

Sedation in fMRI : An unsolved challenge

Byron Bernal *, MD Nolan Altman**, MD

There are many medications that can be utilized to sedate children undergoing fMR examinations. The most frequently used drugs are chloral hydrate, thiopental, phenobarbital, propofol, and fentanyl. These medications have some secondary effects on the electrical and metabolic activity of the cortex, cerebral blood flow(CBF), cerebral blood volume(CBV), and tissue oxygen extraction. These effects are of no concern in regular MRI (Magnetic Resonance Imaging), however, may have a significant contribution in fMR performed in the sedated child. Since fMRI is based on the hemodynamic and metabolic response of the brain to a given stimulus the selection of the sedation medication seems crucial. The following reviews the current knowledge regarding the relation of these drugs to these physiological parameters.

Chloral Hydrate.- Chloral hydrate (CH) does not reduce brain cortex activity. This is demonstrated on EEG where it is widely used. Thoresen M and Henriksen O (1997) did not find changes on the EEGs in 9 out of 13 children with epileptic seizures, before and after CH was administered. We do not know of any reported studies relating CBF, CBV, or cerebral regional metabolism changes, and CH in humans.

Propofol.- Propofol has been used as a sedative in children undergoing EEGs. Low propofol doses (0.5-1 mg/kg) show an increase in the number of beta-waves and a significant reduction of alpha- and theta-waves. Larger doses of propofol (total dose of 2-2.5 mg/kg), the number of beta-waves decreased and delta-waves appeared. The effects of propofol on the cerebral blood-flow have been tested in pigs (Lagerkranser M. et al, 1997). Propofol caused a substantial reduction in the cerebral metabolic rate of oxygen, which was accompanied by an increase in cerebrovascular resistance and a decrease in CBF.

Propofol in clinical dosage does not affect auto-regulation in the pig model, although there is reduction in cerebral metabolic rate. In humans, experiments have demonstrated that propofol induced a reduction of 35% in CBF velocity, and a 10% decrease in cerebral oxygen extraction (Ederberg S et al, 1998).

Barbiturates.- These drugs produce vasoconstriction of the cerebral vascular bed, which is the reason it is used in children with increased intracranial pressure. In neonates, phenobarbital is not associated with significant changes in cerebral flow velocity (Saliba E et al, 1991); but significantly reduces local cerebral glucose utilization in the mammillary nuclei, the anterior, lateral and ventral thalamic nuclei, and the geniculate nuclei (Ableitner A & Herz A., 1987). Chloral hydrate and Phenobarbital do not appear to blunt the cortex activity in our experience. On the contrary, it seems that intensity is better in evoked potentials obtained in sedated patients with these two medications without modification of the latencies.

Pentobarbital is widely used to sedate children for radiological procedures. Pentobarbital reduces CBF in rats, although in high doses (Todd MM & Weeks J, 1996). Others have shown in rats that pentobarbital anesthesia reduces the microregional venous O₂ saturation inhomogeneity in the brain, producing a balance of oxygen supply and consumption, without change in O₂ extraction (Sinha AK et al, 1992). The regional metabolic rate of glucose does not change despite the overt generation of primary evoked cortical potentials in the somatosensory cortex of rats sedated with pentobarbital (Ueki M et al, 1992). We do not know studies of this type conducted in normal human beings.

Neuroleptanalgesia.- As the name implies these are analgesia that takes place in cerebral nervous system (CNS). There are two groups of these agents.. The first group is that of the major tranquilizers such as chlorpromazine, phenergan, and droperidol. The second group is the opiates such as fentanyl or morphine (and more recently omnopon). Alpha-adrenergic blockage, hypothermia and extra-pyramidal effects are seen most often with chlorpromazine. Droperidol produces marked tranquilization and sedation. Droperidol should not be administered to children 2 years of age or under because safety has not been established. Very rarely droperidol or chlorpromazine may produce the Neuroleptic Malignant Syndrome (NMS). NMS is potentially fatal and requires symptomatic treatment and immediate discontinuation of neuroleptic treatment. Fentanyl produces transient increase in intracranial cerebral pressure (ICP) when administered by bolus injection in patients with increased ICP (Albanese J et al, 1999). Large doses of fentanyl in dogs have little effect on the cerebral circulation in the absence of other anaesthetic agents which might influence cerebral haemodynamics and metabolism (Milde LN et al,

1989). Young rats show more cerebrovascular and cerebral metabolic depression than older ones with fentanyl (Baughman VL et al, 1987). In humans the cerebral metabolic rate of oxygen (CMRO₂) does not change with light levels of anesthesia using fentanyl (5-6 mcg/kg bolus) compared with halothane or isoflurane (Young W et al, 1989). We do not know of reports on CVB, CVF or Oxygen extraction studies in healthy human beings.

Ketamine.- Ketamine is a chemical derivative of phencyclidine (PCP). Ketamine appears to selectively depress normal function of the association cortex and thalamus while enhancing activity in the limbic system. A opiate receptor interaction is suggested by the reversal of its effects by naloxone. Also, norepinephrine, serotonin, and muscarinic acetylcholine receptors may be involved. Ketamine produces a state termed "dissociative anesthesia" characterized by the maintenance of reflexes (e.g., corneal and cough) and coordinated but purposeless movements. Ketamine has been used for conscious sedation in pediatric patients undergoing minor procedures, and radiological studies. The most prominent adverse effect resulting from the use of ketamine is the emergence delirium, manifested as confusion, illusions, euphoria, and fear. The frequency of presentation of this reaction is greater in adults (Stoelting RD, 1991). Ketamine supposedly increases intracranial pressure, and CBF. This effect is now questioned. At least, this effect is not seen when this drug is given along with propofol. Albanese et al (1997) found that ketamine decreases the intracranial pressure when used with propofol sedation (doses between 1.5 and 5 mg/kg). In the same study there was no significant difference in cerebral perfusion pressure, jugular venous bulb oxygen saturation, and middle cerebral artery blood flow velocity. A previous study, however, had found that Ketamine increased the intracranial blood flow velocity (Koch et al, 1991). They also described increased brain electrical activity, which closely correlated to an increase in neuronal activity.

Midazolam.- Midazolam is a benzodiazepine that produces sedation, amnesia, and relief of anxiety. This agent has been used for conscious sedation of children before diagnostic or therapeutic procedures or pre-induction of anesthesia. The recommended dose for children is a single dose of 0.25 to 0.5 mg/kg to a maximum dose of 20 mg of the syrup. The most serious side effect of midazolam is respiratory depression or arrest. Midazolam causes dose-related changes in rCBF in brain regions associated with the normal functioning of arousal, attention, and memory (Veselis R. et al, 1997). Other previous studies have found that midazolam decreases cerebral blood flow (CBF) by increasing cerebral vascular resistance (CVR) (Cheng M et al, 1993). This finding has not been verified by others who found, that brain perfusion and cerebral oxygenation was reduced while cerebral vascular resistance was not significantly changed in dogs (Yeh F. et al, 1988). Midazolam has been used blended with ketamine with good results (Parker et al, 1997).

Isoflurane.- Isoflurane blunts cerebral responses to somatosensory stimuli in fMRI (Antognini JF, 1997). It is expected that the same results could be observed in other tasks involving auditory systems already saturated by the noise of the gradient coils. Incremental doses of isoflurane caused a stepwise decrease in frequency of oscillations in auditory evoked potentials (AEP), at least in doses high enough to perform intraabdominal surgery (Madler C. et al, 1991). In animal tests isoflurane tends to disrupt synchronized neural oscillations in the medial geniculate nucleus and consequently the transfer of auditory information (Tennigkeit F et al, 1997). Increasing concentrations of isoflurane produced a clear sequence of EEG changes, decreasing fast and increasing slow components (Lloyd-Thomas AR et al, 1990).

In conclusion, it appears that sedation can alter the activation of the cortex by means of reduction of the metabolism, decrease of CBF, blood volume or both. This can have significant implications for fMRI in the sedated child. There is no ideal drug. Theoretically the best drugs to achieve activation should be Ketamine, Propofol and pentobarbital as they seem to have the least effect on cortical activity, CBV or O₂ saturation. More research has to be done in these fields.

References:

Thoresen M; Henriksen O; Wannag E; Laegreid L: Does a sedative dose of chloral hydrate modify the EEG of children with epilepsy? *Electroencephalogr Clin Neurophysiol*, 1997; 102:152-7

Lagerkranser M; Stange K; Sollevi A: Effects of propofol on cerebral blood flow, metabolism, and cerebral autoregulation in the anesthetized pig. *J Neurosurg Anesthesiol*, 1997;9:188-93

Ederberg S; Westerlind A; Houltz E; Svensson SE; Elam M; Ricksten SE: The effects of propofol on cerebral blood flow velocity and cerebral oxygen extraction during cardiopulmonary bypass. *Anesth Analg*, 1998; 86:1201-6

Saliba E; Autret E; Khadirly L; Chamboux C; Laugier J: Effects of phenobarbital on cerebral hemodynamics in preterm neonates. *Dev Pharmacol Ther*, 1991; 17:133-7

Todd MM; Weeks J: Comparative effects of propofol, pentobarbital, and isoflurane on cerebral blood flow and blood volume. *J Neurosurg Anesthesiol* ,1996; 8:296-303

Ableitner A; Herz A: Influence of meprobamate and phenobarbital upon local cerebral glucose utilization: parallelism with effects of the anxiolytic diazepam. *Brain Res*, 1987; 403:82-8

Sinha AK; Chi OZ; Weiss HR Effect of pentobarbital on cerebral regional venous O₂ saturation heterogeneity. *Brain Res* ,1992 ;591:146-50

Ueki M; Mies G; Hossmann KA: Effect of alpha-chloralose, halothane, pentobarbital and nitrous oxide anesthesia on metabolic coupling in somatosensory cortex of rat. *Acta Anaesthesiol Scand*, 1992 ;36:318-22

Albanese J; Viviani X; Potie F; Rey M; Alliez B; Martin C: Sufentanil, fentanyl, and alfentanil in head trauma patients: a study on cerebral hemodynamics. *Crit Care Med* 1999 ;27:407-11

Milde LN; Milde JH; Gallagher WJ: Cerebral effects of fentanyl in dogs. *Br J Anaesth* 1989; 63:710-5

Baughman VL; Hoffman WE; Albrecht RF; Miletich DJ: Cerebral vascular and metabolic effects of fentanyl and midazolam in young and aged rats. *Anesthesiology*, 1987 ;67:314-9

Young WL; Prohovnik I; Correll JW; Ornstein E; Matteo RS; Ostapkovich N: Cerebral blood flow and metabolism in patients undergoing anesthesia for carotid endarterectomy. A comparison of isoflurane, halothane, and fentanyl. *Anesth Analg* 1989 ;68:712-7

Stoelting, RD, ed. *Pharmacology and Physiology, In: Anesthetic Practice*. 2nd Edition. JB. Lippincott, Philadelphia, 1991

Albanese J; Arnaud S; Rey M; Thomachot L; Alliez B; Martin C: Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. *Anesthesiology* 1997; 87:1328-34

Koch E, Werner C, Hoffman We. Et al.: Concurrent increases in brain electrical activity and intracranial blood flow velocity during low-dose ketamine anaesthesia. *Can J Anaesth* , 1991; 38:826-830

Veselis RA; Reinsel RA; Beattie BJ; Mawlawi OR; Feshchenko VA; DiResta GR; Larson SM; Blasberg RG: Midazolam changes cerebral blood flow in discrete brain regions: an H₂(15)O positron emission tomography study. *Anesthesiology*, 1997; 87:1106-17

Cheng MA; Hoffman WE; Baughman VL; Albrecht RF: The effects of midazolam and sufentanil sedation on middle cerebral artery blood flow velocity in awake patients. *J Neurosurg Anesthesiol* 1993; 5:232-6

Yeh FC; Chang CL; Chen HI: Effects of midazolam (a benzodiazepine) on cerebral perfusion and oxygenation in dogs. *Proc Natl Sci Counc Repub China [B]* 1988;12:174-9 (Abstract)

Parker RI; Mahan RA; Giugliano D; Parker MM: Efficacy and safety of intravenous midazolam and ketamine as sedation for therapeutic and diagnostic procedures in children. *Pediatrics* 1997; 99:427-31

Antognini JF; Buonocore MH; Disbrow EA; Carstens E Isoflurane anesthesia blunts cerebral responses to noxious and innocuous stimuli: a fMRI study. *Life Sci* 1997;61:349-54

Madler C; Keller I; Schwender D; Poppel E: Sensory information processing during general anaesthesia: effect of isoflurane on auditory evoked neuronal oscillations. *Br J Anaesth* 1991; 66:81-7

Tennigkeit F; Ries CR; Schwarz DW; Puil E: Isoflurane attenuates resonant responses of auditory thalamic neurons. *J Neurophysiol* 1997; 78:591-6

Lloyd-Thomas AR; Cole PV; Prior PF: Quantitative EEG and brainstem auditory evoked potentials: comparison of isoflurane with halothane using the cerebral function analyzing monitor. *Br J Anaesth* 1990; 65:306-12

* Neurologist, fMRI, Radiology Department. Research Director

** Neuroradiologist, Chief of the Radiology Department, Miami Children's Hospital