TOTAL INTRAVENOUS ANESTHESIA: TIVA

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Evolution of Intravenous Anesthesia

- Incremental methohexital
  - Drummond-Jackson
  - Foreman
  - Hubbell

- Drug combinations
  - Jorgensen
  - Monheim

- Conscious-sedation
  - Bennett

- Dissociative sedation
  - Bennett

- Deep sedation
  - Continuous infusion
  - TIVA
Total Intravenous Anesthesia (TIVA)

- Unconsciousness
  - Propofol, thiopental, methohexital
- Analgesia
  - Opioids
- Amnesia
  - Benzodiazepines
- Muscle relaxation
  - Muscle relaxants
- Attenuation of autonomic response to noxious stimulation
  - Opioids, benzodiazepines, propofol, dexmedetomidine

Intravenous Anesthetics

- Historically used to induce sleep
  - Smooth and quick induction
- Pharmacological advances have increased their use for maintenance of deep sedation and general anesthesia
Distribution

Intravenous Anesthetics

- Propofol
- Etomidate
- Thiopental
- Methohexital
- Opioids
- Ketamine
- Benzodiazepines
- Dexmedetomidine

- Induction agents
- Adjunctive agents
Thiopental (Pentothal®)

- Ultra-short acting barbiturate first administered by Ralph Waters in 1934
- Thiobarbiturate
  - Sulfur analog of pentobarbital
- Rapidly achieves therapeutic plasma concentrations after IV administration
  - Induces sleep within 15-30 seconds
- 4 mg/kg adults
- 6 mg/kg children

Thiopental

- Influx of chloride ion results in hyperpolarization and an increased threshold of excitability
- At high doses, barbiturates directly activate chloride channels without binding with the receptor acting as direct agonists
- “Barbiturate anesthesia”
Thiopental

- Termination of activity due to redistribution from brain to other tissues
  - Distribution half-life 2-4 minutes
- Clinical duration of anesthesia 20-30 minutes
- Distributes ultimately into fatty tissues
- Repeated administration results in accumulation and prolonged anesthesia due to gradual release of the drug from fat

Thiopental

- Cardiovascular Effects
  - Peripheral vasodilation is primary effect
  - Decreased myocardial contractility is secondary effect
  - MAP is maintained or slightly decreased
  - Reflex increase in heart rate (10%-36%)
  - Cardiac index is maintained or slightly decreased
Thiopental

- Respiratory Effects
- Dose-dependent central respiratory depression
- Decreased minute ventilation
- Apnea

Thiopental

- Other Effects
- Anticonvulsant
- Hyperalgesia
- pH > 10
  - Subcutaneous or intraarterial injection, or extravasation may result in pain, vasospasm, and tissue necrosis
- Histamine release
  - Urticaria, hives, bronchospasm
- Garlic or onion taste (40%)
Thiopental

- Contraindications
- Poor airway
- Cardiovascular instability or shock
  - “the ideal form of euthanasia in war surgery”
- Status asthmaticus
- Porphyria
  - Acute intermittent
    - Accumulation of porphyrins and porphyrin precursors (aminolevulinic acid and porphobilinogen)
  - Variegate
    - Barbiturates stimulate ALA-synthetase and increase ALA levels

Methohexital (Brevital®)

- Ultra-short acting barbiturate
- Oxybarbiturate
- Similar in effects to thiopental
  - 2.7 x more potent
  - Shorter duration of action
- 1-2 mg/kg induction dose
Methohexital

- Advantages over thiopental
- Rapid recovery
- May be used as a continuous infusion for maintenance of anesthesia
  - More rapid clearance
  - Less accumulation and saturation of peripheral sites
  - 50-150 mcg/kg/min
- More suitable for outpatient procedures

Methohexital

- Disadvantages
- Increased incidence of excitatory phenomena (5 x)
  - Coughing
  - Hiccough
  - Tremors and/or twitching (Brevital® shakes)
  - Possible seizure activity with high doses
- Increased pain on injection (12%)
- Increased incidence of phlebitis (8%)
Propofol (Diprivan®)

- 2,6-diisopropylphenol
- Non-barbiturate anesthetic, chemically unrelated to other anesthetics
- Rapid IV induction 2-2.5 mg/kg
  - Loss of consciousness within 40 seconds
- Recovery 10 x more rapid than thiopental
- Minimal postop confusion
- Antiemetic properties

Propofol

- Formulated in an oil in water emulsion
  - Soybean oil
  - Glycerol
  - Egg lecithin (egg yolks)
- Potential culture medium
  - Propofol by Zeneca contains EDTA which slows microorganism growth
  - One generic contains sodium metabisulfite
  - Another generic contains benzyl alcohol
Propofol

- Inhibits NMDA subtype of glutamate receptors
- Agonistic activity at the β1 subunit of GABAA receptor
- Rapid redistribution
  - Distribution half-life 2-4 minutes
  - Elimination half-life 3-12 hours
- Metabolized in the liver
  - Clearance of propofol exceeds liver blood flow suggesting extrahepatic metabolism

Propofol

- Cardiovascular Effects
  - 30% reduction in systemic blood pressure with induction and/or maintenance doses
  - Decreased cardiac output secondary to decrease in stroke volume
  - Peripheral vasodilation
  - No change in heart rate
  - Significant hypotension in the elderly, hypovolemic, and patients with limited cardiac reserve
Propofol

- Respiratory Effects
  - Decreased tidal volume
    - Apnea with induction dose (30%)
  - No histamine release

Propofol

- Other Effects
  - Amnesia
  - Antiemetic
  - Pain on injection
    - Irritates venous intima and activates kallikrein-kinin system to increase bradykinin production
    - Large vein, rapid infusion and slow administration, lidocaine may help
Propofol

- Other Effects
- Propofol infusion syndrome
  - MI, hyperkalemia, metabolic acidosis, rhabdomyolysis, heart failure
- Most often associated with prolonged, high-dose infusions ( > 5 mg/kg/h for more than 48h)
  - May occur with high dose, short-term infusion during surgery
- Most often in children
WOULD YOU LIKE SOME PROPOFOL WITH YOUR EGGS?

“Diprivan® Injectable Emulsion is contraindicated in patients with allergies to eggs, egg products, soybeans or soy products”

Propofol Allergy

- 2,6-diisopropylphenol formulated in a lipid emulsion
- 10% soybean oil
- 2.25% glycerol
- 1.2% egg lecithin
- Incidence of propofol allergy during anesthesia
  - 1:60,000
- Isopropyl groups (dermatological products)
- Phenols

Propofol Allergy

- Vast majority of patients with egg allergy are allergic to the ovalbumin found in egg whites
- Egg lecithin is found in egg yolks and is highly purified in propofol preparations


- 25 patients with documented egg allergy were tested for propofol allergy by skin prick and intradermal testing
  - All were negative
- MMR vaccine contains ovalbumin and has been given to egg-allergic patients without an allergic response
- Egg-allergic patients are not more likely to develop anaphylaxis than non-egg-allergic patients when given propofol
Context-Sensitive Half-Time

Time required for the plasma level of the drug to drop 50% after cessation of infusion

Opioids

• “Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.”

• -Sydenham, 1680

-Diazepam
-Thiopental
-Midazolam
-Ketamine
-Propofol
-Etidazote
Opioid Receptors - 1973

- µ1
  - Analgesia (supraspinal, spinal)
  - Miosis
  - Urinary retention
  - Nausea and vomiting
  - Pruritis
- µ2
  - Sedation
  - Respiratory depression
  - GI motility decrease
- κ
  - Analgesia (supraspinal, spinal)
  - Sedation
  - GI motility decrease
  - Psychotomimesis
- σ
  - Dysphoria
  - Psychotomimesis
- δ
  - Analgesia (supraspinal, spinal)
  - Alterations of affective behavior
  - Primary site of opioid activity
    - CNS
    - Bowel

Analgesia and Sedation

- Analgesia, drowsiness, changes in mood, mental clouding without loss of consciousness
- Relieves most types of pain regardless of origin or intensity
- Increases pain threshold
- Affective pain response is altered
Respiratory Effects

- Primary and continuous depressant of respiration
  - Depresses central ventilatory drive
  - Dependency on hypoxic drive
- Dose-dependent depression
- Decreases rate, tidal volume, minute volume

Factors Affecting Opioid-Induced Respiratory Depression

- High dose
- Elderly
  - Fewer receptors, more sensitive
  - Higher plasma concentrations on a weight basis
- Other CNS depressants
- Renal insufficiency
- Hyperventilation
Effect on Cardiovascular Stress Response

• Attenuation
  • μ-receptor mediated action on the hypothalamic-pituitary-adrenal axis
    • Prevent ACTH release
    • Attenuate surgical stress response
  • Reduction in sympathetic tone
  • Enhance vagal and parasympathetic tone
• Hypotension and bradycardia

GI Effects

• Decrease gastrointestinal motility
  • Antidiarrheal effects
  • Constipation
• Lower esophageal sphincter activity
• Delayed gastric emptying
  • "Full stomachs" regardless of NPO status with preoperative parenteral opioids
• Increase biliary duct pressure and sphincter of Oddi tone
• Stimulate the CTZ
  • δ–receptor mediated nausea and vomiting
**Intracranial Pressure**

- Minimal effect on ICP
- Use with caution in cases of head injury with increased ICP
  - Hypoventilation will raise CO2 and increase cerebral blood flow and ICP

**Muscle Rigidity**

- Increases muscle tone
  - Vocal cord closure
  - Chest-wall rigidity
  - Decrease pulmonary compliance
  - Decrease FRC
  - Increase ICP
- Usually associated with high doses and rapid administration
- Pretreatment with muscle relaxants, benzodiazepines
## Ocular Effects

- Prevent increases in intraocular pressure
- Pupillary constriction (miosis)
- Parasympathetic stimulation mediated through the Edinger-Westphal nucleus of the oculomotor nerve
- Triad of overdose
  - Coma
  - Pinpoint pupils
  - Respiratory depression

## Thermoregulation and Shivering

- Reduces thermoregulation thresholds similar to potent inhalation agents
- Meperidine is unique in terminating shivering in 70-80% of patients
- Related to $\kappa$-receptor mediated reduction in the shivering threshold and to $\alpha_{2b}$-receptor agonism
Allergic Reactions

- True allergic reactions rare
- Histamine-related wheal and flare reactions
- Dilation of cutaneous blood vessels
  - Face, neck, upper thorax flushing
- Pruritus
  - Histamine release
  - Non-histamine releasing opioids also produce pruritis
    - \( \mu \)-receptor mediated
    - Facial itching common

Tolerance

- Opioids inhibit adenyl cyclase
- Long term exposure results in an increase in adenyl cyclase and tolerance develops
- Withdrawal syndrome results from increased adenyl cyclase activity
- Lasts until adenyl cyclase returns to normal
Acute Tolerance

• Controversial
• Associated primarily with remifentanil infusion
• 0.3 µg/kg/min for abdominal surgery had higher postop pain and morphine requirement compared with 0.1 µg/kg/min


Idiosyncrasy

• Dysphoria
  • Especially in the absence of pain
• Focal neuroexcitation
• Meperidine
  • Normeperidine metabolite is twice as potent in as meperidine in causing CNS excitation and convulsions
• Constipation
• Urinary retention
  • Stimulates ADH
  • Increased tone and amplitude of ureter and bladder contractions
• Reverse with atropine, naloxone
Precautions for Use

- Head injury with increased ICP
- Hypothyroidism
- Multiple sclerosis
  - Sensitivity to depressant effects
- Decreased respiratory reserve
  - Emphysema
  - Kyphoscoliosis
  - Morbid obesity
  - Cor pulmonale
  - Asthma
    - Histamine releasers
- Drug interactions
  - Meperidine with MAOI

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<thead>
<tr>
<th></th>
<th>Meper</th>
<th>Morph</th>
<th>Fent</th>
<th>Sufent</th>
<th>Alfent</th>
<th>Remifent</th>
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<tbody>
<tr>
<td>Comparative Potency</td>
<td>0.1</td>
<td>1</td>
<td>75-125</td>
<td>500-1000</td>
<td>10-25</td>
<td>250</td>
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<td>Peak Effect (min)</td>
<td>5-7</td>
<td>20-30</td>
<td>3-5</td>
<td>3-5</td>
<td>1.5-2</td>
<td>1.5-2</td>
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<tr>
<td>Duration (hr)</td>
<td>2-3</td>
<td>3-4</td>
<td>0.5-1</td>
<td>0.5-1</td>
<td>0.2-0.3</td>
<td>0.1-0.2</td>
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<tr>
<td>Half-life (hr)</td>
<td>3-4</td>
<td>2-4</td>
<td>1.5-6</td>
<td>2.5-3</td>
<td>1-2</td>
<td>0.15-0.3</td>
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Morphine

- Dose 10 mg (0.1 mg/kg)
- Onset 5-10 minutes
- Duration 2-4 hours
- Analgesia
- Sedation
- Euphoria
- Histamine release
- Postural hypotension
- Nausea and vomiting

Phenylpiperidine Series

- Meperidine
- Fentanyl
- Sufentanil
- Alfentanil
- Remifentanil
Meperidine (Demerol®)

- Dose 80-100 mg
- Onset 3 minutes
- Duration 45 min-1.5 hours
- Sedation
- Analgesia
- Dysphoria
- Nausea and vomiting
- Control of postop shivering
- Atropine-like effect
  - Tachycardia
  - Antisialogogue
Fentanyl (Sublimaze®)

- Dose 100 mcg
- Onset 30 seconds
- Duration 30 minutes
- Analgesia
- No euphoria
- Respiratory depression
- Bradycardia

Sufentanil (Sufenta®)

- Dose .25-2 mcg/kg
- Onset 30 seconds
- Maintenance 0.5-1.5 mcg/kg/hr
- Additional boluses 2.5-10 mcg
- Ultrapotent
- Respiratory depression

- Sedation doses
  - Dilute to final concentration of 5 mcg/ml
  - 5 mcg sufentanil is equivalent to 50 mcg fentanyl
### Alfentanil (Alfenta®)

- Dose 25 mcg
- Onset 30 seconds
- Maintenance 0.5-2 mcg/kg/min
- Less potent than fentanyl

- Sedation doses
  - 500 mcg alfentanil is equivalent to 50 mcg fentanyl

### Remifentanil (Ultiva®)

- Dose 0.5-1 mcg/kg for GA induction
- No bolus for sedation
- Onset 30 seconds
- Maintenance 0.05-2 mcg/kg/min
- Ultrashort acting
- Ester linkages result in rapid hydrolysis by non-specific esterases
- Sedation doses
  - 0.05-0.1 mcg/kg/min
**Context-Sensitive Half-Time**

![Graph showing context-sensitive half-time](image)

**Ketamine (Ketalar®)**

- Phencyclidine derivative (1963)
- Water soluble
- Lipid soluble
- Dissociation
  - Analgesia
  - Amnesia
  - Catalepsy
“Nothing in my wildest dreams of minimal equipment ever approached the simplicity and the safety of the ketamine technique under these true test conditions.”

Dr. Roy Wilson,
aftermath of 1976 Guatemala earthquake

Ketamine

- Pharmacokinetics
  - Peak plasma concentration
    - 1 minute IV
    - 5 minutes IM
    - 30 minutes oral
  - Redistribution
    - 15 minutes IV
    - 30 - 120 minutes IM
- 1-2 mg/kg IV
- 4-6 mg/kg IM
  - 2-3 mg/kg IM “stun dose”
Ketamine

- Respiratory effects
  - Upper airway reflexes intact
  - Spontaneous ventilation
  - Bronchodilation

- Cardiovascular effects
  - Increases BP, HR, CO
  - Weak antidysrhythmic
  - Increases coronary perfusion
  - Increases myocardial oxygen consumption
Ketamine

• Emergence phenomena
  • Psychic reactions
    • 0 - 50% in adults
    • 0 - 10% in children
  • Risk factors
    • Suppression by benzodiazepines
    • Incidence related to dose and rate of administration

• Nausea and vomiting
  • 0 - 43%
  • Late occurrence

The Ketamine Dart

• Ketamine
  • 2 – 3 mg/kg
• Glycopyrrolate
  • 0.003 mg/kg
• Optional midazolam
  • 0.05 mg/kg

Woke up an hour later, cavity filled, teeth cleaned.
Benzodiazepines

- Benzodiazepine receptor
  - Facilitates GABA-mediated chloride ion influx
- Favorable therapeutic index
- Anxiolysis
- Sedation
- Amnesia
- Anti-convulsant
- Muscle relaxation

Benzodiazepines

![Chemical Structures]

- Diazepam
- Lorazepam
- Midazolam
- Flumazenil
Diazepam

- High lipid solubility
- Elimination half-life ranges from 22-100 hours
- Active metabolites (hangover effect)
  - Nordiazepam
  - Desmethyldiazepam
  - Oxazepam
- Soluble in propylene glycol
  - Water insoluble
  - Venous irritation (phlebitis) and pain on injection
  - Poor uptake after IM injection

Midazolam

- Water soluble
  - No venous irritation or phlebitis
  - Improves IM uptake
- High lipid solubility when injected
  - Closure of benzodiazepine ring at physiologic pH
- No active metabolites
- Elimination half-life 2.5 hours
- CYP 3A4 inhibitors intensify and prolong the effects of benzodiazepines
Dexmedetomidine

- Dexmedetomidine
  - Alpha2-adrenergic receptor agonist
- α2/α1-receptor selectivity
  - Dexmedetomidine
    - 1600/1
  - Clonidine
    - 220/1

α2 Adrenergic Receptor

- Adrenergic receptors
  - Regulate release of neurotransmitters
  - Control epinephrine, norepinephrine release
  - Modulate sympathetic response "negative feedback loop"
Mechanism of Action

- Sites of action
  - Brain (locus ceruleus)
  - Spinal cord
  - Autonomic nerves
- CNS
  - Sedation/hypnosis
  - Anxiolysis
  - Analgesia
- Autonomic nerves
  - Sympathetic activity
  - ↓ BP, ↓ HR
Pharmacokinetics

- Rapid distribution ($t_{1/2\alpha}$)
  - 6 minutes
- Terminal elimination half-life ($t_{1/2\beta}$)
  - 2 hours

Respiratory Effects
Cardiovascular Effects

![Graph showing cardiovascular effects over time.](image)

Cardiovascular Effects

![Graph showing cardiovascular effects over time.](image)
Dexmedetomidine

- Use with caution in patients with advanced heart block
- Use with caution in hypovolemic patients
- Do not use if the patient is in shock
- Transient increases in blood pressure may occur during the loading infusion

Dexmedetomidine may potentiate the effects of other agents
- Opioids
- Sedatives/hypnotics
- Anesthetics
- Vasoactive agents
Dexmedetomidine Administration

- Loading dose
  - 1 mcg/kg over 10 min
- Maintenance infusion
  - 0.2 to 0.7 mcg/kg/hr
- Administer using a controlled infusion device or a slow, controlled bolus
Dexmedetomidine for Emergence Delirium

- 100 mcg/ml
  - 2 ml vial
  - 200 mcg
- Dilute vial to 50 ml
  - 200 mcg in 50 ml
  - 4 mcg/ml
- 0.25 mcg/kg bolus
  - Administer half and observe response

Future Trends in Sedation

- Single drug techniques
- Patient-controlled sedation
WORDS OF WISDOM

Never be the first to use a new drug, or the last to use an old one.