Bull Yamaguchi Med Sch 29 : 67-74, 1982

Cerebral and Systemic Effects of Hypotension Induced by Trimethaphan or Nitroprusside in Dogs

Kiyoshi Okamoto

Department of Anesthesiology, Yamaguchi University School of Medicine, Ube, Yamaguchi 755, Japan

(Received November 27 ; revised December 2, 1982)

Abstract The effects of hypotension induced by trimethaphan (TMP) or nitroprusside (NTP) together with controlled hemorrhage on cerebral electrical activity, cerebrospinal fluid pressure and systemic circulatory and metabolic variables were measured in 10 mongrel dogs anesthetized with halothane (end-tidal, 0.88±0.03%). Induced hypotension was maintained at cerebral perfusion pressure of 45 mmHg for 45 min and then at 30 mmHg for 45 min. In 5 TMP dogs, there were significant decreases in EEG-power and slowing of peak power frequency from the frontal area, but not from the occipital area. The cerebrospinal fluid pressure did not change significantly except for an increase during induction stage of hypotension. In 5 NTP dogs, there were no significant changes in EEG-power and peak power frequency throughout the study from both frontal and occipital areas, but cerebrospinal fluid pressure increased significantly. With both drugs, an increase in glucose, lactate and lactate pyruvate ratio, and a decrease in Pao_2 were more pronounced at 30 mmHg than 45 mmHg. With NTP, there were sustained increases in lactate and lactate pyruvate ratio even after restoration of arterial pressure. The same magnitude and duration of the decrease in cerebral perfusion pressure induced by either TMP or NTP produced different effects on cerebral and systemic function.

Key Words: Vasodilator; trimethaphan, nitroprusside, Brain; cerebral electrical activity, cerebrospinal fluid pressure

Introduction

Trimethaphan (TMP) and nitroprusside (NTP) are widely used as hypotensive drugs in clinical practice. A number of investigations have shown that cerebral oxygenation[1] and adequacy of perfusion[2,3] during hypotension are better maintained with NTP than TMP. However, electrical activity during drug-induced hypotension has been controversial[4-9] and there was no study which examined possible differences in electrical activity of the brain between techniques of induced hypotension with different drugs except for a recent study by Ishikawa & McDowall[10]. They demonstrated that neuronal function in cats, as assessed by a cerebral function monitor, was better maintained with NTP than TMP due to better cerebral perfusion at the same arterial blood pressure level. Michenfelder & Theye[11] studied the cerebral and systemic metabolic effects of

hypotension induced by TMP or NTP, and found that at 50 mmHg of mean arterial pressure (MAP) the detrimental effects of hypotension were more marked with TMP than with NTP, but at 40 mmHg there was no difference between the two drugs. It has been shown that cerebrospinal fluid pressure (CSFP) increases with NTP, but changes little with TMP[12,13]. In previous reports, cerebral effects of drug-induced hypotension have been tested by measuring MAP, not cerebral perfusion pressure (CPP). During hypotension, an increase in CSFP, if it occurs, can not be ignored since MAP is markedly reduced. The present study was designed to examine different effects of hypotension induced by TMP or NTP on cerebral and systemic circulatory and metabolic variables at a comparable level of CPP.

Materials and Methods

Ten dogs weighing 8.0 to 18.0 kg were anesthetized with 2 to 3% halothane and 60% nitrous oxide in oxygen, followed by intramuscular 2 mg/kg succinylcholine to facilitate endotracheal intubation, after which the halothane concentration was reduced to 1 to 1.5% for maintenance. Succinylcholine was administered intravenously at 4±1 mg/kg to maintain muscle relaxation. Thereafter, ventilation was controlled with a Harvard pump to maintain normocapnia (Paco2, 35±2 torr). End-tidal CO_2 and halothane concentrations were monitored with a mass spectrometer (Medspect; MS-8, Scientific Research Instruments, Maryland, USA) throughout the study.

Bilateral catheterization of the femoral arteries and veins was performed for blood sampling, blood pressure monitoring and infusion of lactated Ringer's solution (4±1 ml/kg/h) and of hypotensive drugs. A catheter was inserted through the right facial vein to measure the central venous pressure.

Catheters were inserted into both ureters for timed collection of urine. ECG (lead V5) was monitored and the height of the T-wave in mV was measured. Skin and muscle reflected from the skull and metal screw electrodes for EEG recording were placed on the dura of the frontal and occipital areas of the right hemisphere. A 20 gauge needle was inserted into the cisterna magna and fixed with a metal holder for the measurement of CSFP.

Arterial blood pressure and CSFP were measured with a pressure transducer (Nihon Koden, MPU-0.5-200-0-Ⅲ, Tokyo, Japan) with zero reference at the level of the external auditory canal.

The CPP was calculated as the difference between MAP and CSFP. After completion of surgical preparation, the inspired halothane concentration was reduced to 0.9% at least for 1 hour, and Fio_2 was kept constant at 0.4.

Trimethaphan solution was prepared by diluting Arfonad (Hoffmann-La Roche, Switzerland) with 5% glucose solution.

Nitroprusside was prepared 30 min before infusion by diluting sodium nitroprusside crystals (Nakarai Chemical, Kyoto, Japan) in 5% glucose solution. TMP was infused at a maximum rate of 10 mg/kg/h and NTP was infused in a total dose of less than 1 mg/kg. The rate of decrease in the CPP was controlled by changing the rate of infusion. When necessary, blood was withdrawn; the volume removed in the TMP group was 7±1 ml/kg and in the NTP group 5±1 ml/kg and PEEP of 5 cmH_2O was used to achieve the desired CPP. All dogs were rendered hypotensive to 45 mmHg of CPP for 45 min, and then to 30 mmHg of CPP for 45 min. The drugs were discontinued and 30 min were allowed to elapse for the restoration of CPP. When CPP did not return to control within 30 min, phenylephrine (0.5 to 2.5 mg in total) was administered. Measurements were performed before hypotension, at 45 mmHg of CPP, at 30 mmHg of CPP and when CPP had returned to 90% of the control value and had been stabilized. In each stage of CPP, measurements in triplicate of all parameters were made at 5, 15 and 40 min after the desired CPP levels had been obtained.

The EEG was recorded continuously on both paper and magnetic tape (Sony, NFR-3915, Tokyo, Japan) along with arterial blood pressure and CSFP. The computer (Facom, U-200, Fujitsu, Tokyo, Japan) generated power spectra (Fourier analysis) for each 10-second -epoch of EEG data and then calculated an integrated power with a range of 0.5 to 25 Hz, peak power frequency and median power frequency in Hz. Date for more than 10 power spectra were averaged at each stage.

The CSFP signal was converted to digital with a

sampling interval of 1 second by a digital voltmeter (Eto Denki, EO-80, Tokyo, Japan) and the distributions of CSFP and mean CSFP values were calculated with a computer (Hitac 10, Hitachi, Tokyo, Japan). This process allowed us to examine the trend of CSFP during hypotension, but in the table the computed mean CSFPs are tabulated.

Arterial blood samples were taken for blood gases and pH analysis, and for determination of hemoglobin, glucose, lactate and pyruvate. Po_2, Pco_2 and pH were measured with appropriate electrodes (IL meter 313, Instrumentation Laboratory, Mass., USA). Hemoglobin concentration was determined with a CO-Oximeter (IL 182, Instrumentation Laboratory. Mass., USA). The concentrations of glucose, lactate and pyruvate were determined by enzymatic methods. Esophageal temperature was kept at 38±0.2°C using an electric heating blanket. Sodium bicarbonate was given to correct metabolic acidosis.

The results were subjected to one-way analysis of variance with critical-difference testing and $P<0.05$ was considered to be significant.

Results

The effects of hypotension on EEG and CSFP are shown in Table 1. During hypotension produced by either TMP or NTP, EEG showed variable decreases in frequency with decreased or increased amplitude. During hypotension induced by TMP, the mean EEG-power and peak power frequency in the frontal area decreased significantly while it remained unchanged in the occipital area. In three of five dogs, EEG returned to control within 2 hours, whereas in the remaining two dogs high-voltage slow-wave activity continued for more than 2 hours after restoration of blood pressure, resulting in a significant decrease in the mean peak power frequency in both frontal and occipital areas. During hypotension induced by NTP, the mean EEG-power, peak power frequency and median power frequency remained unchanged at all stages, and returned to control within 2 hours after restoration of blood

Table 1 Effect of induced hypotension on CSFP and EEG-Power (Mean±SE)

	Trimethaphan				Nitroprusside			
	Before	Hypotension		After	Before	Hypotension		After
CPP mmHg	103±0.5	47±1.6*	31±1.2*	102±3.9	99±3.7	45±0.8*	32±0.4*	98±6.7
MAP mmHg	108±5.9	52±1.2*	36±0.4*	105±3.6	104±3.1	56±2.1*	42±2.0*	103±5.6
CSFP mmHg	5.3±0.9	5.6±0.7	5.1±1.3	3.3±1.0	5.3±0.9	10.7±2.2*	10.1±2.2*	6.0±1.4
EEG-Power								
Frontal	2703±641	1731±518	1646±515*	3164±821	3825±613	3421±459	3577±441	4120±661
Occipital	2651±624	2108±653	1853±479	4204±706	5015±784	4254±784	4341±1174	4866±880
Peak power frequency Hz								
Frontal	3.6±0.3	2.9±0.4*	2.5±0.2*	2.2±0.1*	3.5±0.2	3.3±0.3	3.1±0.2	3.3±0.04
Occipital	5.2±0.8	6.7±1.8	5.8±0.6	2.7±0.3*	4.1±0.2	4.7±0.5	3.9±0.5	3.7±0.3
Median power frequency Hz								
Frontal	5.3±0.9	5.5±1.0	5.6±1.0	4.8±0.6	5.5±0.6	6.4±0.8	5.0±0.6	6.3±0.5
Occipital	8.3±1.3	9.0±1.1	10.5±1.2	6.0±0.5	6.6±0.6	6.4±0.3	5.3±0.5	6.2±0.7

* Significantly different from before hypotension ($P<0.05$).

CPP: Cerebral perfusion pressure; MAP: Mean arterial pressure; CSFP: Cerebrospinal fluid pressure.

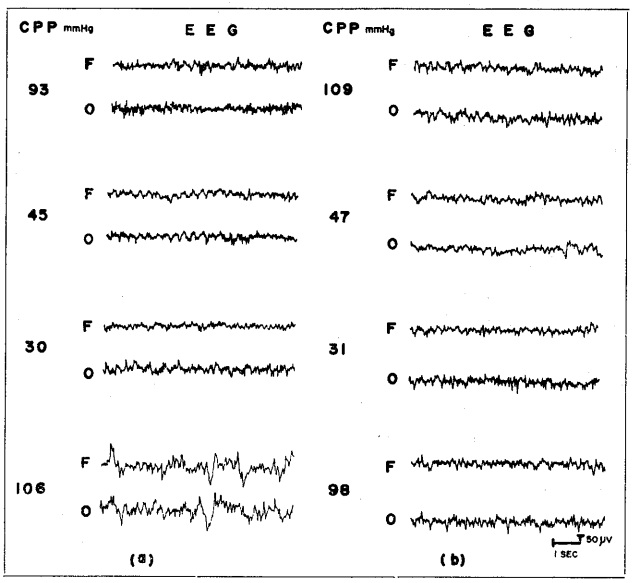

Fig. 1 Representative EEG before, during and after hypotension with TMP (a) and NTP (b). In this TMP dog, EEG did not return to control within 2 hours after restoration of blood pressure. CPP: Cerebral perfusion pressure; F: Frontal; O: Occipital.

Table 2 Systemic circulatory effects of induced hypotension (Mean±SE).

	Trimethaphan				Nitroprusside			
	Before	Hypotension		After	Before	Hypotension		After
CPP mmHg	103±0.5	47±1.6*	31±1.2*	102±3.9	99±3.7	45±0.8*	32± 0.4*	98±6.7
MAP mmHg	108±5.9	52±1.2*	36±0.4*	105±3.6	104±3.1	56±2.1*	42± 2.0*	103±5.6
Heart rate beats/min	118±3.1	107±7.4	82±6.5*	107±4.7	108±5.7	121±5.1	143±10.8*	151±6.3*
Central venous pressure cmH_2O	4.9±0.6	4.2±0.3	5.4±0.5	6.5±0.9	5.1±0.5	3.6±0.7	3.1± 0.8*	7.1±0.9*
T-height in ECG mV	0.30±0.07	0.34±0.07	0.53±0.08	0.60±0.07	0.37±0.03	0.50±0.15	0.52± 0.15	0.30±0.05
Urine output ml/kg/h	2.9±0.5	0.8±0.3*	0.5±0.2*	0.5±0.3*	3.7±0.8	1.2±0.3*	0.1± 0.1*	1.5±0.5*

* Significantly different from before hypotension ($P<0.05$).
For abbreviations, see Table 1.

Table 3 Experimental conditions and systemic metabolic effects of induced hypotension (Mean±SE).

	Trimethaphan				Nitroprusside			
	Before	Hypotension		After	Before	Hypotension		After
MAP mmHg	108±5.9	52±1.2*	36±0.4*	105±3.6	104±3.1	56±2.1*	42±2.0*	103±5.6
PaO_2 torr	205±4	189±6*	187±5*	197±3	206±5	199±6	195±5*	194±2*
$PaCO_2$ torr	34.5±1.5	35.3±0.8	35.3±1.5	34.5±1.5	34.5±0.0	35.3±0.8	35.3±0.8	35.3±0.8
pHa	7.42±0.01	7.37±0.02	7.40±0.02	7.35±0.02	7.43±0.02	7.39±0.02	7.37±0.01	7.40±0.02
Bicarbonate meq/L	21±1	20±1	21±1	19±1	23±1	20±1	20±0	21±1
Hemoglobin g/dl	12.1±0.6	11.7±1.0	10.3±0.7	13.6±0.7	13.2±0.5	12.9±0.5	13.1±0.4	12.7±0.6
Glucose mg/dl	114±11	132±20	178±36*	125±12	92±8	122±27	181±37*	163±34*
Lactate mmol/L	2.2±0.4	2.7±0.6	3.8±0.8*	3.3±0.5*	2.2±0.2	2.9±0.2	3.3±0.3*	4.1±0.7*
Lactate/ pyruvate ratio	11.2±1.1	16.3±2.5	20.2±4.4*	15.4±1.7	14.3±1.3	20.7±2.4	25.8±7.3*	35.0±5.2*
End-tidal halothane %	0.84±0.02	0.85±0.02	0.89±0.05	0.87±0.02	0.87±0.01	0.90±0.02	0.87±0.02	0.90±0.02
Body temperature °C	37.7±0.3	37.3±0.3	37.2±0.2	37.5±0.2	37.3±0.3	37.5±0.3	37.7±0.3	38.0±0.3

* Significantly different from before hypotension ($P<0.05$).
For abbreviations, see Table 1.

pressure. Representative EEGs before, during and after hypotension with TMP or NTP are shown in Figure 1.

A significant increase in the mean CSFP was observed at all stages of hypotension with NTP, but not with TMP except for a temporary increase during the induction stage of hypotension. TMP increased mean CSFP from 6.0±0.9 to 11.7±3.5 mmHg within 5 min after the start of infusion and returned to the control value within 20 min. This increase is not shown in Table 1, since the first measurement during hypotension was obtained 20 min after the start of infusion.

Systemic circulatory and metabolic variables are shown in Table 2 and 3. With both drugs at 30 mmHg of CPP, there were significant increases in glucose, lactate and lactate pyruvate ratio in the arterial blood and a decrease in Pao_2 and urinary output. After restoration of CPP, significant increases in heart rate, central venous pressure, glucose and lactate pyruvate ratio, and decrease in Pao_2 were still present with NTP, but not with TMP.

Discussion

In the present study, the cerebral effects of hypotension with either TMP or NTP were examined at a comparable level of CPP. Inspired halothane concentration was kept constant (end-tidal, 0.88±0.03%) throughout the observation in both groups. Blood removal was allowed only after establishing the maximum rate of TMP or NTP infusion, but there was no significant difference in the volume of blood removal between TMP and NTP groups. Thus, experimental conditions were identical in both groups.

The significant decrease in the mean EEG -power and peak power frequency in TMP dogs suggested a more pronounced alteration of EEG than in NTP dogs. However, it was

significant only in the frontal area, suggesting a regional difference in the effect of hypotension on electrical activity of the brain. The effects of TMP on EEG have been studied by the following investigators. In monkeys, Meldrum & Brierley[4] reported that hypotension induced by TMP combined with hemorrhage produced electrical silence or marked depression of EEG at MAP of 25 mmHg. Gamache et al.[5] observed decreases in frequencies (by 38%) and amplitudes (by 25%) during a 30-min period hypotension at MAP of 25 mmHg. Selkoe & Myers [6] reported that during TMP hypotension slowing and diminished amplitude of EEG appeared below MAP of 28 to 32 mmHg and electrical silence appeared below 21 to 22 mmHg. They also found close correlation between EEG changes and neuropathologic outcome and pointed out that threshold for development of brain injury would be at MAP of 25 mmHg. In dogs, Wiederholt et al.[7] found flat EEG at MAP of 30 to 40 mmHg and no return of EEG to the control when hypotension was maintained for longer than a 30-min period. Magness et al.[8] consistently showed burst-supression or high voltage and slow wave at MAP of 40 to 47 mmHg and flat EEG at MAP of 30 to 47 mmHg. In the latter two studies, arterial blood gas tensions were not described in detail, making it difficult to evaluate the possible contribution of changes in blood gas tensions to EEG. Other factors affecting EEG change during hypotension may include background anesthesia and decreasing rate of blood pressure. In the studies cited above pentobarbital was exclusively used as background anesthesia. The maintenance of constant level of anesthesia with intravenous anesthetics may be difficult. Furthermore, it is known that barbiturates decrease cerebral oxygen consumption[14,15] and hence may protect ischemic brain[16]. In most of the previous studies, blood pressure was lowered rapidly within 2 min from more than 100 mmHg to the desired hypotensive levels. Schallek & Walz[9] suggested that the infusion of TMP must be controlled so that blood pressure does not fall more rapidly than 10 mmHg/min to avoid drastic EEG changes. In the present study, arterial blood gas tensions and anesthetic level were carefully controlled and MAP was reduced at a rate of about 5 mmHg/min, and it was found that modest EEG abnormalities appeared in the frontal area with TMP. Although the underlying mechanism is unclear, EEG slowing for at least 2 hours after the restoration of blood pressure suggested a detrimental effect of TMP on EEG.

In the literature there was no report comparing the effects of TMP and NTP on electrical activity of the brain except for Ishikawa & McDowall's work[10]. They studied the effect of hypotension induced by either TMP or NTP in cats anesthetized with N_2O and halothane on electrical power as assessed by the cerebral function monitor. Their results suggested better maintenance of electrical power with NTP than TMP at MAP of 36 to 30 mmHg. Furthermore, in three of five TMP cats EEG became isoelectric, a result not seen in any of the NTP cats. The present study is in partial agreement with their results, though in no animal did the EEG become isoelectric with TMP. This lesser depression of electric activity than that reported by Ishikawa & McDowall[10] may be due to species difference, or to difference in experimental methods. In their study beta blockers were given in addition to TMP. Finally, they used an open skull preparation in which cerebral perfusion pressure would equal blood pressure.

It is believed that increase in CSFP with NTP can be explained by dilatation of cerebral vessels with consequent increase in cerebral blood flow[17]. Stullken & Sokoll[18] reported that TMP may increase intracranial blood volume due to its blocking effect on the sympathetic nerve of the cerebral vessels.

This may explain the initial transient CSFP increase with TMP, which disappeared as blood pressure fell further. In this respect the dog appears to differ from man; Turner et al.[12] saw no transient increase in intracranial pressure when TMP was used in patients. This could reflect differences in the degree of sympathetic innervation of the cerebral vessels between dog and man. With NTP there was a significant increase in CSFP which made an appreciable difference to the calculated CPP values at low blood pressure. Failure to take CSFP changes into account makes comparison between studies in the literature difficult.

Systemic circulatory and metabolic effects were predictably more pronounced at 30 mmHg than 45 mmHg in both groups. In TMP groups, there was a tendency in T-height to increase which may indicate myocardial ischemia, but the increase did not reach statistical significance. We are unaware of any report which describes circulatory and metabolic effects of drug-induced hypotension after the restoration of CPP. With NTP, significant increases in heart rate and central venous pressure continued after the restoration of CPP, suggesting more prolonged effects of NTP than TMP. The observed increase in glucose may be secondary to increased sympathoadrenal activity, to increased secretion of insulin antagonist and/or decreased secretion of insulin. The increases in lactate and lactate pyruvate ratio became pronounced with decreasing CPP.

Michenfelder & Theye[11] studied the cerebral and systemic effects of TMP- or NTP-induced hypotension and found that at low MAP (40 mmHg) the deleterious effects were unaffected by the drugs used for hypotension, but at higher perfusion pressure hypotension induced by NTP appeared superior to that produced by TMP. However, they cautiously pointed out that the differences were quantitatively small and therefore of only questionable significance. The observed increases in glucose and lactate pyruvate ratio even at the recovery stage in NTP dogs must be considered as the result of its protracted detrimental effects. In NTP dogs, cyanide toxicity can not be ruled out, though the dose was restricted to less than 1 mg/kg which is known to be the toxic threshold of NTP in dogs[19]. Three of eight NTP dogs were discarded from study because more than 1 mg/kg was given for reduction of CPP. It must be added the dogs rendered hypotensive with either TMP or NTP according to the same protocol as present study can recover without neurological sequelae within 7 hours (unpublished data). In summary the present study revealed different effects of the two drugs on EEG, CSFP and glycolytic metabolism.

The author greatfully acknowledges the suggestion and encouragement of Prof. H. Takeshita, Department of Anesthesiology. (This work is a thesis of the Graduate School of Medicine, Yamaguchi University.)

References

1) Maekawa, T., McDowall, D.G. and Okuda, Y.: Brain-surface oxygen tension and cerebral cortical blood flow during hemorrhagic and drug-induced hypotension in the cat. *Anesthesiology*, 51 : 313–320, 1979.
2) Stoyka, W.W. and Schutz, H.: The cerebral response to sodium nitroprusside and trimethaphan controlled hypotension. *Can. Anaesth. Soc. J.*, 22 : 275–283, 1975.
3) Fitch, W., Ferguson, G.G., Sengupta, D., Garibi, J. and Harper, A.M.: Autoregulation of cerebral blood flow during controlled hypotension in baboons. *J. Neurol. Neurosurg. Psychiatry*, 39 : 1014–1022, 1976.
4) Meldrum, B.S. and Brierley, J.B.: Brain damage in the rhesus monkey resulting from profound arterial hypotension. Ⅱ. Changes in the spontaneous and evoked electrical activity of the neocortex. *Brain Res.*, 13 : 101–118, 1969.
5) Gamache, F.W., Dold, G.M. and Myers, R.E.: Changes in cortical impedance and EEG activity induced by profound hypotension. *Am. J.*

Physiol., 228 : 1914-1920, 1975.
6) Selkoe, D.J. and Myers, R.E.: Neurologic and cardiovascular effects of hypotension in the monkey. *Stroke*, 10 : 147-157, 1979.
7) Wiederholt, W.C., Locke, G. and Yashon, D.: Hypotension and its effect on EEG activity in the dog. *Neurology*, 22 : 717-725, 1972.
8) Magness, A., Yashon, D., Locke, G., Wiederholt, W. and Hunt, W.E.: Cerebral function during trimethaphan-induced hypotension. *Neurology*, 23 : 506-509, 1973.
9) Schallek, W. and Walz, D.: Effects of drug-induced hypotension on the electro-encephalogram of the dog. *Anesthesiology*, 15 : 673-680, 1954.
10) Ishikawa, T. and McDowall, D.G.: Electrical activity of the cerebral cortex during induced hypotension with sodium nitroprusside and trimetaphan in the cat. *Br. J. Anaesth.*, 53 : 605-611, 1981.
11) Michenfelder, J.D. and Theye, R.A.: Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimethaphan, halothane, or nitroprusside. *Anesthesiology*, 46 : 188-195, 1977.
12) Turner, J.M., Powell, D., Gibson, R.M. and McDowall, D.G.: Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br. J. Anaesth.*, 49 : 419-425, 1977.
13) Rogers, M.C. and Traystman, R.J.: Cerebral hemodynamic effects of nitroglycerin and nitroprusside. *Acta. Neurol. Scand.*, 60 : 600-601, 1979.
14) Michenfelder, J.D.: The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. *Anesthesiology*, 41 : 231-236, 1974.
15) Miyauchi, Y.: Relationship between the electroencephalogram, cerebral metabolism and blood flow during thiopental anesthesia in the dog. *Bull. Yamaguchi Med. Sch.*, 28 : 41-48, 1981.
16) Michenfelder, J.D. and Theye, R.A.: Cerebral protection by thiopental during hypoxia. *Anesthesiology*, 39 : 510-517, 1973.
17) Ivankovich, A.D., Miletich, D.J., Albrecht, R. F. and Zahed, B.: Sodium nitroprusside and cerebral blood flow in the anesthetized and unanesthetized goat. *Anesthesiology*, 44 : 21-26, 1976.
18) Stullken, E.H. and Sokoll, M.D.: Intracranial pressure during hypotension and subsequent vasopressor therapy in anesthetized cats. *Anesthesiology*, 42 : 425-431, 1975.
19) Michenfelder, J.D.: Cyanide release from sodium nitroprusside in the dog. *Anesthesiology*, 46 : 196-201, 1977.