GENERAL ANESTHETICS

History of early anesthetics: Early drugs essentially provided "controlled suffocation" of the patient
- No longer used: Ether (explosion danger); chloroform (carcinogen, explosion danger)
- Still used: Nitrous oxide – see below

FOUR DESIRED COMPONENTS OF GENERAL ANESTHESIA

1. *Unconsciousness*
2. *Amnesia* – Patient doesn't remember what happened just before, during, or right after surgery
3. *Analgesia* – Lack of pain and autonomic *stability* (generally go hand-in-hand)
    a. Intact autonomic responses can indicate pain or discomfort via changes in heart rate, BP, etc.
4. *Muscle relaxation* – Especially important for orthopedic and abdominal surgery

INHALATION ANESTHETICS – GENERAL PRINCIPLES

MAC (Minimum alveolar concentration)	The concentration of anesthetic that prevents response to a standard painful stimulus in 50% of subjects ▪ Expressed as % of inhaled anesthetic gas or vapor mixed in O2 ▪ 1/MAC ≅ potency (smaller MAC = more potent anesthetic)
Dose altering factors (MAC-altering factors)	Many factors, including but not limited to body temperature, pregnancy, age, concomitant use of other anesthetics or adjuncts
Blood/Lipid solubility & pharmacokinetics	*Blood solubility*: ↑ blood solubility → slower induction (onset of anesthesia) *Lipid solubility*: ↑ lipid solubility → faster induction (and longer duration) ▪ Imagine the blood as a sponge for the inhaled anesthetic; the anesthetic travels from the lungs, saturates the blood, and finally gets to the brain to induce anesthesia ▪ High blood solubility is kind of like a super-absorbent sponge. Anesthetic will take a long time to saturate the "blood compartment" and "spill out" into the brain. ▪ With low blood solubility, lesser amounts of local anesthetic are needed to saturate the "blood compartment" before the anesthetic can "spill out" into the brain.
Mechanism(s) of action are *unclear*	▪ Most probable explanation – Selective effects on specific neurons, and more specifically some "potentiation" of GABA's neuronal inhibitory effects ▪ Other potential explanations: ↑ membrane fluidity, membrane hyperpolarization
"Stages & Planes" of general anesthesia	Outmoded "indicator" of adequacy or degree of general anesthesia (don't memorize!!) ▪ Analgesia (w/o amnesia) ▪ Excitement – Initially, inhibitory neuronal pathways are selectively put to sleep ▪ Surgical anesthesia – Entire CNS depressed ▪ Medullary depression, coma, death

IV INDUCTION DRUGS – GENERAL PRINCIPLES

- Good to excellent amnesia and unconsciousness (some give anterograde & retrograde amnesia)
- Virtually no analgesic or muscle relaxant activities
    - Adjuncts for surgical anesthesia

MALIGNANT HYPERTHERMIA, HALOTHANE, AND SUCCINYLCHOLINE

- Results from interaction of any volatile liquid anesthetic and any neuromuscular blocker
  - Interaction of halothane and succinylcholine is most common
- Incidence & outcome: 1/50000 adult cases and 1/15000 peds cases; fatal 80% worldwide, 10-20% in U.S.
- Genetic predisposition: Family history and screening important
- *Timeframe*: Can occur *intra-operatively or post-operatively* several hours after drug exposure
- *Pathophysiology*: ↓ sarcoplasmic reticulum Ca uptake → titanic muscle contraction → profound, rapidly developing fever → K+ may leak out due to sarcolemma damage
  - Leads to ventilatory impairment, hyperkalemia, arrhythmias, fever-induced seizures
- *Management*: Dantrolene sodium, oxygen, ↓ body temperature, supportive care and other drugs as needed

IV INDUCTION-MAINTENANCE DRUGS ARE SHORT-ACTING NARCOTICS → FENTANYL (PROTOTYPE)

- Similar to morphine but more potent
- Neuroleptic analgesia: **Fentanyl** combined with **Droperidol** (Tranquilizer)
- Can be given transdermally for chronic pain management
- High IV doses used as primary anesthetic for special procedures (e.g. cardiac surgery)

Class / prototype	Pharmacokinetics & use	Effects	Interactions and negative effects
INHALED VOLATILE LIQUID AGENTS **- Halothane** Others include **Isoflurane** (most widely used in US), **Enflurane**, and **Sevoflurane**.	*MAC < 1% inspired air* - VERY potent *Administration*: Usually 0.5-1% Halothane + 60-70% NO + balance O2 *Excretion*: 70-80% unchanged by lungs *Use*: Maintenance of surgical anesthesia	**Dose-dependent organ system effects** **CNS** - Excellent amnesia, unconsciousness, analgesia - Cerebral vasodilation → ↑ ICP (bad w/ stroke & cancer pts) **CV-RENAL** - ↓ HR, ↓ SV, ↓ CO, ↓ BP, ↓ urine output - Potential (intrinsic) arrhythmogenicity; catecholamines can exaggerate this effect *Pulmonary*: Bronchodilator; reverses/prevents bronchospasm **SKELETAL MUSCLE** - Relaxation insufficient for surgery - Malignant hyperthermia risk w/ succ. (See p. 1) *Uterine*: Relaxant *Hepatic*: "Rare" fulminant hepatotoxicity +/- necrosis	↑ Risk of catecholamine-induced arrhythmias - ↑ Cardiac depression when used w/ b-blockers or Ca-channel blockers - ↑ Respiratory depression w/ narcotics - Need for intubation, ventilator - ↑ Action of nondepolarizing (curare-like) NMJ blockers; prolonged muscle paralysis - Malignant hyperthermia risk w/ succinylcholine (see p. 1) Acute OD/toxicity: CV depression

INHALED GASES **- Nitrous oxide**	*MAC = 105% inspired air* - Not potent enough to get analgesia in 50% of pts, even at 100% NO w/ no O2!! *Administration*: See above See *rapid onset and recovery*	Gives modest analgesia, amnesia, unconsciousness, but no muscle relaxation **Organ system effects** - Modest cardiovascular depression - Little/no uterine effects	Long-term/repeat exposure → Neurologic Sx that look like vitamin B12 deficiency Additional concerns about mutagenicity, carcinogenicity, and teratogenicity - Why OR ventilation is so good

IV INDUCTION DRUGS

BARBITURATES Thiopental, Thiamylal, Methohexital	- Ultra-short acting - Good to excellent amnesia and unconsciousness w/ virtually no analgesic or muscle relaxant activities	- ↓ Cerebral blood flow, metabolic rate, ICP (desirable) - Induction risks - CV depression - Laryngospasm + resp. depression / apnea
BENZODIAZEPINES Midazolem, Diazepam, Lorazepam	Midazolem - Used for induction and "conscious sedation" - Good sedation, excellent amnesia	- See under barbiturates) - Diazepam, Lorazepam – limited use - Slow onset and long actions
KETAMINE	- "Dissociative" anesthetic w/ excellent amnesia, analgesia, unconsciousness - Good for high risk pts (hypovolemic, hypotensive), children (eases induction), asthmatics (bronchodilator), burn pts (grafts, debridement)	Autonomic reflexes intact; often activates sympathetics Potential psychomimetic actions (PCP relative)
ETOMIDATE	Good for short procedures or pts at risk for benzodiazepines - Rapid onset, brief duration - Excellent amnesia, unconsciousness - No analgesia, muscle relaxation	Negligible CV or respiratory effects Potential myoclonus on injection
PROPOFOL	- Chemically unrelated to others - Rapid onset (<1min), short duration (<10-15 min) - Excellent amnesia, unconsciousness - Little/no analgesia, muscle relaxation - Popular for ambulatory surgery	Blunts autonomic-CV responses to intubation

PHARMACOLOGY OF ANALGESICS

Narcotic Analgesics	**Competitive agonists**	**Mixed agonists-antagonists**
•*Morphine* (prototype) •Levophanol •*Meperidine* •*Methadone* •Etorphine	•*Naloxone* •*Naltrexone*	•Nalorphine •Pentazocine •*Nalbuphine* •Butorphanol •*Buprenorphine*

• *Codeine* • *Propoxyphene* • *Fentanyl* **RELATED SPECIFIC AGENTS** • Apomorphine • *Dextromethorphan* • Diphenoxylate • Loperamide		A.k.a partial agonists - Can activate same receptors as full agonists with smaller effects - Antagonize the actions of the agonists (so that agonists give lesser effect) - Therapeutically, the least interesting

** Drugs to know…they are italicized on this table…not in the table → *Alfentanil* and *tramadol*

Narcotics act via receptor-mediated actions
- Opioid receptor types: m (named for morphine; tolerance inducing); k
- Tolerance, dependence, cross-tolerance, and cross-dependence – More on this later

Characteristic morphine-like effects of narcotic analgesics

Analgesia	**STRONGEST ANALGESICS KNOWN** Effective when pain comes from injury or inflammation; mechanism poorly understood ▪ Not effective for deafferentation pain Two components of morphine analgesia ▪ *Reduction in pain sensation*: Quantitatively reduces pain neurotransmission - Pre-emptive pain relief: Certain pain receptors uncovered only w/ inflammation; dripping morphine into surgical wound sites can prevent these receptors from getting activated ▪ Reduction in the subjective distress produced by the pain sensation
Subjective effects	- *Distinctive* - *Situationally dependent*: Addicts get a "good sick," those w/ pain have less pain, those w/o pain primarily experience side effects
Overall sedation	*Occurs at all doses where pain relief occurs*: Includes ↓ most behaviors, ↓ muscle tone, ↑ dozing, waxing/waning awareness, mental clouding, staring into space; sedation → severe depression → coma w/ ↑ dose ▪ Effect on sleep: Unnatural form of sleep w/ no REM activity ▪ Species difs in char of effect: Primates & humans similar; cats & rodents get stimulant effects
Respiratory depression	*Strong respiratory depressants* → Dose-dependant reduction in medullary sensation of CO2 ▪ Occurs at standard clinical analgesic doses ▪ *Small margin of safety*: Slight OD can lead to severe respiratory depression, including apnea ▪ W/ morphine, 4x the analgesic dose is lethal for most people ▪ Potentiation factors: Debilitating conditions, administration of barbiturates or phenothiazines
Other CNS effects	- *N/V*: Common - *Vertigo* (ambulatory pts) - *Miosis* - *Release of ADH* (get tolerance) - *Cough suppression* - *Truncal rigidity* (prob in OR) - *Convulsions w/ overdose or abuse* (e.g meperidine, propoxyphene)

Morphine-like effects of narcotic analgesics under ANS control

GI tract	*Constipation*: Occurs at ↓ doses than used for pain relief; *dose-related effect*; *no dev. of tolerance*
Smooth muscle	*↑ tone of biliary tract muscle*: ↑ pressure in bile ducts; sometimes get biliary colic ▪ Also see ↑ tone in bronchial smooth muscle, ureters, and urinary bladder
Cardiovascular	Dose-dependent; not usually a major problem ▪ Large doses given IV → Hypotension via ↓ peripheral vascular resistance ▪ *Standard clinical doses → May produce orthostatic hypotension*
Neurohumors and transmitters	*Rat facts* → Don't help us understand how narcotics act in CNS ▪ Inhibit ACTH release, Ach release from certain post-ganglionic parasymp fibers (similar effect in rodent CNS), and NE release from some post-ganglionic symp fibers ▪ Release of adrenal epinephrine, histamine (asthma probs) ▪ Increased synthesis and turnover of NE in rodent CNS

Pharmacokinetics of narcotic analgesics using morphine as prototype

Mechanism of action	Identification of receptors in CNS ▪ Techniques: Use radiolabeled morphine stereoisomers; active form binds receptors ▪ Distribution: All over, but esp. in the head (in general) and the base of the brain (specific) *Receptor effector mechanisms (opioid receptors)*: G protein-linked, inhibition adenylyl cyclase, activation of K+ channels, suppression of voltage-gated Ca++ channels ▪ Leads to blockade of NT release (e.g. glutamate, substance P) → Block pain transmission Endogenous opiates: Identification of morphine-like substances ▪ *Pro-opiomelanocortin*: Active form b-endorphin; mimics morphine better than any other endogenous opiate ▪ *Proenkephalin*: Met-Enk or Leu-Enk domain ▪ *Prodynorphin*: Dynorphin has slight preference for k receptor; may be k endogenous ligand ▪ Physical and pharmacological properties: Brief & small biological activity; only pathological activity/injury results in measurable (but small) levels of these compounds ▪ Modulation of pain experience not well-understood: Concept of "runner's high" pharmacologically shaky
Absorption, distribution, and fate	*Absorption*: Poor from GI tract; relatively well subcutaneously or IM *Distribution*: Onset of action (by subcutaneous route) related to lipid solubility ▪ Controls access to central receptors; ↑ solubility → ↑ absorption **ELIMINATION/DETOXIFICATION** ▪ Major path: *Conjugation w/ glucuronic acid* to morphine 6-glucuronide (more active than morphine) or morphine-3-glucuronide (inactive) ▪ Minor path: N-demethylation to inactive form ▪ *Duration of action*: 4-6 hours
Pharmacologic principles of morphine-like narcotic analgesics	- Produce morphine-like *CNS depression in single doses* - Induce *similar subjective effects* & reinforce self-administration behavior - CNS depressant effects *antagonized by naloxone* (via competitive inhibition at receptor site) - Upon repeated administration, *tolerance develops to CNS depressant effects*

	- Cross-tolerance among drugs, regardless of chemical structure - Tolerance at level of receptor activation (not drug structure) - Upon repeated administration, *drugs produce physical dependence of the morphine type* - *Cross-dependence among narcotic analgesics* ▪ An organism physically dependent on any one narcotic analgesic will have its dependence supported by another drug of this class. ▪ Abstinence syndrome produced by drug withdrawal can be relieved by any compound of this class (similar to cross-tolerance) ▪ W/physical dependence on any narcotic analgesic, *administration of narcotic antagonist will precipitate an abstinence (withdrawal) syndrome*, regardless of chemical structure of the drug
Characteristics of **morphine-type tolerance**	- Origin of tolerance ▪ Metabolic: Narcotics metabolized more rapidly through induced p450 system ▪ Cellular: Involves receptor recycling through cell (can see dependence w/o tolerance) ▪ Learned: Patients w/ pain become tolerant more rapidly than those w/o pain - Magnitude of tolerance: Depends upon specific biological effect ▪ Little tolerance to constipation; considerable tolerance to analgesia - Augmented by ↑ frequency, ↑ dose of narcotic analgesic
Characteristics of **morphine-type dependence**	- *Morphine abstinence syndrome (withdrawal syndrome)*: Wide set of changes produced upon termination of repeated morphine administration ▪ Begins ~ 6 hrs after last dose: Sensation of illness similar to common cold ▪ Restlessness, ↑ distress, anorexia, rhinorrhea, lacrimation, perspiration, abdom cramping ▪ Restless sleep, possible followed by insomnia ▪ Dilated pupils, N/V, diarrhea, spasms of flexor muscles of the legs ▪ Elevated body temperature, heart rate, systolic & diastolic blood pressure ▪ *Peak severity*: 36-48 hrs following last dose; recovery requires ~ 2 wks - Dependence w/ shorter[longer]-acting narcotics: Peak withdrawal severity sooner [delayed]

Other Morphine-like agonists

Levorphanol	- Morphinan: Similar chemical structure to morphine - *Full spectrum of morphine-like effects w/ better oral-parenteral potency ratio* - **Dextromethorphan**: Prototype *non-narcotic antitussive* - Dextro isomer of the codeine analogue of levorphanol - Suppresses cough by central mechanisms not well understood (and not that great, either) - In therapeutic doses, produces little sedation or GI disturbance - High doses produce respiratory depression - Actions are unaffected by narcotic antagonists; shows *no cross-tolerance to morphine* - Low risk with regard to abuse liability
Meperidine	- *Shorter duration of action than morphine*: Frequently used by dentists - Phenylpiperidines w/ *full spectrum of morphine effects* - Concurrent MAO inhibition produces a *severe state of CNS excitation* w/ delirium, hyperpyrexia, and convulsions, *or respiratory depression* w/

	hypotension - N-demethylation produces a metabolite that has stronger excitant property - **Dephenoxylate and Loperamide (Imodium)**: Meperidine congeners - *Constipating agents used as antidiarrheal agents* - Diphenoxylate tablets contain an inactive amount of atropine - Highly insoluble salts: Activate opiate receptors in GI tract but not centrally - Antagonizable by narcotic antagonists
Methadone	- Structure / actions: Has pseudopiperidine ring; a m agonist *full morphine-like actions* - Well absorbed orally w/ slightly less sedative effect claimed by advocates - Use in treatment of heroin abuse - Given orally 1/day to sustain morphine dependence w/o withdrawal induction - Considered an effective public health measure, but it's a long-term treatment w/ frequent relapses as methadone doses reduced - **a-acetylmethadol**: Recently approved agent for use in treatment of heroin abuse - Similar to methadone but longer-acting; patients could come to clinic less often
Etorphine	- Structure / actions: Oripavine structure; highly potent, short-acting drug - Used as an immobilizing agent (veterinary practice) - Marketed as a package w/ its "own" antagonist, diprenorphine
Fentanyl **VERY WIDELY USED**	- Structurally related to phenylpiperidines (e.g. meperidine) - *Produces strong analgesia*, similar to morphine - Combined w/ a butyrophenone (Droperidol): Produces neurolept analgesia, and can be used for major surgery w/o any other kinds of drugs - Patches and lollipops available for chronic pain and children's surgeries, respectively - Related compounds ▪ Sufentanil ▪ *Alfentanil*: Ultra-short-acting compound, w/ action rapidly terminated by metabolism ▪ *Remifentanil*: Most widely used short-acting m agonist; rapid metabolism means administration requires an infusion pump
Apomorphine	- Similar chemical structure to morphine - *Stimulates CTZ to induce N/V w/ little other narcotic-like effects* - Investigational use as a dopamine-receptor stimulant - Use in treatment as an emetic - Emetic effect antagonized by narcotic antagonists (acoording to some "authorities")
"Weak" agonists Use in milder forms of pain	- Codeine ▪ Structure: Morphine w/ methyl in 3 position; weak affinity for m receptor ▪ High oral: parenteral potency ratio ▪ Low doses relieve cramps, earaches (in children) w/ relatively small risk of abuse ▪ *Striking CV effects occur w/ non-oral administration* - Porpoxyphene (Darvon) ▪ Structure: Similar to methadone ▪ Side effects: Similar to narcotics ▪ High doses: Excitant effects culminate in convulsions w/ respiratory depression ▪ *Slight risk of abuse*, esp. considering wide use in medicine and dentistry

Characteristics of pure narcotic antagonists (naloxone, naltrexone, nalmefene are prototypes)

- Surmountable antagonists of the specific effects of narcotics (reduces potency of agonist)
  - Little effect when given alone, showing that endogenous opiates are not very active under normal circumstances

- In narcotic-dependent patient, narcotic antagonist administration elicits a syndrome resembling narcotic withdrawal.
  - Syndrome obtainable w/ very small doses of antagonists.
- Duration of action differentiates the three antagonists.
  - Naloxone: Short duration of action; multiple doses may be required to control agonist overdose; should only be used to diagnose narcotic intoxication.
  - Naltrexone: Longer-acting; approved for treatment of alcoholism (unclear mechanism)
  - Nalmefene: Slightly longer-acting than naltrexone
- When administered to normal, drug-free individuals, they are w/o effect except at very high doses.
- Use in diagnosis and treatment of overdose; suggested as diagnostic aid in methadone programs.
- All three antagonists more active in reducing m receptor effects than k receptor effects.

Char. of Morphine-like agonist/antagonists (Nalbuphine, butorphanol, dezocine, buprenorphine, tramadol)

Variable effects	- Partial agonist activity at m receptor - Can have other effects at other receptors ▪ e.g. buprenorphine is competitive antagonist at k receptor
Agonist actions	- Respiratory depression is limited - Analgesia is adequate, but may be limited as well - Pattern of adverse reaction is similar to Morphine - Subjective effects similar to Morphine, although limited (actions present in reduced form) - Reinforce self-administration behavior
Antagonist actions	- Precipitate withdrawal in Morphine-dependent patients - High dose effects of Morphine-like agonists are antagonized
Cardiovascular actions	Different: Not yet clear whether the differences are related to opioid receptor actions
Drug classification	Currently marketed compounds not classified under the Controlled Substances Act ▪ Exception: Buprenorphine

Kappa-receptor mediated agonist actions

- Analgesia
- Diuresis/water type
- Tolerance, dependence, but no cross-tolerance or cross-dependence w/ morphine
- Subjective effects that are "dysphoric"
- Fail to reinforce drug-taking behavior
- Absence of significant respiratory depression (kill animals by induced convulsions; unclear if these convulsions are receptor-mediated)
- All actions reversed by narcotic antagonists (w/ possible exception of convulsant action)

Char. of narcotic antagonists w/ Morphine-like agonist effects (nalorphine, cyclazocine, levalorphan)

- Some mixed agonists/antagonists have action at k receptor (pentazocine)
- Some produce nalorphine-like actions mediated at a k receptor – CNS depression, analgesia, sedation, depression of respiration, and ataxia, along w/ dysphoria and hallucination
- Pharmacologic prototypes; not marketed
- Do not reinforce self-administration behavior
- CNS depressant effects cannot be antagonized by nalorphine, but can be blocked by large doses of naloxone (surmountable antagonist)
- Cross-tolerance develops for compounds that work at the k receptor, but not for those w/ morphine-like actions, suggesting that the receptors do not have any significant cross-talk w/ each other
- Physical dependence develops but not cross-dependence w/ m-like compounds.