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SEDATIVE, ANALGESIC AND CLINICO-BIOCHEMICAL EFFECTS OF ROMIFIDINE IN DONKEYS

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ABSTRACT

Romifidine (ROMI), an α_2 – adrenergic agonist has been used in different animal species, but its clinical use for donkey surgery is not well documented. The purpose of this study was to evaluate clinically the sedative, analgesic and biochemical effects of ROMI in donkeys undergoing surgical operation. Ten clinically healthy donkeys weighing between 150 and 250 kgs, and aging between 4 and 7 years old were used in this investigation. The recommended dose was 80 µg/kg of romifidine HCl, diluted in 4 ml saline and administered intravenously in donkeys undergoing castration prior animal preparation for aseptic surgery. Sedative, analgesic and clinico-biochemical effects were recorded at 0 (base value) and 15, 45, 75 and 120 min. post ROMI injection. Sedation was determined by the changes in animal behavior after drug administration. Onset and duration of analgesia was assessed using pin pricking. Respiratory rate (RR), rectal temperature (RT) and pulse rate (PR) were also recorded. Blood samples were collected at the same intervals for hemato-biochemical analysis. Descriptive statistical analysis was performed. Sedation was proved in all donkeys characterized by drooping in head and neck, relaxation of lower lip with great reduction of eye alertness within two minutes and lasted for 86.33 ± 0.88 min. It was enough to handle and prepare the animal for aseptic castration. Analgesia with ROMI occurred at 2.0 ± 0.54 min. and persisted for 68.33 ± 4.40 min. Slight ataxia was observed in three donkeys during standing, characterized by reduction in co-ordination. Salivation and urination were recorded. No significant changes were revealed in clinical or hemato-biochemical findings except significant decrease in creatinine and significant hyperglycemia during the period of the experiment. It was concluded that ROMI (80 µg/kg) proved as an effective sedative and analgesic and used safely for undertaking elective surgery in donkeys.

INTRODUCTION

In veterinary practice, the major α_2 agonists are xylazine, detomidine, medetomidine and romifidine. The major actions and side effects are similar although there are, may be, differences in length of action, and in the extent and significance of some side effects ***(Hall and Clarke, 1991)***. Chemical restraint drugs i.e. sedatives, have been used in veterinary medicine for over three decades. During this time, several drugs have been introduced; xylazine was synthesized in 1962, as a sedative purely intended for animals and has become one of the sedatives most widely used in veterinary practice ***(Vainio, 1985)***. Later on further efforts by chemists and pharmacologists resulted in the development of additional α_2-adrenergic molecules including detomidine, medetomidine and romifidine. Romifidine (2-bromo-fluoro-2-imidazolidinhylidene-benzamine) is potent α_2 agonist that produces pharmacologic effect typical for this group of drugs and characterized by sedation, muscle relaxation, reluctance to move, reduced responsiveness to environmental stimuli, bradycardia, decreased cardiac output and reduced respiratory rate ***(Freeman et al., 2002).*** Romifidine is potent and selective α_2 agonists, has been used recently for both sedation and premedication ***(Voeglti, 1988)***. Romifidine, a new α_2 agonist has become available and it is claimed that doses of 40, 80 and 120 µg/kg provide light, deep and deep prolonged sedation. Significant levels of ataxia were observed ***(Hamm et al., 1995 and Mohsen et al., 2007)***. Maximum sedation with romifidine was achieved with IV doses of 80 µg/kg in horses ***(Hall and Clarke, 1991).*** Romifidine was recently used spinally alone in female

goats ***(Amarpal et al., 2002),*** in combination with morphine spinally in cattle ***(Fierheller et al., 2004),*** parentrally alone in cats ***(Selmi et al., 2004)*** and with lidocaine in goats ***(Kinjavdekar et al., 2006)***. Donkeys may metabolize some drugs faster than horses, which will affect anesthetic duration ***(Matthew et al., 1997)***. The present study ***aimed*** to evaluate clinically the sedative, analgesic and biochemical effects of ROMI given intravenously in donkeys.

MATERIALS AND METHODS

The present study was performed on ten apparently healthy donkeys (aging 4 - 7 years and weighing 150 – 250 kgs). Romifidine hydrochloride (Sedivet, Boehringer ingelheim Vet medica, Inc., Saint Jseph, Mo, USA, 2-bromo-6-floro-2-midazolinnhylidene-Benzamine monohydrochloride) was given by intravenous route in jugular vein. ***80 µg/kg*** of ROMI was selected as a recommended dose diluted in 4 ml saline, according to ***Hall and Clarke (1991), England et al. (1992), Freeman and England (2000) and Nouh and Abdel-Wahed (2000).*** Signs, onset, degree and duration of sedation were assessed depending on the behavioral changes. Onset and duration of analgesia were determined according to response to a standard painful stimulus by pin pricking. Respiratory rate (RR), rectal temperature (RT) and pulse rate (PR) were determined and recorded 5 minutes before injection and repeated at 15, 45, 75 and 120 minutes post injection. Blood samples were collected from jugular vein at the same previous intervals for haematological and biochemical analysis, including values of hemoglobin (Hb %), heamatocrite (PCV %) and differential leukocytic count (DLC %) according to ***Dacia and Lewis (1975).*** Glucose concentration was

assessed according to ***Dubowski (1962).*** Creatinine was assessed according to ***Faulkner and King (1976).*** Urea was assessed according to ***Fawcett and Scott (1960).*** Meanwhile**,** Aspartate transaminase (AST) and Alanin transaminase (ALT) were assessed according to ***Reitman and Frankel (1957).*** Statistical analysis of the collected data was carried out using the analysis of variance procedure of the Statistical Analysis System computer package ***(SAS, 1987).***

RESULTS

Sedative and analgesic effects:

Signs of sedation and analgesia were observed in all animals post ROMI injection. Signs of Sedation included; reduced awareness of the environment, relaxation of penis and anal sphincter, frequent urination and watery salivation, decrease in frequency and velocity of movement, lowering of head and neck (Fig., 1), dropping of ear, reduced eye alertness and extreme lip separation after 1.16 ± 0.44 min post ROMI injection and continued for 86.33 ± 0.88 min (table, 1). Ataxia was slightly observed characterized by swaying and leaning on stanchion with flexion of all joints of hind limbs and the animal has a tendency to fall down (Fig., 1). The analgesic effect of ROMI appeared after 2.00 ± 0.54 min. and persisted for 68.33 ± 4.40 min. (table, 1).

Clinico-biochemical effects:

Changes in values of respiratory rate (RR), rectal temperature (RT) and pulse rate (PR) following IV injection of ROMI are summarized in table (2). Values of Hb, PCV and DLC are summarized in table (3). Meanwhile, values of blood glucose, Urea, Creatinine, ALT and AST following IV injection of ROMI are summarized in table (4).

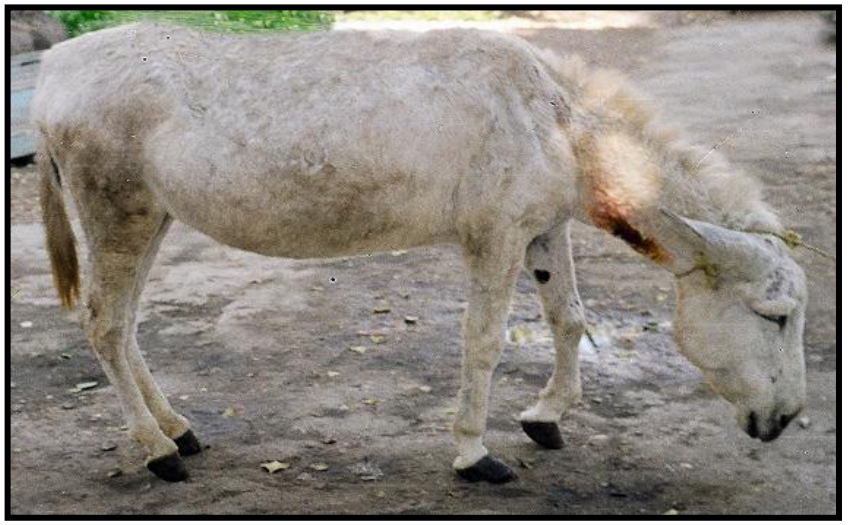

Fig. (1): Showing signs of sedation of 5 years old donkey characterized by drooping of head with a degree of ataxia.

DISCUSSION

α2-agonists are generally regarded as sedative and hypnotics and are commonly administered to induce sedation. They are also considered a potent analgesic agent, especially in horses. Romifidine, representing α2-agonists binds with and intrinsically changes the membrane of α2-adrenoceptors preventing further release of norepinepherine which is necessary for arousal. If its release is blocked, the net result is sedation ***(Sinclair, 2003)***. In this study, rapid onset of sedation (1.16 ± 0.44 min.) and longer duration (86.33 ± 0.88 min.) following IV injection of ROMI coincided with the findings of ***Hall and Clarke (1991) and England et al. (1992)*** who noticed that romifidine has longer duration and maximum sedation than xylazine and detomidine. Greater head lowering may be attributed to excellent muscle relaxation of head and neck followed by dropping of head, neck, ears and lips. This muscle relaxation also resulted in protrusion of penis and relaxation of anal sphincter. Similar

findings were recorded by ***Hoffman (1974)***, ***Hamm et al. (1995), England and Clarke (1996) and Nouh and Abdel-Wahed (2000)***. Incidence of ataxia in few cases in this study coincided with the results described by ***Hall and Clarke (1991), England et al. (1992) and Hamm et al. (1995)***. On the other hand, **Clarke (1988)** reported that the degree of ataxia produced with xylazine was more severe. Frequent urination and watery salivation were noticed with similar frequency following romifidine injection. ***Vainio (1985)*** obtained the same result. Analgesia produced by intravenously injected ROMI appeared to be most satisfactory. This analgesic effect appeared to be a result of both cerebral and spinal effects, possibly in part mediated by serotonin and the descending endogenous analgesia system ***(Benson, 1999).*** Longer duration of analgesia (68.33 ± 4.40mins) is referred to that ROMI has longer potency and greater specificity at central α2-adrenoceptor sites ***(Virtanen and MacDonald, 1985). Hamm et al. (1995)*** found that romifidine (20, 40 and 120µg/kg) had no analgesic effect at any of the site stimulated at any time. The sedative effect of α2-agonists appeared to be longer in its duration than analgesic one. ***Short (1992)*** advised that the predominant effect of α2-agonists is to produce sedation with associated analgesia. ***Nilsfors et al. (1989)*** demonstrated that higher doses of α2-agonists were required to provide analgesia than to provide sedation. Decrease in respiratory rate at 45 min. post injection and pulse rate allover the observation period consistent with ***England et al. (1992),*** but not agreed with ***Nouh and Abdel-Wahed (2000)***. These differences may be attributed to individual and environmental variations. Reduction in body temperature could be attributed to C.N.S depression in combination with reduction in muscular activity ***(Virtanen, 1989)***. On the other hand ***Sinclair (2003)*** mentioned that α2-agonists may allow

better maintenance of body temperature due to peripheral vasoconstriction and central redistribution of the blood with a consequent reduction in cutaneous heat loss. Decrease in pulse rate may be due to induced vagally mediated reflex bradycardia, secondary to increased arterial blood pressure and partly from direct central sympathetic depression ***(Clarke and Hall, 1969, Kerr et al., 1972, Hall and Clarke, 1991 and Sinclair, 2003). Hall and Clarke (1991)*** attributed increased urine production following α2-agonists to inhibition of ADH release. Non significant decrease of Hb was observed post IV injection of Romifidine in donkeys representing the results reported by ***Vainio (1985)***. Concerning PCV%, the result of this study agreed with ***Wagner et al. (1991)*** who reported significant reduction in PCV% in horses. ***Kumar and Singh (1978)*** explained the decrease in PCV% to an increased accumulation of erythrocytes into the spleen by splenic relaxation. Concerning serum analysis, IV injection of Romifidine resulted in significant hyperglycemia**.** ***Shokry et al. (1976), Symonds (1976), Symonds and Mallinson (1978) and Hsu and Hammel (1981)*** attributed this increase to increased hepatic glucose production, hypoinsulinemia or inhibition of insulin release.

Table (1): Showing mean values ± SE of sedation and analgesia following IV injection of ROMI in donkeys.

Parameter \ Time	Onset (min.)	Duration (min.)
Sedation	1.16 ± 0.44	86.33 ± 0.88
Analgesia	2.00 ± 0.54	68.33 ± 4.40

Number of animals per group = 5

Table (2): Showing mean values ± SE of RR, RT and PR following IV ROMI injection in donkeys.

Time (min.)	Respiratory rate (RR)	Rectal temperature (RT)	Pulse rate (PR)
Before 5 min	23.66 ± 0.88	37.63 ± 0.14	44.00 ± 1.15
After			
15 min	20.66 ± 0.88	37.43 ± 0.14	38.00 ± 1.15*
45 min	18.66 ± 0.88*	36.73 ± 0.14*	38.66 ± 1.45*
75 min	19.00 ± 0.57	36.63 ± 0.14*	35.66 ± 1.45*
120 min	21.00 ± .57	36.70 ± 0.36*	36.33 ± 1.45*

* Significantly different to the value before injection (P<0.05).

Number of animals per group = 5

Table (3): Showing mean values ± SE of Hb, PCV % and DLC following IV ROMI injection in donkeys.

Time (min.)	Hb (g/dl)	PCV (%)	DLC (%)			
			Neutrophil	Eosinophil	Lymphocyte	Monocyte
Before 5 min	9.4 ± 0.05	36 ± 0.57	46 ± 0.57	9 ± 0.57	45 ± 0.57	3 ± 0.57
After						
15 min	8.6 ± 0.05*	30 ± 0.59*	37 ± 0.59*	4 ± 0.47*	41 ± 0.37	4 ± 0.50
45 min	8.9 ± 0.05*	29 ± 0.58*	34 ± 0.57*	2.3 ± 0.37*	45 ± 0.55	2 ± 0.55
75 min	9.2 ± 0.05	28 ± 0.57*	37 ± 0.55*	3 ± 0.54*	37 ± 0.58*	4 ± 0.54
120 min	9.4 ± 0.05	32 ± 0.52	41 ± 0.51	7 ± 0.58	37 ± 0.57*	3 ± 0.47

* Significantly different to the value before injection (P<0.05).

Number of animals per group = 5

Table (4): Mean values ± SE of Glucose, Urea, Creatinine, ALT and AST following IV ROMI injection in donkeys

Time (min)	Glucose (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	ALT (u/l)	AST (u/l)
Before					
5 min	75 ± 0.56	30 ± 0.57	0.90±0.047	17 ± 0.77	85 ± 0.56
After					
15 min	105 ± 0.58*	32 ± 0.67	0.50 ± 0.06*	10 ± 0.59*	84 ± 0.59
45 min	120 ± 0.56*	29 ± 0.59	0.52 ± 0.05*	14 ± 0.51	95 ± 0.50*
75 min	135 ± 0.50*	34 ± 0.50	0.62 ± 0.05*	14 ± 0.53	83 ± 0.67
120 min	140 ± 1.15*	28 ± 0.53	0.50 ± 0.07*	15 ± 0.55	94 ± 0.37*

* Significantly different to the value before injection (P< 0.05).

Number of animals per group = 5

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التأثير المهدئ والمسكن والبيوكيميائى للروميفيدين فى الحمير

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لما كان الروميفيدين كأحدث عقار فى مجموعة منبهات ألفا2 والذى لم يتم استخدامه حقليا فى الحمير فقد استهدفت هذه الدراسة القاء الضوء على التأثير المهدىء و التأثير المسكن للألم وكذلك التغيرات البيوكيميائيه عقب حقن الروميفيدين فى الوريد فى الحمير. تم اجراء هذه الدراسة على عدد 10 من الحمير السليمه اكلينيكيا والتى تراوحت أعمارها بين 4 الى 7 سنوات ووزنها بين 150 و 250 كجم. تم حساب الجرعه اللازمه من الروميفيدين (80 ميكروجرام/كجم مخففه فى 4 سم3 من محلول

الملح) وحقنها فى الوريد ثم ملاحظة التغيرات الاكلينيكية مثل معدلات التنفس والنبض ودرجات الحرارة ودراسة التأثير المهدئ والمسكن من خلال التغيرات فى سلوك الحيوان ومدى احساسهوذلك قبل وبعد الحقن. كما تم سحب عينات من الدم لقياس معدل التغير فى وظائف الكبد والكلى وجلوكوز الدم ونسبة الهيموجلوبين و حجم الخلايا المنضغطة وكذلك نسب خلايا الدم البيضاء المختلفة. وقد أوضحت النتائج أن علامات الهدوء والسكينة قد لوحظت على الحمير خلال دقيقتين من الحقن الوريدى للعقار والتى استمرت 86.33 ± 0.88 دقيقة. أما فترة التخدير (فقد الألم) فقد بدأت بعد 2.00 ± 0.54 دقيقه واستمرت 68.33±4.40 دقيقه مع عدم القدرة على التحكم فى الجسم وعدم الاتزان أحيانا. بملاحظة التأثير الاكلينيكى وجد أن التغيرات فى النبض والتنفس ودرجة حرارة الجسم كانت حول المعدلات الفسيولوجيه وعادت الى أو بالقرب من هذه المعدلات أثناء أو بعد انتهاء مدة التخدير. كما لوحظ زيادة معدل التبول ونزول اللعاب من الفم. أما التغيرات المسجله فى نتائج تحليل الدم فلم تكن معنويه باستثناء الكرياتينين وسكر الدم. نستخلص من هذه الدراسة أن الروميفيدين له تاثير مهدىء ومسكن قوى وآمن للاستخدام قبل العمليات الجراحيه فى الحمير.