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Cerebral Hemodynamic Effects of Vasodilating Drugs in the Dog

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Abstruct Cerebral hemodynamic effects of continuous infusion of vasodilating drugs, hydralazine; 10 μg/kg/min, nitroprusside; 5 μg/kg/min, nitroglycerin; 5 μg/kg/min, trimethaphan; 5 μg/kg/min, were studied in twenty dogs anesthetized with halothane (0.28% end-tidal). With hydralazine, the mean arterial pressure (MAP) maximally decreased to 88% of the control, and cerebrospinal fluid pressure (CSFP) and cerebral blood flow (CBF) increased to 231% and 180% of the control, respectively. With nitroprusside, MAP maximally decreased to 78% of the control, and CSFP increased to 140% of the control with unchanged CBF. With nitroglycerin, MAP maximally decreased to 87% of the control, and CSFP and CBF increased to 168% and 108% of the control, respectively. With trimethaphan, MAP maximally decreased to 90% of the control, and both CSFP and CBF remained unchanged. It was concluded that vasodilating drugs had differential cerebral hemodynamic effects and there was no consistent relationship between CSFP and CBF during infusion.

Key Words: Brain; cerebrospinal fluid pressure, blood flow, perfusion pressure, Vasodilating drugs; hydralazine, nitroprusside, nitroglycerin, trimethaphan

Introduction

Vasodilating drugs which include hydralazine (HYD), nitroprusside (NTP), nitroglycerin (TNG) and trimethaphan (TMP) have been widely used in clinical practice. However, their effects on cerebral hemodynamics have received only recent attention. HYD, NTP and TNG have been reported to increase cerebrospinal fluid pressure (CSFP) in man[1)-7)] and animals[8)-14)] with or without intracranial pathology. It has been believed that the qualitative effect of drugs on CSFP can be predicted from the drug's effect on cerebral blood flow (CBF) and cerebral vascular resistance (CVR)[15)]. If this is applicable to vasodilating drugs, there should be interdependency between CSFP and CBF. However, except for few reports, there is no study which measured CSFP and CBF simultaneously. Overgaard and Skinhøj[4)] found that a single injection of HYD increased CSFP and CBF in three patients with intracranial lesions. In dogs, Rogers and Traystman[10)] preliminarily reported that with NTP or TNG injections, CSFP increased, while

CBF remained unchanged or decreased depending on whether or not CSFP had been increased before the single injection of the drugs. Simultaneous measurement of CSFP and CBF during TMP administration has not been made. Thus, there is a lack of knowledge concerning the cerebral hemodynamic effects of these drugs, particularly when these drugs are administered by continuous infusion. Accordingly, the present study was designed to measure CSFP and CBF simultaneously during continuous infusion of HYD, NTP, TNG or TMP, and the study revealed differential effects of these drugs on cerebral hemodynamics.

Materials and Methods

Twenty unpremedicated mongrel dogs weighing 6 to 20 kg were anesthetized with halothane, 1 to 1.5%, and nitrous oxide, 60%, in oxygen. Succinylcholine was given to facilitate tracheal intubation, 2 mg/kg intramuscularly, and administered at 4 mg/kg/h to maintain muscle paralysis. Ventilation was controlled with a Harvard pump to maintain $Paco_2$ at 33±1 (mean±SEM) torr. Pao_2 was maintained at 199±8 torr by adjustment of inspired oxygen concentration. An esophageal thermistor was placed to monitor body temperature, which was maintained at 37.2±0.3°C by a warming pad. Hemoglobin levels were maintained at 14±1 g/dl by blood transfusion or hemodilution with 10% hydroxyethyl starch solution. Base deficits more than 5 mEq/L were corrected by sodium bicarbonate.

In the supine position, catheters were inserted into both femoral veins for drugs, blood and lactated Ringer's solution infusions, into both femoral arteries for pressure measurements and blood sampling, and into the left facial vein for returning drained blood from the brain. Thereafter, animals were placed in the prone position with the head supported by bilateral ear bars, and then the surgical preparation for the measurement of CBF was made by the method described by Michenfelder, et al[16]. Briefly, the skin of the head was incised and the parietal and temporal muscles were reflected. The sagittal sinus was exposed and isolated from extracerebral communications. After the animal was heparinized by an initial dose of 2 mg/kg (1 mg/kg/h, subsequently), the tapered cannula was inserted into the sagittal sinus. The drained blood was returned to the facial vein. An electromagnetic flowmeter probe (Nihon Kohden MFV-1100, lumen diameter 3 mm) was incorporated 1 cm away from the draining portion of the sinus. To ensure accurate measurements, the electromagnetic flowmeter incorporated a nonocclusive zero and a 3-sec time constant. In addition, the electromagnetic flowmeter was frequently calibrated by direct timed measurements of the sagittal sinus blood flow. The percentage of the brain weight drained from the sagittal sinus was determined by injecting vinyl acetate at the completion of each experiment. This figure was used to convert flow from units of ml/min to ml/100g/min. For the measurement of CSFP, muscles were retracted to expose the atlanto-occipital membrane and a 20 gauge needle was inserted into the cisterna magna. Lidocaine, 5 mg/kg, 0.5% solution, was injected into the skin and muscle of the head and at the area where cannulae were placed. Additional lidocaine (half of the initial dose) was given hourly. All the pressures were zero-refered at the level of the external auditory cannal. The mean arterial pressure (MAP) and CSFP were measured by a pressure transducer (Statham P23 ID). The MAP, CSFP, CBF, ECG and end-tidal CO_2 concentration (Gould Godart Capnogram MK Ⅱ) were simultaneously recorded on a polygraph recorder (Nihon Kohden RM-6000). Cerebral perfusion pressure (CPP) was calculated as the difference between MAP and the mean CSFP. CVR was calculated as the ratio of CPP to CBF. Pao_2, $Paco_2$, pH values were measured with appropriate electrodes, and hemoglobin was measured by IL-182, Co-oximeter. After the completion of the surgical preparations, nitrous oxide was substituted by nitrogen and end-tidal halothane concentration analyzed by gas chromatography (Shimadzu GC-4A) was decreased to 0.28±0.03% and at least 1 h was allowed before the measurement commenced. Animals were then randomly divided into four groups: HYD, NTP, TNG and TMP, with five animals in each. Control measurements were obtained over a 15-min period and mean values were calculated from seven consecutive measurements (four measurements for blood gas analyses). Thereafter, the constant infusion of vasodilating drugs was started: 10 μg/kg/min for HYD, 5 μg/kg/min for NTP, TNG and TMP. Drugs were diluted in 5% glucose solution

and their concentrations were adjusted for each dog to allow constant infusion rate (Harvard Infusion/Withdrawal Pump, 902: 1.15 ml/min). Infusion was continued for 30 min. Measurements were performed at 5, 10, 15, 20, 30 min after the start of infusion (during) and 5, 10, 15, 20, 30, 45, 60 min after the end of infusion (after). Results were analyzed statistically using Student's t test for pared data to compare control values with values during or after infusion. $P<0.05$ was considered significant.

Results

The physiological parameters of each drug group are summarized in Table 1. There were no significant changes in physiological parameters during and after infusion from the control. Table 2 summarizes cerebral hemodynamics and Figure 1 shows per cent control in mean values of MAP, CVR, CSFP and CBF. With HYD, MAP maximally decreased to 88% of the control at 10 min-after infusion, and CSFP and CBF increased to 231% and 180% of the control, at 30 min-during and at 20 min-after infusion, respectively. The average MAP, CSFP, CBF and CVR from 15 min-during to 30 min-after infusion were 93, 180, 161 and 57% of the control, respectively. With NTP, MAP maximally decreased to 78% of the control at 15 min-during infusion and CSFP increased to 146% of the control at 20 min-during infusion, while CBF remained unchanged. The average MAP, CSFP and CVR during infusion were 81, 142 and 75% of the control, respectively. These changes returned to the control level at 5 min-after infusion. CPP and CVR increased significantly at 60 min-after infusion. With TNG, MAP maximally decreased to 87% of the control at 15 min-during infusion, and CSFP and CBF increased to 168 and 108% of the control at 5 min- and 10 min-during infusion, respectively. The average MAP, CSFP, CBF and CVR during infusion were 89, 146, 112 and 79% of the control, respectively. These changes returned to the control at 10 min-after infusion. MAP and CVR increased significantly at 60 min-after infusion. With TMP, CSFP and CBF remained unchanged throughout the experiment, while MAP and CVR maximally decreased to 90 and 86% of the control at 30 min-during infusion, respectively.

Table 1 Physiological Parameters

Drugs	Time	Pao_2 (torr)		$Paco_2$ (torr)		pH		Temperature (C)	
		Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Hydralazine (n=5)	Control	201	7	33	1	7.40	0.02	37.4	0.1
	During	203	3	33	1	7.40	0.02	37.5	0.1
	After	200	2	34	1	7.38	0.01	37.6	0.1
Nitroprusside (n=5)	Control	206	5	33	1	7.43	0.02	36.3	0.4
	During	201	2	33	1	7.41	0.01	36.6	0.3
	After	209	3	33	1	7.41	0.01	36.8	0.3
Nitroglycerin (n=5)	Control	204	13	33	1	7.40	0.03	37.7	0.4
	During	202	7	33	1	7.39	0.01	37.7	0.4
	After	205	6	33	1	7.39	0.01	37.7	0.4
Trimethaphan (n=5)	Control	185	7	34	2	7.42	0.02	37.3	0.3
	During	183	3	35	1	7.42	0.01	37.3	0.3
	After	186	6	36	1	7.42	0.01	37.2	0.3

Table 2 Effects of Vasodilating Drugs on Cerebral Hemodynamics

Drugs	Time (min)	MAP (torr)		CSFP (torr)		CPP (torr)		CBF (ml/100g/min)		CVR (torr/ml/100g/min)	
		Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Hydralazine (n=5)	Control	111	9	11	2	100	10	60	5	1.7	0.1
	During 5	113	9	12	2	100	10	60	7	1.7	0.1
	10	112	8	13	2	99	9	62	6	1.6	0.1
	30	104	4	26*	4	78*	7	102	24	0.9*	0.2
	After 10	97*	6	21*	3	76*	8	110	24	0.8*	0.1
	30	100	3	15*	2	84	5	101*	19	0.9*	0.1
	60	101	5	12	2	89	6	85*	8	1.1*	0.1
Nitroprusside (n=5)	Control	116	8	10	1	107	7	55	3	2.0	0.2
	During 5	102	8	13*	1	89*	7	54	3	1.7*	0.1
	10	93*	7	14*	2	80*	6	55	3	1.5*	0.1
	30	92*	4	13*	2	80*	3	55	3	1.5*	0.1
	After 10	109	6	8	1	101	5	56	5	1.9	0.1
	30	122	8	8	1	113	7	51	1	2.3*	0.2
	60	124	8	9	1	115*	7	50	2	2.3*	0.2
Nitroglycerin (n=5)	Control	126	7	9	1	117	7	58	3	2.0	0.2
	During 5	115	10	14*	2	100*	10	64	5	1.6*	0.2
	10	113*	8	12*	2	101*	9	63*	4	1.6*	0.2
	30	113*	8	12*	1	101*	8	65	5	1.6*	0.2
	After 10	124	8	9	1	115	7	63	4	1.9	0.2
	30	126	7	10	1	117	7	58	4	2.1	0.3
	60	131*	7	10	1	121	8	52	3	2.4*	0.3
Trimethaphan (n=5)	Control	120	7	8	1	112	6	62	5	1.9	0.2
	During 5	112	6	8	1	104	6	62	5	1.7	0.1
	10	115*	6	8	1	107*	6	62	5	1.8	0.1
	30	108*	5	8	1	99*	5	64	5	1.6*	0.2
	After 10	121	6	8	1	113	6	60	4	1.9	0.2
	30	118	5	8	1	110	5	57*	5	2.0	0.2
	60	121	7	8	1	113	7	55	3	2.0	0.2

*Significantly different from the control ($P<0.05$)

Discussion

The present study demonstrated differential effects of vasodilating drugs on cerebral hemodynamics. Physiological parameters, especially Pao_2, $Paco_2$ and hemoglobin concentration, which may modify cerebral hemodynamic effects of these drugs[11], were carefully controlled. Background anesthesia, 0.28% halothane, was kept constant throughout the measurement, and was considered to be minimal in its cerebral vasodilating effect[16]. These well-controlled conditions made it possible to compare the drug's effects per se among groups.

With a single injection of HYD, Overgaard and Skinhøj[4] reported an increase in CSFP

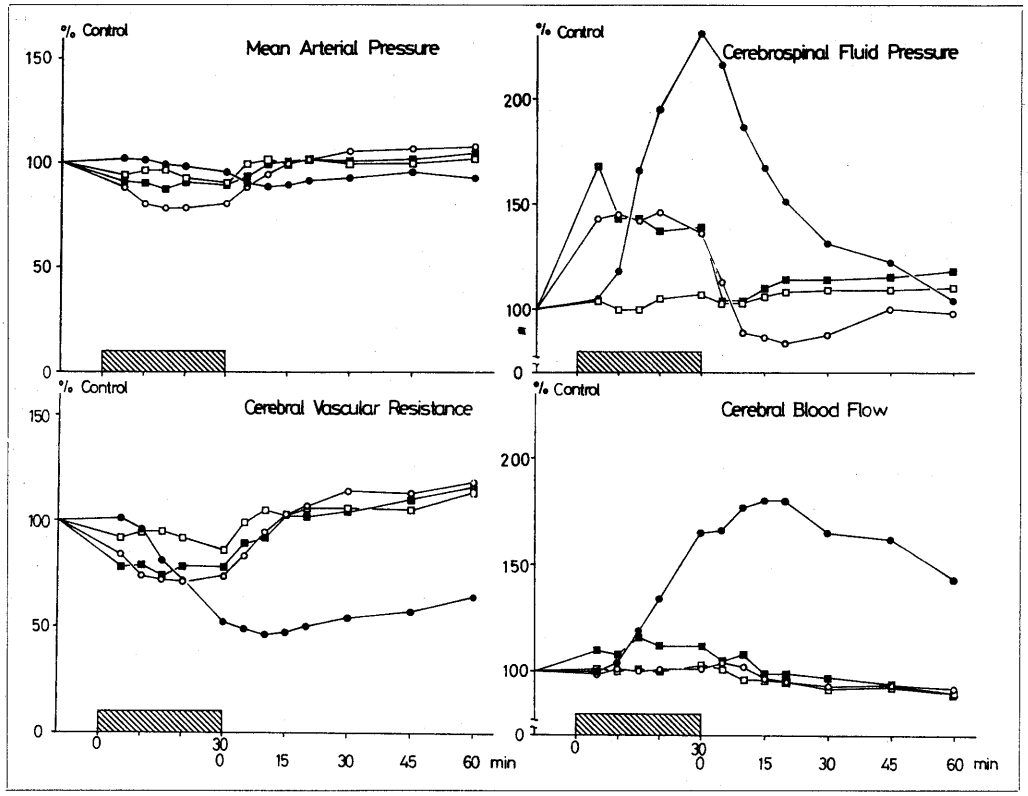

Fig. 1 Per cent control of mean arterial pressure (MAP), cerebral vascular resistance (CVR), cerebrospinal fluid pressure (CSFP) and cerebral blood flow (CBF) during and after infusion of hydralazine (●), nitroprusside (○), nitroglycerin (■) and trimethaphan (□). Shaded area indicates infusion period.

to 210% of the control in patients with intracranial pathology. However, CBF increased to only 108% of the control in their study. The difference in the degree of an increase in CBF between their and the author's studies can be interpreted as a result that some of their patients had already increased CSFP. It is generally accepted that larger changes in CBF hence cerebral blood volume (CBV) would have to occur in subjects with normal intracranial compliance than in subjects with decreased intracranial compliance. They also suggested that HYD initially had a more potent effect upon capacitance vessels than upon resistance vessels, because of the early and persistent increase in CSFP in spite of spontaneous hypocapnia which might have constrict cerebral resistance vessels through an increase in pH of perivascular space. However, their evidence for a dilating effect on capacitance vessels was indirect. In contrast, Johansson, et al.[13] measured vessel calibres of pial veins and arteries after the administration of dihydralazine, an analogus of HYD, and concluded that dihydralazine did not dilate venules and the dilatation of arteries was accompanied by an increase in CSFP. If this is applicable to HYD, an increase in CBF and a decrease in CVR, which relates inversely to the dia-

meter and total blood volume of cerebral resistance vessels[17], may be responsible for an increase in CSFP in the present study. The slow recovery of systemic and cerebral effects of HYD as compared to other drugs indicated long duration of action of this drug.

With NTP or TNG, an increase in CSFP reached to the plateau during infusion and appeared to be essentially independent of changes in CBF. Moderate decrease in CVR may be explained by autoregulatory changes in cerebral resistance vessels, which alone is not likely to increase CSFP, as in the case with TMP. Thus, NTP or TNG may increase CBV, and hence CSFP by changing cerebral venous capacitance. Rogers and Traystman[10] reported that CSFP increased to 180-270% of the control with TNG, and to 140-190% of the control with NTP, by a single injection, 5 to 50 μg/kg in the dog. In the present study, NTP and TNG had similar effects on CSFP, while TNG's effect on MAP was less than that of NTP at a given dose. Although direct comparison between two studies is difficult because of lack of detail information in their data, it is suggested that TNG has more pronounced effect on cerebral hemodynamics than NTP. In addition, the small increase in CSFP in our results emphasizes importance of the rate of administration of these drugs.

TMP is a ganglionic blocking agent that produces systemic vasodilatation but variable changes in CSFP have been observed. TMP induced no increase in CSFP and CBF with mild decrease in CVR which might be a simple manifestation of the autoregulatory changes in cerebral resistance vessels, in the present study. Turner, et al[1], found no consistent increase in CSFP in neurosurgical patients, while Stullken and Sokoll[8] reported an increase in CSFP with TMP in the cat. This discrepancy might be due to species difference in the degree of cerebrovascular control by the autonomic nervous system, and more importantly, due to dose and the rate of administration. No significant increase in CSFP with a decrease in CVR and MAP indicated that the dilatation of resistance vessels due to autoregulatory mechanism does not cause an increase in CSFP at least in dogs with normal intracranial compliance. Conversely, an increase in CSFP with NTP or TNG can not be explained by a decrease in CVR observed and is more likely due to the dilatation of capacitance vessels as mentioned above. In the present study, significant increase in CVR after NTP infusion was accompanied by an increase in MAP. However, it was difficult to assume this small increase in MAP to be a rebound phenomenon repeatedly reported[18),19].

In order to clarify the mechanism of the increase in CSFP, direct effects of vasodilating drugs on cerebral arteries and veins must be studied both in vivo and in vitro. Regadless of the mechanism, the following clinical interpretation can be made. The magnitude of CSFP changes observed in the present study would be probablly exaggerated and lead precipitous fall of CPP and hence cerebral ischemia in patients with decreased intracranial compliance. Special caution should be exercised in continuous infusion of drugs with cerebral hemodynamic effects, in the patients with increased CSFP.

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