Influence of Dopamine on Cerebral Blood Flow, and Metabolism for Oxygen and Glucose Under Barbiturate Administration in Cats

M. Sato, K. Niiyama, R. Kuroda, and M. Ioku

Department of Neurosurgery, Kinki University Medical School, Osaka, Japan

Summary

The effect of dopamine during barbiturate therapy was investigated in 29 cats including 5 sham-operated cats. According to Kiersey's classification of electro-encephalographic patterns, physiological variables, cerebral metabolic rates for oxygen and glucose, cerebral blood flow (CBF), and intracranial pressure (ICP), etc. were evaluated in each electro-encephalographic pattern. Oxygen-glucose index was calculated and used as an indicator for aerobic or anaerobic metabolism of glucose.

Group 1 (12 cats), to which only thiamylal was administered, maintained aerobic glycolysis due to a parallel reduction of cerebral metabolic rates for oxygen and glucose (about half of the initial value at Kiersey's fifth pattern) in spite of reduction of CBF and mean arterial blood pressure (MABP).

Group 2 (12 cats), to which dopamine was administered in addition to thiamylal due to a reduction of MABP, showed anaerobic glycolysis though MABP and CBF were maintained.

These findings are ascribed to an increase of cerebral metabolic rate for glucose up to 130% of the initial value though cerebral metabolic rate for oxygen decreased down to half of the initial value: The beneficial effect of barbiturate on cerebral metabolism was reduced by use of dopamine. ICP was reduced in both groups. Our result indicates that administration of extracellular fluid may be preferable for treatment of hypotension during barbiturate therapy than dopamine medication.

Keywords: Barbiturate therapy; cerebral metabolism; dopamine; electro-encephalogram.

Introduction

The beneficial effects of barbiturate treatment have been proven in both clinical and experimental work. However, during clinical application severe complications have sometimes been inevitable\(^{23}\). Except severe complications such as pulmonary, renal, hepatic failure, and opportunistic infections, a common phenomenon during barbiturate therapy was a reduction of systemic blood pressure. For the treatment of hypotension agents to increase the blood pressure, such as catecholamines, were generally used. Ward et al.\(^{30}\) reported that hypotension (systolic blood pressure < 80 mmHg) occurred in 54% of the 27 head-injured patients during barbiturate treatment and dopamine was used. Similarly, Samson et al.\(^{22}\) reported that hypotension occurred in 3 patients among 7 patients with subarachnoid haemorrhage and dopamine was used for 2 patients showing a progressively severe hypotension. The problem caused by use of catecholamines is that catecholamines increase cerebral blood flow (CBF) and cerebral metabolism, and it might result in a reduction of the beneficial effect of barbiturates.

This study was aimed to investigate the possibility of reducing the beneficial effect of barbiturates by using catecholamines. Dopamine and thiamylal, both of which were frequently used during barbiturate treatment\(^{21}\), were chosen for this purpose. Another purpose of this study was to clarify the relationship between the electro-encephalogram (EEG) patterns associated with barbiturate dosage\(^{12}\) and change of the variables consisting of CBF, intracranial pressure (ICP), cerebral metabolic rates for oxygen (CMRO\(_2\)) and glucose (CMRGL), etc., which would be influenced by dopamine.

Material and Methods

Animal Preparation

The experiment described here was conducted according to the principles set forth in the “Management of experimental animals” described in Notification No. 6 of the Prime Ministers Office of Japan, and “Guideline on the animal experiment” in the draft by the Science Council of Japan.

Twenty-nine cats of either sex were used weighing 1.8-3.0 kg. All were initially anaesthetized with ketamine hydrochloride intraperitoneally (30 mg/kg body weight). Catheters were inserted into
the brachial veins bilaterally for drug administration and into the descending aorta via the femoral artery for continuous blood pressure monitoring, measurement of blood gas, haematocrit, haemoglobin, glucose, and blood concentration of barbiturate. Following tracheostomy the animals were paralyzed with repeated doses of pancuronium bromide (0.12 mg/kg body weight every 1 hour) and artificially ventilated with a ventilator (Model 665, Harvard Apparatus, USA). Anaesthesia was maintained with a 3 to 1 mixture of nitrous oxide and oxygen. The surgical procedures were done after local infiltration with 0.5% xylocaine to avoid any pain. Rectal temperature was kept at 38–39°C by means of a heating blanket. Then, the animal’s head was fixed in a head holder, and burr holes were made in the frontal bones bilaterally, left parietal bones, and the midline of the parietal bone at the torcular Herophili.

Measurement of CBF by Hydrogen Clearance Method and EEG

After incising the dura, a paint-insulated platinum electrode (measuring 50 μm in diameter and 1 mm in length exposed) was inserted into the left ectosylvian gyrus for the measurement of CBF by means of the hydrogen clearance method (BIA-1, Biomedical Science CO., LTD., Japan), and for EEG (Polygraph 141-6, type 1205C, Sanei Instrument CO., LTD., Japan). CBF was measured after inhalation of a gas mixture containing 5–10% hydrogen gas. Flow values were calculated from hydrogen clearance curves starting 40 seconds after terminating hydrogen inhalation by using the initial slope method.

Measurement of CBF by Thermal Diffusion Method

A thermal diffusion flow probe, 8 mm in diameter, constructed from a Peltier stack (Biomedical Science CO., LTD., Japan) was placed to touch the cortex of the left ectosylvian gyrus just near the point of insertion of the hydrogen electrode. The probe created a temperature gradient between the two sensors, one cooled and the other heated, where a current was supplied using a semiconductor. The values obtained by the thermal diffusion method were calibrated by the absolute values of CBF obtained by the hydrogen clearance method: The measurement of CBF by the hydrogen clearance method was done before the administration of thiamylal and it was done also after the administration in some cats. Thus, continuous change of the absolute values of CBF was evaluated in combination with the thermal diffusion and hydrogen clearance method.

Measurement of ICP

ICP was continuously recorded by a pressure transducer (ICT/ b, Gaeltec CO., LTD., England) inserted epidurally through a right frontal burr hole.

Sinus Canulation

A thin canula (23 gauge) was inserted into the venous sinus at the torcular Herophili. The venous blood which was withdrawn from the torcular Herophili was used for the measurement of venous blood gas and glucose. After these procedures the burr holes were sealed by dental cement.

Measurement of Cerebral Metabolism

Serum glucose concentration was measured by the glucose-oxidase method. Arterio-venous difference of glucose (AVDG) was calculated by the difference of serum glucose concentration between the systemic arterial blood and venous blood obtained from the torcular Herophili. Arterio-venous difference of oxygen (AVDO2) was calculated from the oxygen saturations measured in systemic arterial blood and venous blood obtained from the torcular Herophili, with corrections for physically dissolved oxygen, according to the formula:

$$AVDO_2 = [1.34 \times Hb \times 0_2 \text{ saturations (AV)}/100] + 0.003 \times P_0_2$$

where Hb = haemoglobin, CMRG and CMRO2 were calculated as the product of CBF and the values of arterio-venous difference, and expressed as a percent change of the initial values because CBF in this study was local CBF, not total CBF.

The oxygen-glucose index (OGI) was calculated by the formula,

$$OGI = (AVDO_2 / 6 \times AVDG) \times 100\%.$$  

The normal value of OGI was 85–95%.

Experimental Groups

The cats were divided into three groups: group 1 comprising 12 cats, to which only thiamylal was administered, group 2 comprising 12 cats, to which dopamine was administered in addition to thiamylal, and the sham operation group comprising 5 cats, which served as controls.

Administration of Agents

After the measurement at the normal condition thiamylal was administered intravenously using an automatic infusion pump (SP-60, Nipro CO., LTD., Japan). According to the Kiersey’s classification of the EEG pattern (Table 1)12 each pattern was maintained for at least 15 minutes and the measurement was done thereafter: Each pattern was maintained totally for 20–25 minutes including the time spent for the measurement. After the measurements during the fifth pattern of EEG, thiamylal was continuously administered by 25 mg/kg body weight for 20 minutes, and the same measurements were performed thereafter. In this study this stage was defined as the deeper fifth stage, where low voltage EEG of the fifth pattern continued. The total dose of thiamylal used ranged from 130 to 160 mg/kg body weight. The blood concentration of thiamylal was measured by means of gas-liquid chromatography at each pattern. In group 1 thiamylal was kept administering according to the EEG pattern in spite of a reduction of mean arterial blood pressure (MABP); dopamine was not used. In group 2 dopamine was used to maintain MABP at more than 80% of initial MABP in order to

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