Title: LOCAL CEREBRAL BLOOD FLOW DURING HIGH DOSE FENTANYL IN THE RAT

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Introduction: High-dose fentanyl anesthesia technique has been advocated for cardiac surgery because of its cardiovascular stability and its reversibility by naloxone. This anesthetic technique is usually associated with EEG slowing and reductions in cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$)(1). When fentanyl seizures occur in rats, total $CMRO_2$ and CBF are increased. In humans, high doses of fentanyl can cause sharp waves and seizure activity in EEG. In the present study, local CBF (l-CBF) was measured to identify the distribution characteristics of blood flow and to examine the coupling between l-CBF and EEG activity during high-dose fentanyl induced seizures.

Methods: Twenty-three Sprague-Dawley rats were anesthetized with 1.5% halothane and 70% N_2O in O_2. They were paralyzed with pancuronium and ventilated via a tracheostomy to maintain normocapnia (37±0.4mmHg). Femoral arteries and veins were cannulated for arterial blood pressure measurement, blood sampling, and infusion of drugs and ^{14}C-iodoantipyrine tracer. EEG and body temperature were also monitored. After the completion of the operation, halothane was discontinued and at least 60 minutes were allowed for stabilization. The rats were randomized into 5 groups, based on characteristic EEG patterns, i.e. control, initial suppression of frequency, spike, burst, and suppression groups. These EEG patterns developed as a fentanyl infusion ($11\mu g/kg\text{-}1\ min^{-1}$) was maintained. Local-CBF was measured by quantitative autoradiography. N_2O was replaced by N_2 5 minutes before the start of fentanyl infusion, when the control l-CBF was obtained. Statistical significance was tested using one-way analysis of variance ($P<0.05$=significance).

Results: The measured physiological parameters in the fentanyl groups were not statistically significant from the control group. The total dose of fentanyl for frequency suppression, spike, burst and suppression group was 11,75,220 and 164µg/kg, respectively. Local-CBF of selected representative structures are shown in the table. In the spike and the burst groups, l-CBF is increased in hippocampus (191% of control in both groups) and septal nucleus (163% and 236% of control, respectively). In the suppression group, l-CBF is increased in hippocampus and amygdala (371% and 287% of control, respectively).

Discussion: Fentanyl produces 3 dose-related stages of EEG patterns: I.Initial suppression of frequency, II.Spike and burst activation and III.Suppression. In stage II activation, l-CBF was significantly elevated in the hippocampus and septal nucleus regions. These regions are known to be metabolically activated in fentanyl and other depressant drug related subcortical seizure activity. This increase in subcortical l-CBF probably represents an appropriate compensatory flow response to enhanced metabolic activity. However, in stage III suppression, characterized by minimal EEG activity, l-CBF was increased to its highest levels in the hippocampus and amygdala. The coupled relationship between EEG function and metabolism-flow appears disturbed during post-seizure suppression, i.e. low function-high flow. This uncoupling may represent reactive hyperemia secondary to inadequate l-CBF compensation during phase II spike-burst activity. Since the hippocampus is known to be expecially vulnerable to hypoxic-ischemic insults, fentanyl enhanced activity in this region could be harmful, especially if low perfusion pressures limit the l-CBF autoregulatory response.

Reference:

1. Carlsson C, Keykhah MM, Smith DS, et al Cerebral blood flow and oxygen consumption after fentanyl. Anesthesiology 55(Suppl): A193, 1981.

Table: Local-CBF in 6 brain structures as correlated with EEG patterns occurring during fentanyl infusion. The values are mean ±SEM. *Significantly different from control ($p<0.05$)

	CONTROL n=4	LOW-DOSE n=5	SPIKE n=4	BURST n=5	SUPPRESSION n=5
Frontal Cortex	279±31	339±34	430±61	386±73	401±60
Amygdala	203±11	211±11	238±21	264±38	582±105*
Hippocampus	240±20	327±38	457±36*	459±51*	890±150*
Septal Nucleus	160±12	192±17	261±12*	377±17*	321±77
Caudate-Putamen	244±10	305±34	349±43	357±96	344±34
Corpus Callosum	88±5	88±8	103±7	106±11	104±14

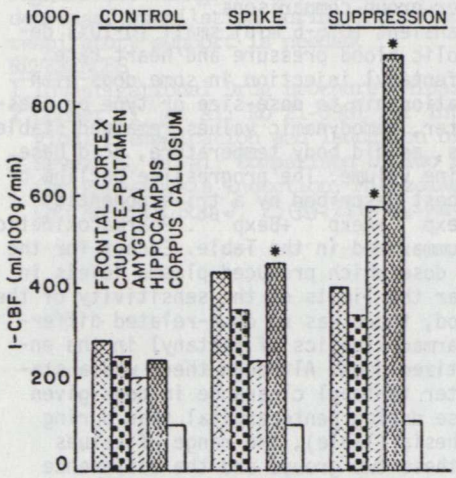

Figure: l-CMRg in 6 brain structures during different electrophysiological states.

*Significantly different from control ($p<0.05$)