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THE EFFICACY OF INTRANASAL ADMINISTRATION OF DEXMEDETOMIDINE, KETAMINE AND MORPHINE COMBINATION TO RABBIT

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ABSTRACT

The sedative effects of intranasal dexmedetomidine, ketamine and morphinecombination were evaluated in rabbits. A combination of 0.1 mg/kg dexmedetomidine, ketamine 20 mg/kg and 0.4 mg/kg morphine was administered by inserting a lubricated catheter in intranasal. The sedation score was classified as 'deep' from 2 to 20 minutes, 'moderate' from 20 to 30 minutes, the sedation level was insufficient from 30 to 45 minutes. The rabbits were all awake at 60 minutes. The analgesic score stayed highest (absence of Pedal withdrawal reflex) from 2 to 20 minutes. Heart rate and rectal temparature did not change significantly from baseline at any time. Respiratory frequency decreased significantly ($P<0.05$) from baseline. Also SpO2 progressively dropped 10- 15 minutes when O2 supplementation was started, increasing significantly. PaCO2 enhanced significantly ($P<0.05$) at 15, mins and PaO2 lessening significantly ($P<0.05$) at 15, mins compared with baseline value. The intranasal dexmedetomidine-ketamine–morphine combinations has been successfully used for deep sedation for 20 minutes in rabbits.

INTRODUCTION

The studies have shown that transnasal route is an effective way to administer sedation and premedication to human (Henderson *et al.,* 1998; Rey *et al.,* 1991; Kendall *et al.,* 2001). It is a easy non-invasive route and rapid onset of action comparable to that of IV administration because of the rich blood supply of the airway mucosa and bypassing the first pass hepatic metabolism. Also, this route is not painful and does not require trained personnel (Hadley *et al.,* 2004). Intranasal administration may be an acceptable route of administration for bird (Vesal and Eskandari, 2006; Vesal and Zare, 2006; Moghadam *et al.,*2009; Mans *et al.,* 2012), tortoise (Schnellbacher *et al.,*2012), dog(Eagleson, 2012),cat(Marjani, 2015) and rabbits (Robertson and Eberhart 1994).Limited information is available on rabbits (Raekallio *et al.,* 2002; Santangelo *et al.,* 2015; Santangelo *et al.,* 2016).In rabbits, intranasal administration of 25 mg/kg ketamine has an onset time of 1,2 minutes and duration of approximately 25 minutes.1.0 mg/kg midazolam and 25 mg/kg ketamine combinations has an onset time of 2 minutes and duration of approximately 52.5 minutes (Robertson and Eberhart, 1994). Dexmedetomidine is specific α2 adrenoreceptor agonist that has both sedative and analgesic effects and reduction of anesthetic requirements together with increased hemodynamic. The respiratory depressant effects of dexmedetomidine have been studied in rabbits by Nishida *et al.,* (2002). Dexmedetomidine can be effectively administered via the intranasal route in humans and animals (Yuen *et al.,* 2008; Schnellbacher *et al.,* 2012). Ketamine hydrochloride produces dissociative anaesthesia that is characterized by catatonic, amnesia and analgesia with or without actual loss of consciousness. In rabbits, intranasal ketamine or ketamine / midazolam combinations have been used for preinduction of anesthesia (Robertson and Eberhart 1994). Morphine, produce their pharmacological actions, including potent analgesia, as shown by its intranasal administration in humans (Kendall *et al.,* 2001). But clinical trials that investigate the sedative effect of a mixture of intranasal dexmedetomidine,ketamine and morphine are absent.The aim of this study was to investigate the analgesic and sedative effect of intranasal dexmedetomidine, ketamine and morphine combinations in rabbits.

MATERIALS AND METHODS

Experiment was conducted in the Animal Hospital of Veterinary Faculty of the Firat University of Turkey and the protocol for the use of animals was approved by the National

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Table 1. Effects of combination of dexmedetomidine, ketamine and morphine intranasal anesthesia on hematological and clinical parameters in rabbits

Time (mins)	0	5 mins	10 mins	15 mins	20 mins	25 mins	30 mins	35 mins	40 mins	45 mins	50 mins	60 mins
RT	39±0.6	39±0.4	39±0.5	38.8±0.8	38.6±0.6	38.5±0.5	38.4±05	38.3±06	38.1±02	38±0.5	38±0.4	37,8±0.6
HR	182±22	178±23	186±24	173±23	176±24	175±22	174±18	172±22	170±21	173±23	177±25	179±22
RR	100±15	98±12	85±21*	64±24*	60±18*	60±21*	62±22*	63±21*	64±23*	68±24*	69±24*	74±24*
SpO2	96± 5	92± 12	90±8*	87±7*	87±8*	92± 12	93± 14	94± 11	94± 8	95± 12	95± 11	94± 8
PaCO2	60±6			70±8*			65±5			63±4		62±4
PaO2	95±12			86±12*			92±13			94±11		93±12

Values are expressed as mean ± SD, n = 8; *Values decreased significantly (P<0.05) from baseline.

Institute of Health and the Local Committee on Animal Research. Experiments were performed eight New Zealand White rabbits (male) with a mean 12±3 months and body weight of 2.5 ±0.4 kg.A combination of 0.1 mg/kg dexmedetomidine (Precedex 100µ/ml, Meditera,US), ketamine 20 mg/kg (1ml/100mg, Ketasol, Richter Pharma Ag, Austria) and0.4 mg/kg morphine (1ml/10mg, Morphine HCL, Galen, Turkey) was administered by inserting a lubricated catheter in intranasal. The level of sedation was assessed by recording the rabbit's position, the loss of the righting reflex, the palpebral reflex and reactions to other stimuli using a modified numeric rating scale (0–12) for rabbits (Raekallio *et al.,* 2002).

This individual sedation score was assessed every 5 minutes by the same operator in all rabbits and was classified as insufficient (0–3), moderate (4–7) or deep (8–12). Analgesia was scored by the pedal withdrawal reflex (PWR) on a 0–2 scale as part of the sedation score. Rectal temperature (RT, °C), and heart (HR, beats/min), SPO2 (%) and respiratory rates (RR, breaths/min) were recorded pre anesthesia and 5 minutes intervals. The respiratory rate was determined by direct observation of the thoracal movements. Vital parameters (heart rate, rectal temperator and SPO2 (%)) were continuously monitored by a multiparametric monitor (Sino-Hero S80 VET China). The blood samples were taken at ear vein at 0, 15, 30, 60 minutes period during sedation in injectors (Gas-lyte 2,5 ml. containing heparin) and later analyzed. The parameters assessed were venous blood gases (PaCO2, PaO2), by analysed a portable blood gas analyser (Edan I15 VET China).

Statistical analysis

The data for parametric or nonparametric observations analyzed using IBM SPSS 22 Statistics program. The data were presented as the mean ± SE. Significance was accepted at P<0.05.

RESULTS

Normally distributed data are expressed as the mean _ SD, whereas non-parametric data are reported as the median (range), as summarized in Table 1. The sedation score was classified as 'deep' from 2 to 20 minutes, 'moderate' from 20 to 30 minutes, the sedation level was insufficient from 30 to 45 minutes. The rabbits were all awake at 60 minutes. The analgesic score stayed highest (absence of Pedal withdrawal reflex) from 2 to 20 minutes. Heart rate and rectal temparature did not change significantly from baseline at any time. Respiratory frequency decreased significantly (P<0.05) from baseline.

Also SpO2 progressively dropped 10-15 minutes when O2 supplementation was started, increasing significantly.PaCO2 enhanced significantly (P<0.05) at 15, mins and PaO2 lessening significantly (P<0.05) at 15, mins compared with baseline value.

DISCUSSION

In the present study, we demonstrated that intranasal dexmedetomidine-ketamine–morphine combinations can provide sedation sufficient for completing routine chlinical examinations in rabbits. Nasal catheterization is an easily performed and well-tolerated procedure in rabbits. The analgesic dose of intranasal dexmedetomidine-ketamine–morphine combinations in the present study was lower than reported in previous rabbits studies with either combination of dexmedetomidine, midazolam and butorphanol. Also the sedation score was classified as 'deep',modarate time to take longer (Santangelo, 2016). Intranasal dexmedetomidine-ketamine–morphine combinations decreased the respiratory rate in rabbits but had no significant effect on heart rate and rectal temparature. In this study, respiratory frequency was severely reduced, although hypoxemia was lessened by O2 supplementation. Significant changes in venous oxygen saturation (SpO2) and partiel saturation (PaO2) have been observed 10-15 minutes in rabbit. The intranasal dexmedetomidine-ketamine–morphine combinations has been successfully used for sedation in rabbits, as it avoids the discomfort associated with IV or IM injection.

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