The Sedative and Analegesic Effects of Romifidine in Donkeys

El-Maghraby, H.M.¹, Al-Akraa, A. M.² and Ghanem, M.M.²


Summary
Romifidine was administered intravenously in twelve donkeys in a dose rate of 35, 70 or 100 μg/kg body weight. The levels of sedation and analgesia were recorded and graded. The sedative effect persisted for 66±4.3, 72±2.3 and 91±5.1 minutes after intravenous injection of romifidine at 35, 70 and 100 μg/kg b.w., respectively. The degree of sedation was more or less dose dependent and rated from grade I to grade III. The depth of sedation induced by 100 μg/kg was greater than that induced by either 35 or 70 μg/kg. There was a marked analgesic effect for romifidine in all of the three tested doses. The period of analgesia was shorter than that of sedation. The analgesic effect persisted for 39±2.3, 55±4.2 and 77±4.5 minutes after intravenous injection of romifidine at 35, 70 and 100 μg/kg b.w., respectively. Intravenous administration of romifidine in a dose rate of 35 and 70 μg/kg induced analgesic effect of grade II. The analgesic effect of romifidine in a dose rate of 100 μg/kg b.w. was excellent (Grade III) as indicated by lack of response to painful external stimulations. Slight drooping of the head and upper eyelid, increasing of the distance between the ear tips, thickness of the lips, partial prolapse of the penis and frequent urination were all recorded. Significant bradycardia and respiratory depression as well as ataxia were also recorded. It is concluded that romifidine is a potent analgesic and sedative agent in donkeys. Intravenous administration of romifidine at a dose rate of 70 μg/kg produced good sedation and analgesia with mild ataxia and minimal side effects.

Introduction
Romifidine, iminoimidazolidinone derivative, is a relatively recent α2-adrenoceptor agonist. The other members of this group including xylazine, detomidine and medetomidine have been extensively used in the field of veterinary anesthesia for their sedative properties. Romifidine as well as xylazine and detomidine causing a temporary increase in nociceptive thresholds. However, these drugs have a dose related effect with an increase in dose resulting in an increase in their degree and duration of action.

Romifidine can be included in analgesic and anesthetic protocols to provide additional analgesia in horses. Romifidine has a longer period of sedation and analgesia than that of detomidine. Instability and ataxia were less pronounced with romifidine than with detomidine.

Although all of the α2-agonists exert a marked increase of the urinate pressure, romifidine showed a less urinate pressure duration and strength than that occurred with xylazine and detomidine. However, these differences are not significant.

Romifidine has been used for sedation of horses, dogs and goats. However, evaluation of romifidine in donkeys had not been found in the available literature. The purpose of this controlled study is to evaluate objectively the sedative and analgesic effects of various doses of romifidine in donkeys.

Materials and Methods
Twelve adult healthy donkeys (7 females and 5 males), aged about 7 years and ranged from 100 to 180 kg body weight were used in this study. These animals were kept for a week before experimentation for acclimation to local conditions. Resting rectal temperature, pulse and respiratory rates were measured and complete blood count was made, before each treatment, to assess animals' health. These animals were randomly divided into three equal groups (4 animals each). Romifidine was administered intravenously in a dose rate of 35, 70 or 100 μg/kg body weight respectively.

Sedation was assessed and graded from 0 to 3 as described by 20. The shine ground distance (head pupils, distance from the lower lip to the floor) as well as the distance between the tips of the concha were measured just before administration of romifidine and every 15 minutes (From time 0 to recovery). Dropping of the external conchas of the ear and/or upper eyelids, prolapse of the penis and frequency of urination were also observed.

Analgesia was detected and assessed by recording the response of the animal to needle pricks at the same regular intervals. Needle pricks were applied at the shoulder, flank gres and perineum. The analgesia was graded from 0 to 3 as described by 19.

The time of onset, degree, and duration of sedation and analgesia were recorded for 3 hours after drug administration. Heart and respiratory rates were recorded at 0, 15, 30, 45, 60 min. and at apparent recovery time.

Electrocardiography (ECG): An electrocardiographic examination was conducted on a donkey injected with 70 μg/kg body weight just before injection, and 30 and 90 minutes post injection. The electrocardiographic traces were obtained using EC 60 cardiac and respiratory monitor, DR-6290, Marleve, Denmark. The base-speed lead system was applied as previously mentioned 12, 18. Briefly, the right forelimb electrode (RA) was placed along the jugular groove one third of the way up the neck from the torso. The left forelimb electrode (LA) was placed on the ventral midline under the apex of the heart. Both hind limbs (RL and LL) electrodes were attached to the skin over the stifles joints. Alligator clips moisten with alcohol were used.

Biochemical Analysis: Blood samples were collected at 0, 5, 15, 30, 45, 60, 90 minutes and 24 hours after administration of romifidine. Serum samples of all animals were separated and used directly for determination of glucose, insulin hormone, urea and creatinine.

Results
Sedative Effect: Intravenous injection of romifidine induced a rapid loss of coordination and apparent sedative effect within 1-3 minutes. The mean of maximum sedation as indicated by minimal distance between the lower lip and the ground was (15-25 cm), (10-20 cm) (0 - 10 cm) respectively. The maximal drooping of the head was achieved at 14±1.3, 11±1.9 and 7±1.5 minutes after intravenous injection of romifidine respectively. The sedative effect was persisted for 66±4.3, 72±2.3 and 91±5.1 minutes respectively (Table 1). The degree of sedation was more or less dose dependent and rated from (Grade I) to (Grade III). The depth of sedation induced by 35 μg/kg (Grade I) was less than that induced by 70μg/kg (Grade II) or 100 μg/kg (Grade III).

During the period of sedation there was marked drooping of external conchas of the ear, increasing of the distance between the ear tips, thickness of the lips, drooping of the upper eyelids and partial prolapse of the penis.

Increased urination commencing about 70 to 100 minutes after administration of romifidine was observed along this study in all groups.

In all of the examined groups the degree of analgesia was more pronounced at the level of the head, neck, shoulder, and thoracic and abdominal walls. The degree of analgesia was less pronounced at the perineum and the hind limbs.

Ataxia was variable from mild to moderate in animals treated with romifidine. While transient and mild ataxia were associated with lower doses (35 and 70 μg/kg), moderate ataxia recorded mostly at the higher dose (100 μg/kg). None of the treated donkeys of the three groups along this study showed recumbence.

Bradycardia was also observed in all animals which received romifidine (Table 2). Heart rates were significantly reduced 5 minutes.
after i.v. injection of romifidine in all groups where the means of heart rate were 26.4 ± 2.0, 33.5 ± 2.5 and 28.3 ± 3.2 in the three groups respectively. Twenty five beats/minute was the lowest heart rate recorded. Ataxia/ataxia showed a irregular rhythm and droopy eyes. The heart rates returned to its normal levels after 60 to 90 minutes of induction of sedation.

Intravenous injection of romifidine in a dose rate of 35 μg/kg body weight showed a slight decrease in the respiratory rate which extended up to the end of observation period (Table 3). Intravenous injection of romifidine in a dose rate of 70 or 100 μg/kg body weight showed a significant decrease in the respiratory rate which also extended up to the end of observation period. The respiratory rate didn’t return to the normal level in all of the three examined doses.

Increased urination was frequently observed in all of the three groups in this study. The time from intravenous injection of romifidine to first urination ranged between 70 to 100 minutes. Animals received romifidine showed no signs of sweating or erection. Moreover, recumbency did not occur even in deeply sedated animals (100 μg/kg) but protrusion of the penis was observed in some animals.

**Effect of Romifidine on ECG Findings:**

ECG findings of Romifidine injected dosing showed a marked reduction in the heart rate (bradycardia) due to prolongation of the R-R interval (period between 2 successive R waves). The myocardial contraction is markedly reduced as denoted by reduction in the amplitude of R wave (30 minutes after romifidine injection). The ventricles start to regain their contraction 75 minutes after romifidine injection although the heart rate was not regained. Ninety minutes after romifidine injection, the ventricular contraction increases but the bradycardic picture (Figures 1A-D)

**Biochemical Analysis:**

Result of biochemical analysis (Table 4 and 5) revealed a significant increase in serum glucose level that extended from 30 to 90 minutes. This increase become non significant at 24 hr from injection of romifidine in the first group (G1) and remain significant at 24 hr in the second (G2) and third groups (G3).

Insulin hormone showed significant decrease that extended from 15 to 90 min in the first and second groups, this decrease became non significant at 24 hr, when compared with the control level (Table 4).

There was non significant increase in the levels of serum urea and creatinine in (G1) and (G2) while (G3) revealed a significant increase in serum urea nitrogen level were only recorded at 60 and 90 min. (Table 5).

**Table 3: The effect of various doses of Romifidine in the duration and grade (Mean ± SD) of sedation and sedation.**

<table>
<thead>
<tr>
<th>Drug / Dose</th>
<th>Duration (minutes)</th>
<th>Grade</th>
<th>Sedation l</th>
<th>Analgesia</th>
<th>Sedation 2</th>
<th>Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romifidine (35 μg/kg)</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>5.0 ± 1.5</td>
<td>7.0 ± 1.0</td>
</tr>
<tr>
<td>Romifidine (70 μg/kg)</td>
<td>10</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>7.0 ± 1.0</td>
<td>8.0 ± 1.0</td>
</tr>
<tr>
<td>Romifidine (100 μg/kg)</td>
<td>15</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>9.0 ± 1.0</td>
<td>9.0 ± 1.0</td>
</tr>
</tbody>
</table>

**Table 4: Mean ± SD serum glucose (mg/dL) and insulin (μU/mL) concentration in male donkeys.**

<table>
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<tr>
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<td>5</td>
<td>2</td>
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</tr>
</tbody>
</table>

- Significant at (P<0.05)

**Table 5: Mean ± SD serum glucose level and creatinine in male donkeys.**

<table>
<thead>
<tr>
<th>Drug / Dose</th>
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<th>Analgesia</th>
<th>Sedation 2</th>
<th>Analgesia</th>
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<tbody>
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<td>3</td>
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- Significant at (P<0.05)
Discussion

Romifidine is one of the relatively new agents of α2-adenreceptor agonist. This study demonstrated the potent sedative and analgesic effects of romifidine in donkeys. The onset of sedation started soon after intravenous injection of romifidine (1:3 minutes). There was no difference in latency in animals injected with the three doses of romifidine.

The result of this study proved that the degree of sedation and analgesia of romifidine in donkeys was dose dependent. A positive correlation between its doses and degrees of sedation and analgesia was recorded.

Sedative effect of romifidine in horses is similar to xylazine and detomidine but is longer lasting and produces less ataxia. The result of this study showed that the grade of sedation was dose dependent and rated from grade I to grade III. The depth of sedation induced by 25 μg kg (grade I) was less than that induced by 70 μg kg (Grade II) or 100 μg kg (Grade III). This result agrees with previous reports in horses and disagrees with others. The later authors reported that a dose of 120 μg kg body weight romifidine was only equal to, or even less effective than dose 80 μg kg body weight.

Head height, distance between the ear tips, thickness of the lips, drooping of the upper eyelids and partial protrusion of the penis were all recorded in this study as signs of muscle relaxation that is associated with romifidine. These findings are in consistent with that recorded in horse. The observed thickening of the lip is attributed to the development of head edema that is associated with drooping of the head. Dropping of the head may lead to reduction in the cerebral blood flow and subsequent cerebral edema.

Romifidine has a marked analgesia in the three tested doses of romifidine in donkeys. The degree and duration of analgesia was more or less dose dependent. The durations of analgesia were between 39±2.3, 55±4.2 and 77±4.5 min in the three groups respectively. This result disagrees with another report, who stated that romifidine unexpectedly has no analgesic effects at any time in horses. However, our result agrees with other reports who stated that romifidine can be included in anesthetics and analgesic protocols to provide additional analgesia in horses. Moreover, the analgesic effects of romifidine were similar to that produced by detomidine that characterized by prolonged and intense analgesia.

Marked levels of ataxia were observed with romifidine in this study especially in the higher dose (100 μg/kg). The degree of ataxia seems to be dose dependent. This result might agree with that described in horses. The used doses of romifidine didn't lead to recumbency or falling down of any of the animals of this study. This result might disagree with that reported in horses who recorded recumbency with romifidine in some cases. However, romifidine produces less severe ataxia than that recorded with detomidine.

The increased frequency of urination associated with romifidine is possibly through inhibition of antidiuretic hormone (ADH) release.

Using high doses of α2-adrenoceptor agonists is usually associated with diuresis that possibly assisted by hyperglycemia. The increase of urine production over 90 minutes is accompanied by an increase in glucose excretion. The renal clearance of glucose remains constant.

Substantial cardiovascular changes specially bradycardia had been observed after administrations of Romifidine. Similar findings had been reported in horses. A significant bradycardia was recorded 5 minutes after administration of romifidine in all groups. The bradycardia was significant even in the low dose (35 μg/kg). The cardiovascular depression including bradycardia and initial hypotension followed by hypotension was dose dependent in horses. Intravenous injection of romifidine showed a decrease in the respiratory rate which extended up to the end of observation period in all groups. Similar respiratory depression had been reported in horses.

ECG findings showed that romifidine injection induced marked bradycardia in donkeys indicated by prolongation of the R-R interval. Previous researches showed that romifidine reduced the heart rate in dogs in a dose-dependent manner and in horses. Electrocardiographic examination of a donkey from the second group was conducted to investigate whether romifidine produce changes in heart contraction similar to those of horses. Consistently with this finding, noticed a reduction of the heart rate following IV injection of romifidine with doses of 40 and 120 μg/kg. As a member of Alpha2 adrenoceptor agonists, romifidine reduces the heart rate via vagally-mediated reflex bradycardia and partly from central sympathetic depression.

The ECG tracing showed also a reduction in the R wave amplitude which indicates suppression of the myocardial contraction during systole, and hence the cardiac output. Similar findings had been reported in small animals. Further studies are required to completely investigate the effect of romifidine on the ECG findings in donkeys.

Regarding the biochemical analysis, the hyperglycemia recorded following the administration of romifidine may be attributed to increase adrenal activity, decrease in the secretion or the effect of insulin or increase in the secretion or effect of glucagon. There is a recognized effect of α2 agonist on stimulation of growth hormone and suppression of insulin through direct inhibitory effect of Romifidine on β cell of pancreas. Hyperglycemia was also recorded after administration of detomidine in donkeys and horses. Changes in creatinine and urea levels was non significant in groups I and II. However, there was a significant increase in serum urea nitrogen level at 60-90 minutes in group III. This increase became non significant at 24 hours of romifidine administration.

The result of this study proved that romifidine is a potent sedative and analgesic drug in donkeys. Although the recommended dose of romifidine in horses ranged between 40 to 120 μg/kg body weights, the result of this study showed that the recommended intravenous dose of romifidine in donkeys is 70 μg/kg. This dose was associated with marked degree of sedation and analgesia with minimal side effects.

Acknowledgement

The authors would like to thank the anonymous reviewers for their helpful comments. They also would like to thank Mr. G. F. A. Bekele and Mr. A. A. Bekele for their technical assistance. This work was supported by the University of Veterinary Medicine, Addis Ababa, Ethiopia.