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SEDATIVE AND ANALGESIC EFFECTS OF DETOMIDINE WITH AND WITHOUT BUTORPHANOL IN DONKEYS

(With 3 Tables)

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التأثير المهدئ والمسكن لعقار الديتومدين مع أو بدون عقار البيوترفانول فى الحمير

حسين المغربى ، عطيه عطا

تم فى هذه الدراسه الحقن الوريدى لعقار الديتومدين اما بمفرده أو بالاضافه الى عقار البيوترفانول فى أربع مجموعات من الحمير. وقد حقنت جميع المجموعات بعقار الديتومدين بجرعه مقدارها ١٠ ميكروجرام لكل كيلو جرام من وزن الحيوان ثم حقنت المجموعه الثانيه والثالثه والرابعه فى الوريد بعقار البيوترفانول بجرعات مقدارها ٢٥ أو ٥٠ أو ٧٥ ميكروجرام لكل كيلو جرام من وزن الحيوان على التوالى. وقد كررت هذه التجربه مرتين باستخدام عقار الديتومدين بجرعة مقدارها ٢٠ أو ٤٠ ميكروجرام لكل كيلو جرام من وزن الحيوان بدلاً من الجرعه السابقه (١٠ ميكروجرام من وزن الحيوان). وقد تبين من هذه الدراسه انه بالرغم من ان التأثير المهدئ لعقار الديتومدين كان قوياً الا أن التأثير المسكن له كان ضعيفاً نسبياً ولقد تم الحصول على درجة أعلى بكثير من التسكين والهدوء باستخدام عقار البيوترفانول مع عقار الديتومدين، ولقد تبين من هذه الدراسه ان استخدام الديتومدين بجرعه مقدارها ٢٠ ميكروجرام لكل كيلوجرام من وزن الحيوان مع البيوترفانول بجرعه مقدارها ٥٠ ميكروجرام لكل كيلوجرام من وزن الحيوان ذو فاعليه عاليه ولا يحدث مضاعفات جانبيه كبيره.

SUMMARY

Detomidine either 10,20 or 40 µg/kg was administered intravenously alone or in combination with butorphanol in 3 different doses (25,50 or 75 µg/kg) in donkeys. The levels of sedation and analgesia were graded and recorded. Sedation and analgesia were mostly dose dependent. Detomidine at a dose rate of 20 µg/kg together with butorphanol in a dose of 50 µg/kg produced optimal sedation and analgesia with mild ataxia. It is concluded that detomidine/butorphanol combination accentuates the degree of sedation and analgesia as well as minimize the adverse effects of both drugs.

Key words: *Donkey - Analgesia - Detomidine.*

INTRODUCTION

α-2 adrenoceptor agonists have been extensively used their sedative properties (Hall and Clarke, 1991). However, the depth of sedation produced with α- 2 agonists alone may very and some adverse effects such as occasional violent episodes and kicking out with limbs may occur (Browning and Colines, 1994). Usually increasing the dose of α- 2 agonist increases ataxia without preventing the response of the animal to painful stimulation (Short, 1992). Moreover, other consequences of peripheral adrenergic stimulation including swaying sweating, piloerection and increased of micturition were reported (Einstein et al, 1994). To avoid some of these unpredictable effects, α- 2 agonists often used in conjunction with an opiate to produce a state of neuroleptanalgesia (Browing & Collines, 1994). Neuroleptanalgesia has been widely used in horses to induce a greater degree of sedation tha can be achieved with either drug alone (Taylor, 1985; Hall & Clarke, 1991).

Detomidine is a relatively new α- 2 adrenoceptor agonist that has been used as a sedative in equines (Clarke and Gerring, 1990; Mostafa et al, 1995). In horses, detomidine induces stronger and longer lasting sedation and analgesia in comparison with other members of the same group such as xylazine (Jochle and Hamm 1986, Jockle et al, 1989). Its analgesic effect either superficially (skin) or abdominally (equine cloic) was inconsistent (Lowe and Hilfiger, 1986). It has been reported that a more satisfactory effect can be achieved in horses by administration of detomidine with an opoid (Clarke and Paton, 1988 Taylor et al 1988).

Butorphanol is an opioid analgesic that has agonistc and antagonistic properties (Lavoie, et al 1996). It is usually administered to provide adequate analgesia in horses (Hall and Clarke, 1991). Instead of inducing drowsiness, as in people, butorphanol produce shivering, muscular tremors, ataxia, restlessness and locmotor activity (Robertson, et al 1981; Kalpravidh et al, 1984 and Nolan et al, 1994). These adverse effects limit the use of butorphanol as a sole agent in equines (Lavoie et al, 1996). The combination of detomidine and butorphanol had been used to sedate horses for a variety of surgical or diagnostic procedures (Taylor et al, 1988; Lavoie et al, 1996). However, evaluation of detomidine/ butorphanol combination 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 detomidine/ butorphanol combination in comparison with those induced by detomidine alone in donkeys.

MATERIALS and METHODS

Twenty mature healthy donkeys, twelve females and eith males, aged two to seven years and ranged from 120 to 180 kg body weight were used along this study. These animals were kept for a week before experimentation for acclimatization to local conditions. Before sedation, a 14- gauge, 8 cm long catheter was inserted into jugular vein of each animal for administration of drugs and for blood collection. Resting rectal temperature, pulse and respiratory rates were measured and a complete blood count was made, before each treatment, to asses animals health.

Animals were divided randomly into four equal groups. Animals of the first group were only given a single i.v. dose of 10 ug/kg detomidine (Domosedan: Orion Corporation Animal Health Division). Animals of the second, thirr and fourth groups were injected with the same dose of detomidine and one minute later, they were injected with butorphanol (Torbugesic: Willows Francis Veterinary) in a single i.v. dose of either 25, 50 or 75 µ/kg respectively. This protocol was repeated twice with an interval of 10 days but detomidine was used in a dose of 20 µg/kg or 40 µg/kg in the second and third trials respectively.

Sedation was assessed and graded from 0 to 3 as described by Johle and Hamm (1986). The distance from the lower lip to the floor was measured just before adminstration of sedative and every 15 minutes. Dropping of the external concheae 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 neddle pricks and to electrical stimulation at the same regular intervals. Needle pricks were applied at the shoulder, flank area and perineum. Electrical stimulation was appllied through two electrods fixed around closely clipped coronary bands of both fore limbs and connected to a variable output stimulator (BioScience stimulator, 10550). The amplitude of the electrical current output were increased until the animal responded by moving or raising one of the examined limbs. The amplitude of the current to which response occured was recorded and accordingly analgesia was graded from 0 to 3 as described by Jochle and Hamm (1986). 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. Blood samples were collected at 0,30,60 min and at apparent recovery tiime for determination of hemoglobin (Hb%), Packed cell volume (PCV%) and RBCs and WBCs counts. Blood serum was also analyzed for blood urea nitrogen and creatinine concentrations. Statistical analysis was carried out where appropriate using Student test.

RESULTS

Sedative effect:

Intravenous injection of detomidine alone 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 group (27, 32 and 10 cm) was achieved 18,20 and 12 min. after i.v. injection of detomidine at 10,20 or 40 µg/kg b.w. respectively. The sedative effect persisted for 43 ± 2.53, 58 ± 3.41 and 72 ± 2.11 minutes respectively (Table 1). The degree of sedation was more or less dose dependent and rated from grade 1 to grade 2. The depth of sedation induced by 10 and 20 µg/kg (grade 1) was less than that induced by 40 µg/kg (grade 2).

Intravenous injection of detomidine / butorphanol combinations induced marked sedation within 1-2 minutes. Maximal sedation after using this combination as indicated by minimal distance between the lower lip and the ground (0-15 cm) was achievd (5-25 min.) after i.v. administration of the combination. The duration of sedation induced by detomidine at 10, 20 or 40 µg/kg in combination with butorphanol at its three dosage levels was dose depndent (Table 1) All animals treated with detomidine at 10 µg/kg with

butorphanol at each of its three dosage levels showed a sedative effect of grade 2. Animals received detomidine at 20 µg/kg and butorphanol exhibited a sedative effect of grade 2 to grade 3, while those given detomidine at 40 µg/kg and butorphanol at any of the used doses revealed sedation of grade 3 (Table 1).

Analgesic effect:

The abalgesic effect of detomidine alone or detomidine/ butorphanol combination was recorded in table 1. Injection of detomidine at 10 or 20 µg/kg b.w. induced poor analgesic effect (grade 0-grade 1). Meanwhile, the higher dose (40 µg/kg) induced a satisfactory level of analgesia (grade 2). The analgesic effect persisted for 23 ±3.17, and 34 ± 3.40 minutes following i.v. injection of detomidine at a dose rate of 20 or 40 µg/kg respectively. Most of these animals, even in deeply sedated ones, were able to raise their hind limbs and to kick when painful stimulation was applied.

Intravenous injection of detomidine (10 µg/kg) with butorphanol (25, 50 or 75 µg/kg) induced an analgesic effect for 22 ± 4.11, 28 ± 2.15 and 43 + .06 min. respectively. The degree of analgesia was rated from fair (grade 1) to satisfactory (grade 2; table 1). Animals sedated with detomidine at 20 ug/kg and butorphanol (25, 50 or 75 µg/kg) showed analgesic effect (grade 2-grade 3) persisted for 41 ± 3.11,54 ± 1.12 and 63 ± 1.05 min. respectively. The duration of analgesic effect was increased to 48 ± 6.11, 59 ± 2.14 and 62 ± 4.87 min following i.v. injection of detomidine at 40 ug/kg in combination with butorphanol (25, 50 or 75 µg/kg) respectively. This analgesic effect was excellent (grade 3) as indicated by lack of response to painful and electrical stimulation. All animals sedated with detomidine / butorphanol combinations were unable to kick even when painful stimulation was applied.

Ataxia was variable from mild to sever in animals treated with detomidine alone. While transient and mild ataxia were associated with lower doses (10 and 20 µg/kg), Sever ataxia was recorded mostly at the higher dose (40 µg/kg). In animals sedated with detomidine / butorphanol combinations, locomotor ataxia was also observed. The degree of ataxia increased by increasing the dose of either drug. Moreover, a slight walking behavior appeared in some of these groups (20 µg/kg detomidine + 75 µg/kg butorphanol and 40 µg/kg detomidine + 50 or 75 µg/kg butorphanol).

Bradycardia was also observed in all animals which received either detomdine alone or in combination with butorphanol (Table 2). Heart rates were significantly reduced after i.v. injection of detomidine. Twenty two

beats/minute was the lowest rate recorded. Auscultation showed also irregular rhythm and drooped beats. This cardiovascular changes were not exacerbated by addition of butorphanol. Minimal depression in the respiratory rate was also observed in the animals treated with detomidine alone While those received i.v. injection of detomidine/butorphanol showed significant decrease in the respiratory rate which extended up to the end of observation period.

Increased urination commencing about 1 hour after administration of either detomidine alone or in combination with butorphanol was observed along this study. Animals received detomidine with or without butorphanol showed no signs of sweating or piloerection. Moreover, recumbency did not occur even in deeply sedated animals but protrusion of the penis was observed in some animals.

Intravenous administration of detomidine alone (10, 20 or 40 ug/kg b.w.) or in combination with butorphanol (25, 50 or 75 µg/kg b.w.) did not produce significant changes in PCV%, Hb%, W.B.Cs., R.B.Cs. counts and blood creatinine or blood urea nitrogen levels. Blood parameters following 40 ug/kg detomidine with or without butorphanol (75 µg/kg) were illustrated in table 4.

DISCUSSION

It is not always possible to complete anticipated procedures in equines with a single agent, successful equine practice often combine the effects of two or more agents to achieve desirable end results (Short, 1992). Combinations of α-2 agonists with opioids have been administered in horses and are in common practice as a neuroleptanalgesic (Taylor et al, 1988 and Browning and Collins, (1994).

This study demonestrated the potent sedative effect of either detomidine alone or when combined with butorphanol in donkeys. The onset of sedation started soon after intravenous injection of detomidine alone (1-3 minutes) or in combination with butorphanol (1-2 minutes). The difference of latency in animals injected with detomidine alone or in combination with butorphanol was minimal (1 min.). Taylor et al, (1988) recorded a latent period of 2-3 min. in horses sedated with detomidine / butorphanol combination. Also, 2-5 min. latent period was observed by Clarke and Taylor (1986) in horses sedated with detomidine alone at dosage level of 5 to 20 µg/kg b.w.

Effective sedation in donkeys i.v. injected with detomidine / butorphanol lasted for a period of 1.5-3 times as long as that observed in those i.v. sedated with detomidine alone depending on the dose levels of both drugs. For example when detomidine was used at 10 µg/kg followed by butorphanol (25 µg/kg), the duration of sedation was 69 ± 1.43 min *vs* 43 ± 2.53 min for detomidine alone (10 µg/kg). This period was extended to 180 ± 8.43 min. vs 58 ± 3.41 min. when detomidine (20 µg/kg) was given with butorphanol (75 µg/kg) as compared with detomidine alone at the same level. These findings indicate a positive correlation between the doses of either drug and duration of sedation. Taylor et al (1988) reported that effective sedation in horses lasted approximately 1 hour following administration of detomidine and butorphanol at a dose level of 12.7 and 26.3 µg/kg respectively.

The depth of sedation for either detomidine alone or in combination with butorphanol was to a less extend dose dependent. Similar observation has been reported for detomidine in donkeys (Mostafa et al, 1995) and for detomidine / butorphanol in horses (Taylor et al, 1988).

The analgesic effect of detomidine was nearly dose dependent. While lower doses (10,20 µg/kg) showed no (grade 0) to fair (grade 1) analgesic effect, higher dose (40 µg/kg) revealed only a satisfactory level of analgesia (grade 2) which is slightly lower than that previously reported in donkeys (Mostafa et al, 1995). It should be pointed out that such higher dose (40 µg/kg) was associated with high degree of ataxia. Addition of butorphanol to detomidine markedly increased depth and duration of analgesia which ranged from satisfactory (grade 2) to excellent (grade 3). These findings agree with that reported in horses (Taylor et al, 1988).

Despite detomidine demonstrated a potent sedation in donkeys; deeply sedated ones were able to react and deliver violent, well aimed kicks on painful stimulations. This result might differ than that reported by Mostafa et al (1995) who stated that donkeys showed no inclination to kick at different dosage level of detomidine (5-40 µg/kg). However, this response was not seen in all animals which received detomidine and butorphanol combinations. This is in agreement with that reported in horses (Clarke and Taylor, 1986; Taylor et al, 1988).

In horses, it has been reported (Hall and Clarke, 1991) that excitement after butorphanol administration could be seen in various ways from muzzle twitching, muscular spasms, ataxia, snatching at food, uncontrolled walking through to violent excitment. However, except ataxia and aimless walking, excitement was not observed in all of the sedated

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Tabel 1 : The effect of detomidine with or without three different dosage of butorphanol on the grade and duration (mean ± SD) of sedation and analgesia.

Drug	Dose(μ g/kg)	Sedation		Analgesia		Recovary (min)
		Duration (min)	Grade	Duration (min)	Grade	
Detomidine	10	43±2.53	1		0	57±7.11
Detomidine + Butorphanol						
	10+25	69±1.43	2	22±4.11	1	83±3.14
	10+50	72±3.17	2	28±2.15	2	97±4.13
	10+75	93±2.15	2	43±4.06	2	105±2.11
Detomidine	20	58±3.41	1	23±3.17	1	82±3.11
Detomidine + Butorphanol						
	20+25	89± 4.11	2	41± 3.11	2	102± 5.06
	20+50	95± 3.17	3	54± 1.12	3	120± 2.11
	20+75	180± 8.43	3	63± 1.05	3	190± 2.03
Detomidine	40	72± 2.13	2	34±3.40	2	89±6.14
Detomidine + Butorphanol						
	40+25	142±4.11	3	48±6.11	3	165±3.67
	40+50	151±2.13	3	59±2.14	3	174±4.11
	40+75	182±2.15	3	62±4.87	3	211±7.11

Table 2. Shows the Mean ±SD of heart and respiratory rates in donkeys injected i.v. with different doses of either detomidine alone or detomidine butorphanol combination.

Drugs and doses (μ g /kg)	Heart rate (beats /min) Time(min)						Respiratory rate (breath / min) Time (min)					
	0	15	30	45	60	Recovary	0	15	30	45	60	Recovary
Detomidine												
10	43 ±2	30 ±4*	38 ±2*	38 ±7	42 ±3	44 ±4	12 ±4	12 ±4	11 ±5	10 ±8	12 ±2	10 ±7
20	46 ±1	25 ±1*	30 ±3*	42 ±1*	36 ±2*	42 ±4	14 ±5	12 ±4	10 ±2	10 ±4	15 ±3	13 ±4
40	48 ±2	26 ±2*	28 ±6*	28 ±4*	46 ±4	47 ±2	11 ±4	10 ±2	9 ±3	11 ±2	12 ±4	10 ±2
Detomidine + Butorphanol												
10 + 25	47 ±2	33 ±4*	36 ±3*	35 ±6*	41 ±8	39 ±8	17 ±5	12 ±2	11 ±4	10 ±3*	8 ±2*	9 ±1*
10 + 50	53 ±4	34 ±5*	35 ±4*	38 ±6*	41 ±6*	49 ±4	19 ±2	16 ±3	17 ±1	14 ±2*	11 ±1*	11 ±3*
10 + 75	46 ±5	36 ±2*	36 ±5*	36 ±8*	38 ±5*	44 ±2	20 ±5	16 ±4	16 ±1*	10 ±1*	11 ±4*	8 ±4*
20 + 25	48 ±4	29 ±1*	28 ±2*	34 ±2*	46 ±3	49 ±3	22 ±2	18 ±4	19 ±3	17 ±1*	14 ±2*	20 ±1
20 + 50	47 ±3	37 ±4*	39 ±3*	40 ±2	44 ±3	46 ±4	14 ±5	10 ±2	10 ±4	8 ±1*	7 ±2*	12 ±1
20 + 75	45 ±5	26 ±6*	31 ±3*	25 ±4*	45 ±2	47 ±3	17 ±4	14 ±9	12 ±3	10 ±4*	9 ±2*	8 ±2*
40 + 25	54 ±4	40 ±2*	41 ±4*	43 ±4*	46 ±8	49 ±4	18 ±3	14 ±4	14 ±2*	15 ±2*	11 ±1*	11 ±2*
40 + 50	48 ±4	23 ±3*	39 ±3*	40 ±8	40 ±7	42 ±6	14 ±2	13 ±4	11 ±1*	10 ±1*	10 ±2*	9 ±2*
40 + 75	43 ±3	23 ±1*	23 ±3*	40 ±4	39 ±4	40 ±4	16 ±2	14 ±8	12 ±2*	12 ±3*	10 ±3*	7 ±2*

* Significant at $P < 0.05$

Tabel 3: Some haematological and biochemical values (mean ± SD) after i.v adminstration of either detomidine alone (40 μg/kg) or detomidine / butorphanol combination in donkeys.

Drug	Time(min)	Hb %	PCV%	RBCs x$10^6/\mu$L	WBCs x$10^5/\mu$L	creatinin (mg/dL)	BUN (mg/dL)
Detomindine 40μg / kg	0	9.8 ±0.73	28.8 ±0.86	5.08 ±0.11	10.95 ±0.48	2.17 ±0.69	27.1 ±1.43
	30	8.9 ±1.16	27.5 ±0.14	4.84 ±0.18	10.57 ±0.42	2.11 ±0.14	25.6 ±0.12
	60	9.5 ±0.14	29.1 ±0.24	4.70 ±1.11	10.12 ±0.73	2.42 ±0.24	24.9 ±2.17
	Recovary	9.3 ±0.21	28.1 ±0.24	4.92 ±0.25	9.95 ±0.11	2.08 ±0.15	26.3 ±0.08
Detomidine 40 μg/ kg + Butorphanol 75 μg / kg	0	9.5 ±0.25	30.1 ±0.16	4.81 ±0.99	11.40 ±0.	2.31 ±0.17	37.8 ±0.32
	30	9.5 ±1.14	28.4 ±0.19	4.99 ±0.15	12.10 ±0.	2.19 ±0.51	35.1 ±0.20
	60	9.1 ±0.37	29.1 ±0.21	4.73 ±1.12	11.60 ±	2.45 ±0.04	35.7 ±1.10
	Recovary	8.7 ±3.35	30.3 ±0.21	4.50 ±1.14	12.30 ±	2.35 ±0.14	36.4 ±1.03