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Antagonistic Effects of Atipamezole and Yohimbine against Anesthesia with Medetomidine and Ketamine Combination in Pigs

Jae-Yeon Lee and Myung-Cheol Kim[1]

College of Veterinary Medicine, Research Center for Transgenic Cloned Pigs, Chungnam National University, Daejeon 305-764, Korea

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Abstract : The aims of the present study were to investigate the anesthetic and hemodynamic effects of medetomidine-ketamine combination and to compare antagonistic effects of atipamezole and yohimbine on the recovery of pig from anesthesia induced by medetomidine-ketamine combination. Landrace and Yorkshire cross-bred pigs were evaluated in the present study. Pigs (n = 8) received three different treatments (one treatment per 14 days in a random order). All pigs were injected intramuscularly with medetomidine, and ketamine in a single syringe. Intravenous injections of atipamezole (MKA), yohimbine (MKY), or a control saline solution (MK) were administered 20 minutes after the medetomidine-ketamine combination injection. The intravenous antagonist injections quickly reversed the medetomidine-ketamine induced sedation in the pigs, resulting in a significantly shorter duration of anesthesia in the MKA and MKY groups compared to the MK group. Mean arterial pressure (MAP) levels were significantly lower in the MKA and MKY groups compared to the MK group. Scores for posture and responses to noxious stimuli after atipamezole and yohimbine administration were significantly lower in the MKA and MKY groups than in the MK. In conclusion, the sedative effects and increases in blood pressure induced by a medetomidine-ketamine combination were quickly and smoothly reversed by atipamezole or yohimbine.

Key words **:** medetomidine, ketamine, atipamezole, yohimbine, pigs.

Introduction

Pigs are frequently used in clinical research, including human organ transplant research. However, it is difficult to effectively restrain and anesthetize them. Chemical restraint is a valuable tool in veterinary research and management since it facilitates easy handling of animal for medical procedures and experiments. Many drugs are administered intramuscularly for immobilization and anesthesia induction. There are many established intramuscular anesthetic combination protocols in pigs, including medetomidine-butophannol-ketamine (13), tiletamine/zolazepam-ketamine-xylazine, and guaifenesin-ketamine-xylazine (2). Medetomidine and ketamine are commonly used in combination with one another to immobilize and anesthetize pigs and other companion animals. A combination of medetomidine and ketamine potentially enhanced the sedative and analgesic actions of the individual drug in pigs (12). However, few controlled studies have evaluated the cardiorespiratory effects of injectable drug combinations in pigs. The effect of intramuscular anesthesia is not as easily controlled as intravenous or inhalant anesthesia. Therefore, antagonist drugs and combination would allow for better control.

Antagonism may be required when anesthetized animals demonstrate profound depression of vital signs, adverse effects against anesthetic agents, and delayed anesthetic recovery. Anesthesia with drug combinations (with specific antagonists) would be significantly advantageous. Each component may potentiate the other's actions, lower individual dose requirements, and produce safe surgical anesthesia (3). The determination of a suitable antagonist for rapid recovery of anesthetized veterinary patients is therefore very important. Alpha adrenergic antagonists including yohimbine and atipamezole have been effectively used in ungulates for antagonism of the anesthetic effects of α_2-adrenoceptor agonist- based combinations (5,15). The actions of medetomidine can be reversed by α_2-adrenoceptor antagonists, including the highly receptor-specific atipamezole or the less specific yohimbine (13). However, there is minimal available information describing the effects of the medetomidine-ketamine combination and reversal in pigs. We investigated the anesthetic and hemodynamic effects of the medetomidine-ketamine combination in the present study, and compared the antagonistic effects of atipamezole and yohimbine on anesthetic recovery.

Materials and Methods

Animals

The present study was performed with 4-to-5 months old Landrace and Yorkshire cross-bred pigs (four females and four males). All pigs were obtained from the experimental live-

[1]Corresponding author.
E-mail : mckim@cnu.ac.kr

stock farm of the College of Agriculture, Chungnam National University (CNU). Experimental and housing protocols were approved by the CNU Animal Care and Use Committee, and the study was performed 14 days after obtaining pigs. The pigs were maintained in a quiet room to avoid stress-inducing factors during this period. Pigs were fed a wheat-based diet in accordance with previous feeding regimens, and were fasted 12 hours prior to experimentation. Water was withheld 2 hours prior to anesthesia in order to prevent adverse effects, including vomiting and regurgitation.

Instrumentation and drugs administration

A sterile, 22-gauge catheter (BD IV Catheter; Becton Dickinson) was inserted percutaneously into the left dorsal metatarsal artery of each pig prior to experimentation; pigs had been anesthetized with isoflurane masks for the measurement of arterial blood pressure (Forane; Choong Wae). The catheter was connected to a pressure transducer with a noncompliant tube (Pulscan-Component; Scionic), and the transducer was attached to a physiological monitor (Pulscan-Component; Scionic). Isoflurane was discontinued after catheter insertion, and pigs recovered for 60 minutes prior to drug administration. Pigs were restrained for measurement of baseline data.

Each pig (n = 8) received one treatment per 14 days in a random order, for a total of three different treatments. Pigs in all groups were injected intramuscularly with medetomidine (Domitor®, Orion Pharma, Finland, 0.08 mg/kg), and ketamine (Ketamin 50®, Yuhan Co, Seoul, Korea, 10 mg/kg) in a single syringe. Intravenous injections of atipamezole (Antisedan®, Orion Pharma, Finland, 0.24 mg/kg, MKA), yohimbine (Yobin®, Lloyd Laboratories, Iowa, USA, 0.15 mg/kg, MKY), or a control saline solution (MK) were injected 20 minutes after the medetomidine-ketamine combination injection. Injections were given in the trapezius muscles, and animals were positioned in right lateral recumbency. Level of analgesia and hemodynamic data were determined and recorded.

Induction and recovery

Times to induction, anesthesia, sternal recumbency, standing, and walking were recorded for each pig. Induction time was the time from medetomidine-ketamine injection to complete immobilization. Complete immobilization was defined as a lack of response to handling. Anesthesia time was defined as the time interval between complete immobilization and the first attempt by the pig to lift its head. Sternal recumbency time was defined as the time from medetomidine-ketamine injection to sternal recumbency. Standing time was defined as the time from medetomidine-ketamine injection to the ability to stand without assistance for longer than 10 seconds. Walking time was defined as the time from medetomidine-ketamine injection to the ability to walk without knuckling.

Heart rates, blood pressure and rectal temperature

Variables were measured at time 0 (pre-injection) and at 5, 10, 20, 30, and 40 minutes after drug administration. The heart rate (HR) was measured by a transducer attached to a physiological monitor (Pulscan-Component®, Scionic, Seoul, Korea). The mean arterial pressure (MAP) was measured with a patient monitor (Pulscan-Component®, Scionic, Seoul, Korea) and were recorded. The left scapulohumeral joint was used as the zero reference point for MAP measurement. Rectal temperature (RT) was continuously recorded using a digital thermometer (Pulscan-Component®, Scionic, Seoul, Korea) with a rectal thermocouple probe.

Evaluation of sedation and response to noxious stimulus

Level of sedation (spontaneous posture) and responses to noxious stimuli (pedal withdrawal) were assessed at designated times during anesthesia (Table 1).

Statistical analysis

Data were expressed as median (range), and Mann-Whitney U-test was used as appropriate. A p-value of < 0.05 was considered as significant. All statistics were performed using a computer statistical package (Statistics Package for the Social Sciences, version 17.0; SPSS Inc., IL, USA).

Table 1. Subjective criteria used to score levels of sedation and response to noxious stimulus in pigs treated with medetomidine/ketamine (MK), medetomidine/ketamine-atipamezole (MKA) and medetomidine/ketamine-yohimbine (MKY)

Variable	Score	Criteria
Sedative score	0-5	
Spontaneous posture		
	0	Normal
	1	Being able to stand or sit on their hind legs
	2	Keeping the position of ventral recumbency
	3	Lateral recumbency with apparent spontaneous movement (head lifting or struggling)
	4	Lateral recumbency with subtle spontaneous movement (ear and nose twitching or blink)
	5	Lateral recumbency without spontaneous movement
Score of response to noxious stimulus	0-3	
Pedal withdrawal response to pinching of a digit or interdigital web		
	0	Hypersensitive or normal
	1	Slightly impaired
	2	Clearly weak
	3	Absent

Results

Pigs in all groups became sedated after the intramuscular injection of medetomidine-ketamine, and all were laterally recumbent within three minutes without excitement signs. Induction time was similar in all groups (Table 2). Administration of medetomidine-ketamine to 8 pigs induced a mean duration of anesthesia of 46 (40-51) minutes. Intravenous antagonist injections quickly reversed the medetomidine-ketamine induced sedation in pigs, giving the MKA and MKY groups a significantly shorter duration of anesthesia than the MK group. Times to sternal recumbency and standing and walking times in MKA and MKY group were significantly faster than those of the MK group during anesthetic recovery (Table 2). There were no significant differences in anesthetic recovery between the MKA and MKY groups.

HR, MAP, and RT values were summarized in Table 3. There were no significant differences in heart rate (compared to baseline values) after MK administration in all groups. Significant increases in blood pressure were observed in all groups after MK administration (compared to baseline values). The mean arterial blood pressure increased significantly in the MK group ($p = 0.004$) within 5 minutes of MK administration, and remained consistently elevated above baseline for 40 minutes. The MAP peak occurred 40 minutes after MK administration in the MK group, and the MAP peak in the MKA and MKY groups occurred 20 minutes after MK administration; the peak decreased after antagonist administration. MAP levels were significantly lower in the MKA and MKY groups compared to the MK group at 30 and 40 minutes ($p = 0.041$). There were no significant differences among rectal temperature values compared with baseline values after MK administration in all groups.

Medetomidine-ketamine administration in the three groups produced satisfactory sedation for all pigs in the study. However, posture scores and responses to noxious stimuli were significantly lower at 30 and 40 minutes in the MKA and MKY groups, respectively, than in the MK group (Table 4).

Table 2. Time for induction, duration of anesthesia and recovery times in pigs after administration of medetomidine/ketamine (MK), medetomidine/ketamine-atipamezole (MKA) and medetomidine/ketamine-yohimbine (MKY)

	MK	MKA	MKY
Induction time	2 (2-3)	2 (2-3)	2 (2-4)
Duration of anesthesia	46 (40-51)	23 (17-27)*	25 (17-30)*
Time to sternal recumbency	62 (56-67)	38 (31-44)*	35 (30-42)*
Time to standing	76 (64-87)	54 (42-67)*	51 (39-61)*
Time to walking	104 (75-134)	67 (54-79)*	59 (47-71)*

Data are expressed as median (range) (n = 8).
*Significantly different ($p < 0.05$) from MK.

Discussion

The α_2-adrenoceptor agonists are commonly used in clinical practice, and are frequently used for reliable dose-dependent sedation, analgesia, and muscle relaxation in a variety of domesticated and wild species. The α_2-adrenergic receptor agonistic properties may result in clinicophysiological side effects and central nervous system depression (4). Therefore, the prevention or reversal of α_2-agonist induced effects may be accomplished with α_2-adrenergic antagonists. The results of this study suggested that both atipamezole and yohimbine have similar antagonistic effects on medetomidine-ketamine-induced anesthesia in pigs. Antagonist administration quickly reversed the effects induced by medetomidine-ketamine; recumbency time, standing time, and total anesthesia time were signifi-

Table 3. Heart rate, mean arterial blood pressure and rectal temperature in pigs after administration of medetomidine/ketamine (MK), medetomidine/ketamine-atipamezole (MKA) and medetomidine/ketamine-yohimbine (MKY)

	Group	Pre	5 min	10 min	20 min	30 min	40 min
HR (beats/minutes)	MK	115 (100-128)	115 (103-127)	114 (102-124)	110 (101-123)	111 (95-127)	109 (95-127)
	MKA	115 (101-125)	110 (93-125)	113 (91-127)	114 (93-131)	115 (105-129)	112 (91-129)
	MKY	113 (97-125)	119 (99-135)	115 (101-127)	115 (96-128)	118 (102-132)	113 (97-131)
MAP (mmHg)	MK	88 (74-96)	110 (94-130)*	109 (88-122)*	114 (103-119)*	114 (107-121)*	116 (105-125)*
	MKA	87 (75-93)	114 (99-123)*	112 (102-124)*	114 (108-123)*	98 (89-105)*,a	93 (89-101)*,a
	MKY	84 (69-93)	111 (100-120)*	107 (96-122)*	114 (102-124)*	94 (86-104)*,a	95 (89-105)*,a
RT (°C)	MK	39.4 (38.8-39.6)	39.4 (38.9-39.7)	39.3 (39.0-39.4)	39.0 (38.9-39.3)	39.1 (38.8-39.2)	39.3 (39.0-39.4)
	MKA	39.7 (38.9-40.1)	39.6 (38.8-40.0)	39.6 (38.9-40.1)	39.8 (38.4-40.4)	39.2 (38.8-40.0)	39.7 (38.8-40.0)
	MKY	39.7 (39.1-39.9)	39.4 (38.9-40.1)	39.6 (38.9-40.1)	39.6 (38.7-40.1)	39.9 (39.0-40.6)	39.5 (39.0-40.4)

Data are expressed as median (range) (n = 8).
*Significantly different ($p < 0.05$) from baseline.
[a]Significantly different ($p < 0.05$) from MK.

Table 4. Scores of sedation (spontaneous posture) and response to noxious stimulus (pedal withdrawal) after the administration of medetomidine/ketamine (MK), medetomidine/ketamine-atipamezole (MKA) and medetomidine/ketamine-yohimbine (MKY)

	Group	5 min	10 min	20 min	30 min	40 min
Spontaneous posture	MK	5 (4 - 5)	5 (4 - 5)	5 (4 - 5)	5 (4 - 5)	5 (4 - 5)
	MKA	5 (4 - 5)	5 (4 - 5)	5 (4 - 5)	2 (1 - 3)[*,a]	2 (1 - 2)[*,a]
	MKY	5 (4 - 5)	5 (4 - 5)	5 (4 - 5)	2 (1 - 3)[*,a]	2 (1 - 2)[*,a]
Response to noxious stimulus	MK	3 (2 - 3)	3 (2 - 3)	3 (2 - 3)	2 (2 - 3)	2 (1 - 3)
	MKA	3 (2 - 3)	3 (2 - 3)	3 (2 - 3)	1 (0 - 1)[*,a]	0 (0 - 1)[*,a]
	MKY	3 (2 - 3)	3 (2 - 3)	3 (2 - 3)	1 (0 - 1)[*,a]	0 (0 - 1)[*,a]

Data are expressed as median (range) (n = 8).
[*]Significantly different ($p < 0.05$) from baseline.
[a]Significantly different ($p < 0.05$) from MK.

cantly reduced compared to pigs treated with the saline control.

The α_2-adrenoceptor agonist medetomidine was introduced as a sedative analgesic agent for both small and large animals (14); it is a highly complete and selective central α_2-adrenergic receptor agonist and is superior to xylazine. It has significant dose-dependent sedative effects that are more potent than xylazine effects in pigs (11). Ketamine is a dissociative anesthetic that has been used clinically for immobilization and anesthesia; it is effectively used in combination with medetomidine for anesthesia in pigs (16). Intramuscular medetomidine (80 μg/kg) combined with butorphanol (200 μg/kg) and ketamine (10 mg/kg) provided appropriate anesthesia and analgesia in pigs for approximately 30-40 minutes (13). In this study, medetomidine (0.08 mg/kg) and ketamine (10 mg/kg) administration resulted in 45 minutes of anesthesia with a 2.6 minute induction period. The duration of non-responsiveness to noxious stimuli applied to the pelvic digit and the ears ranged from 5-40 minutes. Pigs had minimal responses to the noxious stimuli, and most pigs had an anesthetic score of 4 or high after MK administration (range, 5-40 minutes). This suggested that MK produced good short-term sedation and mild-to-moderate analgesia in the pigs.

Antagonism may be required when anesthetized animals demonstrate profound depression of vital signs, adverse effects from administered agents, and delayed anesthetic recovery. Anesthesia with combinations of agents has potential advantages. Each component may potentiate the other agent's actions and may lower individual dose requirements, collectively resulting in greater safety of anesthetic agents (3). The α_2-adrenoceptor agonist medetomidine has been successfully antagonized with atipamezole in pigs (9). Ketamine is a non-competitive N-methyl D-aspartate (NMDA) antagonist, and can bind to naloxone-insensible sigma receptors, inducing hallucinogenic effects. However, a specific ketamine antagonist does not exist. Alpha adrenergic antagonists such as yohimbine and atipamezole have been effectively used in ungulates α_2-adrenoceptor agonist- based combinations antagonism. The atipamezole dose (0.24 mg/kg) in this study was selected for optimal reversal of medetomidine (0.08 mg/kg), since the effective reversal dose of atipamezole in pigs ranges from 2-4 times that of medetomidine. The yohimbine dose (0.15 mg/kg) was determined based on a preliminary study from our group, since we could not find any reference for an adequate yohimbine dose for optimal reversal of medetomidine in pigs. Atipamezole or yohimbine administered as single agents markedly antagonized medetomidine-ketamine anesthesia in the present study. Atipamezole or yohimbine quickly reversed the effects of medetomidine-ketamine. Times to recumbency, standing, and anesthesia were significantly reduced compared to the control group. Medetomidine effects can be reversed by α_2-adrenoceptor antagonists, including the highly receptor-specific atipamezole or the less specific yohimbine (8). In previous study (6), yohimbine was less effective than atipamezole in reversing medetomidine induced sedation in lambs because of yohimbine's lower specificity towards α_2- adrenoceptors. Another study demonstrated that yohimbine at 0.5 mg/kg reversed the anesthetic effects of medetomidine (0.08 mg/kg) and ketamine (5 mg/kg), although a lower yohimbine dose (0.25 mg/kg) was not effective in cats (17). However, medetomidine-induced sedation and central nervous system depression were equally reversed within 2 to 5 minutes by atipamezole or yohimbine in the present study. Intravenous administration of atipamezole or yohimbine resulted in an immediate awakening in this study, corresponding to earlier reports (7). This suggested a rapid equilibration of atipamezole or yohimbine in the central nervous system. The reversal was lasting with no relapses into deeper stages of sedation. Salivation and tremors were observed in a few pigs after reversal of medetomidine-ketamine-induced sedation by atipamezole or yohimbine.

Intramuscular administration of medetomidine-ketamine produced a decrease in heart rates at sedative dose in rabbits (1) and Yucatan mini pigs (16). The α_2-agonists may produce marked bradycardia, but there were no significant changes in heart rate after medetomidine-ketamine injection in the present study.

There was a lasting and significant rise in blood pressure after injection of medetomidine-ketamine in the present study. It is notable that MAP remained consistently elevated above baseline for approximately 50 minutes when medetomidine-

ketamine was used; however, atipamezole and yohimbine treatments resulted in reductions below unconscious levels soon after injection of antagonists. Similar results were displayed by Nishimura *et al*. (1994) in laboratory pigs (10). The increases in MAP in the present study were statistically significant with little clinical significance.

The sedative effects and the increases in blood pressure induced by a medetomidine/ketamine combination could be reversed quickly and smoothly by administration of atipamezole or yohimbine alone. The antagonistic actions were seen with atipamezole (dose, 0.24 mg/kg) and yohimbine (dose, 0.15 mg/kg) administration; the doses were 2-3 times higher than the preceding medetomidine dose. The possible use of antagonists might enhance the value and availability of medetomidine/ketamine for chemical restraint in pigs.

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돼지에서 Medetomidine-ketamine 마취에 대한 Atipamezole과 Yohimbine의 길항효과

이재연 · 김명철[1]

충남대학교 수의과대학

요 약 : 돼지에서 medetomidine-ketamine (MK) 합제에 대한 마취효과와 이 합제에 대한 atipamezole (MKA) 과 yohimbine (MKY)의 길항효과를 비교하였다. 24 마리 Landrace - Yorkshire 혼혈 종 돼지를 사용하였다. Medetomidine-ketamine 는 한 주사기로 근육주사 하였고 atipamezole 과 yohimbine 은 마취 후 20 분에 정맥 주사 하였다. 평균마취시간, 평균흉와시간, 평균기립시간 및 평균보행시간은 MKA와 MKY군에서 MK군보다 유의적으로 짧았다. 그러나 MKA군과 MKY군간의 유의적인 차이는 없었다. 평균혈압은 MKA와 MKY군에서 MK군보다 유의적으로 낮았다. 결론적으로 Medetomidine-ketamine 에 의한 마취 및 혈압 상승 효과는 atipamezole과 yohimbine 에 의해 안전하고 빠르게 길항되었다. 따라서 atipamezole과 yohimbine은 돼지에서 Medetomidine-ketamine 마취를 길항하는 데 안전하고 효과적으로 사용될 수 있다.

주요어 : atipamezole, medetomidine, ketamine, yohimbine, 돼지