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Clinical Antagonistic Effect of Atipamezole in Cats Anesthetized with Tiletamine-Zolazepam and Medetomidine

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Abstract : The purpose of the study is to evaluate the clinical antagonistic effect of atipamezole(0.25 mg/kg, IM) in cats anesthetized with tiletamine-zolazepam (zoletil®, 10 mg/kg, IM) and medetomidine (0.05 mg/kg, IM). Twelve healthy 1 year old Korean mixed breed cats were used for this study. They were 4 males and 8 females. These cats were randomly assigned to two groups. One was control group (Zoletil® + medetomidine, ZM), and the other was treatment group (Zoletil®+medetomidine and antagonism by atipamezole, ZMA). All cats were examined 15 minutes before, 5, 25, 65 and 105 minutes after administration of tiletamine-zolazepam and medetomidine. Atipamezole was injected intramuscularly 20 minutes after ZM administation. Recovery time, heart rate, respiratory rate, total plasma protein and blood glucose were significantly different between ZM group and ZMA group ($P < 0.05$). However, rectal temperature was not significantly different between ZM group and ZMA group. Two groups were able to induce sternal recumbency within 2 minutes and lateral recumbency within 4 minutes after the anesthetics injection. Mean sternal position time (mean ± SD) was 174.0 ± 44.6 and 116.2 ± 27.3 minutes, and mean standing position time was 210.8 ± 45.6 and 154.2 ± 21.1 minutes in ZM and ZMA group, respectively. In these two groups, adverse effects during recovery time from anesthesia were not seen. As a result, the ZMA group had a faster recovery than the ZM group. Thus it was concluded that atipamezole could exert a useful reversal effect in cats anesthetized with medetomidine-tiletamine/zolazepam combination.

Key words **:** cat, atipamezole, tiletamine/zolazepam, medetomidine.

Introduction

So often in the past domestic cats have been regarded as being simply small dogs, but this attitude has gradually changed and it is now recognized that cats are unique among domestic animals. Cat object to being restrained and even friendly cats have been proved difficult to anesthetize effectively unlike other animals (8,11).

Tiletamine and zolazepam are used a 1 : 1 combination (1). Tiletamine[2-(ethylamino)-2-(2-thienyl)cyclohexanonehydrochloride] was first reported in 1969. It is a dissociative anesthetic agent with pharmacologic properties similar to those of ketamine, but it has longer duration of action and greater analgesic effect than that of ketamine (12). Zolazepam [4-(o-fluorophenyl)-6,8-dihydro-1,3,8-trimethyl-pyrzole [3, 4-e]diazepine-7(1H)-one] is a benzodiazepine derivative with pharmacologic properties similar to those of diazepam (8). Zolazepam induces muscle relaxation and tranquilization. Tiletamine quickly induces satisfactory levels of anesthesia, but it has short duration of anesthesia, poor muscle relaxation and ineffectiveness upon visceral pain. On the other hand, zolazepam was chosen to combine with tiletamine because of its effectiveness as an anti-convulsant and muscle relaxant (8). Zoletil® (Virbac, France) is a 1 : 1 mixture by weight of tiletamine and zolazepam. It has been proved to be a very useful drug for an induction of anesthesia in a wide variety of wild and domestic animals (3-5).

The adverse effects include respiratory depression, erratic vocalization and/or prolongation of recovery, involuntary muscular twitching, cyanosis, cardiac arrest, pulmonary edema and either hypertension or hypotension. Pain after IM injection, especially in cat, has been noted which may be a result of the low pH of the solution (9).

Medetomidine [4-(1-(2,3-dimethylphenyl)ethyl)-1H-imidazole] is a specific $alpha_2$-adrenoceptor agonist and sedative-analgesic intended for use in dogs and cats, but also may be useful in other pets and exotics (1,2). It is commonly used as a preanesthetic prior to ketamine or mask induction agent with an inhalation anesthetic. It has an $alpha_2/alpha_1$ selectivity factor of 1620, and shows 10 times higher selectivity for $alpha_2$, receptors compare to xylazine. Xylazine has an $alpha_2/alpha_1$ selectivity factor of 160 (7).

The adverse effects reported with medetomidine are basically an extension of its pharmacologic effects including bradycardia,

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occasional AV blocks, decreasing respiration, hypothermia, urination, vomiting and hyperglycemia, and pain on injection. But medetomidine is commonly used sedative analgesic and preanesthetic in veterinary medicine (12).

Atipamazole HCL [4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole] was synthesized in the course of a project to find a potential medetomidine antagonist for use in veterinary practice (11). It is a specific and competitive alpha$_2$-antagonistic drug which is able to inhibit the sedation, analgesic and other effects of medetomidine and xylazine. Net pharmacologic effects of atipamezole are reduction of sedation, blood pressure decrease, heart and respiratory rate increase, and reduction of the analgesic effect of alpha$_2$-adrenergic agonist. The peak plasma levels occur about 10 minutes after IM administration in the cat. The drug has an average plasma elimination halflife of about 2-3 hours. The alpha$_2$/alpha$_1$ selectivity ratio of atipamezole is 200 to 300 times higher than either idazoxan or yohimbine (7,11). Potential adverse effects include occasional vomiting, diarrhea, hypersalivation and tremor (12).

The cat is easily excited unlike the other pets and still has wildness themselves, so that it's difficult to restrain them under anesthesia, and sometimes need assistants to do that.

The purpose of this study is to recognize clinical antagonistic effects of atipamezole on Zoletil® and medetomidine anesthesia in cats. Thus, induction and recovery time values, and vital change values were monitored in cats administered with atipamezole after Zolitil® and medetomidine anesthesia.

Materials and Methods

Experimental Design

Twelve healthy 1 year old mongrel breed cats were used for this study. These were consist of 4 males (33.3%) and 8 females (66.6%). They were fed a dry food (Science diet®, Hill' pet company, USA) and a moist food (Cesar®, Uncle ben's company, USA) from 1 month before experiment. Food and water were withheld for 12 hours prior to the experiments.

These cats were randomly assigned to two groups. One was control group (Zoletil®+medetomidine, ZM), and the other was treatment group (Zoletil®+medetomidine and atipamezole, ZMA). The control group cats (ZM group) with weight of 3.62 ± 0.52 (mean ± SD) kg received 10.0 mg/kg of Zoletil® and 0.05 mg/kg of medetomidine (Domitor®, Orion Pharma, Finland). The treatment group cats (ZMA group) with weight of 3.65 ± 0.48 kg received 10.0 mg/kg of Zoletil® and 0.05 mg/kg of medetomidine and were antagonized by 0.25 mg/kg atipamezole (Antisedan®, Orion Pharma, Finland). All drugs were injected intramuscularly. Atipamezole was injected 20 minutes after medetomidine and Zoletil® injection.

All cats were examined 15 minutes before, 5, 25, 65 and 105 minutes after Zoletil® and medetomidine administration.

Recordings and Evaluations

Induction and recovery time

Induction time was the sternal recumbency time (from injection to sternal recumbency position) and lateral recumbency time (from injection to lateral recumbency). And recovery time was sternal position time (from injection to sternal position) and standing time (from injection to standing position).

Vital signs

Physiological parameters were monitored. Rectal temperature was measured with a digital thermometer (Kruuse digital thermometer®, Kruuse, Denmark) and heart rates was measured by a stethoscope. Respiratory rates were measured by observing the abdominal movement. Points of evaluation time for rectal temperature, heart rates and respiratory rates were at 15 minutes before, 5, 25, 65 and 105 minutes after tiletamine/zolazepam and medetomidine administration.

Statistical Analysis

All data were expressed as mean ± standard deviation. Induction and recovery time, vital signs (rectal temperature, heart rates and respiratory rates) were analyzed by two-way ANOVA analysis. The significance level of all tests was set at $p < 0.05$.

Results

1. Observation of induction and recovery

Both control and treatment groups were induced by rapid onset of sedation following the intramuscular injection in the biceps femoris muscle. After injection, all cats in both groups were very sensitive and rough. Tiletamine/zolazepam and medetomidine anesthesia were able to induce sternal recumbency within 3 minutes and lateral recumbency within 4 minutes after drug injection in both groups. Induction time of both groups had not significant difference. But recovery time had significant difference between control and treatment group. Mean recovery time to sternal position was 174.0 ± 44.6 minutes in ZM group and 116.2 ± 27.3 minutes in ZMA group, respectively. Mean recovery time to standing position

Table 1. Effect of atipamezole on induction and recovery variation in cats anesthetized with tiletamine/zolazepam and medetomidine

Group	Sternal recumbency time -induction(min)	Lateral recumbency time -induction(min)	Sternal position time -recovery(min)	Standing position time -recovery(min)
ZMA	2.2 ± 0.6	3.2 ± 0.7	116.2 ± 27.3*	154.2 ± 21.1*
ZM	1.4 ± 0.1	2.3 ± 0.9	174.0 ± 44.6	210.8 ± 45.6

*Significant difference between ZM group and ZMA group ($p < 0.05$).
ZM: Tiletamine/zolazepam and medetomidine, ZMA: Tiletamine/zolazepam and medetomidine and antagonism by atipamezole.

was 210.8 ± 45.6 minutes and 154.2 ± 21.1 minutes in ZM group and ZMA group, respectively. As a result, ZMA group was faster recovery than ZM group. And time from sternal recumbency to standing position in ZMA group was significantly shorter ($p < 0.05$) than ZM group (Table 1).

2. Changes of rectal temperature

The mean rectal temperature of the two groups (ZM, ZMA group) was gradually increased until 5 minutes after drug injection. In the ZM group, the rectal temperature showed a tendency to decrease from 5 minutes after injection to the end of experiment. But, In the ZMA group, rectal temperature was slightly increased after 65 minutes. Rectal temperature was not significantly different between ZM group and ZMA group (Fig 1).

3. Changes of Heart Rate

All groups revealed a rapid decrease in heart rate up to 25 minutes following anesthetic drug injection. After 25 minutes, ZMA group showed a tendency to increase at experiment ending time. The heart rate was significantly different between ZM group and ZMA group (Fig 2).

4. Respiratory rate

The mean respiratory rates of ZM and ZAM group were decreased until 25 minutes after anesthetic drug injection. After that, respiratory rates in both groups were gradually increased until 65 and 105 minutes. The respiratory rate was significantly different between ZM group and ZMA group (Fig 3).

Discussion

In this study, Zoletil® and medetomidine combination were effective in anesthetizing cats, and atipamezole was effective in shortening sternal position time and standing time by this combination.

Medetomidine binds to membrane-associated receptors on presynaptic and postsynaptic nerves. So, this drug modulates the release of norepinephrine, results in sedation, decreases locomotor activity, and suppresses conditioned responses. However, complete anesthesia for general surgery requires the addition of other anesthetic combinations such as Zoletil®, ketamine and butophanol, etc (2,6). Tiletamine is an cyclohexamine that provides analgesia and immobilization, whereas zolazepam, a benzodiazepine derivative, provides smooth muscle relaxation, anti-

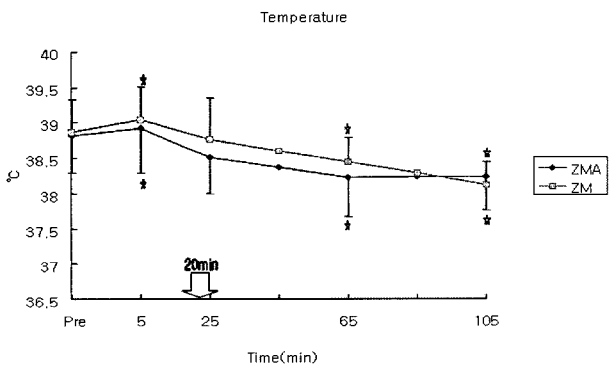

Fig 1. Effect of atipamezole on temperature in cats anesthetized with tiletamine/zolazepam and medetomidine.
Rectal temperature was not significantly different between ZM group and ZMA group.
ZM : Tiletamine/zolazepam and medetomidine, ZMA : Tiletamine/zolazepam and medetomidine and antagonism by atipamezole.
*Significantly different from baseline ($p < 0.05$).

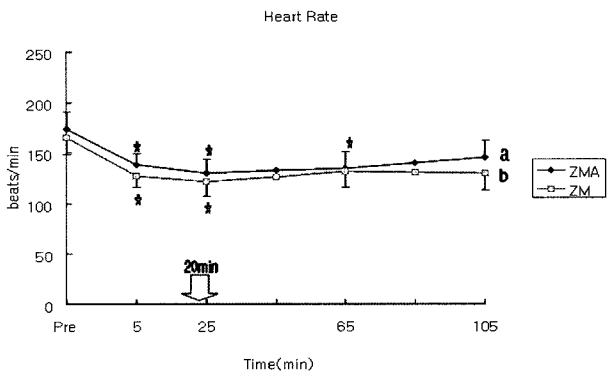

Fig 2. Effect of atipamezole on heart rate in cats anesthetized with tiletamine/zolazepam and medetomidine.
Heart rate was significantly different between ZM group and ZMA group.
ZM : Tiletamine/zolazepam and medetomidine, ZMA: Tiletamine/zolazepam and medetomidine and antagonism by atipamezole
a, b : Values marked with different letters represent significant difference statistically. ($P < 0.05$).
*Significantly different from baseline ($p < 0.05$).

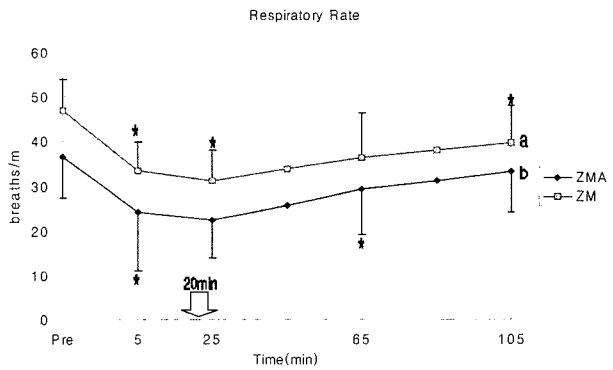

Fig 3. Effect of atipamezole on respiratory rate in cats anesthetized with tiletamine/zolazepam and medetomidine.
Respiratory rate was significantly different between ZM group and ZMA group.
ZM : Tiletamine/zolazepam and medetomidine, ZMA : Tiletamine/zolazepam and medetomidine and antagonism by atipamezole.
a, b : Values marked with different letters represent significant difference statistically. ($P < 0.05$).
*Significantly different from baseline ($p < 0.05$).

convulsant activity and tranquilization (8). Zoletil® and medetomidine anesthesia were able to induce sternal recumbency within 3 minutes and lateral recumbency within 4 minutes after drug injection in each group. Mean recovery to sternal position time was 174.00 ± 44.61 minutes in ZM group. Generally, this anesthesia time is enough for abdominal surgery in cats.

As a result, ZMA group had faster recovery than ZM group. During Zoletil® and medetomidine anesthesia, reversal effect of atipamezole is probably due to its antagonism on medetomidine effects in this study. Both medetomidine and atipamezole compete at alpha$_2$-adrenergic receptors (10). Pharmacologic effects of atipamezole are reduce sedation and anlagesic effect alpha$_2$-adrenergic agonist (10). Atipamezole is a specific and competitive alpha$_2$-antagonistic drug which is able to inhibit the sedative, analgesic and other effects of medetomidine and xylazine. Similar results were observed in the study with other animals. In dog, higher dose of atipamezole was more effective in reducing the anesthetic time, but induced rougher recovery (7). The values for the retal temperature were decreased in both groups at 5 to 65 minutes. Heart rate and respiratory rate in both group were decreased up to 25 minutes following anesthetic drug injection. These results are similar to the previous report, medetomidine induced hypothermia, bradycardia and respiratory depression (9).

In conclusion, Zoletil® and medetomidine combination were effective in anesthetizing cats. And the results of this study showed that atipamezole is considerd to have a useful reversal effect in cats anesthetized with medetomidine-tiletamine/zolazepam combination.

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고양이에서 tiletamine-zolazepam과 medetomidine 마취에 대한 atipamezole의 임상적 길항 효과

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요 약 : 연구의 목적은 고양이에서 Zoletil® 과 medetomidine 약물 마취 시 atipamezole의 임상적 길항 효과를 보기 위함이다. 마취를 하고 다시 회복 되는 동안에 체온, 심박수, 호흡수를 측정하였다. 이 연구에는 12 마리의 건강한 한국 잡종 고양이를 사용하였다. 각 6마리씩 무작위로 선별하여 대조군(Zoletil® 과 medetomidine, ZM)과 실험군(Zoletil®, medetomidine 과 길항제인 atipamezole, ZMA) 두 군으로 나누었다. 모든 고양이들은 투여 전 15분, 주사 후 5분, 25분, 65분, 105분에 평가하였으며, 길항제인 atipamezole은 마취 주사 후 20분에 근육 주사 하였다. 회복 시간, 심박수, 호흡수는 두 군간 유의성이 있는 결과를 보였고 체온은 유의성을 나타내지 않았다. 두 군 모두 Zoletil® 과 medetomidine 마취 주사 후 4분 내에 횡와 되는 결과를 보였고 마취 시간도 3시간 가까이 지속해 고양이에 있어서 이들 약물이 좋은 마취 효과가 있음을 보여 주었다. 회복 시 마취 부작용은 거의 보이지 않았다. 고양이가 마취에서 회복되어 기립 자세를 하기까지 걸리는 시간이 ZM 군에서는 210.8 ± 45.6 시간으로 나타났고, ZMA 군에서는 154.2 ± 21.1 시간으로 나타났다. 길항제를 투여한 ZMA 군에서 회복시간이 거의 한 시간 가까이 단축되어 ZMA 군이 ZM 군보다 회복이 빠르다는 결과를 보였다. 본 연구에서 atipamezole은 medetomidine-tiletamine/zolazepam으로 병용 마취된 고양이에서 유용한 회복효과를 발휘하였다.

주요어 : 고양이, atipamezole, tiletamine/zolazepam, medetomidine