NEUROPHARMACOLOGY

ISNACC

Qualifications for inclusion into the neuroanesthesia drug club:

- Controllability (e.g. rapid onset and offset of effect)
- Stability of intracranial homeostasis
- Hemodynamic stability
- Noninterference with neurophysiologic monitoring
- Neuroprotection
- Antinociception

Barbiturates

- Thiopental decreases CBF and CMRO2 paralel to the point of isoelectricity on the EEG.
- Change in CBF secondary to the change in CMRO2 (a couple decrease in flow and metabolism).
- Thiopental, even in high dose, does not appear to abolish cerebral autoregulation or CO2 reactivity.

Barbiturate

- Effect of CSF dynamics.
- Effect on ICP: as a result of reduction both CBF anf CBV, barbiturate lower ICP.
- Effect on Spinal Cord Blood Flow (SCBF) and metabolism: reduce significant SCBF, autoregulation remain intact (autoregulation 60-120 mmHg).

Intravenous anesthetics

Barbiturate

- Ca influx ↓
- Block Na channel
- Free radicals inhibition formation.
- ↓ Extracellular lactate, glutamate, aspartat

Propofol: ↑ glutamate excotoxicity
↑ neuronal damage.
propofol infus syndrome

Etomidate

- Reduce CBF and CMRO2.
- Myoclonus has the disadvantage of being misinterpreted as seizure activity.
- Prolonged used may supresse the adrenocortical response to stress.
- Less cardiovascular effect as compared to thiopental.

Etomidate

- Effect on autoregulation has not been evaluated.
- Reactivity to CO2 is maintained.
- Effect on CSF dynamic.
- Reduced ICP without decreasing CPP.

Effect etomidate to CNS

- A potent cerebral vasoconstrictor and like thiopental, is capable of decreasing ICP.
- Like methohexital, may activate seizure foci in patients with focal epilepsy versus facilitate location of seizure focus in patients undergoing cortical resection of epileptogenic tissue.

etomidate

- Has been advocated for neuroanesthesia, because of its similar cerebral metabolic profile compared with barbiturates without cardiovascular side effect.

  Cheng et al. Crit Care Clin 1997.

- Decrease CBF, CMRO2, ICP. In contrast to barbiturate the cerebral metabolic effect are regionally, reduction of CMRO2 greater in the forebrain.

  Davis. Anesthesiology 1986

- Etomidate reduce CBF and oxygen consumption, which attenuates elevated ICP and limits ICP spikes associated with intubation
- Unlike thiopental and propofol, etomidate reduce ICP without decreasing ABP and CPP

Bergen et al, J Emerg Med 1997

Wadbrook. Emerg Med Clin North Am 2000

Giese et al. Pharmacotherapy 1983

Etomidate brain protection

- Decreased CMRO2, reduction in intracranial blood volume, decrease ICP, decrease or redistribution of CBF, membrane stabilization, inhibition of free radical liberation.
- Several studies in animal models → etomidate provides protection during incomplete global ischemia and severe hypoxemia.

Cottrell JE, Smith DS. Anesthesia & Neurosurgery. 1994

Propofol

- Produces dose-related reductions in both CBF and CMRO2.
- Has been use as sedation in awake craniotomy.
- Propofol infuse syndrome.
- Autoregulation and CO2 response are preserved.

Propofol

- Effect on CSF dynamic.
- Reduces ICP.
- Because reduced MAP, its effect on CPP must be carefully monitored.
- Decreases local spinal cord metabolism as expressed by local reductions in glucose utilization.

Narcotics

- Effect on CBF are difficult to characterize accurately because of cnflicting experimental report.
- Low dose of narcotics have little effect on CBF and CMRO2 whereas higher dose progressively decrease both of CBF and CMRO2.
- Autoregulation and CO2 reactivity are maintained.
- Effect on CSF dynamics.
- Produce either no change or slight decrease in ICP.

Ketamine

- Produces an increase in CBF and CMRO2.
- Mechanism : respiratory depression with milh hypercapnia, regional neuroexitation, direct with concomittant increase in cerebral metabolism, direct cerebral vasodilatation, seizure.
- Cerebral autoregulation and CO2 reactivity are maintained.
- Increase PaCO2 and ICP in both presence and absence of preexisting intracranial hypertension.

Effect of anesthetic agent on CBF, CMRO2, ICP

Anesthetic	CBF	CMRO2	ICP
Thiopental	Decrease	Decrease	Decrease
Etomidate	Decrease	Decrease	Decrease
Propofol	Decrease	Decrease	Decrease
Fentanyl	0/Decrease	0/Decrease	0/Decrease
Sufentanyl	0/Decrease/increase	0/Decrease	0/Decrease/increase
Ketamine	Increase	0/increase	Increase
Midazolam	Decrease	Decrease	0/decrease

Choice of inhalation anesthetics

- Inhalation anesthetic should be evaluated effect on ICP and cerebral vasculature.
- All inhalation anesthetic has cerebral vasodilatation effect, will increase CBF, CBV and ICP.
- Must be know the effect on cerebral autoregulation, response to CO_2 reactivity and $CMRO_2$, brain protection effect.

N2O

- 60% N2O : CBF 100% ↗
  CMR O2 20% ↗
- Can decrease by Pentothal, Opioid, Hypocapnia.
- Frequent of emesis 90%
- Avoid in aerocele, until 5 days after pneumoencephalography, risk of air embolism, redo craniotomy < 3 weeks.
- Don’t use N2O (Cottrell, 2001,2002)

N2O

- Increases neurotoxicity of NMDA in rats
- Potentiated the NMDA damage
- Adding ketamine worsens damaged neuron.

  Cottrell. ESA 2004
- Adding a nontoxic dose of N2O to midazolam/isoflurane anesthetic resulted in a robust neurodegenerative reaction more severe in the thalamus and parietal cortex

  Jevtovic et al. J neuroscience 2003

Halothane :

- Smallest decrease CMR O_2
- CBF increase – 3 x isoflurane
- With N_2O, CBF increase 300%
- Autoregulation loss at > 1 MAC and persistent until post operative period.
- CSF : production and absorption increase
- ICP increase whereas hypocarbia
- BBB & B-CSF barierre : destroyed
- Increase brain water, permeability BBB, edema
- concentration 2% mitochondria destroyed
- myocardium sensitization to catecholamine

Stone DJ et al : The Neuroanaesthesia Hand Book, 1996
Cottrell JE : Anesthesia and Neurosurgery, 1994

Enflurane :

- Can produce EEG seizure at moderate dose (1,5 - 2 MAC) and hypocapnia.
- CMR O_2 decrease
- CSF : increase production, decrease absorption
- cerebral ischemia protection better than halothane but less than isoflurane.
- Loss autoregulation : 1 MAC
- Not advised for neuroanesthesia

Isoflurane :

- concentration 0,5% ⟶ CBF decrease
  0,95% ⟶ CBF increase
- Increased ICP with Isoflurane 1% easy reduce with hypocapnia / pentothal
- Autoregulation intact until 1,5 MAC
- CO_2 Response intact until 2,8 MAC
- CSF : production : no change
  absorption increase
- Increase ICP caused by
  Isoflurane : 30 minutes
  Enflurane/halothane : 3 hours

Stone D.J et al : The Neuroanaesthesia Hand Book, 1996
Cottrell : Anesthesia and Neurosurgery, 1994

Isoflurane

- Isoflurane only transient protective against a severe focal ischemic insult.
- Isoflurane did not inhibit postischemic neuronal apoptosis.
- Conclusion: Isoflurane have not brain protection effect.

Werner C. AOSRA Nov 2003, WCA 2004, ESA 2004.

Cottrell JE: WCA 2004, ESA June 2004

Kawaguchi et al. Anesth Analg 2004

Warner DS.Anesth Analg 2004

sevoflurane

- Sevoflurane improves neurological outcome following incomplete cerebral ischemia in rat.

  Werner C et al.Br J Anesth 1995;83
- Isoflurane delay but does not prevent cerebral infarction in rats subjected to focal ischemia.

  Kawaguchi et al. Anesthesiology 2000;92
- Sevoflurane provides sustained anti necrotic and anti apoptotic effect.

  Engelhard et al. ASA Annual meeting 2003. Abstract A 740

Sevoflurane:

- Have advantages performance for Neuroanesthesi.
- Faster recovery Sevoflurane than Isoflurane → faster neurologis evaluation post operative period.
- Cerebral vasodilatation effect less than halothane, isoflurane.
- Effect to blood circulation less than isoflurane
- More advantages than TIVA.

Nathanson, *WCA-Montreal*, 2000

Cardiovascular effect of volatile inhalation anesthetics at 1-1,5 MAC

Variable	Halothane	Enflurane	Isoflurane	Sevoflurane
BP	↓↓	↓↓	↓↓	↓
Vascular resistance	0	↓	↓↓	↓↓
Cardiac output	↓↓	↓↓	0	0
Cardiac contraction	↓	↓↓	0	0
CVP	↑	↑	0	0
Heart rate	0	↑	↑↑	0↑
Sensitization of the heart to epinephrine	↑↑↑	↑	0?	0

0 = no change (<10%)

↓ = 10-20% decrease

↓↓ = 20-40% decrease

↑ = increase

Effect of volatile anesthetic agent on CBF, CMRO2, ICP

Anesthetic	CBF	CMRO2	ICP
N2O	Increase	0/Decrease	Increase
Isoflurane	Increase	Decrease	Increase
Desflurane	Increase	Decrease	Increase
Sevoflurane	Increase	Decrease	Increase

Effect of Anesthetics on Physiological Responses and Ion and Metabolite Levels

	Anoxia				NMDA/AMPA
	Protect Response	Improve NA^+	Improve ATP	Improve Ca^+	Protect Response
Thiopental (600 µM)	Yes	Yes	No/Yes[1]	Yes	Yes
Midazolam (100 µM)	Yes	-	Yes	Yes	-
Propofol (20 µg/ml)	No	Yes	Yes	Yes	No
Lidocaine (10 µM)	Yes	Yes	Yes	No	-
Isoflurane (1,5%)	No	No	No	No	-
Sevoflurane (4%)	Yes	Yes	Yes	Yes	-
Etomidate					
3 µg/ml	No	No	No	-	-
30 µg/ml	No	Yes	No	-	-
Nitrous oxide (50%)	No	No	No	No	-

[1]Worsens ATP after 3.5 minutes of anoxia: improves ATP after 10 minutes of anoxia.

Cottrell JE. ESA, 2004,Lisbon

Muscle relaxant

- Do not cross the blood-brain-barriere
- Any cerebral effect are thus secondary to histamine release, systemic hemodynamic changes, actions of metabolites, and altered cerebral afferent input.

Succinylcholine

- Can cause increase in CBF and ICP.
- This is secondary to increases in muscle spindle activity, which increase cerebral afferent input.
- The change in ICP are modest and transient.
- Exaggerated release of potassium.

Atracurium

- Causes histamin release when given in large bolus dose.
- Laudanosin, a metabolit Hoffman elimination of atracurium causes seizure in laboratory animal.
- Cisatracurium not cause histamin release and is not associated with the formation metabolit toxic.

Vecuronium

- Has advantages of maintaining stable hemodynamic even when given in large doses.
- Bradycardia may occur when vecuronium combined with large dose of narcotic.
- Not alter ICP or CSF dynamic.
- Popular choice in neuroanesthesia

Rocuronium

- Weakly vagolytic.
- Not associated with the production of active metabolit.
- Rapid onset → exelent choice for intubation.

Pancuronium

- Decreases MAC volatile anesthetics.
- Large dose cause hypertension and tachycardia, which could increase CBF and ICP.

Effect of muscle relaxant to hemodynamic and ICP

Drugs	MAP	HR	ICP
Succynilcholine	-	↓	↑
Atracurium	↓	↑	-
Vecuronium	-	-	-
Pancuronium	↑	↑ ↑	-

dexmedetomidine

- Anesthesia sparring effect.
- Have sedative, analgesic effect
- Dose 0.2-0.7 ug/kg/h
- Blunt laryngoscopy-intubation effect.
- Have brain protection effect.

Neuroprotective effects of Dexmedetomidine

- Inhibition of ischemia induced NE release may be associated with neuroprotection
- Dex prevents delayed neuronal death after focal ischemia
- Dex decreased total ischemic volume by 40% compared to placebo

  Jolkkonen J et al. Euro J Pharm 1999

  Hoffman WE et al Anesthesiology 1991

- Dex enhances glutamine disposal by oxydative metabolism in astrocytes

  Huang R et al. J Cereb Blood Metab 2000

Effect of intravenous drugs on rate of CSF formation (Vf), resistance to reabsorption (Ra), and predicted effect on ICP

Intravenous drug	Vf	Ra	Predicted ICP effect
Thiopental			
Low dose	0	+,0*	+,0*
High dose	-	0,-*	-
Etomidate			
Low dose	0	0	0
High dose	-	0,-*	-
Propofol	0	0	0
Ketamine	0	+	+
Midazolam			
Low dose	0	+,0*	+.0*
High dose	-	0,+*	-,?*

0=no change ; - decreased; * effect dependent on dose; ? uncertain

Effect of narcotic on rate of CSF formation (Vf), resistance to reabsorption (Ra), and predicted effect on ICP

Narcotics	Vf	Ra	Predicted ICP effect
Fentanyl, alfentanil, sufentanil (low dose)	0	-	-
Fentanyl (high dose)	-	0,+*	-,?*
Alfentanil (high dose)	0	0	0
Sufentanil (high dose)	0	+,0*	+,0*

0=no change ; - decreased; * effect dependent on dose; ? uncertain

Effect of inhaled agent on rate of CSF formation (Vf), resistance to reabsorption (Ra), and predicted effect on ICP

Inhaled agent	Vf	Ra	Predicted ICP effect
Nirous Oxide	0	0	0
Isoflurane			
Low dose	0	0,+*	0,+*
High dose	0	-	-
Desfluranr	0,+*	0	0,+*
Sevoflurane	-	+	?

0=no change ; - decreased; * effect dependent on dose; ? uncertain

Conclusion

- Anesthetic management of neurosurgical patient is based on the knowledge of drugs's influence to CNS physiology.
- Effect to cerebral hemodynamic, cerebral metabolism, intracranial pressure, CSF volume, and effect brain protection.

Thank you very much