	128±38	94±39‡	77±40‡
0	60±11	31±9	118±18	75±13	67±14
5	72±5‡	66±5‡	124±20	89±19‡	82±17‡
15	51±7	63±18‡	156±14‡	113±12‡	100±15‡
30	54±8	54±22‡	138±32‡	125±22‡	101±14‡
MKA-5	57±7	35±14	138±31‡	101±25‡,#	83±25‡,#
MKA-15	51±7	31±10#	130±22	95±23‡,#	82±21‡,#

§Significant decrease from baseline (time-0) values.
‡Significant increase from baseline (time-0) values.
#Significant difference from the values recorded at 30 minutes following MK administration.

Table 4. Mean values (± SD) for acid-base status (pHa and base excess [BE]), and arterial blood gases ($PaCO_2$, PaO_2, and SaO_2) in calves receiving yohimbine (MKY; 0.25 mg/kg, IV), tolazoline (MKT; 2.2 mg/kg, IV) or atipamezole (MKA; 60 μg/kg, IV) 30 minutes following medetomidine (20 μg/kg, IV) and ketamine (2.2 mg/kg, IV) anesthesia.

Time(min)	pHa	BE	$PaCO_2$	PaO_2	SaO
0	7.41±0.04	0.82±2.95	40±4	81±6	96±1
30	7.37±0.03	0.83±2.83	46±6‡	69±8§	92±2§
MKY-15	7.38±0.04	1.77±3.29	47±9‡	70±3§	93±1§
0	7.41±0.03	0.92±2.87	40±2	86±7	96±1
30	7.36±0.02§	1.28±1.91	49±4‡	68±9§	92±3§
MKT-15	7.41±0.04#	2.55±1.78	44±4‡,#	81±8#	96±1#
0	7.42±0.03	0.55±2.19	39±2	83±11	96±2
30	7.35±0.04§	-0.2± 2.91	47±4‡	64±14§	76±32§
MKA-15	7.42±0.04#	0.43± 2.27	39±5#	84±4#	96±1

§Significant decrease from baseline (time-0) values.
‡Significant increase from baseline (time-0) values.
#Significant difference from the values recorded at 30 minutes following MK administration.

increased significantly during MK anesthesia but returned to baseline following administration of atipamezole. Arterial blood pressures (SAP, MAP, and DAP) were increased either from 15 to 30 or 5 to 30 minutes during MK anesthesia. These values remained increased after administration of atipamezole , even though the values of MAP and DAP were lower than those recorded at 30 minutes during anesthesia. Decreases in pHa, PaO_2, and SaO_2 and an increase in $PaCO_2$ were observed during anesthesia, and they had returned to baseline values after administration of atipamezole . Base excess remained unchanged during the course of the study. The duration of recumbency in MKA calves was 34 ± 3 minutes with calves standing 4 ± 3 minutes after administration of atipamezole. The calves stood significantly sooner following the administration of atipamezole than those receiving yohimbine or tolazoline.

Discussion

The results of this study showed that MK combination can be used effectively in calves to induce

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recumbency for 94 ± 25 minutes. The antagonistic effects of tolazoline and atipamezole were faster acting and more effective than yohimbine.

The dosages of antagonists used in this study were determined based on the recommendations reported by other studies and our clinical experience with these drugs. Variable results have been reported on the effectiveness of yohimbine in reversing xylazine-induced sedation.[16,19] While Kitzman et al[19] indicated that 0.125 mg/kg of yohimbine IV significantly reduced the duration of sedation in cattle, the study conducted by Hsu et al[16] showed that a dose of 0.2 mg/kg was not effective in reversing xylazine-induced sedation in sheep. However, when a higher dose of 0.375 mg/kg was administered to unsedated cattle, yohimbine caused anorexia, moderate sedation, and rear limb ataxia.[19] Therefore, a moderate dose of 0.25 mg/kg of yohimbine was used in this study. Calves receiving 2 to 4 mg/kg of tolazoline were reported to have a shorter recovery to standing time from xylazine sedation than those receiving a lower of dose of 1 mg/kg.[26] Our clinical experience suggests that 2 mg/kg of tolazoline is adequate for use in cattle. The recommended dose ratio of atipamezole to reverse medetomidine-induced sedation in cattle is 2 to 3 : 1,[1,27] which is similar to the dose ratio (3 : 1) we used in this study. The results of our study on the effectiveness of these three antagonists agrees with studies reported by other investigators.[1,16,26,27]

In ruminants, xylazine alone or in combination with other anesthetics is widely used to induce dose-dependent sedation, analgesia and immobilization for various surgical procedures.[3] Ruminants are very sensitive to the effects of xylazine, requiring only one tenth to one twentieth of the dose used in horses and one thirtieth of the dose used in swine.[12] Therefore, overdosing due to preexisting illness or human error is a potential problem associated with the use of xylazine in ruminants. It appears that medetomidine, though very similar to xylazine, does not share the same species variation. Lack of species variation is also observed with detomidine in ruminants in that 2.5-10 μg/kg is used to produce dose-dependent sedation,[28] similar to the dose range used in horses. While the exact mechanism for this variation is unknown, the higher α_2/α_1 selectivity ratio of detomidine (260) and medetomidine (1620) compared to xylazine (160) may contribute to the lack of species variation seen with these two drugs.[43]

In 1994, Sharma et al[a] reported that IM administration of 30 μg/kg of medetomidine to calves induced recumbency, muscle relaxation, and analgesia for 60 to 75 minutes. When a lower dose (20 μg/kg, IV) was combined with ketamine (0.5 mg/kg, IV), the duration of anesthesia lasted from 26 to 39 minutes.[27] In this study, the duration of recumbency was 94 ± 25 minutes, which may be due to the higher dose of ketamine (2.2 mg/kg, IV) used. The lack of painful stimuli during anesthesia may have been a contributing factor for the longer duration of recumbency seen in our study.

In Treatment 1 calves, heart rate remained mostly unchanged during anesthesia with a slight decrease occurring at 60 minutes. However, an increase in heart rate was observed at 5 minutes after MK administration for Treatment 2, 3, and 4 calves. The reason for the discrepancy in changes of HR between treatments following MK administration is unclear. However, large individual variations and small sample size may be the attributable factors. Even though the α_2-agonists are known to induce bradycardia, simultaneous administration of ketamine is able to minimize or prevent the decrease in heart rate with these α_2 drugs.[29,41] Increases in arterial blood pressures occurred with all four treatments prior to the administration of antagonists. Intravenous administration of medetomidine alone is often associated with an increase, followed by a decrease, in blood pressure. The initial increase is attributed to the stimulation of the postsynaptic α_2-adrenoceptors located in the peripheral vessels and the secondary decrease is believed to result from CNS depression of sympathetic output caused by the stimulation of presynaptic α_2-adrenoceptors.[7,33] In this study, the hypertensive effect appears to be longer lasting than that observed in dogs[34] and sheep[39] and persisted throughout most of the anesthetic period. It seems that when administered simultaneously, the secondary hypotension induced by medetomidine was offset by the increase in central sympathetic outflow resulting from CNS stimulation by ketamine and inhibition of neuronal uptake of catecholamines into sympathetic nerve endings.[20]

Administration of yohimbine or atipamezole returned the blood pressure to baseline values. Yohimbine and atipamezole are both classified as selective α_2-adrenoceptor agonists. Atipamezole has an affinity for α_2-adrenoceptors that is approximately 100 times more potent than yohimbine and an α_2/α_1 selectivity ratio that is 200-300 times (8256) higher than yohimbine (40).[46] Yohimbine, with its lower α_2/α_1 selectivity ratio, is more effective in blocking α_1-adrenoceptor-mediated vasoconstriction induced by phenylephrine than atipamezole in pithed rats.[46] Changes in arterial blood pressures following the administration of yohimbine and atipamezole in our study were in agreement with this observation, where more effective antagonism was evident with yohimbine, as reflected in lower arterial blood pressure.

In this study, neither tachycardia nor excitement was observed in calves receiving atipamezole. This was likely due to the low dose (60 μg/kg, IV) of the drug being

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used. However, heart rate was not monitored beyond 15 minutes after administration of atipamezole.

Tolazoline is reported to have vasodepressant effects similar to that of histamine and α-adrenoceptor blocking action.[38] Administration of tolazoline is sometimes associated with cardiovascular changes like vasodilation, cardiac stimulation, coronary vasodilation, and increased cardiac output. Tachycardia and gastrointestinal distress are the most common side effects of this drug.[47] When tolazoline was used to antagonize the anesthetic effects of medetomidine/ketamine in this study, heart rate increased significantly within 5 minutes after the administration of tolazoline, but returned to baseline at 15 minutes. Interestingly, arterial blood pressure did not decrease by administration of tolazoline as predicted,[38] instead, it remained increased above baseline values. This response may be attributable to the increase in heart rate and the resultant increase in cardiac output.

Significant increases in respiratory rate in response to hypoxemia (significantly decreased PaO_2 and SaO_2) and hypoventilation (increased $PaCO_2$) occurred in all calves during MK anesthesia. Similar changes in the respiratory function have been observed in MK-anesthetized calves[27] and sheep,[39] but not in dogs[34] and llamas.[40] Celly et al[5] studied the hypoxemic effect of four α_2-agonists: xylazine, romifidine, detomidine, and medetomidine. Their results showed that all four drugs caused significant decreases in PaO_2 in sheep. The authors indicated that the duration of hypoxemia outlasted the duration of sedation.[5] No similar observation was recorded in our study, however, we did not monitor arterial blood gases beyond 60 minutes after injection of MK. The possible mechanisms of the hypoxemic effect induced by α_2-agonists include: constriction of the bronchial musculature,[25] platelet aggregation,[11] and increased right-to-left pulmonary shunt flow.[5] It appears that the hypoxemia is mediated primarily through α_2-adrenoceptors, since it can be prevented by pretreatment with an α_2 antagonist.[25,42] The results of our study confirm this observation. Reversal of hypoxemia in these calves did not occur with the administration of yohimbine, and prolonged recumbency associated with ineffective antagonism by yohimbine is believed to be the primary cause for the continuous hypoxemia we observed. In sheep, yohimbine administered 5 or 20 minutes after administration of xylazine failed to antagonize hypoxemia.[8,16] The administration of atipamezole and tolazoline was able to antagonize the hypoxemia and hypoventilation that occurred during MK anesthesia, which gradually returned the increased respiratory rate to, or at least toward, baseline values. The respiratory rate of anesthetized calves given yohimbine also returned to pre-MK values even though PaO_2 and SaO_2 remained significantly decreased. Mild changes in pHa and base excess corresponded with the changes in PaO_2 and $PaCO_2$, which returned to baseline values after the administration of an antagonist.

The results of our study show that both tolazoline and atipamezole are far more effective in decreasing the recovery time from MK anesthesia than is yohimbine. Atipamezole is the most effective of these drugs. In calves, yohimbine causes antagonism of xylazine-induced bradycardia and ruminal stasis, but not sedation.[14] In our previous study, tolazoline was shown to be a more effective antagonist than yohimbine in xylazine-sedated calves.[b] Atipamezole, with its greater α_2/α_1 selectivity ratio, reverses α_2-agonist induced sedative effects more effectively than the bradycardic and ruminal effects, whereas tolazoline and yohimbine, with their lower α_2/α_1 selectivity ratio, seem to reverse ruminal hypomotility better than the CNS depressant effects.[37]

The administration of an antagonist is not completely without risk. Studies have shown that anesthesia alone or with surgery with potential complications of hypercapnia, hypoxemia, hypotension, hypovolemia, pain, acid-base disturbance, and electrolyte imbalance may precipitate a stress response in the anesthetized animal.[22,30,31,35,36] Administration of anesthetic antagonists induces rapid return of consciousness promoting arousal and shortening recovery time. This rapid arousal will consequently result in immediate awareness of pain associated with surgery and thus, predispose the animal to stress as indicated by increases in cortisol, glucose, and free fatty acid following administration of tolazoline.[4] Brief period of seizures or muscle tremors occurred when 5 times the recommended dose of yohimbine was given to dogs.[h] Three out of four sheep died after receiving an IV dose of 0.8 mg/kg of yohimbine.[17] In another study, one ewe died of severe tachycardia following rapid IV injection of 2 mg/kg of tolazoline.[17] Ruminants and llamas may be very sensitive to tolazoline because death has been reported in several animals following its use (personal communication). Nevertheless, unfavorable effects of α_2-antagonists are extremely rare in healthy animals when administered by slow IV injection at appropriate doses.

Conclusion

Medetomidine and ketamine can be used effectively in combination to induce recumbency for a period of 94 ± 25 minutes in dairy calves. Although there may be some concern about the significant decreases in PaO_2 and SaO_2 during anesthesia, the values of PaO_2 remained above 60 mm of Hg. Supplementation of 100% O_2 can be used to maintain

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adequate PaO_2 level if needed. Yohimbine is ineffective in decreasing the recovery time from MK anesthesia, but atipamezole and tolazoline can be used effectively to antagonize the anesthetic effect and induce a rapid recovery.

Footnotes

[a] Domitor, Orion Corporation, Orion-Farmos, Espoo, Finland; U.S. Distributor: Pfizer Animal Health, Exton, PA 19341.

[b] Sharma SK, Nigam JM, Kumar A, Varshney AC, Singh M: Preliminary studies on the use of medetomidine in calves and its reversal by atipamezole. Proc 5th Intl Cong Vet Anesth, 121, 1994.

[c] Yobine, Lloyd Laboratories, Shannandoah, IA 51601.

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[f] Thurmon JC, Lin HC, Tranquilli WJ, Benson GJ, Olson WA: A comparison of yohimbine and tolazoline as antagonist of xylazine sedation in calves. Proc 4th Ann Mtg Vet Midwest Anesth Conf, 14, 1988.

[g] Abbocath®-T, Abbott Ireland, Sligo, Rep. Of Ireland for Abbott Laboratories, North Chicago, IL 60064, USA.

[h] Ketaset, Fort Dodge Laboratories, Inc., Fort Dodge, IA 50501.

[i] Dinamap, Veterinary Blood Pressure Monitor 8300, Critikon, Inc, Tampa, FL.

[j] Surflo® I.V. Catheter: Terumo Medical Corporation, Elkton, MD 21921.

[k] Spacelab, A Squibb Co, Redmond, VA.

[l] SAS/STAT User's Guide, Version 6, ed. Cary, NC; SAS Institute, Inc; 1990, 210-244.

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Micotil® 300 Injection
Tilmicosin Phosphate

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Human Warnings: Not for human use. Injection of this drug in humans may be fatal. Keep out of reach of children. Do not use in automatically powered syringes. Exercise extreme caution to avoid accidental self injection. In case of human injection, consult a physician immediately. Emergency medical telephone numbers are 1-800-722-0987 or 1-317-276-2000. Avoid contact with eyes.

Note to Physician: The cardiovascular system appears to be the target of toxicity. This antibiotic persists in tissues for several days. The cardiovascular system should be monitored closely and supportive treatment provided. Dobutamine partially offset the negative inotropic effects induced by Micotil in dogs. ß-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil-induced tachycardia in dogs. Epinephrine potentiated lethality of Micotil in pigs.

For Subcutaneous Use in Cattle Only. Do Not Use in Automatically Powered Syringes.

Indications: For the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica*. For the control of respiratory disease in cattle at high risk of developing BRD associated with *Pasteurella haemolytica*.

Description: Micotil is a solution of the antibiotic tilmicosin. Each mL contains 300 mg of tilmicosin base as tilmicosin phosphate in 25% propylene glycol, phosphoric acid as needed to adjust pH and water for injection, q.s. Tilmicosin phosphate is produced semi-synthetically and is in the macrolide class of antibiotics.

Actions: Activity — Tilmicosin has an *in vitro** antibacterial spectrum that is predominantly gram-positive with activity against certain gram-negative microorganisms. Activity against several mycoplasma species has also been detected.

Ninety-five percent of the *Pasteurella haemolytica* isolates were inhibited by 3.12 µg/mL or less.

Microorganism	MIC (µg/mL)
Pasteurella haemolytica	3.12
Pasteurella multocida	6.25
Haemophilus somnus	6.25
Mycoplasma dispar	0.097
M. bovirhinis	0.024
M. bovoculi	0.048

*The clinical significance of this *in vitro* data in cattle has not been demonstrated.

Directions — Inject Subcutaneously in Cattle Only. Administer a single subcutaneous dose of 10 mg/kg of body weight (1 mL/30 kg or 1.5 mL per 100 lbs). Do not inject more than 15 mL per injection site.

If no improvement is noted within 48 hours, the diagnosis should be reevaluated.

Injection under the skin behind the shoulders and over the ribs is suggested.

Note — Swelling at the subcutaneous site of injection may be observed but is transient and usually mild.

CONTRAINDICATION: Do not use in automatically powered syringes. Do not administer intravenously to cattle. Intravenous injection in cattle will be fatal. Do not administer to animals other than cattle. Injection of this antibiotic has been shown to be fatal in swine and non-human primates, and it may be fatal in horses.

CAUTION: Do Not Administer to Swine. Injection in Swine Has Been Shown to be Fatal.

WARNINGS: Animals intended for human consumption must not be slaughtered within 28 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of tilmicosin in this class of cattle may cause milk residues. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

CAUTION: The safety of tilmicosin has not been established in pregnant cattle and in animals used for breeding purposes. Intramuscular injection will cause a local reaction which may result in trim loss.

How Supplied: Micotil is supplied in 50 mL, 100 mL and 250 mL multi-dose amber glass bottles.

Storage: Store at room temperature, 86°F (30°C) or below. Protect from direct sunlight.

Literature revised December 30, 1996

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