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Research Article

A Comparison between Medetomidine-Ketamine and Xylazine-Ketamine Anaesthesia in Rabbits

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Abstract: The anaesthetic and cardiopulmonary effects of medetomidine-ketamine (MK) and xylazine-ketamine (XK) combinations were compared in rabbits. A total of 18 rabbits were randomly assigned to 2 different groups. The rabbits in the MK group (n = 9) were given 0.25 mg/kg of medetomidine and 50 mg/kg of ketamine intramuscularly. The XK group was given 4 mg/kg of xylazine and 50 mg/kg of ketamine via the same route. Data on reflexes (righting, ear pinch and pedal withdrawal) and cardiopulmonary parameters (heart rate, respiratory rate, mean blood pressure, and blood gas values) were recorded before and 5, 10, 15, 30, 45, 60, 75, 90 and 120 min after anaesthesia. Total sleep time, mean duration of loss of ear pinch reflex and mean duration of pedal withdrawal reflex were significantly longer in the MK group than in the XK group ($P < 0.05$). Duration of surgical anaesthesia was significantly longer in the MK group than in the XK group ($P < 0.05$). Both combinations caused moderate bradycardia, moderate or marked hypoxaemia, moderate hypercapnia and moderate acidosis. It was concluded that the MK combination provided suitable anaesthesia for rabbits, characterised by rapid induction and recovery as the arterial oxygen tension is reduced to hypoxaemic levels during the use of this combination, and the supplemental administration of oxygen is recommended.

Key Words: Medetomidine, xylazine, ketamine, anaesthesia, rabbit.

Tavşanlarda Medetomidin-Ketamin ve Xylazin-Ketamin Anestezisinin Karşılaştırılması

Özet: Bu çalışmada, tavşanlarda medetomidin-ketamin kombinasyonu ile ksilazin-ketamin kombinasyonunun anestezik ve kardiyopulmoner etkileri karşılaştırılmıştır. Toplam 18 tavşan iki farklı gruba ayrıldı. Grup MK'ye (n = 9) 0,25 mg/kg medetomidin ve 50 mg/kg ketamin kas içi yolla uygulandı. Grup XK (n = 9)'deki hayvanlara aynı yolla 4 mg/kg xylazine ve 50 mg/kg ketamine uygulandı. Anestezi öncesi ve anesteziden 5, 10, 15, 30, 45, 60, 75, 90 ve 120 dakika sonra refleksler (ayakta kalma, kulak ve arka pedal) ve kardiyopulmoner parametreler (kalp frekansı, solunum frekansı, ortalama kan basıncı, kan gazları seviyesi) her iki grupta incelendi. Anestezi süresi, arka pedal ve kulak reflekslerinin kaybolma süresi MK grubunda XK grubuna nazaran önemli derecede uzundu ($P < 0,05$). Ayrıca cerrahi anestezi süresinin MK grubunda XK grubuna nazaran istatistiksel olarak anlamlı derecede uzun olduğu tespit edilmiştir ($P < 0,05$). Her iki grupta da hafif dereceli bir bradikardi, hafif veya orta dereceli bir hipoksemi, hafif dereceli hiperkapni ve asidozis tespit edilmiştir. Sonuç olarak, anesteziye giriş ve anesteziden hızlı bir çıkış sağladığı için tavşanlarda medetomidin-ketamin kombinasyonunun kullanılması uygun bulunmuştur. Ayrıca medetomidin-ketamin hipoksiye neden olduğundan oksijenasyonun mutlaka sağlanması gerektiği anlaşılmıştır.

Anahtar Sözcükler: Medetomidin, ksilazin, ketamin, anestezi, tavşan.

Introduction

The rabbit is widely used as a laboratory animal for experimental surgery. It has also gained increasing popularity among urban families as a domestic pet. A safe anaesthetic method is therefore needed both for surgeons untertaking research and for practising veterinarians. Especially in veterinary practice anaesthesia of the rabbit may present problems unless the method is easy to apply and efficient and safe to use. Intubation of the rabbit and use of a volatile anaesthetic agent, possibly in combination with muscle relaxants, may be too complicated and time-consuming for the practitioner and sometimes even for scientists or surgeons who often perform experimental surgical research alone without any sophisticated devices (1).

Among the many methods of anaesthetising the rabbit described in the literature a combination of several injectable drugs (fentanyl/fluanisone, ketamine/acepromazine, and ketamine/diazepam) seems to be the most popular (2,3). Fentanyl, fluanisone and diazepam combinations have been used in 565 rabbits for experimental orthopaedic surgery (4). Although this

combination is safe in comparison with other techniques, it produces a relatively long recovery period (2,4).

When ketamine is used as a sole anaesthetic agent it tends to cause hypertonus, poor muscle relaxation, persistent pain reflex responses and violent recovery from anaesthesia (5). To counteract these undesirable side effects various drugs such as xylazine, an α_2-agonist compound, have been used in combination with ketamine. Ketamine combined with xylazine has been reported to produce good anaesthesia in the rabbit, but with some mortality (6).

Medetomidine is a potent α_2-adrenoceptor agonist that induces sedation, analgesia and muscle relaxation (7). Its mechanism of action is similar to that of xylazine and it has been successfully combined with ketamine for anaesthesia in a range of species (8-17). In rabbits, medetomidine has been reported to produce sedation and some analgesia at doses of 0.25, 0.35 and 0.50 mg/kg IM (13). Dose rates of 0.25 mg/kg and 0.50 mg/kg produced a moderate depression in heart rate, blood pressure and arterial PO_2 (13). When combined with ketamine, moderate surgical anaesthesia is produced, although a wide range of dose rates have been reported as being effective. In an initial evaluation, ketamine and medetomidine at 25 mg/kg + 0.5 mg/kg and 60 mg/kg + 0.5 mg/kg IM doses produced surgical anaesthesia in some but not all animals (7). Ketamine (20 mg/kg), medetomidine (0.3 mg/kg) and diazepam (0.75-1.5 mg/kg) administered subcutaneously to rabbits undergoing orthopaedic surgery resulted in a surgical plane of anaesthesia, but with serious hypoxia and moderate hypercapnia (14).

Although a range of different injectable agents can be used in the rabbit, ketamine/medetomidine offers the advantage of relatively rapid recovery, since the effect of medetomidine can be reversed using the specific antagonist, atipemazole (1-3,17).

The aim of this study was to evaluate the anaesthetic and cardiopulmonary effects of the MK combination and to compare it with the XK combination in rabbits.

Materials and Methods

Animals

The study was performed in 18 young female adult chinchilla rabbits with a mean body weight of 3.0 ± 0.5 kg. The rabbits were kept in a controlled environment (room temperature, 18-21 °C; humidity, 55-65%), fed a commercial pellet diet (Kaninchen Haltung 2020, Altromin) and allowed ad libitum access to water. A standard clinical examination preceeded general anaesthesia.

Anaesthetic protocol

The rabbits were randomly assigned to 2 different groups. The rabbits in group MK (n = 9) were given 0.25 mg/kg of medetomidine (Domitor, Smith Kline Beacham, 1 mg/ml) and 50 mg/kg of ketamine (Narketan 10, Chassot, 100 mg/ml) intramuscularly (IM). Group XK was given 4 mg/kg of xylazine (Xylapan, Chassot, 20 mg/ml) and 50 mg/kg of ketamine via the same route. All drugs were mixed in a single syringe for injection.

Local anaesthetic cream (Xylocain 2%, Astra) was applied to the rabbits' ears 45 min before induction of anaesthesia to prevent pain during catheter insertion. Prior to induction of anaesthesia a catheter (Venflon 22 SWG, Ohmeda, Helsingborg, Sweden) was placed in the ear artery and connected to a pressure transducer (Statham, USA) to monitor arterial blood pressure.

After placement of the catheters, baseline recordings of respiratory rate, mean arterial blood pressure (MAP) and heart rate were obtained for a 2 min period. An arterial blood sample (0.5-1 ml) was then obtained for blood gas analysis and the anaesthetic combination was administered. Depth of anaesthesia was assessed by recording the presence or absence of a righting response (the animal showing the ability to spontaneously right itself after being placed on its back), an ear pinch response (shaking the head or vocalisation when the pinna was pinched using the investigator's fingernails) and pedal withdrawal response (PWR) (withdrawal of the hind limb in response to pinching 1 digit with the investigator's fingernails). Simple eye ointment (Bepanthene, Roche) was administered in both eyes to prevent drying of the corneal surface. Recordings of heart rate and MAP were made for a 2 min period prior to withdrawal of additional blood samples at 5, 10, 15, 30, 45, 60, 75, 90 and 120 min during anaesthesia for blood gas analysis (using an IL Blood Gas Analyzer, Instrumentation Laboratory, USA). Monitoring was continued until the animal regained its righting reflex. At the end of the study, the rabbits were re-homed.

Statistical evaluation and data processing

Statistical analyses were performed using SPSS software. Data were recorded as mean ± SD. Student's t-test was applied to unpaired data for comparisons within the group.The MK combination was compared with the xylazine-ketamin combination using the paired Student's t-test. Values of $P < 0.05$ were considered statistically significant.

Results

Depth of anaesthesia

Both groups lost the righting reflex and ear pinch response. The righting reflex was lost within 5 min in all rabbits. The time of loss of the righting reflex did not differ significantly between the groups (Table 1). Total sleep time was significantly longer in MK (150 ± 30 min) than in XK (120 ± 25 min, $P < 0.05$). The duration of loss of the ear pinch reflex was significantly greater in MK (55 ± 19 min) than in XK (30 ± 15 min, $P < 0.05$). A similarly longer PWR loss occurred with MK (50 ± 28 min) compared with XK (28 ± 19 min, $P < 0.05$). Duration of surgical anaesthesia was significantly longer for the MK group (45 ± 26 min) than for the XK group (20 ± 11 min, $P < 0.05$) (Table 1).

Cardiorespiratory effects

Pre-induction heart rate (HR) varied between 200.3 ± 20.5 and 203.3 ± 15.6 beats per minute for MK and XK, respectively. HR was significantly below the baseline value during anaesthesia in both groups. Both combinations caused moderate bradycardia, the lowest rates being 143.2 ± 23.5 and 153.4 ± 22.8 for MK and XK, respectively. HR was significantly higher in rabbits given XK than in those given MK at 5, 10, 15, 30 and 45 min ($P < 0.05$) (Table 2). The resting respiratory rate (RR) of chinchilla rabbits, observed undisturbed, has been recorded as 59 ± 9 breaths per minute. All rabbits were tachypnoeic before induction, varying between 187.3 ± 25.5 and 182.3 ± 30.8 breaths per minute. The lowest respiratory rates during anaesthesia were 30.2 ± 7.5 and 30.8 ± 7.5 breaths per minute (between 15 and 60 min after induction) for MK and XK, respectively. The RR in the XK group was significantly higher compared with the MK group between 45 and 75 min after application ($P < 0,05$). Mean arterial blood pressure (MAP) before induction varied between 82.0 ± 10.1 mm Hg for MK and 83.2 ± 8.2 mm Hg for XK. The effects of MK administration in rabbits were minimal, the lowest MAP values over the first 90 min being recorded as 69.9 ± 9.7 mm Hg. The XK combination caused moderate hypotension, the lowest MAP values being 59.3 mm Hg (Table 2). The MAP in group MK was significantly higher compared with that in group XK between 5 and 90 min after application ($P < 0.05$).

Effect on blood gas values

All blood gas values are shown in Table 3. Before induction of anaesthesia, arterial PaO_2 and $PaCO_2$ varied between 83.3 ± 3.5 and 80.1 ± 6.5 and 28.7 ± 2.1 and 29.7 ± 2.6 mm Hg for MK and XK, respectively. Arterial pH varied between 7.48 ± 0.02 for MK and 7.48 ± 0.03 for XK, respectively. Both combinations produced moderate hypoxaemia between 5 and 90 min after application. All rabbits were visibly cyanotic shortly after

Table 1. The mean times (± SD) to loss of the righting reflex, sleep time, duration of loss of ear pinch and duration of loss of pedal withdrawal response in 18 chinchilla rabbits after the intramuscular injection of a combination of medetomidine-ketamine or a combination of xylazine-ketamine.

Anaesthetic combination	MK	XK
Time to loss of righting reflex (minutes)	1.8 ± 0.4	2.0 ± 0.4
Sleep time (minutes)	150 ± 30	120 ± 25*
Duration of loss of ear pinch (minutes)	55 ± 19	30 ± 15*
Duration of loss of pedal withdrawal response (minutes)	50 ± 28	28 ± 19*
Surgical anaesthesia (minutes)	45± 26	20± 11*

MK= Medetomidine 0.25 mg/kg + ketamine 50 mg/kg

XK = Xylazine 4 mg/kg + ketamine 50 mg/kg

*Mean value differs significantly ($P < 0.05$) from MK

Table 2. Effects of IM administration of medetomidine (0.25 mg/kg)-ketamine (50 mg/kg) and xylazine (4 mg/kg)-ketamine (50 mg/kg) on cardiorespiratory values in chinchilla rabbits.

Time	HR (beats/min)		RR (breaths/min)		MAP (mm of Hg) (min)	
(min)	MK	XK	MK	XK	MK	XK
0	200.3 ± 20.5	203.3 ± 15.6	187.3 ± 25.5	182.3 ± 30.8	82 ± 10.1	83.2 ± 8.2
5	160.2 ± 22.0†	191 ± 25.1†*	56.3 ± 17.5†	50.3 ± 16.2†	89.3 ± 10.2	68.8 ± 13.0†*
10	158.3 ± 21.8†	180.3 ± 25.5†*	50.8 ± 13.2†	44.2 ± 8.5†	88.5 ± 9.8	73.3 ± 10.6†*
15	155.7 ± 20.7†	170.6 ± 24.5†*	48.3 ± 11.5†	42.5 ± 7.5†	88.9 ± 10.5	74.1 ± 10.5†*
30	145.6 ± 20.3†	153.4 ± 22.8†*	30.3 ± 12.7†	30.8 ± 10.5†	89.4 ± 10.5	73.7 ± 12.1†*
45	143.2 ± 23.5†	154.0 ± 25.9†*	30.2 ± 7.5†	38.3 ± 13.5†*	86.2 ± 11.4	70.2 ± 12.1†*
60	148.7 ± 23.8†	158.3 ± 21.0†	35.3 ± 7.9†	47.8 ± 15.5†*	80.1 ± 12.1	65.4 ± 11.2†*
75	150.3 ± 3.5†	158.6 ± 19.2†	40.3 ± 14.5†	59.3 ± 17.4†*	78.3 ± 12.8†	65.1 ± 10.3†*
90	155.2 ± 22.3†	160.2 ± 19.1†	52.7 ± 22.5†	58.3 ± 20.7†	69.6 ± 9.7†	59.3 ± 8.5†*
120	152.3 ± 22.5†	158.3 ± 20.9†	59.9 ± 29.8†	58.1 ± 30.5†	62.3 ± 10.5†	61.7 ± 10.5†

Values reported are mean ± SEM (range). *Mean value differs significantly ($P < 0.05$) from MK. † Mean value differs significantly ($P < 0.05$) from baseline value. MK = medetomidine 0.25 mg/kg + ketamine 50 mg/kg. XK = xylazine 4 mg/kg + ketamine 50 mg/kg. HR = heart rate; RR = respiratory rate; MAP = mean arterial blood pressure

Table 3. Effects of IM administration of medetomidine (0.25 mg/kg)-ketamine (50 mg/kg) and xylazine (4 mg/kg)- ketamine (50 mg/kg) on blood gas values in chinchilla rabbits.

Time	Arterial pH		PaO_2		$PaCO_2$	
(min)	MK	XK	MK	XK	MK	XK
0	7.48 ± 0.02	7.48 ± 0.03	83.3 ± 3.5	80.1 ± 6.5	28.7 ± 2.1	29.7 ± 2.6
5	7.38 ± 0.04†	7.41 ± 0.03†*	40.1 ± 3.1†	47.9 ± 5.8†*	36.8 ± 5.7†	35.6 ± 2.8†
10	7.36 ± 0.04†	7.41 ± 0.04†*	41.3 ± 3.0†	50.4 ± 5.5†*	39.5 ± 4.4†	35.8 ± 3.4†*
15	7.29 ± 0.03†	7.36 ± 0.04†*	42.1 ± 4.5†	44.8 ± 5.8†	37.7 ± 2.2†	34.7 ± 5.1†*
30	7.31 ± 0.03†	7.43 ± 0.06†*	44.3 ± 6.2†	46.3 ± 7.9†	38.4 ± 3.1†	35.1 ± 6.0†*
45	7.34 ± 0.04†	7.44 ± 0.04†*	52.7 ± 8.5†	55.7 ± 9.5†	46.2 ± 5.6†	34.7 ± 7.6†*
60	7.37 ± 0.04†	7.45 ± 0.05*	55.6 ± 10.7†	61.8 ± 11.7	45.7 ± 6.1†	35.7 ± 8.1†*
75	7.39 ± 0.03†	7.44 ± 0.03†*	67.4 ± 12.5	77.8 ± 8.6	43.8 ± 7.1†	35.3 ± 4.2†*
90	7.40 ± 0.03†	7.44 ± 0.04†*	67.4 ± 8.6	77.9 ± 9.2	42.7 ± 6.4†	35.2 ± 4.1†*
120	7.40 ± 0.02†	7.44 ± 0.03†	74.5 ± 8.5	79.1 ± 6.4	39.4 ± 4.8†	33.8 ± 3.8*

Values reported are mean ± SEM (range). *Mean value differs significantly ($P < 0.05$) from MK. † Mean value differs significantly ($P < 0.05$) from baseline value.

MK = medetomidine 0.25 mg/kg + ketamine 50 mg/kg

XK = xylazine 4 mg/kg + ketamine 50 mg/kg

induction. Hypoxaemia was reversed within 15 min in all cases. Both groups produced moderate hypercapnia, the highest means varying between 46.2 ± 5.6 for MK and 35.8 ± 3.4 mm Hg for XK (at 5-60 min of anaesthesia). The lowest arterial pHs varied between 7.29 ± 0.03 and 7.36 ± 0.04 for MK and XK, respectively and were reached between 5 and 45 min of anaesthesia. The pH value in the XK group was significantly higher compared with that of the MK group between 5 and 90 min after application ($P < 0.05$).

Discussion

Medetomidine formed a suitable combination with ketamine for anaesthesia of chinchilla rabbits. It greatly potentiated the anaesthetic effect of ketamine, since 50 mg/kg of ketamine combined with 0.25 mg/kg of medetomidine produced a more prolonged anaesthesia than 50 mg/kg of ketamine combined with 4 mg/kg of xylazine. For the purposes of comparison the medetomidine-ketamine combination can be considered as approximately equivalent to the xylazine-ketamine combination, which is in agreement with the findings in dogs and cats (12,16). Ketamine and medetomidine have been tested in New Zealand white rabbits in 4 different combinations (18). It was suggested that 15 mg/kg of ketamine and 0.25 mg/kg of medetomidine was appropriate for most common surgical procedures (e.g., ovariohysterectomy and castration). It is possible that strain variation in response may necessitate the administration of a higher or lower dose. For example, the pigmented outbred rabbits anaesthetised by Nevalainen et al. (7) were not all surgically anaesthetised, even at the higher dose rates of ketamine used (60-75 mg/kg). Rabbits that received this increased dose of ketamine (60 mg/kg) combined with 0.5 mg/kg of medetomidine showed fewer anaesthetic effects, while in the present study increasing the dose of ketamine alone increased the duration of surgical anaesthesia. When evaluating anaesthetic depth, it was noted that when the pedal withdrawal reflex was absent a positive response was sometimes observed when the stimulus was repeated (1,2). The first stimulus seemed to arouse the animal to a state in which a repeated stimulus evoked a response. Since most surgical procedures include repetitive nociceptive stimulation, it seems logical to evaluate reflexes by repeating the stimulus when evaluating anaesthetic depth.

In these studies, the positive chronotropic effect of ketamine temporarily counterbalanced the bradycardiac effect of the α_2-agonist medetomidine in a dose dependent manner, as has already been reported in dogs and cats (12,16). The significantly higher heart rates in the rabbits anaesthetised with XK compared with the rabbits anaesthetised with MK could have been due to the shorter bradycardiac effect of xylazine.

Xylazine-ketamine and medetomidine-ketamine combinations depressed respiratory rates in the same way. Nevertheless, in this and other previously published studies of ketamine and medetomidine in rabbits, moderate to marked hypoxia, moderate hypercapnia and moderate acidosis have been noted (14,18,19) and it is recommended that oxygen supplementation be provided when these agents are used for anaesthesia. It should be noted that this depression of respiratory function is not unique to the use of ketamine-medetomidine, but also occurs with other injectable anaesthetic regimens in this species (19,20).

Previous studies (5,6) have indicated that the administration of xylazine in rabbits produces a decrease in blood pressure. Medetomidine exhibits similar effects (7,10,12). Therefore, in combination, the centrally stimulating effects of ketamine balance the depressive effects of α_2-agonist compounds, as was evident with the medetomidine-ketamine combination tested in this study. Indeed, increasing the dose of ketamine cancelled the hypotension related to medetomidine administration.

An obvious advantage with the technique described is that the effects of medetomidine can be reversed rapidly and completely by the administration of atipemazole (1,7,17). With reversal of anaesthesia, the sleep time is reduced, and the animal returns to a normal physiological state much faster. Since atipemazole reversed all of the analgesic effects of medetomidine, additional analgesia should be provided, for example by administration of an NSAID such as carprofen before reversal of anaesthesia (21).

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