

Antagonistic Effects of Atipamezole and Flumazenil on Medetomidine-Midazolam Induced Sedation in Laboratory Pigs

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ABSTRACT. Antagonistic effects of atipamezole (80, 160 and 240 $\mu\text{g/kg}$, im), and flumazenil (100 $\mu\text{g/kg}$, iv) or atipamezole (80 $\mu\text{g/kg}$) and flumazenil (100 $\mu\text{g/kg}$) on medetomidine-midazolam induced sedation were evaluated in laboratory pigs. Atipamezole at each dose effectively reversed sedation, and the arousal time, standing time and total recovery time were significantly shortened. The optimal action of atipamezole was seen at a dose of 160 $\mu\text{g/kg}$. At this dose recovery from the sedation was quick and smooth, and adverse effects such as hyperactivity or tachycardia were minimal. Flumazenil reversed sedation temporary, but the pigs went back to moderate sedation soon after arousal. The combination of atipamezole and flumazenil most effectively reversed the sedation, however atipamezole (160 $\mu\text{g/kg}$) alone was thought to be practically potent enough to antagonize sedation induced by medetomidine-midazolam in laboratory pigs.—**KEY WORDS:** atipamezole, flumazenil, medetomidine, midazolam, laboratory pig.

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As we previously reported [5], a combination of medetomidine-midazolam exerted a much more potent sedative effect than that induced by a medetomidine alone, while the dose of medetomidine was reduced to one half. Pigs given this combination were induced to sedation accompanied with good muscle relaxation and moderate analgesia smoothly and very quickly, even if they were stimulated continuously during the induction phase. During being sedated the arousal reaction induced by sensory stimuli were depressed profoundly and pigs could be placed in dorsal recumbency without any resistance. If the sedative condition induced by this combination can be reversed quickly and smoothly, this combination should be more valuable and more widely available in pigs.

Atipamezole is a highly selective and specific α_2 -adrenoreceptor antagonist and has been reported to have the ability to reverse the effects of medetomidine even if medetomidine was used with other drugs [11]. Flumazenil is a potent and specific benzodiazepine antagonist and is now being widely employed to reverse the effects of midazolam in medical practice [3].

The purpose of this study was to evaluate and compare the antagonistic effects of atipamezole and flumazenil on a sedative effect induced by medetomidine-midazolam in laboratory pigs. The present study was also design to determine the optimal dose of an antagonist on this combination.

MATERIALS AND METHODS

Animals: Six castrated mixed breed pigs (Sumichiku Co., Ltd., Japan) in good health were used repeatedly at a week interval in this study. Their mean age was 11.5 weeks (range 9 to 14 weeks) and mean body weight was 17.9 kg (range 15 to 23 kg). During the period of

stabilization (for more than a week), the pigs were fed a commercial ration once a day and given water *ad libitum*. The pigs were fasted for more than 12 hr before the experiments, and each animal was exposed to different regimens in a randomized block design.

Drugs: The drugs used in this study were medetomidine (Domitor, Farnos Group Ltd., Finland), midazolam (Dormicum, Yamanouchi Pharmaceutical Co., Japan), atipamezole (Antisedan, Farnos Group Ltd., Finland) and flumazenil (Hoffman-La Roche, U.S.A.). Flumazenil was dissolved in acidic aqueous solution at the concentration of 0.1 mg/ml (each ml contains 0.1 mg of flumazenil compounded with 9.3 mg of sodium chloride, 0.1 mg of edetate disodium, and 0.1 mg of acetic acid; pH is adjusted to approximately 4 with hydrochloric acid and/or sodium hydroxide). Medetomidine, midazolam and atipamezole were injected into the cervical muscle and flumazenil was injected into the ear vein.

Experimental design: The experiments were performed in a quiet room with a controlled temperature at $24.0 \pm 1.5^\circ\text{C}$ and humidity at $50 \pm 15\%$. The pigs were administered 40 $\mu\text{g/kg}$ of medetomidine and 0.2 mg/kg of midazolam mixed in the same syringe, and were kept in solitary cages to keep the animals from disturbing each other. Thirty min after dosing, these animals were given saline solution as a control, atipamezole at doses of 80, 160 and 240 $\mu\text{g/kg}$, which were two, four and six times higher than the dose of preceding medetomidine, 100 $\mu\text{g/kg}$ of flumazenil or 80 $\mu\text{g/kg}$ of atipamezole and 100 $\mu\text{g/kg}$ of flumazenil. The dose of atipamezole was chosen from the optimal dose of atipamezole against the sedation induced by medetomidine alone [7]. The antagonistic effect of 100 $\mu\text{g/kg}$ of flumazenil to 0.2 mg/kg of midazolam has been certified in a preliminary study using 6 pigs. Saline solution was administered in amount of

0.048 ml/kg which was the same volume as atipamezole at the dose of 240 µg/kg. Antagonistic effects were repeatedly assessed 5, 10, 20, 30, 40, 60, 80, 120, 180, 240 and 300 min after dosing and/or until the animals totally recovered.

Heart rate and rectal temperature were measured before injection of medetomidine-midazolam as base-line values, during which time each pig was kept on a canvas sling. After drug administration, those measurements were repeated 10, 20, 30, 40, 60, 80 and 120 min after dosing at their own cages.

Assessment of antagonistic effect of atipamezole and flumazenil: Antagonistic effects of antagonist(s) were evaluated by the total score for evaluating the sedative character and by arousal time (time from injection of antagonist(s) until the animal could raise the head when stimulated), standing time (time from injection of antagonist(s) until the animal could stand) and total recovery time (time from injection of antagonist(s) until the animal could not be distinguished from untreated animals). Sedative character was assessed as we previously reported [6]: the total score of posture, response to noise (hand clapping), resistance to restraint and resistance to mouth open and to pull tongue outwards. Recovery condition and undesirable side effects were also observed throughout the experiment.

Statistical analyses: Differences of antagonistic effects at corresponding time were assessed by use of Kruskal-Wallis test and Williams Wilcoxon multiple comparison procedure. The data of recumbency time, arousal time, standing time and total recovery time were analyzed by one-way analysis of variance and Duncan's multiple comparison procedure. The data of heart rate and rectal temperature were analyzed by one-way analysis of variance and Duncan's multiple comparison procedure, and by paired-*t* test. In all analyses, values were considered to be statistically significant when $P < 0.05$.

RESULTS

Following the intramuscular injection of medetomidine-midazolam, any of the pigs were quickly and smoothly induced to sedation in all the 36 trials in the same manner. The animals became lateral recumbency in 4 to 11 min (Table 1), and the total score for sedative character went up to full marks soon after that. During being in lateral recumbency, these pigs lost consciousness and the animals were not aroused even when they restrained in dorsal recumbency.

Atipamezole injections at any doses (80, 160 and 240 µg/kg) effectively reversed the medetomidine-midazolam induced sedation (Fig. 1). Pigs were aroused 2 to 7 min after atipamezole injections, and all the pigs rose to standing position within 12 min. The total score for evaluating sedative character in pigs given 160 and 240 µg/kg of atipamezole already decreased significantly as compared with those in control pigs at the first observation time (5 min after administrations of atipamezole). Twenty min after injection, the score in pigs given 80 µg/kg of atipamezole was also significantly different from the score in control pigs (Table 2).

The mean arousal time and the mean standing time in pigs given atipamezole at either dose (80, 160 and 240 µg/kg) were significantly shortened to one-fourth to one-seventh of the values in control pigs. These values were shortened in proportion to the atipamezole dose, however there were no significant differences between each dose group (Table 1). On the contrary, the mean total recovery time in pigs given 80 µg/kg of atipamezole was significantly longer than that in pigs given the higher doses of atipamezole.

Recovery from sedation in pigs given atipamezole at 80 and 160 µg/kg was smooth with minimal adverse effects and with no relapses into sedation, although the animals became slightly ataxic for 20 to 30 min. On the contrary, three of the six pigs given atipamezole at 240 µg/kg appeared mildly hyperactive and had mild muscular tremors for a short duration.

Table 1. Recumbency time, arousal time, standing time and total recovery time in pigs given medetomidine-midazolam and atipamezole and/or flumazenil or saline solution^{a)}

Antagonist(s)	Mean recumbency time(min)	Mean arousal time(min)	Mean standing time(min)	Mean total recovery time(min)
Saline solution	5.3±1.0 ^A	41.2±13.7 ^A	62.7±41.5 ^A	224.4±32.3 ^A
Atipamezole 80 µg/kg	6.8±2.1 ^A	10.5±4.5 ^B	14.7± 6.5 ^B	124.8±27.9 ^B
Atipamezole 160 µg/kg	7.2±2.1 ^A	7.8±2.5 ^{BC}	10.3± 3.2 ^B	68.3±33.7 ^C
Atipamezole 240 µg/kg	6.2±1.2 ^A	5.7±2.0 ^{BC}	9.2± 4.4 ^B	67.3±19.0 ^C
Flumazenil 100 µg/kg	6.7±1.0 ^A	1.0±2.1 ^C	9.0±17.0 ^B	173.3±24.7 ^D
			(38.0± 9.9) ^{b)C}	
Atipamezole 80 µg/kg + Flumazenil 100 µg/kg	7.0±4.0 ^A	1.2±0.4 ^C	2.0± 1.5 ^B	42.3±15.0 ^C

a) Atipamezole, flumazenil, atipamezole and flumazenil or saline solution were administered 30 min after injection of medetomidine at 40 µg/kg and midazolam at 0.2 mg/kg. Data were expressed as mean±standard deviation (n=6).

b) Data of the time when the pigs stood up again.

A, B, C, D: Mean values with same superscripts are not significantly different ($P > 0.05$).

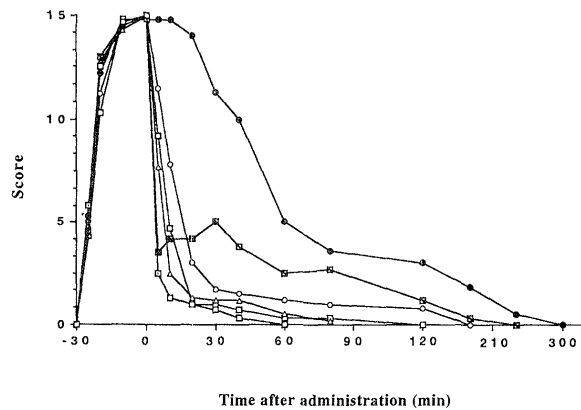


Fig. 1. Effects of atipamezole and flumazenil on sedative variables (full marks = 15) in pigs sedated by medetomidine-midazolam. Medetomidine and midazolam were injected intramuscularly 30 min before injection of antagonist(s). The pigs were given 80 µg/kg of atipamezole (○), 160 µg/kg of atipamezole (□), 240 µg/kg of atipamezole (△), 100 µg/kg of flumazenil (⊠), 80 µg/kg of atipamezole and 100 µg/kg of flumazenil (◻) and saline solution (●). Each symbol represents the mean value of the total score of posture, response to noise, resistance to restraint and resistance to mouth open and to pull tongue outwards.

Intravenous administration of flumazenil at a dose of 100 µg/kg reversed the medetomidine-midazolam induced sedation very quickly. These animals were aroused during or just after injection of the drug and five of the six pigs stood up soon after the arousal. The mean arousal time was significantly shorter than those in pigs given saline solution or 80 µg/kg of atipamezole. However, all the animals relapsed to moderate sedation 5 to 20 min after standing and became dorsal recumbency again. The sedative character score rebounded until 30 min after administration of flumazenil and stood up again approximately 40 min after administration (Table 1). Although the mean total recovery time was slightly shortened by flumazenil from the control value, the value was significantly longer than those in pigs given other antagonists.

Simultaneous administration of 80 µg/kg of atipamezole and 100 µg/kg of flumazenil quickly and effectively reversed the sedation induced by a combination of

medetomidine and midazolam. Sedative character score decreased significantly and most rapidly after administration of these antagonists. Recovery from sedation was smooth and the mean arousal time, mean standing time and mean total recovery time were significantly shortened from control values. However these data were not significantly different from those in pigs given 160 or 240 µg/kg of atipamezole.

Table 3 shows the effects of atipamezole and/or flumazenil on heart rate and body temperature in pigs sedated by a combination of medetomidine and midazolam. Thirty min after administration of medetomidine-midazolam or just before administration of antagonist(s), heart rate of any groups slightly decreased from base-line values. After administrations of atipamezole or atipamezole and flumazenil, heart rate increased in a dose-dependent manner of atipamezole. At the highest dose of atipamezole (240 µg/kg), heart rate significantly increased from the base-line value and caused moderate tachycardia (up to 180 beats/min) in two of the six pigs for less than 10 min.

Body temperature significantly decreased after injection of medetomidine and midazolam in each group. In pigs given saline solution or flumazenil alone, body temperature continued to decrease until 40 to 80 min after injections of antagonists and reached to approximately 36°C. On the contrary, body temperature in pigs given atipamezole or atipamezole and flumazenil was reversed after administrations of antagonists. In these atipamezole or atipamezole and flumazenil treated groups, the values did not significantly differ from each other.

DISCUSSION

In the present study all the pigs tested were constantly induced to a very deep sedation, and there were least variance of induction time or degree of sedation induced between each pig.

Administration of atipamezole quickly and smoothly reversed the effects induced by a combination of medetomidine and midazolam, and the arousal time, standing time and total recovery time were significantly reduced as

Table 2. Statistical analysis of the total scores used for evaluating sedative character in pigs given medetomidine-midazolam and atipamezole, flumazenil, atipamezole and flumazenil or saline solution^{a)}

Antagonist(s)	Time after administration (min)														
	-30	0	5	10	20	30	40	50	60	80	100	120	160	200	240
Saline solution	A ^{b)}	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Atipamezole 80 µg/kg	A	A	AB	AB	BC	B	B	BC	BC	B	BC	B	B	B	A
Atipamezole 160 µg/kg	A	A	B	BC	D	B	C	B	B	D	BC	B	D	C	B
Atipamezole 240 µg/kg	A	A	BC	CD	B	D	B	C	B	B	D	BC	D	C	B
Flumazenil 100 µg/kg	A	A	C	BC	A	C	A	AB	A	C	A	C	A	AB	B
Atipamezole 80 µg/kg + Flumazenil 100 µg/kg	A	A	C	D	D	B	C	B	C	D	C	D	C	B	B

a) Atipamezole, flumazenil, atipamezole and flumazenil or saline solution were administered 30 min after injection of medetomidine at 40 µg/kg and midazolam at 0.2 mg/kg.

b) Same alphabet (A, B, C, D) means that there is no significant difference in posture score between each group ($P > 0.05$).

Table 3. Effects of atipamezole, flumazenil or atipamezole and flumazenil on the changes of heart medetomidine-midazolam in pigs^{a)}

Antagonist(s)	Time after antagonist(s) administration (min)					
	-30	0	10	20	30	40
Heart rate (beats/min)						
Saline solution	104.0±12.4 ^A	87.2±21.0 ^A	87.0±15.1 ^A	86.0±20.3 ^A	82.0±20.7 ^A	81.0±19.6 ^{A*}
Atipamezole 80 µg/kg	100.0±13.5 ^A	95.0±23.2 ^A	99.7±16.9 ^A	104.0±18.5 ^{AB}	95.0±19.1 ^{AB}	95.0±19.1 ^A
Atipamezole 160 µg/kg	97.0± 8.8 ^A	82.0±10.5 ^{A*}	105.0±23.3 ^{AB}	103.0±10.3 ^{AB}	104.0±11.8 ^B	99.0±11.8 ^A
Atipamezole 240 µg/kg	98.0±11.2 ^A	87.0± 7.3 ^A	129.0±35.5 ^{B*}	120.0±16.5 ^{B*}	100.0±14.5 ^{AB}	99.0±10.6 ^A
Flumazenil 100 µg/kg	100.0± 9.8 ^A	93.0±15.1 ^A	91.0±14.9 ^A	97.3±18.0 ^A	88.0±17.7 ^{AB}	ND ^{b)}
Atipamezole 80 µg/kg+	98.0± 9.0 ^A	86.0± 7.3 ^{A*}	97.2± 6.6 ^A	96.0± 7.3 ^A	93.6± 3.3 ^{AB}	88.5± 9.0 ^A
Flumazenil 100 µg/kg						
Body temperature (°C)						
Saline solution	38.7±1.0 ^A	37.8±1.2 ^A	37.3±1.1 ^A	36.9±1.1 ^{A*}	ND	36.3±1.1 ^{A*}
Atipamezole 80 µg/kg	38.6±0.6 ^A	38.1±0.7 ^A	37.2±0.8 ^A	37.1±1.0 ^{A*}	ND	37.3±1.0 ^{AB}
Atipamezole 160 µg/kg	38.5±0.4 ^A	37.6±0.6 ^{A*}	36.9±0.5 ^{A*}	36.9±0.4 ^{A*}	ND	37.4±0.5 ^{BC}
Atipamezole 240 µg/kg	38.5±0.3 ^A	37.7±0.6 ^{A*}	37.1±0.6 ^{A*}	37.3±0.5 ^A	ND	37.8±0.6 ^C
Flumazenil 100 µg/kg	38.8±0.4 ^A	38.1±0.7 ^{A*}	37.4±0.7 ^{A*}	37.1±0.9 ^{A*}	ND	36.4±0.9 ^{AB*}
Atipamezole 80 µg/kg+	38.5±0.3 ^A	37.6±0.3 ^{A*}	37.3±0.5 ^{A*}	37.2±0.4 ^{A*}	ND	37.5±0.3 ^{C*}
Flumazenil 100 µg/kg						

a) Atipamezole, flumazenil, atipamezole and flumazenil or saline solution were administered 30 min after midazolam at 0.2 mg/kg. Data were expressed as mean±standard deviation (n=6).

b) Not detected.

A, B, C: Mean values with same superscripts are not significantly different (P>0.05)

*: significantly different from a base-line value (P<0.05).

compared with those in pigs given saline solution. Atipamezole, 4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride, is a potent and highly selective and specific α_2 -adrenoreceptor antagonist which produces a potent antagonism of the effects of medetomidine in dogs, cats, zoo animals and also in pigs [1, 4, 7, 10]. It has been reported that this antagonistic effect was obtained even if medetomidine was used with ketamine and butorphanol [11], because the administered dose of ketamine which was reduced to one half to one fourth and butorphanol would not produce satisfactory anesthesia or sedation by themselves. As we reported [5], 0.2 mg/kg of midazolam alone exerted minimum sedative effect for the shorter duration. In the present study pigs might be little influenced by residual midazolam when the atipamezole was injected (30 min after administration of medetomidine-midazolam) and the effect of medetomidine was abolished.

The optimal antagonistic action of atipamezole alone against medetomidine-midazolam induced sedation was seen at a dose of 160 µg/kg which was the four times higher than preceding medetomidine dose. The antagonistic effect became more potent in proportion to the increase in atipamezole dose administered, and the mean total recovery time in pigs given 160 µg/kg and 240 µg/kg of atipamezole were significantly shorter than that in pigs given 80 µg/kg of atipamezole. However, there were no significant differences between the antagonistic effect induced by 160 µg/kg of atipamezole and that by 240 µg/kg of atipamezole. And some of the pigs given 240 µg/kg of atipamezole appeared mildly hyperactive during the recovery phase in contrast to very smooth recovery from sedation in pigs given 160 µg/kg of atipamezole. This

excessive effect, which was also observed when a higher dose of atipamezole was administered to the pigs given medetomidine alone [7], was probably caused by the excitatory effects of α_2 -adrenergic antagonist on central nervous system [12]. In addition, heart rate increased in pigs given 240 µg/kg of atipamezole. This change was also partly caused by a central stimulant effect of atipamezole [2]. Those results might indicate that 240 µg/kg of atipamezole alone was slightly excessive for antagonism of medetomidine-midazolam induced sedation.

The pigs given flumazenil at a dose of 100 µg/kg were aroused very quickly and most of the pigs stood up soon after arousal. However, flumazenil might not be valuable as a sole antagonistic agent as compared with atipamezole, because all the animals relapsed to moderate sedation after standing. This relapse effect was apparently induced by residual medetomidine because the total score used for evaluating the sedative character after administration of flumazenil became similar to that in pigs given 40 µg/kg of medetomidine alone [5]. Flumazenil is a specific and exclusive benzodiazepine antagonist with a high affinity for benzodiazepine receptors, where it exerts minimal agonist activity [9]. As a competitive antagonist, flumazenil reverses all the agonist effects of benzodiazepine quickly when used intravenously [3], but does not block the hypnotic response to medetomidine [8].

The sedative effect induced by medetomidine and midazolam was most effectively reversed by a combination of atipamezole and flumazenil in pigs even if the lower dose of atipamezole was used. However, there were no significant differences in the mean arousal time, mean standing time and mean total recovery time between pigs given atipamezole-flumazenil and pigs given 160 and 240

rate and body temperature induced by

60	80	120
81.6±19.6 ^A	86.4±23.1 ^{AB}	93.1±20.5 ^A
92.0±11.8 ^{AB}	90.0±10.0 ^{AB}	95.0±16.3 ^A
86.4±16.2 ^{AB}	93.6± 6.8 ^{AB}	95.0± 1.4 ^A
104.0± 6.2 ^B	102.7± 6.1 ^A	106.0± 2.8 ^A
82.0±15.5 ^A	83.0±13.9 ^B	84.0±17.0 ^A
90.0±10.4 ^{AB}	96.0± 0.0 ^{AB}	ND
36.3±1.1 ^A	36.2±1.0 ^A	36.6±0.7 ^s
37.4±0.8 ^{BC}	37.9±0.8 ^B	38.5±1.3
37.7±0.6 ^C	37.8±0.5 ^B	38.3±0.4
38.1±0.7 ^C	38.1±0.5 ^B	ND
36.6±0.9 ^{AB}	36.5±0.8 ^A	37.7±1.1 ^s
37.7±0.4 ^C	38.0±0.6 ^B	ND

injection of medetomidine at 40 µg/kg and

µg/kg of atipamezole. As it is difficult to concentrate flumazenil solution because of its water insolubility, much injection volume of flumazenil is needed for antagonism against midazolam with a higher cost. Practically, atipamezole alone is thought to be potent enough to antagonize the sedation induced by a combination of medetomidine-midazolam.

In conclusion, the sedative effect and the decrease in body temperature induced by a combination of medetomidine and midazolam could be reversed quickly and smoothly by atipamezole alone. The optimal action was seen at a dose of 160 µg/kg, which was four times higher than the preceding medetomidine dose. The possible use of an antagonist might enhance the value and availability of medetomidine-midazolam for chemical restraint in laboratory pigs.

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