Intravenous Anesthetics

Medical Student Lecture Series
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Pharmacokinetics: What the BODY does to the drug

- Adsorption
- Distribution
- Metabolism (Biotransformation)
- Excretion

  ◦ Elimination: Combined actions of metabolism and excretion
  ◦ Clearance: The rate of elimination
• Adsorption
  ◦ Rate at which drug enters bloodstream from site of administration (IV, PO, IM, SQ, etc.)
  ◦ Influenced by:
    • Site of administration
    • Blood flow
    • Molecular characteristics:
      ◦ Lipid solubility
      ◦ Degree of ionization
      ◦ Concentration of drug
**Pharmacokinetics**

- **Distribution – To the site of action**
  - Organ perfusion: Highly perfused/“vessel rich” group takes up more drug than “vessel poor”
    - Brain, heart, liver, kidneys, lungs vessel rich
      - 10% of entire body mass, but receives 75% of CO
    - Fat is largest vessel poor compartment
  - Protein binding
    - Inhibits cellular uptake of drug, non-active
      - Albumin – Acidic drugs; AAG – Basic drugs
  - Lipid solubility
    - Lipophilic drugs cross cell membrane more easily

- **Volume of distribution – Theoretical concept**
  - $V_d = \frac{[\text{drug dose}]}{[\text{plasma concentration}]}$
  - Small volume for drug properties that promote staying in blood stream (i.e., protein binding, ionization, hydrophilicity)
Pharmacokinetics

- **Metabolism (Biotransformation)**
  - Hepatic metabolism primary mode for anesthetic drugs
    - Glucoronidation and conjugation
    - Hepatic blood flow and extraction ratio determine rate
  - Spontaneous metabolism useful in setting of organ dysfunction
    - Plasma esterases and Hoffman elimination (hydrolysis)
- **Excretion**
  - Primarily via urine, though important exceptions
    - Lungs excrete anesthetic gasses!
    - Some medications may be excreted without metabolism (ie anesthetic vapors, gabapentin)
- **Elimination – Combined effects of metabolism and excretion**
  - Half-time: Time to decrease plasma concentration by 50%
• Context sensitive half-time
  ◦ Takes into account the duration of infusion, elimination, AND the volume of distribution
    • Particularly true of lipophilic substances, represents ‘depot’ accumulation of drug in body stores
  ◦ Propofol and fentanyl are two examples of drugs with a large context-sensitive contribution to half-time
- Context sensitive half-time
Pharmacodynamics: What the DRUG does to the body

- Efficacy – Maximum effect of the drug (ie max analgesia, max sedation)
  - Intrinsic to the drug
- Potency – Dose required to achieve efficacy
  - Intrinsic to the drug
- ED50 – Dose of drug required to produce expected effect in 50% of patients
  - Anesthesia example: MAC for inhalational agents
- Visual representation of efficacy and potency
Mechanism at site of action

- **Agonist**: Activates a specific cell receptor, changing cellular function
  - May be either direct effects on ionic flux or (ie ion channels) through activation of secondary messengers (ie G-protein linked)
- **Antagonist**: Binds to a receptor without activating or changing cellular function
  - Irreversible vs. competitive binding
- **Mixed**: Displays both agonist and antagonist properties on the same receptor
  - Modern example: Buprenorphine
  - Why could this be a problem for surgical patients?
• What is general anesthesia?
  ◦ Amnesia (and hypnosis)
  ◦ Analgesia
  ◦ Immobility

As anesthesiologists, it is our job to determine the most safe, effective, and practical means to achieve the above goals.
Several classes of IV anesthetics

- GABA system
  - Barbiturates
  - Benzodiazepines
  - Propofol
  - Etomidate
- Ketamine
- Dexmedetomidine
- (Opioids)
GABA System

- Principal inhibitory neurotransmitter
- Activation of GABA receptor produces hyperpolarization of cellular membrane
  - In turn, this has an inhibitory effect on any further depolarization
- Two classes of GABA receptors
  - \( \text{GABA}_A \) is a ligand-gated ion channel
    - \( \text{Cl}^- \) ion influx or \( \text{K}^+ \) ion efflux
  - \( \text{GABA}_B \) is a G protein-coupled receptor
Barbiturates

- Clinically relevant medications:
  - Thiopental
  - Phenobarbital
  - Methohexital

- Mechanism of action
  - GABA\(_A\) receptor agonist
  - Depresses reticular activating system (RAS)

- Uses
  - General anesthesia induction agent
  - Potent antiepileptic, capable of causing burst suppression on EEG
  - Generally not utilized in US for anesthesia anymore, with exception of methohexital (ECT procedures)
• Rapid onset and termination
• Primarily hepatic metabolism
• Effect on physiology:
  ◦ CNS: ↓CMRO₂, ↓ICP, ↓CBP, neuroprotective
    • Drop in ICP is more than the drop in MAP, so CPP is preserved
  ◦ Respiratory: apnea, ↓response to hypoxia and hypercarbia, relatively preserved airway reflexes
  ◦ CV: ↓SVR, ↓CO, ↓BP, ↑HR
  ◦ Side effects: onion taste, excitatory symptoms, can precipitate acute intermittent porphyria
Benzodiazepines

- Clinically relevant medications:
  - Midazolam
  - Alprazolam
  - Diazepam

- Mechanism of Action
  - GABA\textsubscript{A} receptor agonist

- Uses
  - General anesthesia induction
  - Sedation
  - Anxiolysis
  - Antiepileptic

- Metabolism
  - Hepatic – Diazepam has active phase I metabolites, leading to long duration of action
  - Midazolam has a very high extraction ratio = short duration

- Excretion
  - Primarily via urine
• Amnesia most useful property
• Effect on physiology:
  ◦ CNS: ↓CMRO₂, ↓ICP, ↓CBP, ↑seizure threshold, neuroprotection
  ◦ Respiratory: apnea in large doses, ↓Response to CO₂, ↓Airway reflexes
  ◦ CV: minimal ↓CO and ↓SVR
• Antagonist for overdose
  ◦ Flumazenil
    • Competitive antagonist at GABAₐ receptor
- **Propofol**

  - **Mechanism of Action**
    - GABA$_A$ (and GABA$_B$?) receptor agonist
    - Recent research suggests Na$^+$ channel blocking and endocannabinoid effects as well (Hot, Horny, and Hungry)

  - **Uses**
    - Induction agent for GA
    - Sedation
    - Antiemetic
    - Antipruritic

  - **Characteristics**
    - Ultra rapid onset
    - Short duration
      - Hepatic and pulmonary metabolism
      - However, duration of action terminated by re-distribution
    - Lipid emulsion can promote bacterial growth
    - Lecithin, derived from egg yolk, is used as an emulsifier
      - Caution in patients with severe egg allergies
Effects on physiology
- CNS: ↓ICP, ↓CMRO2, neuroprotection
- Respiratory: Apnea, Depression of airway reflexes, ↓hypoxic ventilatory drive and response to hypercapnea
- CV: HYPOTENSION due to ↓SVR, ↓cardiac contractility, ↓preload
  - Impaired arterial baroreflex to hypotension
- Potent antiemetic at subanesthetic doses

Side effects
- Pain on injection – Often given with lidocaine
- Myoclonus – More common with etomidate
- Propofol Infusion Syndrome
  - Seen in cases of long-term infusion for sedation, usually in the ICU
    - Usually in combination with catecholamines and/or steroids
• Mechanism of Action
  ◦ GABA$_A$ receptor agonist
• Use
  ◦ Induction agent for GA
  ◦ Procedural sedation
• Characteristics
  ◦ Ultra rapid onset
  ◦ Duration of action terminated due to redistribution
  ◦ Single bolus dose capable of causing adrenal suppression for up to 72 hrs
    • Dose-dependent via 11-beta-hydroxylase inhibition
  ◦ Does not have significant effects on SVR
• Pharmacokinetics
  ◦ Highly protein bound = Small Vd
  ◦ Hepatic metabolism as well as plasma esterases
  ◦ Excretion via urine and biliary system

• Side Effects
  ◦ Pain on injection (Etomidate > Propofol)
  ◦ Myoclonus (Etomidate > Propofol)
  ◦ Nausea and vomiting
  ◦ Propylene glycol toxicity
    • Uncommon as etomidate rarely used as infusion
Dexmedetomidine

- **MOA:** $\alpha_2$ adrenoreceptor agonist
  - $\alpha_2B$ and $\alpha_2C$ - located in brain and spinal cord
    - Responsible for sedative and analgesic properties, decreased sympathetic outflow
  - $\alpha_2A$ - located in periphery
    - Responsible for hypotension

- **Uses**
  - Procedural sedation
  - Adjunct to general anesthesia
  - ICU sedation/Bridge to extubation
  - Management of withdrawal syndromes

- **Unique in that sedation produced much more closely resembles physiologic sleep as opposed to hypnotic state**
  - Via decreased activity of locus ceruleus and increased GABA pathways
• **Characteristics**
  ◦ Highly specific for $\alpha_2$ receptor ($\alpha_2/\alpha_1$ 1600:1)
  ◦ Rapid distribution
  ◦ Medium length duration of action
  ◦ Context sensitive half-time must be observed
  ◦ Hepatic metabolism, renal excretion, highly protein bound

• **Effects on physiology**
  ◦ Analgesia and light to moderate sedation
  ◦ Decreased minute ventilation with preserved response to CO2
  ◦ Bradycardia and hypotension common, especially with loading dose
Ketamine

- **Mechanism of Action**
  - NMDA receptor antagonist (glutamate transmission inhibition)
    - Analog to phencyclidine (PCP), created by the US gov’t

- **Uses**
  - Induction for general anesthesia
  - Procedural Sedation
  - Adjunct to general anesthesia
  - Adjunctive analgesia

- **Characteristics**
  - Dissociative Anesthetic
    - In contrast to other IV anesthetics, primarily causes disruption of communication between thalamus and limbic cortex as opposed to suppression of RAS
  - Rapid onset
  - Short duration of action terminated by redistribution
  - Hepatic metabolism and renal excretion
• **Effects on Physiology**
  ◦ CNS: ↑CMRO₂ from excitatory CNS activity, ↑CBF from ↑CMRO₂ and cerebral vasodilation, ↑IOP, Dilated pupils and nystagmus
  ◦ Respiratory: maintain CO₂ response, relaxation of bronchial smooth muscles, salivation
  ◦ CV: Norepinephrine release leading to ↑SVR, ↑HR, ↑CO, DIRECT myocardial depressant
    † Beware in acutely ill/catecholamine-depleted patients

• **Side effects**
  ◦ Dysphoria and emergence delirium
    † Might want to avoid in comorbid psychiatric disease
    † BZDs can be a useful tool to prevent or treat
  ◦ Salivation
    † Pretreatment with glycopyrrolate
  ◦ Caution in those with elevated ICP/IOP (ie glaucoma, open globe/rupture, intracranial mass)
  ◦ Caution in those with CAD or major vascular disease
• Most IV anesthetics influence the GABA system
• Choice of anesthetic agent determined by goals of anesthetic and patient comorbidities
• Dosing determined by age, physiological function, comorbid disease, and use of adjuncts
• Barbiturates are capable of precipitating AIP though are rarely used anymore
- Flumazenil is a specific antidote for BZD overdose
- Propofol is the workhorse of modern anesthesia, but is not appropriate in every circumstance
- Etomidate is capable of causing adrenal suppression with just one dose
- Dexmedetomidine most closely mimics the state of natural sleep
- Ketamine produces a dissociative state that is unique amongst IV anesthetics

Take Home Points