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Effects of Medetomidine and Atipamezole on Cerebral Perfusion Pressure in Dogs

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Abstract: The effects of Medetomidine (Me) and Atipamezole (Ati) on Intracranial Pressure (ICP) and Cerebral Perfusion Pressure (CPP) were studied in 12 dogs with artificial intracranial space-occupied lesions. The dogs were randomly assigned to a Me-Physiological Saline (PSS) group (n = 6) or a Me-Ati group (n = 6). All dogs were anesthetized with oxygen-isoflurane inhalation anesthesia and received an intramuscular injection of Me (80 μg kg^{-1}) as an initial treatment. At 30 min after administration of Me, the dogs in the Me-PSS and Me-Ati groups received an intramuscular injection of PSS or Ati (400 μg kg^{-1}) as a second treatment, respectively. Me produced a significant decrease of ICP in both groups. The administration of Ati produced a transient decrease in CPP associated with a decrease in arterial blood pressure. The lowest value of CPP (27.8 mmHg) was recorded at 10 min after administration of Ati. These results suggest that adequate cerebral blood flow is temporarily inhibited by Ati administration. Therefore, we conclude that Ati should be used with caution in patients with intracranial lesions.

Key words: Anesthesia, atipamezole, canine, cerebral perfusion pressure, intracranial pressure, medetomidine

INTRODUCTION

Many α2-adrenoceptor agonists have been shown to decrease sympathetic nervous activity, reduce the transmission of pain information and decrease volatile anesthetic requirements during surgery (Doze *et al*., 1989; Milne, 1991; Vahe, 1989). Therefore, α2-adrenoceptor agonists have been used for preanesthetic medication. A major advantage of the use of α2-adrenoceptor agonists is that specific antagonists have been developed to reverse their physiological effects quickly and completely. An α2-adrenoceptor antagonist can produce a rapid recovery from the hypnosis induced by its agonist.

Rapid recovery from anesthesia and prevention of Increased Intracranial Pressure (ICP) are important goals of neurosurgical anesthesia that permit early evaluation of neurologic functions and the preclusion of cerebral ischemic effects on neurological function.

Because, the hypnotic effects of α2-adrenoceptors can be reversed, these agents are useful for neurosurgical procedures in which the subjects are required to promptly awaken from anesthesia. On the other hand, most α2-adrenoceptor agonists decrease cerebral blood flow, which suggests that they may decrease ICP (Ishiyama *et al*., 1995). Recently, some α2-adrenoceptor agonists have been proven to offer efficacies for neuroprotection (Hoffman *et al*., 1991).

Medetomidine (Me), a selective α2-adrenoceptor agonist that is an equal racemic mixture of dexmedetomidine and levomedetomidine has been shown to be effective and convenient for sedation in some species, including dogs (Milne, 1991; Vahe, 1989). Major α2-adrenoceptor antagonists include idazoxane, tolazoline, yohimbine and atipamezole. Atipamezole (Ati) is the most selective of the α2-adrenoceptor antagonists: its α2- to α1- selectivity ratio is 200-300 times higher than that of idazoxane or yohimbine (Virtanen, 1989). Ati is used to reverse the physiological effects of Me in veterinary anesthesia.

However, to the best of our knowledge, little information is available on the effects of α2-adrenoceptor

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antagonists on ICP, although the effects of α2-adrenoceptor agonists have been previously explored (Favre *et al*., 1995; Keegan *et al*., 1995; McCormick *et al*., 1993; Zornow *et al*., 1992). In addition, there is no available information on the effects of α2-adrenoceptor antagonists on ICP in dogs with space-occupied lesions. Therefore, the purpose of this study is to investigate the effects of Me and Ati on ICP in dogs with artificially induced decreased brain compliance.

MATERIALS AND METHODS

Animals and instrumentation: This study was conducted with the prior approval of the animal care committee of Yamaguchi University. Twelve adult beagle dogs (age range, 1.4-4.2 years) of either sex (male = 6, female = 6) and weighing from 7.7-12.1 kg were studied. All the dogs were clinically normal and showed normal ranges in their hematological profiles (complete blood count, blood urea nitrogen, serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, glucose, Na, K and Cl). The dogs were housed individually and fed commercial dry food and water *ad libitum*. Food was withheld for 12 h prior to the experiment.

Anesthesia was induced by the administration of isoflurane with O_2 using a tightly fitting mask. Following intubation, the endotracheal tube was connected to a circle breathing system. The dogs were anesthetized with 1.7 Minimum Alveolar Concentration (MAC) of isoflurane (2.2%) and were mechanically ventilated (Model 2000 Anesthesia Ventilator; Hallowell EMC, Pittsfield, MA).

End-tidal CO_2 tension ($EtCO_2$) and isoflurane concentration, Heart Rate (HR), electrocardiogram (lead II) and percutaneous hemoglobin saturation of oxygen (SpO_2) were continuously measured by a patient monitoring system (BP-508; Colin Medical Technology Corporation Aichi, Japan). Ventilation was controlled to maintain the end-tidal CO_2 tension at about 35 mmHg. The Body Temperature (BT) was continuously checked with a digital rectal thermometer (SK-1250MC; Sato Keiryoki Mfg., Tokyo, Japan) and maintained between 38 and 39°C with an electrically heated water pad.

After the dog had been placed in a suitable surgical position, a No. 8 French polyethylene catheter was inserted into the left femoral artery to measure the arterial blood pressure and obtain arterial blood samples. Arterial blood pressure was displayed continuously and recorded using a pressure transducer (DX-360T; Nihon Kohden, Tokyo, Japan) positioned at the level of the heart.

Finally, the scalp was incised in the midline and reflected laterally to expose the fascia of the temporalis muscle. The temporalis muscle was divided and the cranium was exposed. A cranial burr hole (5×15 mm) was made by craniotomy at 1 cm right lateral to the bregma for the measurement of ICP. An ICP monitoring catheter (TM-200T; Nihon Kohden) was gently placed in the epidural space. The ICP was displayed continuously and recorded by using a pressure transducer (DX-360T; Nihon Kohden) positioned at the level of the ventricle. Pressure-volume compensation was prevented by an epidural balloon that produced an artificial intracranial space-occupied lesion.

A cranial burr hole (5 mm in diameter) was made by craniotomy at 1 cm left lateral to the bregma for the placement of the balloon catheter (No. 4 French). After epidural placement of the balloon catheter, the preincrement value of ICP was recorded. Then, 1 mL of Physiological Saline (PSS) was added gradually over a period of 10 min into the epidural balloon. The dog was then sustained for 60 min until the ICP had returned to its preincrement value (Fig. 1). The results of a preliminary examination showed that a period of 30-40 min was sufficient for this purpose. The animals were randomly assigned to a PSS group (Me-PSS) and an Ati group (Me-Ati).

Experimental design: Sixty minutes after surgical preparation, the first treatment, 80 μg kg^{-1} of Me was given intramuscularly to both groups. The Systolic Arterial Pressure (SAP), Diastolic Arterial Pressure (DAP), Mean Arterial Pressure (MAP), ICP, HR, $EtCO_2$, SpO_2 and BT were recorded prior to (pre-Me) and at 1, 3, 5, 10, 15, 20 and 30 min after Me administration. Cerebral Perfusion Pressure (CPP) was calculated by subtracting ICP from MAP. Arterial blood samples were collected anaerobically into heparinized glass syringes prior to and at 10, 20 and 30 min after Me injection. Arterial oxygen and carbon dioxide partial pressures (P_aO_2 and P_aCO_2, (mmHg) respectively), arterial standard bicarbonate $(HCO_3^-)_a$ (mmol L^{-1}) and arterial pH (pH_a) were measured with a blood gas analyzer (iSTAT; iSTAT Corporation, Princeton, NJ) at 37°C. These values were corrected for the BT of each dog. After recording the data at 30 min after Me administration, PSS and Ati was administered to the dogs of the Me-PSS and Me-Ati groups, respectively, as the second treatment.

The administration volume of PSS was same as that of Ati (400 μg kg^{-1}). After the second treatment, the same measurements were recorded at the same times as those used after Me administration. The values recorded 30 min after administration of Me to each group were used as pre-second-treatment values (pre-PSS or pre-Ati values) (Fig. 1).

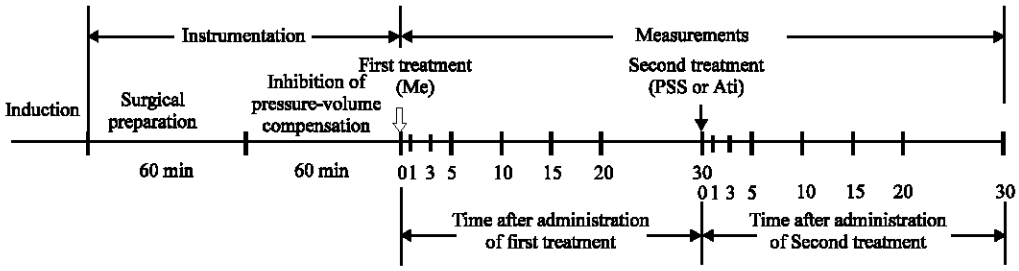

Fig. 1: Summary of experimental protocol. The values recorded 30 min after administration of the first treatment [Medetomidine (Me)] were used as the pre-second treatment values of each group. The time scale shows the time after administration of each treatment. The white arrow (⇩) and black arrow (↓) show the administration time point of the first and second treatment, respectively. The first treatment consisted of Me for both groups and the second treatment consisted of Physiological Saline (PSS) for the Me-PSS group and Atipamezole (Ati) for the Me-Ati group

Statistical analysis: Differences among the time-related variables within each treatment group were tested for significance by repeated measures of Analysis of Variance (ANOVA) this was followed by Bonferroni's multiple comparison test. All time-related variables within each treatment group were compared with the pre-Me administration values. In addition, time-related variables after administration of the second treatment were also compared with the pre-Ati and pre-PSS values. For unpaired comparisons between treatment groups, the data were tested by ANOVA.

When the F value was not significant, the Student's t-test was used to identify significant differences. When the F value was significant, the Wilcoxon test was used for statistical evaluation. The significance level of all tests was set at $p<0.05$.

RESULTS AND DISCUSSION

During the course of this study, there were no significant differences in SpO_2, SaO_2, pH_a, $[HCO_3^-]_a$, PaO_2 and $PaCO_2$ values between the Me-PSS and Me-Ati groups, as well as no significant time-related changes in these measurements (Table 1 and 2).

HR was significantly reduced in both groups after the administration of Me. A comparison of HR values pre and postadministration of the second treatment revealed no significant changes after either of the second treatments (Fig. 2a). However, there were significant differences in HR values between the groups at 30 min after administration of Me and at 1 min after administration of the second treatment.

Compared with the pre-Me values, MAP was significantly reduced in the Med-Ati group within 30 min after administration of Me. In the Me-PSS group, MAP showed a significant change after administration of PSS when compared with the pre-Me values. When MAP values before and after the second treatment was compared: only the Me-Ati group showed a significant decrease at 3-10 min after the second treatment. Between 3 and 10 min after administration of the second treatment, dogs that received Me-PSS had significantly higher MAP values than those that received Me-Ati. The time-related changes of SAP and DAP showed similar patterns to that of MAP (Fig. 2b, c and 3a).

ICP significantly decreased at 3-5 min after administration of Me in the Me-PSS group and at 3-15 min in the Me-Ati group. When ICP values before and after the second treatment were compared and ICP was found to significantly increase at 15-20 min after administration of the second treatment in only the Me-Ati group; no change was observed in the Me-PSS group. Between 20 and 30 min after administration of the second treatment, the ICP in the Me-Ati group was significantly higher than that in the Me-PSS group (Fig. 3b).

When compared with the pre-Me values, the CPP was significantly reduced in the Me-PSS group at 5-20 min and in the Me-Ati group from 30 min after the second treatment. The Me-Ati group showed a rapid change in CPP at 3-10 min after administration of the second treatment; the CPP values were significantly different from the pre-Ati values. The smallest value for mean CPP was 27.8 mmHg at 10 min after administration of Ati. The CPP of the Me-Ati group tended toward recovery from 10 min after Ati administration.

To the knowledge, the present study is the first to evaluate the effect of Ati on CPP in dogs treated with Me. In this study, Me (80 μg kg^{-1}) was given intramuscularly to both groups as the first treatment. The dose-dependent effect following Me administration has been reported in twitch response in mice (Virtanen *et al*., 1988), vigilance in cats (Stenberg *et al*., 1987), sedation in pigs (Sakakibara *et al*., 1982) and sedation in dogs (Vainio and Vahe, 1990).

Table 1: Time-related changes of SpO_2 and Me-Ati groups

Groups	Min	0	1	3	5	10	15	20	30	1*	3*	5*	10*	15*	20*	30*
Me-PSS	Mean	97.0	97.8	98.0	98.0	97.8	97.6	96.6	96.8	96.8	97.4	97.4	97.8	97.6	97.6	97.2
	SD	1.00	1.48	0.71	0.71	0.84	0.89	1.52	1.48	1.48	1.14	1.14	0.84	1.14	1.14	1.30
Me-Ati	Mean	97.7	98.0	98.8	98.8	98.0	97.8	97.0	97.8	97.3	96.7	97.0	97.5	97.7	97.7	97.2
	SD	1.37	1.10	0.75	0.75	0.63	0.41	1.55	0.75	0.52	1.03	0.89	0.55	0.52	1.21	1.72

*Time after administration of second treatments; SD: Standard Deviation

Table 2: Time-related changes of arterial blood gas and acid-base values in Me-PSS and Me-Ati groups

Groups	Min.	0	10	20	30	10*	20*	30*
PCO_2								
Me-PSS	Mean	33.2	34.4	34.4	34.4	34.6	33.8	33.9
	SD	0.8	1.1	0.9	0.5	0.5	1.2	1.5
Me-Ati	Mean	32.6	32.8	32.4	33	32.6	34.2	34.6
	SD	3.4	2.3	3.1	3.7	3.6	1.3	0.9
pHa								
Me-PSS	Mean	7.366	7.362	7.357	7.362	7.367	7.348	7.355
	SD	0.031	0.032	0.035	0.028	0.029	0.032	0.035
Me-Ati	Mean	7.343	7.345	7.361	7.352	7.357	7.381	7.376
	SD	0.054	0.062	0.070	0.059	0.069	0.051	0.049
$(HCO^-_3)_a$								
Me-PSS	Mean	22.0	22.0	21.75	22.25	22.25	21.5	22.0
	SD	2.8	0.8	1.0	1.0	1.0	1.3	2.4
Me-Ati	Mean	22.5	22.5	23.0	22.7	22.5	22.7	23.0
	SD	2.3	2.1	2.0	2.1	2.1	2.4	1.7

*Time after administration of second treatments; SD: Standard Deviation

On the other hand, the large amount of Me administered over the recommended dose did not produce deep sedation in pigs (Sakaguchi *et al*., 1992). Similarly, the previous report showed a ceiling effect on sedation levels, as evaluated with electroencephalography. In Itamoto (2001)'s report, the maximum sedative effect of Me was observed at the dose of 80 μg kg^{-1} in dogs.

The α2-adrenoceptor antagonists, including Ati are widely exploited in veterinary anesthesia. Ati can fully reverse the sedative and sympatholytic effects of the α2-adrenoceptor agonists not only in animals but also in humans. Ati is the most selective of the a2-adrenoceptor antagonists and its α2- to α1- selectivity ratio is 8,526, whereas idazoxane and yohimbine show a ratio of 27 and 40, respectively (Virtanen *et al*., 1988).

In this study, Me produced a significant decrease in HR. The precise mechanisms of HR reduction by administration of an α2-adrenoceptor agonist are still unknown, although it is suspected that this agonist may exert effects on the baroreceptor reflex, on the depression of norepinephrine release or on the imidazoline receptor (Maze, 1989). However, the increment of blood pressure causing baroreceptor reflex was observed to be very small in this study. In addition, a reduction in HR was observed at the hypotension phase that occurred after the transient induction of hypertension by Me administration. Therefore, these results suggest that the baroreceptor reflex was not a factor in HR reduction.

In this study, blood pressure showed a transient increase after administration of Me, after which the

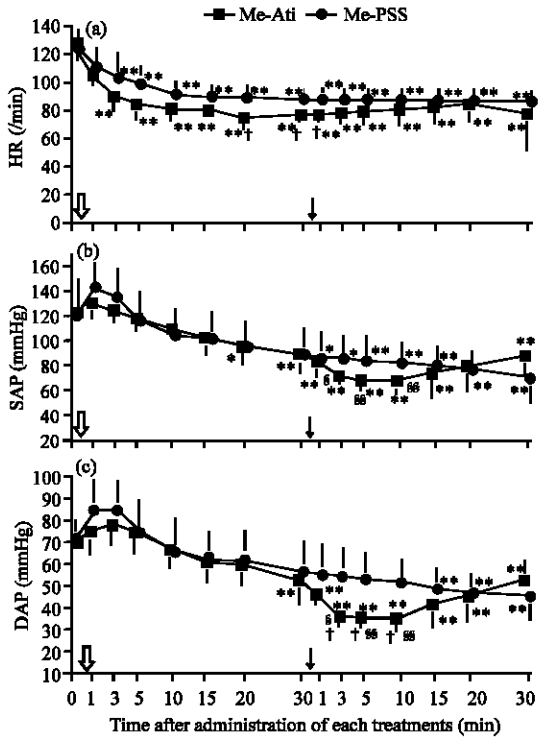

Fig. 2: Time-related changes of Heart Rate (HR) (a), Systolic Arterial Pressure (SAP) (b), Diastolic Arterial Pressure (DAP) (c) in Medetomidine (Me) Physiological Saline (PSS) and Me-Atipamezole (Ati) groups. Explanatory notes have been added to DAP values (c). The white arrows (⇩) and black arrows (↓) show the administration time points of the first and second treatments, respectively. The time scale shows the time after administration of each treatment. *Significantly different from pre-Me value ($p<0.05$), **significantly different from pre-Me value ($p<0.01$), §significantly different from pre-second treatment value ($p<0.05$), §§significantly different from pre-second treatment value ($p<0.01$) and †significantly different from Me-PSS group ($p<0.05$)

subjects became hypotensive. The hypertensive effects of α2-adrenoceptor agonists have been well documented (Bergström, 1988; Hayashi *et al*., 1995; Ko *et al*., 1996; Nichols *et al*., 1988; Vahe, 1989). In vascular smooth-muscle cells of peripheral tissues, α2-adrenoceptors mediate vasoconstriction (Nichols *et al*.,

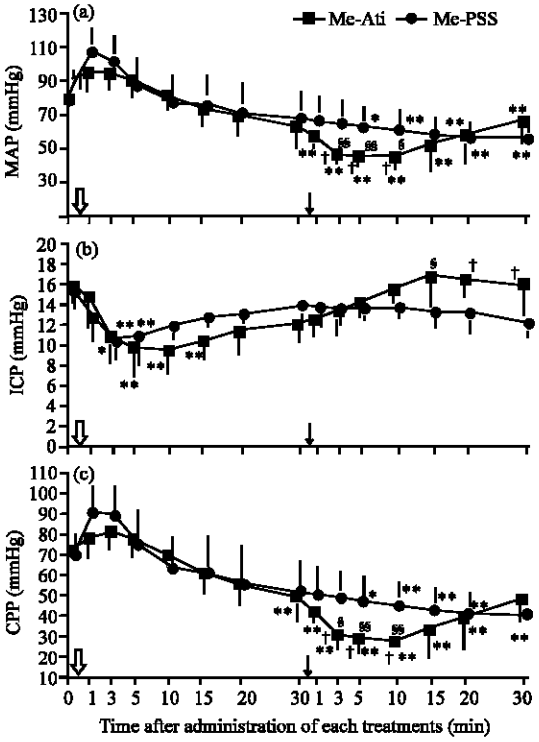

Fig. 3: Time-related changes of MAP (a), Intracranial Pressure (ICP) (b), Cerebral Perfusion Pressure (CPP) (c) in Medetomidine (Me)-Physiological Saline (PSS) and Me-Atipamezole (Ati) groups. Explanatory notes have been added to CPP values (c). The white arrows (⇩) and black arrows (↓) show the administration time points of the first and second treatment, respectively. The time scale shows the time after administration of each treatment. *Significantly different from pre-Me value ($p<0.05$), **significantly different from pre-Me value ($p<0.01$), §significantly different from pre-second treatment value ($p<0.05$), §§significantly different from pre-second treatment value ($p<0.01$) and †significantly different from Me-PSS group ($p<0.05$)

1988). However, the transient increase in blood pressure was not significant in this study. We suspect that isoflurane, acting as a background agent, might have prevented the hypertensive effect of the α2-adrenoceptor (Hysing *et al*., 1992).

After recovery from the transient increase in blood pressure produced by Me, hypotension was observed in the Me-PSS group after administration of PSS. However, we believe that this hypotension was due to Me and the use of isoflurane as a background anesthesia. The α2-adrenoceptor agonist has long been used as an antihypertensive drug (Khan *et al*., 1970). It is thought that the hypotensive effects of α2-adrenoceptor agonists might be the result of their imidazoline receptor selectivity with an imidazoline structure or their ability to reduce the secretion of norepinephrine (Khan *et al*., 1999). Me has an imidazoline structure that is active in the rostroventrolateral medulla and nucleus reticularis lateralis, regions that are associated with central antihypertensive effects (Bousquet *et al*., 1981, 1984; Ernsberger *et al*., 1990). On the other hand, extreme hypotension was observed in the Me-Ati group. This extreme hypotensive effect may be due to the vasodilative effect of Ati, since a difference in hypotension levels was noted between the Me-PSS and Me-Ati groups in the present study. It is well recognized that Ati introduces hypotensive effects in many species, including humans. Ati is also believed to cause vasodilative effects via α2-adrenoceptors on the smooth muscle of peripheral vessels.

The α-adrenoceptors that mediate the constriction of brain arteries of cats (Skärby *et al*., 1981), pigs (Busija and Leffler, 1987), dogs (Sakakibara *et al*., 1982; Tsukahara *et al*., 1986), cattle (Tsukahara *et al*., 1983) and humans (Usui *et al*., 1985) are predominantly α2-adrenoceptors. Furthermore, Ishiyama *et al*. (1995) has confirmed the cerebrovascular constrictive effect of α2-adrenoceptors on the pial vein and artery in both large and small pial vessels by using direct topical application of dexmedetomidine on pial vessels in canine *in vivo* models (Ishiyama *et al*., 1995). On the other hand, dexmedetomidine decreased cerebral blood flow in isoflurane-anesthetized dogs (Zornow *et al*., 1990). Theoretically, selective cerebral blood volume reduction by the use of α2-adrenoceptor agonists may reduce ICP. There have been reports about the effects on ICP or cerebrospinal fluid pressure of α2-adrenoceptor agonists, including dexmedetomidine in humans (Talke *et al*., 1997) and in rabbits (Zornow *et al*., 1992), medetomidine in dogs (Keegan *et al*., 1995), xylazine in dogs (McCormick *et al*., 1993) and clonidine in humans (Favre *et al*., 1995). Some of these reports documented the reduction effect of α2-adrenoceptor agonists on ICP in experimental animals with intracranial occupied lesions. The results suggest that Me also decreases ICP when compared with preadministration values.

The effect of the α2-adrenoceptor antagonist tolazoline on ICP has been reported in dogs (McCormick *et al*., 1993). In that report, tolazoline inhibited the ICP drop induced by xylazine. Similarly, we observed in the present study that ICP was increased to pre-Me values in the Me-Ati group after Ati administration, whereas the decrease in ICP continued

after administration of PSS in the Me-PSS group. This result suggests that the decrease in ICP by Me was antagonized by Ati without excess of ICP over pre-Me values in dogs with intracranial occupied lesion. However, the vasodilative effect of Ati induced hypotension and a transient decrease of CPP. The smallest value of CPP in the Me-Ati group was 27.8 mmHg at 10 min after administration of Ati. The dog that showed the smallest value in the Me-Ati group showed 15 mmHg of CPP at that time. Sufficient CPP is necessary to maintain adequate cranial blood flow and to prevent cerebral ischemia.

In humans, the acceptable lower limit of CPP in adults is 50 mmHg and this value is lower in infants. Cerebral ischemia occurs in dogs as CPP approaches 40 mmHg (Sulek, 1998). It has been recommended that CPP should be maintained at a level >70 mmHg in head-injured human patients to minimize cerebral ischemia and to prevent the cascade events that result from inadequate perfusion (Muizelaar and Schroder, 1994; Rosner and Daughton, 1990). Isoflurane, a background anesthesia, was considered to be the causative factor in the extreme drop in CPP observed in this study. However, it is obvious that Ati also affects CPP. Moreover, it has been reported that Ati shows hypotensive effects in human (Scheinin *et al*., 1998) and in dogs (Vainio, 1990).

CONCLUSION

The administration of Me produced a reduction in ICP, which may have provided a neuroprotective effect. On the other hand, Ati induced an extreme drop in CPP under isoflurane anesthesia in dogs. This drop in CPP may be due to the vasodilative effect of Ati. The lowest value of CPP fell to well below 40 mmHg, which is the level at which cerebral ischemia occurs. Therefore, the present results suggest that Ati should be used with caution in patients with intracranial lesions.

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