Title: EFFECTS OF HIGH-DOSE FENTANYL ON CEREBRAL HIGH ENERGY METABOLITES DURING HYPOXIA

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Introduction: Both barbiturates and hypothermia reduce the cerebral metabolic rate for oxygen ($CMRO_2$), and decrease the fall of high energy cerebral metabolites and elevation of lactate during hypoxia (1,2). Previous studies have shown that fentanyl causes a reduction in $CMRO_2$ of 35% at a dose of 100 µg/kg i.v. (3). This current study was designed to determine if high dose fentanyl also reduces high energy metabolite changes during hypoxia.

Method: Male Wistar rats were anesthetized with halothane, 2%, in N_2O, 70%, and O_2. Following tracheostomy and institution of mechanical ventilation, the left carotid artery was ligated. The femoral vessels were cannulated for monitoring of arterial pressure, measuring arterial blood gases and pH, and drug infusion. The animals were then paralyzed with curare, and a plastic funnel was fixed to the skull. After completion of surgery, the halothane was discontinued, and the animals were ventilated with 70% N_2O and O_2 for 30 min prior to the experiment. The animals were randomly assigned to six different groups, with 10 animals in each group. Group 1 (control group) was ventilated with 70% N_2O and O_2 during the experiment. Group 2 received 100 µg/kg fentanyl i.v. following by i.v. fentanyl infused at 200 µg/kg/hr; in addition, N_2O was replaced by 70% nitrogen (N_2) for the period of the experiment. Animals in the remaining groups were exposed to 20 min of severe hypoxia (PaO_2 18-20 mmHg) induced by partially replacing O_2 with N_2 during the experiment. A slow i.v. infusion of phenylephrine and sodium bicarbonate was given during hypoxia to help maintain MAP at 100 mmHg and normal acid-base balance. These hypoxic groups were treated as follows. Group 3 received no additional treatment. In group 4 the body temperature was reduced to and then maintained at 32°C for the period of experiment. Group 5 received pentobarbital 25 mg/kg intraperitoneally 15 min prior to the onset of hypoxia. Group 6 was given fentanyl 100 µg/kg i.v. followed by i.v. fentanyl infused at 200 µg/kg/hr during the experiment. N_2O was replaced by N_2 in the last two groups during the experiment. At the end of the hypoxic period in the last four groups, and after a corresponding period in the first two groups, the brain was frozen *in situ* by pouring liquid N_2 into the funnel. The brain was then chiseled out and stored in liquid N_2 until the measurement of cortical adenosinetriphosphate (ATP), phosphocreatine (PCr), lactate (Lac), and glucose (Glu) by microfluorometric techniques. Data were analyzed by analysis of variance and with t-test between various groups using the Bonferroni correction; $P < 0.05$ was considered statistically significant.

Results: Mean arterial pressure, $PaCO_2$ and arterial pH were similar in all groups. PaO_2 was 100-120 mmHg before hypoxia in all groups and 18-20 mmHg during the hypoxic period. Except for the hypothermia group (temperature 32°C), rectal temperature was maintained at 37°C throughout the experiment. Table 1 shows the values for ATP, PCr, Lac and Glu from the ligated cerebral cortex. The administration of fentanyl alone caused no alteration in metabolite concentrations when compared to control. Fentanyl pretreatment did not prevent the deterioration of ATP and PCr, nor did it reduce the formation of Lac caused by hypoxia compared to values from hypoxic animals receiving no pretreatment. In contrast, hypothermia and barbiturate preserved cortical tissue ATP and PCr during hypoxia. Although the Lac concentration in hypothermic and barbiturate groups increased significantly when compared to control, this increase was significantly less than those seen in fentanyl hypoxia and hypoxia alone. There was no difference in brain glucose or blood glucose between the various groups.

Discussion: Our results indicate that while hypothermia and barbiturate preserved brain tissue ATP and PCr during hypoxia, fentanyl, at a dose in previous studies that decreased $CMRO_2$ by 35%, had no such effect. The reason for the failure of fentanyl to prevent the reduction in high energy phosphates and the accumulation of lactate in the brain tissue during hypoxia is not known. It is important to note that fentanyl in the normoxic animal had no effect on cerebral energy metabolite concentration, and in the hypoxic animals, the effects were no worse than in the hypoxic animals not receiving fentanyl.

References:

1. Carlsson C, Hagerdal M, Siesjö BK: Protective effect of hypothermia in cerebral oxygen deficiency caused by arterial hypoxia. Anesthesiology 44:27-35, 1976

2. Smith AL: Barbiturate protection in cerebral hypoxia. Anesthesiology 44:285-293, 1977

3. Carlsson C, Smith DS, Keykhah MM, Harp JR: The effects of high-dose fentanyl on cerebral circulation and metabolism in rats. Anesthesiology 57:374-380, 1982

Table 1
Cerebral Cortical Tissue Metabolites From Ligated Hemisphere

Groups	ATP	PCr	Lac	Glu
I. Control (N_2O)	2.86± 0.09	3.83± 0.11	1.68± 0.21	3.3± 0.47
II. Fentanyl (Normoxia)	2.81± 0.06	3.97± 0.13	1.44± 0.30	4.01± 0.30
III. Hypoxia+ N_2O	1.96±* 0.36	2.02±* 0.44	16.33±* 1.63	2.24± 0.65
IV. Hypothermia+ Hypoxia	2.98± 0.08	3.78± 0.02	6.33±* 0.50	3.91± 0.51
V. Barbiturate+ Hypoxia	2.55± 0.20	3.29± 0.27	10.29±* 1.37	4.76 0.04
VI. Fentanyl+ Hypoxia	2.00±* 0.27	2.23±* 0.30	19.33±* 3.16	3.33± 0.66

Values are means ± S.E.M.
*Significantly different from control $P < 0.05$