Title: SUBCORTICAL LOCAL BRAIN METABOLISM INCREASES WITH FENTANYL-INDUCED SEIZURES

Authors: C. Tommasino, M.D., H.M. Shapiro, M.D., and M.M. Todd, M.D.

Affiliation: Veteran's Administration Medical Center and Neuroanesthesia Research Laboratory, University of California at San Diego, La Jolla, CA 92093

Introduction: High doses of fentanyl produce dose dependent reductions in cerebral blood flow (CBF) and cerebral metabolic rate (CMR) similar to that obtained with barbiturates. Even higher doses of some narcotics can elicit convulsions; when this occurs with fentanyl in rats a relative increase in whole brain $CMRO_2$ occurs without a compensatory elevation in total CBF (1). This could represent a potential ischemic-toxic effect of high dose narcotic anesthesia as employed in cardiac surgery. To gather data relevant to this question we examined the neuro-anatomic and quantitative local (1)-CMR response to fentanyl seizures.

Methods: L-CMR-for glucose (1-CMRg) was determined in three groups (n=6) of rats, awake control (C), low dose fentanyl (200µg/kg=LF, and high dose fentanyl (400µg/kg=HF) with the ^{14}C-deoxyglucose (^{14}C-DG) quantitative autoradiographic technique. Sprague-Dawley rats (300g±6(±SE) were briefly anesthetized with halothane for tracheostomy and femoral vessel catheterization to permit pressure measurement, drug administration, and sampling of arterial blood via an arteriovenous shunt. Muscle relaxation was obtained with pancuronium (0.2mg i.v. q 20min) and mechanical ventilation established with O_2/N_2 (30:70) to yield $PaCO_2$ 37±2 torr and PaO_2 between 90-125 torr. The electroencephalogram (EEG) was recorded with subcutaneous platinum electrodes. Temperature was servo-controlled to 37°C and the rats were heparinized (200 I.U. i.v.). Surgical wounds were infiltrated with lidocaine and halothane discontinued for 1 hr prior to 1-CMRg determination. Fentanyl in the LF group was given as 40µg/kg/min infusion for 5 min followed by a continuous infusion of fentanyl over 50 min at 8µg/kg/min. In the HF group the infusion dose was doubled and donor blood was given to maintain mean BP above 100 torr.

Results: High doses of fentanyl induced relatively continuous seizure activity in 11 of 12 rats during the ^{14}C-DG determination. Table 1 and Figure 1 summarize the 1-CMRg effects of high dose fentanyl administration in our animals. In the LF and HF groups 1-CMRg was significantly decreased in all cerebral cortical areas and white matter areas. In the subcortex, during fentanyl anesthesia, 1-CMRg decreased in 3 structures and remained at control levels in limbic structures. Local brain metabolism in subcortical structures in HF rats remained unchanged in 5 subcortical structures. In three limbic system structures there was a tendency for 1-CMRg to increase at both fentanyl doses; this increase was statistically significant in only the hippocampus.

Discussion: Similar patterns of (relative or absolute) subcortical limbic system metabolic activation due to seizures occur with enflurane and lidocaine. Whether the increased local-metabolic demand caused by fentanyl seizures can be satisfied by changes in local brain blood flow remains unanswered. In the absence of this local flow information it seems prudent to monitor the EEG during high dose fentanyl anesthesia during cardiac surgery, and to avoid systemic hypotensive stresses to CBF autoregulation, especially when EEG spike activity is noted.

Reference:

1. Carlsson C, Keykhah MM, Smith DS, et al. Influence of high dose fentanyl on cerebral blood flow and metabolism. Acta Physiol Scand 113:271-272, 1981.

Table 1: Mean local cerebral metabolic rate for glucose (umole/100g/min) (±SE) in conscious restrained rats (control) and those given fentanyl 200µg/kg (LF) and 400µg/kg (HF)

	Control	LF	HF
1.(F) Frontal	67±4	46±5**	49±7*
2.(T) Temporal	71±4	52±5*	51±5*
3.(P) Parietal	65±4	45±4*	45±5*
4 (O) Occipital	70±3	47±6**	45±5**
Sub-Cortex			
5.(Th) Thalamus	53±4	29±3***	29±3***
6.(C-P) Caudate-Putamen	63±3	43±6*	41±5**
7.(H-Th) Hypothalamus	39±4	22±4*	25±5
8.(Hip) Hippocampus	42±3	49±6	80±16*
9.(IN) Interpeduncular N	85±3	59±11	77±6
10.(SN) Septal N	46±3	48±11	68±11
11.(A) Amydgala	30±3	34±3	35±5
12.(PV) Paraventricular	41±4	30±4	33±2
White Matter			
13.(CC) Corpus Callosum	22±4	11±5	8±2**
14.(IC) Internal Capsule	16±4	4±2	2±2**
15.(C) Cerebellar	17±3	12±4	6±2*

(Significant changes from control *=p<.05,**p<.01,***p<.001)

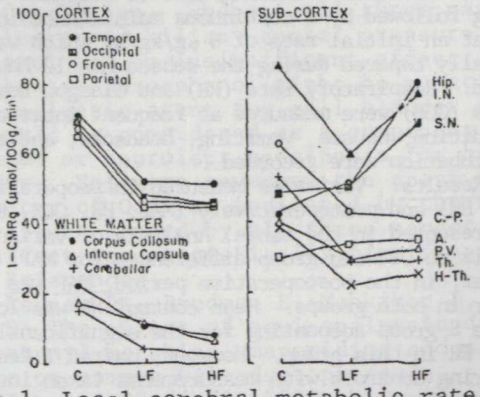

Figure 1: Local cerebral metabolic rate for glucose (1-CMRg) in conscious (C) and in rats given 200 µg/kg fentanyl (LF), and 400µg/kg fentanyl (HF). Refer to table for complete structure names.