IV Induction Agents

Mechanism of Action

- It is widely believed that IV anesthetics exert their sedative and hypnotic effects via their interaction with GABA
  - GABA is the primary inhibitory neurotransmitter in the CNS
  - Activation of receptor causes increased Chloride conductance and therefore, hyperpolarization
- Propofol and the barbiturates decrease the rate of dissociation of GABA and its receptor
- Benzodiazepines increases the efficiency of GABA-receptor coupling

Pharmacokinetic Values for the Currently Available Intravenous Sedative-Hypnotic Drugs

•DRUG NAME	•DISTRIBUTION HALF-LIFE (min)	•PROTEIN BINDING (%)	•DISTRIBUTION VOLUME AT STEADY STATE (L/kg)	•CLEARANCE (mL/kg/min)	•ELIMINATION HALF-LIFE (h)
Thiopental	2-4	85	2.5	3.4	11
Methohexital	5-6	85	2.2	11	4
Propofol	2-4	98	2-10	20-30	4-23
Midazolam	7-15	94	1.1-1.7	6.4-11	1.7-2.6
Diazepam	10-15	98	0.7-1.7	0.2-0.5	20-50
Lorazepam	3-10	98	0.8-1.3	0.8-1.8	11-22
Etomidate	2-4	75	2.5-4.5	18-25	2.9-5.3
Ketamine	11-16	12	2.5-3.5	12-17	2-4

(Clinical Anesthesia 5th Edition; Barash, P.; Lippincott Williams and Wilkins; 2006)

Induction Characteristics and Dosage Requirements for the Currently Available Sedative-Hypnotic Drugs

•DRUG NAME	•INDUCTION DOSE (mg/kg)	•ONSET (sec)	•DURATION (min)	•EXCITATORY ACTIVITY*	•PAIN ON INJECTION*	•HEART RATE†	•BLOOD PRESSURE†
Thiopental	3-6	<30	5-10	+	0-+	↑	↓
Methohexital	1-3	<30	5-10	++	+	↑↑	↓
Propofol	1.5-2.5	15-45	5-10	+	++	0-↓	↓↓
Midazolam	0.2-0.4	30-90	10-30	0	0	0	0/↓
Diazepam	0.3-0.6	45-90	15-30	0	+/+++	0	0/↓
Lorazepam	0.03-0.06	60-120	60-120	0	++	0	0/↓
Etomidate	0.2-0.3	15-45	3-12	+++	+++	0	0
Ketamine	1-2	45-60	10-20	+	0	↑↑	↑↑

*0 = none; + = minimal; ++ = moderate; +++ = severe.

†↓ = decrease; ↑ = increase.

(Clinical Anesthesia 5th Edition; Barash, P.; Lippincott Williams and Wilkins; 2006)

Pharmacodynamics

- The principle pharmacologic effect of IV anesthetics is to produce increasing sedation and eventually hypnosis
- All hypnotics also effect other major organ systems
  - They produce a dose-dependant respiratory depression (exception: Ketamine)
  - They produce hypotension and cardiac depression (Etomidate causes the least cardiac depression)
- Profound hemodynamic effects can be seen with hypovolemia as a higher drug concentration is achieved at the central compartment
  - A large hemodynamic depressant effect can be seen in the eldery and those with pre-existing cardiovascular disease
    - These patients often require a decreased dose requirement

Drug	Dose (mg/kg)	Effects	Pearls
Propofol	1.5-2.5	**Neuro:** Decreases cerebral metabolic O2 requirements, cerebral blood flow, intracranial pressure **CV**: Decreases SVR, direct myocardial depressant **Pulm:** Dose dependant respiratory depression (apnea in 25-35% of patients)	-Pain on injection(32-67%) -can be attenuated with lidocaine -antiemetic properties -anticonvulsant properties
Etomidate	0.2-0.3	**Neuro:** Decreases CMRO2, CBF, ICP **CV**: Maintains hemodynamic stability (minimal cardiac depression) **Pulm:** minimal respiratory depression (no histamine release)	-Pain on injection -High incidence of PONV -myoclonus -inhibits adrenocortical axis
Thiopental	3-5	**Neuro:** Decreases CMRO2, CBF, ICP **CV**: Decreases SVR, direct myocardial depressant **Pulm:** Dose dependant respiratory depression	-anticonvulsant properties -can precipitate when injected with acidic fluids (i.e LR)
Ketamine	1-2	**Neuro:** Increases CMRO2, CBF, ICP **CV**: Cardio-stimulating effects (negatively effects myocardial supply-demand) **Pulm:** minimal respiratory depression; bronchodilation; most likely of all to protect airway reflexes	-good analgesic effects -intrinsic myocardial depressant effects which may be unmasked with depleted catecholamines

Propofol

- Produced in an egg lecithin emulsion because of its high lipid solubility
- Pain on injection occurs in 33-67% of subjects
- Can be attenuated with lidocaine or administering the drug in a larger vein
- Induction dose 1.5-2.5 mg/kg
  - Children require higher doses (larger Volume of Distribution)
  - Elderly require lower doses (smaller Volume of Distribution)
- Decreases cerebral metabolic O_2 requirements, cerebral blood flow, intracranial pressure
- Decreases SVR, direct myocardial depressant
- Dose-dependent respiratory depression
- Has anti-emetic properties
- Anticonvulsant properties

Etomidate

- Can produce pain on injection
- Induction dose 0.2-0.3 mg/kg
- Myoclonus common upon injection
- Decreases cerebral metabolic O_2 requirements, cerebral blood flow, intracranial pressure
- Maintains hemodynamic stability (even in the presence of pre-existing disease)
  - Does not induce histamine release
- Inhibits adrenocortical synthetic function
  - Inhibition for 5-8 hours even after a single induction dose!
- High incidence of PONV

Thiopental

- Highly alkaline (pH 9)
- Can precipitate in acidic solutions
  - DO NOT MIX with Rocuronium
- Induction dose 3-5 mg/kg
- Rapidly redistributed into peripheral compartments
- Accounts for its short duration of action
- Larger doses can saturate the peripheral compartments resulting in a prolonged duration of action
- Decreases $CMRO_2$, CBF, ICP
  - Causes EEG burst supression in larger doses (often used for neurosurgical procedures)
- Decreases SVR, direct myocardial depressant
- Anticonvulsant activity
  - Exception: Methohexital

Ketamine

- Produces a dissociative anesthetic state
  - Profound analgesia and amnesia despite maintainence of consciousness
  - High incidence of psychomimetic reactions
- Induction dose 1-2 mg/kg
- NMDA antagonist
- Increases $CMRO_2$, CBF, ICP
  - Contraindicated in neurosurgical procedures
- Most likely to preserve airway reflexes among the IV anesthetics
- Minimal respiratory depression
- Cardio-stimulating effects
  - Can be unmasked in patients with increased sympathetic outflow
  - Negatively effects myocardial oxygen supply-demand ratio
- Causes bronchodilation

Midazolam

- All benzodiazepines have anxiolytic, amnestic, sedative, hypnotic, anticonvulsant properties
- Premedication dose 0.04-0.08 mg/kg
- Decreases $CMRO_2$, CBF, ICP
  - Does not produce EEG burst supression
- Causes dose-dependant respiratory depression
  - Exaggerated when combined with opioids
- Flumazenil is a specific antagonist
  - Very short acting
  - 45-90 minutes of action following 1-3 mg dose
    - May see resedation as benzodiazepine is eliminated more slowly compared to effects of flumazenil

References

1. Clinical Anesthesia 5th Edition; Barash P., Cullen B., Stoelting R.; Lippincott Williams and Wilkins, 2006
2. Miller's Anesthesia 6th edition; Miller R.; Churchill Livingstone, 2005