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Comparison of Anesthetic Effects Induced by Tiletamine-Zolazepam and Azaperone Plus Tiletamine-Zolazepam in Growing Pigs

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Abstract : The purpose of this study was to determine the anesthetic effects of tiletamine-zolazepam (TZ) alone and azaperone plus tiletamine-zolazepam in growing pigs, and to compare the various physiological parameters in both treatments. Cross experiment was accomplished at 2-week interval. Group 1 (TZ group); six pigs (31.4±4.83 kg) received 4.4 mg/kg of TZ alone. Group 2 (ATZ group); the same six pigs (43.6±4.31 kg) received 4.4 mg/kg of TZ twenty minutes after receiving 2 mg/kg of azaperone. All of the anesthetic drugs were injected into the trapezius muscles. The pigs were fasted for 24 hours before the experiments. Induction and recovery values were determined. Heart rate, respiratory rate, rectal temperature, pO_2, pCO_2 and pH were determined before administration and 5, 25, 45, 65 and 85 minutes after administration. Induction time of ATZ group was more rapid than that of TZ group ($p<0.01$). During recovery, sternal recumbency time, standing time and walking time of ATZ group were longer than those of TZ group ($p<0.01$). Heart rate, respiratory rate, pO_2, pCO_2 and pH did not show especial differences between the two groups. However, rectal temperature was significantly different between the TZ and ATZ group ($p<0.05$). As a result, ATZ group had a faster induction and a longer duration of anesthesia than TZ group did. Thus, it was concluded that ATZ combination could be usefully used for chemical restraint in pigs.

Key words **:** pig, azaperone, tiletamine-zolazepam, anesthetic effect.

Introduction

The pig is an excellent experimental animal in comparative physiology and has thus been widely used in clinical research (4). Recently pigs have been used for organs transplantation or many purposes. However, pigs are not easy to be handled because they vocalize extremely loudly and struggle hardly, when they were restrained. The restraint needs therefore for handling of pigs (9). Various methods for the restraint of pigs have been studied. The effort to find suitable sedative have been continued at the present time. Administration of a sedative might be needed for restraint to complete the minor or non-painful procedures and to induce general anesthesia smoothly (9).

Tiletamine-zolazepam (TZ) (Zoletil® 50 mg/ml, Virbac, France), a non-opioid, non-barbiturate injectable anesthetic, is a 1 : 1 (weight to weight) combination of tiletamine and zolazepam (7,13). Tiletamine, a dissociative anesthetic agent, was selected due to its longer duration of action and greater analgesic effect than that of ketamine (7). Zolazepam, a benzodiazepine tranquilizer, was chosen to combine with tiletamine because of its effectiveness as an anti-convulsant and muscle relaxant (7). The pharmacological actions of these two drugs are complementary, with tiletamine providing analgesia and immobilization and zolazepam contributing to muscle relaxation and tranquilization. TZ has been used either alone or in combination with other anesthetics in laboratory animals including pigs (6,12).

Azaperone (Stresnil® 40 mg/kg, Janssen, Belgium), a butyrophenone derivative, cause tranquilization and sedation, antiemetic activity, reduced motor activity, and inhibition of CNS catecholamines. Azaperone appears to have minimal effects on respiration. Azaperone is officially indicated for the control of aggressiveness when mixing or regrouping weanling or feeder pigs weighing up to 36.4 kg. Azaperone is also used clinically as a general tranquilizer for swine, in aggressive sows to allow piglets to be accepted, and as a preoperative agent prior to general anesthesia or cesarean section with local anesthesia (10).

Many studies about administration of azaperone alone (11) and TZ alone (7) were present, but no data are available on azaperone plus TZ combination (ATZ) administration in growing pigs.

The purpose of this study was to determine the anesthetic effects of TZ alone and ATZ administration in growing pigs, and to compare the anesthetic parameters in both treatments.

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Materials and Methods

In this study, six healthy mixed breed pigs (Landrace and Yorkshire) were used. These pigs were provided from the agriculture livestock farm, at Chungnam National University. Cross experiment was accomplished at 2-week interval.

Group 1 (TZ group); six pigs (31.4 ± 4.83 kg) were received 4.4 mg/kg of TZ alone. Group 2 (ATZ group); the same six pigs (43.6 ± 4.31 kg) were received 4.4 mg/kg of TZ twenty minutes after receiving 2 mg/kg of azaperone. All of the anesthetic drugs were injected into the trapezius muscles. Pigs had fasted for 24 hours before each trial, in order to prevent the possible adverse effects associated with anesthesia.

Induction and recovery values were determined. Heart rate, respiratory rate, rectal temperature, pO_2, pCO_2 and pH were determined before administration and 5, 25, 45, 65 and 85 minutes after administration.

Induction and recovery

Sternal position time (from injection to sternal position for induction), sternal recumbency time (from injection to sternal recumbency for arousal stage), standing time (from injection to standing for arousal stage; if the pigs stood over the ten seconds), and walking time (from injection to walking for arousal stage) were checked with a stopwatch.

Vital signs

Heart rate was measured by stethoscope, respiratory rate was measured by observing of the costo-abdominal movements, and rectal temperature was measured with a electronic thermometer (13).

Blood gas

Arterial blood samples for arterial blood gas analysis were collected from the femoral artery. pH, pCO_2, and pO_2 were measured in each time with a blood gas analyzer (OPTI Critical care analyzer, AVL, USA).

Statistical analysis

Induction and recovery values were compared using a one-way ANOVA analysis. Vital signs (heart rate, respiratory rate and rectal temperature) and arterial blood gases (pO_2, pCO_2 and pH) were analyzed by two-way analysis of variance (ANOVA) for repeated measures to compare time-related variables within each anesthetic group. The comparison of all data with baseline data in same group was assessed by student's *t*-test. The significance level of all tests was set at $p < 0.05$.

Results

Induction and recovery variation

Induction time of ATZ group was more rapid than that of TZ group ($p < 0.01$). Recovery values such as sternal recumbency time, standing time and walking time of ATZ group were longer than those of TZ group ($p < 0.01$). As a result, ATZ group had a faster induction and a longer duration of anesthesia than TZ group had (Fig 1).

Changes of heart rate

Heart rate of both groups was changed a little as compared with baseline value. The heart rate of TZ group was higher than that of ATZ group in each time. But no significant difference was observed between both groups (Fig 2).

Changes of respiratory rate

Respiratory rate of both groups was changed a little as compared with baseline value (Fig 3). The respiratory rate of TZ group was higher than that of ATZ group in each time.

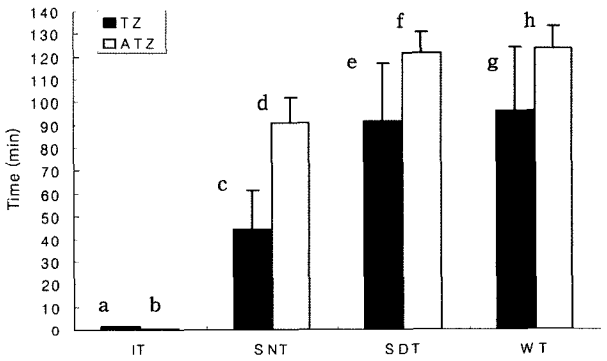

Fig 1. The changes of induction and recovery values in pigs anesthetized with Tiletamine-zolazepam (TZ) group and Azaperone plus tiletamine-zolazepam (ATZ) group. IT; induction time was the time from TZ injection to sternal position, SNT; sternal recumbency time was the time from TZ injection to sternal recumbency in arousal stage, SDT; standing time was the time from TZ injection to standing. WT; walking time was the time from TZ injection to walking. a,b : c,d : e,f : g,h ; different letters means significant difference between the both groups. ($p < 0.01$)

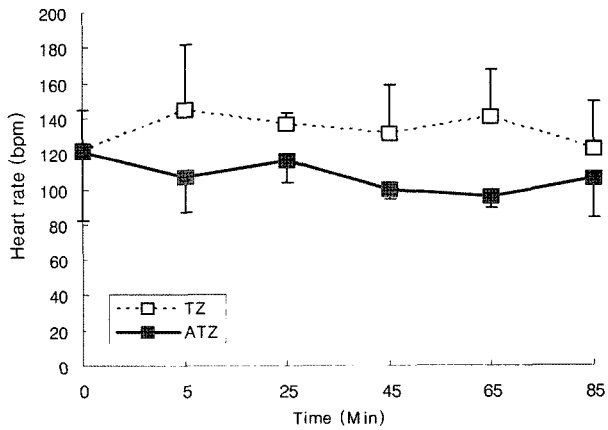

Fig 2. The changes of heart rate in pigs anesthetized with TZ group and ATZ group.

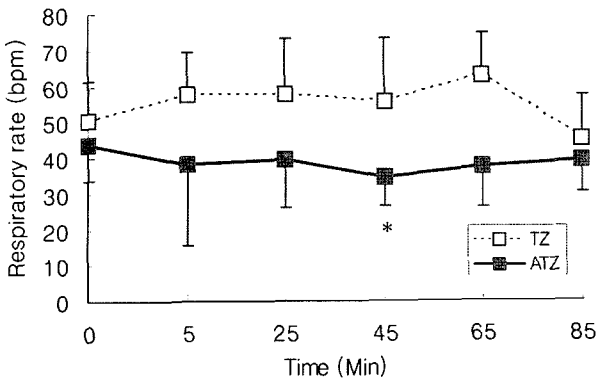

Fig 3. The changes of respiratory rate in pigs anesthetized with TZ group and ATZ group. *Significantly different from baseline ($p < 0.05$).

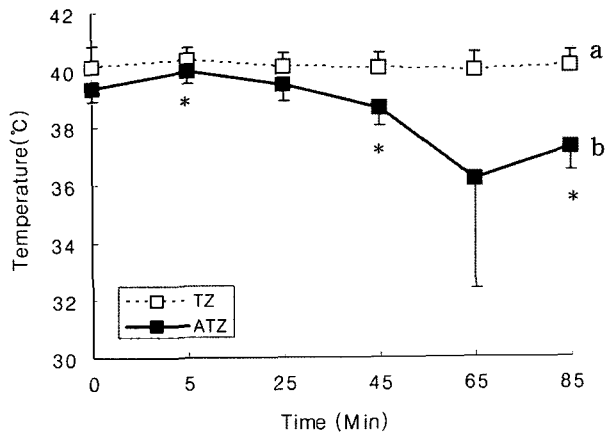

Fig 4. The changes of rectal temperature in pigs anesthetized with TZ group and ATZ group. *Significantly different from baseline ($p < 0.05$). a, b; Different letters means significant difference between the both groups ($p < 0.05$).

Respiratory rate in ATZ group was more stable than that of TZ group. But no significant difference was observed between both groups. Respiratory rate in ATZ group was significantly decreased at 45 minutes as compared with baseline ($p < 0.05$).

Changes of rectal temperature

Rectal temperature was stable through the experiment in TZ group, but gradually decreased at 25, 45 and 65 minutes and increased at 85 minutes after TZ administration in ATZ group. Significant difference was observed between both groups ($p < 0.05$).

Changes of pO_2

Fig 5 shows changes of pO_2 in TZ and ATZ group. In TZ group, pO_2 decreased gradually in 5, 25 and 45 minutes, and then increased at 65 minutes. Although significant difference was observed at 45 minutes in TZ group ($p < 0.05$), the values of ATZ group were stable to appear lineal graph. No significant difference was observed between both groups.

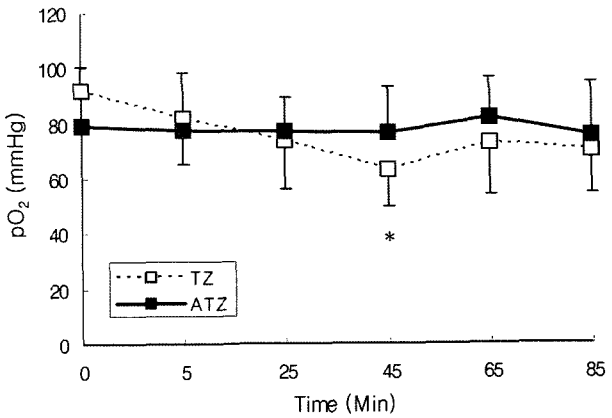

Fig 5. The changes of arterial blood pO_2 in pigs anesthetized with TZ group and ATZ group. *Significantly different from baseline ($p < 0.05$).

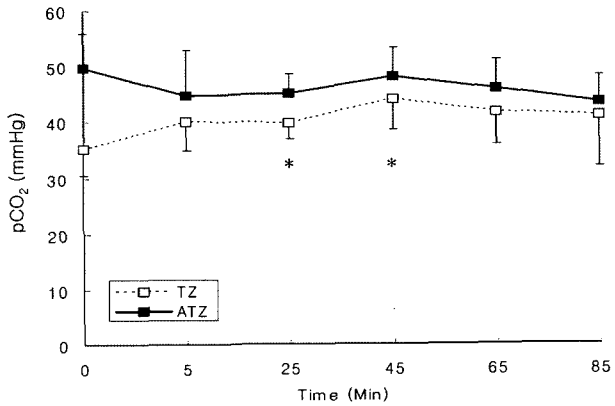

Fig 6. The changes of arterial blood pCO_2 in pigs anesthetized with TZ group and ATZ group. *Significantly different from baseline ($p < 0.05$).

Changes of pCO_2

Fig 6 shows changes in pCO_2 over time in groups TZ and ATZ. pCO_2 was lower in TZ group compared with ATZ group in each time. In both groups, pCO_2 were not changed rapidly. There were significant differences at 25 and 45 minutes as compared with baseline in TZ group ($p < 0.05$). No significant difference was observed between both groups.

Changes of pH

In both groups, pH increased gradually until 65 minutes (Fig 7). At 85 minutes, TZ group had decreased. In ATZ group, pH was increased slowly until 85 minutes. Significant differences were in 5, 25, 45 and 65 minutes to be compared with baseline in TZ group ($p < 0.05$). There were significant differences in 25, 45, 65 and 85 minutes as compared with baseline in ATZ group ($p < 0.05$). No significant difference was observed between both groups.

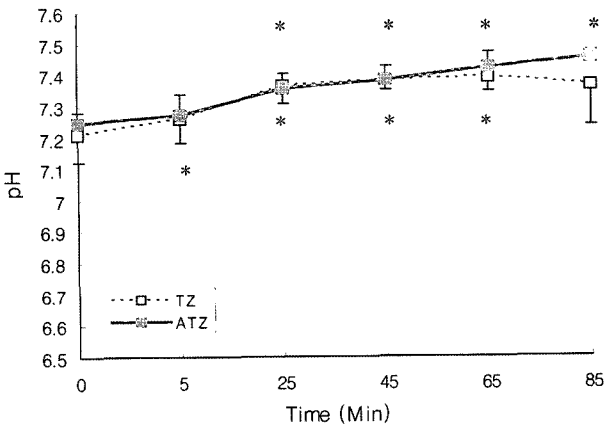

Fig 7. The changes of arterial blood pH in pigs anesthetized with TZ group and ATZ group. *Significantly different from baseline ($p < 0.05$).

Discussion

Azaperone, a neuroleptic agent belonging to the butyrophenone group of compounds, is used alone to induce sedation in swine (11). The drug is considered to have a fairly rapid onset of action following intramuscular injections in pigs (5-10 min) with a peak effect at approximately 30 min post injection (9). So TZ administration was followed azaperone administration after 20 min in this study. It has a duration of action of 2-3 hours in young pigs (10). Ataxia occurred in pigs given 10 mg of azaperone/kg intramuscularly and became severe when the azaperone dosage was increased to 40 mg/kg (5). The degree of sedation was directly proportional to the azaperone dosage. Muscle tremors accompanied by increased respiratory rate and salivation have been reported after administration of 5 to 6 mg of azaperone/kg in pigs (5). In this study, azaperone dosage was 2 mg/kg in the ATZ combination. We did not see any muscle tremors. It is possible that the dose of azaperone used in this study was low not to induce any appreciable side effects. However, we saw a little salivation in ATZ group. We thought that the side effect of salivation was appeared by the side effect of TZ. Although used this small dosage of azaperone (2 mg/kg), we believe the drug contributed some sedative property to the ATZ combination. This is supported by the fact that duration of recover to sternal recumbency was longer in ATZ (90.83 ± 11.17 min)-treated pigs than in those treated with TZ (44.33 ± 17.35 min).

To allow calm induction without elevation of stress hormones and a negative influence on cardiopulmonary function, quick intramuscular administration with a small volume would appear to be less stressful than the restraint required for IV injection. Also the cervical muscle injection causes less whole body movement than the other injection site, middle gluteal muscle, triceps muscles and fascia lata muscle (2). In this study, all of the anesthetic drugs were injected into the trapezius muscles.

Pigs given ATZ showed the strange behavior such as persistent licking or gnawing during recovery phase. It has been known that these drugs produce their sedative effects by antagonism of dopamine as a neurotransmitter which also causes extrapyramidal side effects characterized by abnormal motions (9). These abnormal behavior observed in this study may be related to this neurological side effect. Also, azaperone should not be given IV as a significant excitatory phase may be seen in pigs. In this study. premedication, such as atropine, was not administrated because premedication would interrupt determination of sedation effect by TZ or ATZ administration.

In this study, the heart rate of ATZ group was lower than that of TZ group. This result may express that azaperone premedication inhibited some actions of TZ. Generally TZ increases heart rate and depresses respiratory system, occasionally causes apnea, but respiratory rate remains unchanged or increased in most species (7,8). In this study, respiratory rate of TZ group was higher than that of ATZ group. Azaperone appears to have minimal effects on respiration and may inhibit some of the respiratory depressant actions of general anesthetics (10). Decreased respiratory rate of ATZ group might be occurred by respiratory depression of TZ and minimal respiratory depression of azaperone.

Azaperone causes vasodilatation resulting in a small fall in arterial blood pressure, and vasodilatation of cutaneous vessels makes sedated pigs particularly likely to develop hypothermia in a cold environment (3). In this study, rectal temperature of TZ group was stable in all time. However, rectal temperature of ATZ group was gradually decreased in 25, 45 and 65 minutes after TZ administration. Also, significant difference was observed between both groups ($p < 0.05$). Perhaps this result was due to the effect of vasodilation by azaperone (3).

The pH were increased slowly in both groups. The result is understood that lactic acid released from muscle exercise was increased in bloodstream at restraint for first blood collection (1). And then the pH was increased slowly to normal range (pH 7.4).

Both drug combinations induced effective chemical restraint in pigs. Sternal recumbency or lateral recumbency was achieved within 2 min in all pigs following intramuscular injection, with no signs of excitement. In ATZ group premedicated with azaperone, the onset of sternal recumbency was appeared more rapid than in TZ group. The results of this study indicate that the addition of azaperone to TZ prolongs analgesia without increasing the duration from arousal to standing and from standing to walking. Thus, it was considered that ATZ may be used for deep sedation on induction of anesthesia in pigs.

Acknowledgements

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돼지에서 Tiletamine-Zolazepam 단독과 Azaperone, Tiletamine-Zolazepam 합제의 마취 효과에 대한 비교

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요 약 : 본 연구에서는 돼지에서 tiletamine-zolazepam (TZ) 단독 사용과 azaperone, tiletamine-zolazepam (ATZ) 합제 사용시의 마취효과를 규명하고, 양군에서의 생리학적 parameters를 비교하였다. 두개의 군으로 구분하였으며, 건강한 6두의 랜드레이스와 요크셔 교잡종 돼지를 실험에 사용하였다. 교차실험을 하였으며, 각 군 사이의 휴약기간은 2주로 하였다. 1군 (TZ 군); 돼지 6두 (31.4±4.83 kg)에 TZ 4.4 mg/kg을 투여하였다. 2군 (ATZ 군); 동일한 돼지 6두 (43.6±4.31 kg)에azaperone 2 mg/kg을 투여하고, 20분 후에 TZ 4.4 mg/kg을 투여하였다. 모든 마취약물들은 등세모근에 근육주사를 하였다. 약물 투여 24시간 전부터 절식을 시켰다. 도입 및 회복 시간을 측정하였다. 심박수, 호흡수, 체온, pO_2, pCO_2 및 pH를 투여 전, 투여 후 5분, 25분, 45분, 65분 및 85분에 측정하였다. 도입시간에서는 ATZ 군이 TZ군에 비하여 더 빠른 도입을 나타내었다 ($p<0.01$). 회복에 있어서, 흉와자세 시간, 기립시간 및 보행시간은 ATZ군이 TZ군에 비하여 더 긴 시간을 나타내었다 ($p<0.01$). 심박수, 호흡수, pO_2, pCO_2 및 pH는 두 군간에서 유의차가 인정되지 않았다. 그럼에도 불구하고, 체온은 두 군간 유의성있는 변화가 인정되었다 ($p<0.05$). 이상의 결과를 종합하여 볼 때에, ATZ군이 TZ군에 비하여 빠른 도입과 긴 마취시간을 나타내었다. 따라서, ATZ 병용은 돼지의 화학적 보정에 유용하게 사용될 수 있을 것으로 판단되었다.

주요어 : 돼지, azaperone, tiletamine-zolazepam, 마취 효과