

## Comparative Studies on the Effect of S(+)-Ketamine-Medetomidine and Racemic Ketamine-Medetomidine in Mouse

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### SUMMARY

In this study, the cardiopulmonary and clinical effects of S (+) ketamine/medetomidine (S-K/MED) and ketaminrazemat/medetomidine (K-R/MED) combination on mice for anaesthesia were compared. A total of 20 adult female NMRI-mice (body weight 33-58 g) were used for this trial. Mice were divided into two groups. 75 mg/kg S-K and 0.25 mg/kg MED intraperitoneally (IP) were given to the Group 1 (G1), while 50 mg/kg K-R and 0.25 mg/kg MED intraperitoneally were given to the Group 2 (G2). The efficiency of anaesthetic agents were determined by clinical observations, which duration of induction, analgesia and immobilization, body temperature, respiratory rate (RR), peripheral oxygen saturation (SpO<sub>2</sub>), heart rate (HR). These parameters were measured and recorded at 10-minute intervals before and after administration of the anaesthetic agents. Analgesia lasted as a mean of 25 (15-35) min in G1 and 40 (30-60) min in G2 (p<0.05). The immobilization periods conducted in G1 and G2 were 56 (ranged between 50 and 65) min and 87 (ranged between 75 and 100) min, respectively (p<0.05). Temperatures reduced in both groups during anaesthesia. No significant differences between individual groups in the heart or respiratory rate as well as SpO<sub>2</sub> value. Atipamezole (AT) application resulted in an increase in respiratory rate, and a small numbers of animals showed hyperventilation. As a results, it could be suggested that using S-K in combination with MED causes shorter duration time and less side effects after antagonisation of MED compared with K-R.

**Key words:** S-Ketamine, Ketamine razemat, Medetomidine, Anaesthesia, Mice.

### Farelerde S(+)-Ketamin-Medetomidin ve Ketamin Razemat-Medetomidin'in Etkilerinin Karşılaştırılması

### ÖZET

Bu çalışmada, farelerde anestezi için S(+)-ketamin-medetomidin (S-K/MED) kombinasyonu ile ketaminrazemat-medetomidin (K-R/MED) kombinasyonu klinik ve kardiyopulmoner etkileri yönünden karşılaştırıldı. Toplam 20 erişkin dişi fare iki farklı gruba ayrıldı. Grup 1 (n=10) 0.25 mg/kg MED ve 75 mg/kg S-K intraperitoneal yolla uygulanırken, Grup 2 (n=10)'deki farelere yine aynı yolla 0.25 mg/kg MED ve 50 mg/kg K-R verildi. Anestezik ajanların etkileri; indüksiyon, analjezi, immobilizasyon süreleri, vücut ısısı, kalp frekansı, solunum frekansı ve perifer oksijen saturasyonu gibi klinik gözlemlere göre değerlendirildi. Bu gözlemler anestezi den önce ve anestezi boyunca onar dakikalık aralıklarla yapıldı. Analjezi süresi G1'de ortalama 25 dakika iken (15-35), G2'de ortalama 40 dakika (30-60) olarak ölçüldü (p<0.05). Immobilizasyon süresi G1'de ortalama 56 dakika iken (50-65), G2'de ortalama 87 dakika (75-100) olarak ölçüldü (p<0.05). Her iki grupta da anestezi boyunca vücut ısısında düşüşler tespit edildi. Kalp frekansı, solunum frekansı ve perifer oksijen saturasyonu değerlerinde gruplar arasında istatistiksel farklılıklar gözlenmedi. Atipemazol enjeksiyonundan sonra solunum frekansında artış ve hiperventilasyon gözlemlendi. Sonuç olarak, S-K/MED kombinasyonunun K-R/MED kombinasyonuna göre gerek daha kısa süreli anestezi oluşturması ve gerekse medetomidinin antagonize edilmesinden sonra daha az yan etki göstermesinden dolayı farelerde kullanımı önerilmektedir.

**Anahtar Sözcükler:** S-Ketamin, Ketamin razemat, Medetomidin, Anestezi, Fare.

### INTRODUCTION

That is because of small body size of rodents, some problems arise when anaesthetizing these species. Their high ratio of surface area to body weight makes them particularly susceptible to the development of hypothermia. Due to small size of superficial veins intravenous drug administration is limited. Beside this, relatively inaccessible larynx makes endotracheal intubation difficult. As a frequent cause of anaesthetic deaths is particularly important in small rodents and birds especially during prolonged anaesthesia (2).

The racemic ketamine (K-R) is generally utilised in veterinary medicine as a mixture of two isomers: S-(+)- and R-(-)-ketamine. Studies in human medicine show that the analgesic and anaesthetic potency of S-(+)-ketamine (S-K) are two times higher than of racemic ketamine. The main advantages of using S-K are considered to be as

reduced unpleasant side effects by one third and gaining consciousness earlier (7).

Medetomidine (MED) is sedative and analgesic agent. It is a potent  $\alpha_2$ -adrenoreceptor agonist in laboratory animals, dogs and cats. Similar to xylazine-ketamine combination, medetomidine-ketamine shows anaesthetic properties in animals (4,12,13).

S-K/MED combination has been tested in dogs, cats and hamsters (1,9,10). However studies conducted on ketamine-medetomidine in dogs and cats have shown not to have any advantage of S-K over K-R. In hamsters, the combination of S-K/MED is recommended over K-R/MED because of its significantly shorter duration of action and fewer incoordinate movements following AT.

Atipamezole (AT) is a highly selective  $\alpha_2$ -adrenoreceptor antagonist for reversing the cardiovascular and sedative effects of medetomidine used either alone or in combination (5,8).

The purpose of this study reported here is to compare S-K and K-R, both in combination with MED in NMRI mice.

**MATERIALS and METHODS**

Twenty adult female NMRI-mice were used in this study the mice were divided into two groups (ten mice each). Seventy five mg/kg S-K (Ketanest S25, Parke-Davis AG, Berlin) and 0.25 mg/kg MED (Domitor®, Pfizer GmbH, Karlsruhe), and 50 mg/kg K-R (Narketan 10, Chassot) and 0.25 mg/kg MED were administered intraperitoneally to Group 1 (G1) and Group 2 (G2), respectively.

The efficiency of anaesthetic agents were determined by clinical observations, monitoring and recording duration of induction, analgesia and immobilization, body temperature, respiratory rate (RR), peripheral oxygen saturation (SpO<sub>2</sub>), heart rate (HR). Parameters were recorded at 10-minute intervals before and after administration of agents. Analgesia was tested by using a haemostatic forceps every 10 min on the interdigital skin on a back paw closed to the first notch. Analgesia was assumed to be achieved during the time when no withdrawal reflexes were observed in response to this stimulus. Immobilization was considered to be occurred at the time between the loss of righting reflex and regaining of the reflex. The animal was attached to a pulseoxymeter (Biox™ Handoximeter 3775, Fa. Ohmeda, Erlangen) with an ear probe placed proximal to the tarsal joint for the measurement of peripheral blood oxygen saturation and heart rate.

MED was antagonized using AT 0.25 mg/kg (Antisedan®, Pfizer AG) 50 minutes after injection of the ketamine-medetomidine combination. Clinical observations (reflexes, body temperature, respiratory rate, peripheral oxygen saturation, pulse rate) were recorded 5 minutes before and after injection in both groups.

Statistical analysis was performed using analysis of variance (one-way ANOVA) and Students' t-tests.

**RESULTS**

Induction time was between 1-3 min (mean 1.5 min) and 1-4 (mean 2.1) min in the mice of G1 and G2, respectively. Analgesia lasted for a mean of 25 (15-35) and 40 (30-60) min in G1 and G2, respectively. The animals were immobilized for a mean of 56±9 min and 87±13 min in mice of G1 and G2, respectively. S-K animals showed a shorter recovery period and were able to move in a coordinated way earlier. Anaesthesia was produced in all animals. Body temperature reduced to 36.5±0.4 and 37.0±0.5 °C for G1 and G2, respectively at the beginning of anaesthesia and a slight increase was observed during anaesthesia. A significant decrease in RR (from 180±12 to 140±14) after administration of anaesthetic drugs in the mice of G2 and then remained stable for the rest of the experiment. No significant change in RR was observed in the animals of G1 and G2 at respective time intervals. SpO<sub>2</sub> decreased with the administration of S-K and K-R to values between 70 to 76 % as compared to normal value of 92 %. There were no significant differences between individual groups in the heart or respiratory rate, as well as SpO<sub>2</sub> value.

Table 1. Effects of MED (0.25 mg/kg)/S-K (75 mg/kg) and MED (0.25 mg/kg)/K-R (50 mg/kg) on cardiorespiratory values in mouse.

	G1	G2	G1	G2	G1	G2	G1	G2
0	37.8±0.85	37.7±0.56	187.3±25.5	182.3±30.8	570±78.2	550±90.5	93.2±5.79	94.4±8.36
10	36.94±0.72	36.35±0.92*	176.0±17.5	139.0±16.2*	196.7±43.7***	241.1±14.2***	69.11±13.79**	75.30±9.24*
20	37.44±1.08	36.23±1.29*	176.0±13.2	135.00±8.5*	200.5±30.9***	270.6±52.8***	77.44±13.09*	71.80±10.3**
30	37.56±1.02	35.99±1.30**	167.2±11.5	137.00±7.5*	171.6±27.3***	224.4±56.3***	77.75±13.2*	80.20±12.1
40	37.84±0.83	35.96±1.34**	181.7±12.7	147.20±10.5*	168.0±39.0***	263.3±50.1***	74.17±4.0*	75.00±12.8*
50	37.50±1.17	36.39±1.23*	174.00±7.5	155.20±13.5*	201.0±53.0***	202.8±35.5***	76.00±4.7*	75.00±6.51*
60	36.80±0.42*	36.43±0.49*	150.80±12.1*	140.80±10.2*	182.2±42.1***	220.0±49.3***	82.33±8.7	78.33±15.3
PA	37.0±0.52	37.4±0.70	170.2±12.1	160.8±10.2	370.1±52.1**	415.3±70.2*	91.1±3.1	88.1±11.6*

Values reported are mean± SEM (range). \*Mean value differs significantly (P<0.05) from baseline value (t=0).  
 \*\* Mean value differs significantly (P<0.05) from baseline value (t=0) \*\*\* Mean value differs significantly (P<0.05) from baseline value (t=0).  
 HR = heart rate; RR = respiratory rate; SpO<sub>2</sub>= Peripher oxygen saturation;  
 T = rectal temperature; PA; post atipemazole, Time (min) T (°C) RR (breaths/min) HR (beats/min) SpO<sub>2</sub> (%)

The application of AT caused an increase in respiratory rate and a few of animals showed hyperventilation. The RR (breath/min) values before AT were 150±12.1 and 140±10.2 for G1 and G2, respectively. These values were recorded after AT as 170±12.1 and 160±10.2 for G1 and G2, respectively. HR (beats/min) values before AT were found 182±42.1 and 220±49.3 for G1 and G2, respectively. The HR values after

administration of AT were found to be as 370±52.1 and 415±70.2 for G1 and G2, respectively. SpO<sub>2</sub> (%) levels were recorded as 82±8.7 and 78±15.3 for G1 and G2, respectively, before AT administration, they were found to be as 91±3.1 and 88±11.6 after AT administration. The body temperature (°C) values recorded before AT application were 36.8±0.42 and 36.4±0.49 for G1 and G2, respectively whereas these values were found to be as

37.0±0.52 and 37.4±0.70 after AT administration, for G1 and G2, respectively. After application of AT righting reflex was observed earlier in G1 than in G2. Animals anaesthetized by using S-K showed a shorter recovery period and were able to move in a coordinated way earlier.

## DISCUSSION

Several anaesthetic regiments immobilize mouse, but surgical anesthesia is difficult to achieve, especially a long period of surgical anesthesia.

Ketamine/medetomidine combination at different dosages have been used by various workers in mice (3,6,14). The combination of medetomidine 0.25 mg/kg and ketamine 100 mg/kg seems to be the best combination for minor surgical interventions in NMRI-mice. Increasing the medetomidine dosage causes severe respiratory and cardiovascular depression. If surgery is assumed to last longer, a higher ketamine part is preferable (6).

Animals anaesthetized by using S-K showed a shorter recovery period and were able to move in a coordinated way earlier. The shorter duration of immobilization and recovery period with S-K in compare with K-R has been reported in dogs, cats and hamsters previously (1,9,10).

Decreases in body temperature have also been reported after medetomidine administration in laboratory animals, dogs and cats (11,15,16). Alpha<sub>2</sub>-adrenoreceptor agonists are known to reduce body temperature by an action on the central nervous system.

Both drug combinations produced a decrease of HR at the beginning of anaesthesia and a moderate depression of cardiovascular system was observed in both groups. The effects on the cardiovascular system are probably due to administration of medetomidine, with typical α<sub>2</sub>-adrenoreceptor agonists actions (11-13). The positive chronotropic effect of K-R and S-K counterbalanced temporarily the bradycardiac effect of the α<sub>2</sub>-adrenoreceptor agonists medetomidine in a dose dependent manner has already been reported in dogs and cats previously (15,16).

After application of atipamezole righting reflex was seen earlier in GI than in GII S-K animals showed a shorter recovery period and were able to move in a coordinated way earlier. This shorter recovery period with S-K in compare with K-R after antagonisation of MED has been reported in cats and hamsters (1,9).

As a conclusion, the use of S-K in combination with MED is recommended because of its shorter duration time and less side effects after antagonisation of medetomidine compared with K-R.

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