Anesthesia Student Survival Guide

Created by: Nebiyou Samuel, MS4

Table of Contents

Introduction

At UC San Diego medical school, third year medical students' exposure to Anesthesia is often as part of a two-week selective during their surgery rotation. Students are told to read up on *Miller* or *Bareish* (not for the faint of heart) to understand the foundational knowledge for the rotation. Fourth year medical students often feel like there should be a concise introductory document to help students before the rotation. This document is to provide a brief introduction to the field of anesthesia and ensure students feel more prepared prior to the rotation. This document is intended to be modified and altered as other students find the information outdated or irrelevant to the Anesthesia rotation.

If you are interested in Anesthesia as a career choice (it's a great field), definitely don't rely on this document only. Reading "Miller" or "Bareish" now would go a long way for residency preparation.

Preoperative Evaluation

It is important for anesthesiologists to approach each patient in a systematic way. Part of this preparation includes but not limited to:

- Obtaining through medical history, reviewing previous anesthetic plans, checking for appropriate lab tests, ordering appropriate meds and blood products, performing a detail airway assessment, informing the patient and obtaining consent.

History and Physical

Obtain targeted H&P focusing on airway and organ systems affected by the anesthetic plan, type of surgery and choice of anesthetic agent.

- Common Organ systems Reviewed
  - **Cardiovascular** – History of SOB, dyspnea, chest pain, edema, HTN, MI, Cardiac surgery, anticoagulant use, cardiac medications (i.e. diuretic, antihypertensives), CAD (was there a stress test or prior cardiac intervention, determining functional capacity (energy requirement with activity). Poor man's stress test – feeling after climbing 2 to 3 flights of stairs

  - **Pulmonary** – is patient current smoker? as secretion management can be difficulty (smoking cessation for at least 8 wks.). Hx Asthma? (determine severity and triggers - stimulation during surgery can trigger bronchospasm,

  - **Hepatic/Renal -** anesthetic agents are metabolized differently by liver or kidney, patient conditions might change our agent of choice.

  - **Gastrointestinal** – history of acid reflux makes us worry about aspiration since patients are relaxed, is an indication for RSI (rapid sequence intubation) –

requiring the use of quick acting paralytic succinylcholine and cricoid pressure (occludes the esophagus). Asking about history of Nausea and Vomiting (PONV – post operative nausea and vomiting

- **Endocrine**: Recent steroids use. Glucose monitoring and CAD monitoring in Diabetics (stress from surgery can increase blood glucose concentrations in diabetics and CAD risk factor), Taking insulin? - Take half morning dose of insulin on day of surgery. Thyroid issues creating hyper or hypo metabolic states during surgery.

- **Medications** – chronic pain management with opioids, anticoagulants
- **Allergies** – knowing previous medical reactions is critical
- **Family Hx** – important when it comes to history of Malignant hyperthermia in families lacking pseudocholinesterase.

➢ Physical Exam

- Vitals are always vital
- Establish ease of mask ventilation and intubation
  - **Gross external features** – facial trauma, deviated septum or nasal polyps, prominent incisors, beard, moustache, neck masses, dentures or not? (from personal experience, trying to intubate a patient with Dentures in is a nerve-racking experience).
  - **Neck ROM** – pt. need to assume the sniffing position (cervical flexion and atlanto-occipital extension) allowing the oral, pharyngeal and laryngeal axes to align, facilitating a clear viewing of the glottic opening.
  - **TMJ mobility** –
    - ➢ Measure inter-incisor distance (<3cm or 2 finger breadth will not be adequate)
    - ➢ Upper lip bite test – ask the patient to move the lower incisors as high as possible onto the upper lip – if unable to this might indicate inadequate translation movement of TMJ
  - **Tongue, dentition, oropharynx** – look for macroglossia (too large tongue), micrognathia (small mandible) making intubation difficulty. Have the patient sit and open their mouth as wide as while protruding their tongue, without phonating. Class 3 or 4 may be associated with difficulty with intubation
  - **Thyromental distance** – an assessment for the size of the mandible. Distance between the mentum of the mandible to the thyroid cartilage. 6 cm (= 3 finger breadth) or less associated with receding mandible or short neck, indicating a possible difficult intubation.

❖ **Mallampati Score**

- Mallampati classifications: size of tongue in relation of oral cavity. The greater the tongue, the greater the obstruction.
- May not be sensitive to detecting a difficulty intubation, the absence is predictive for relative ease of intubation.

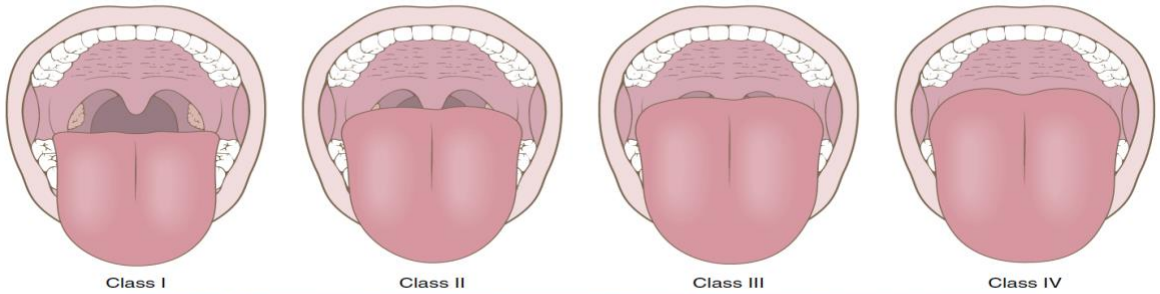


Fig. 16.6 Mallampati classification. (From Samsoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. *Anaesthesia.* 1987;42:487-490, used with permission.)

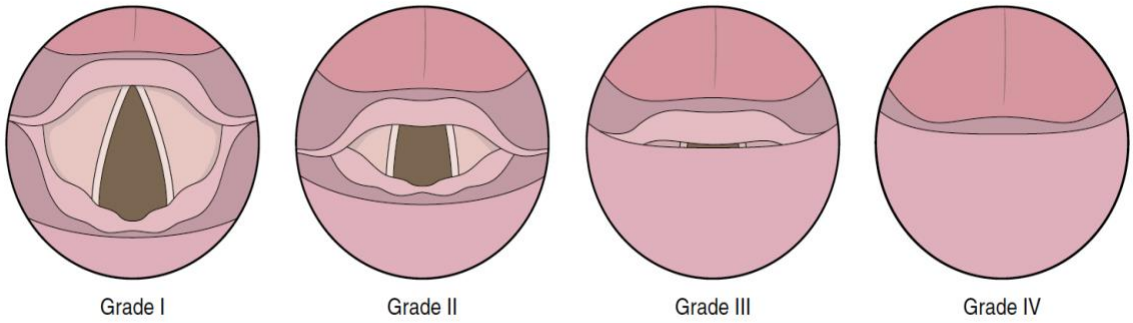


Fig. 16.12 Four grades of laryngoscopic view. Grade I is visualization of the entire laryngeal aperture, grade II is visualization of just the posterior portion of the laryngeal aperture, grade III is visualization of only the epiglottis, and grade IV is visualization of just the soft palate. (From Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia.* 1984;39(11):1105-1111.)

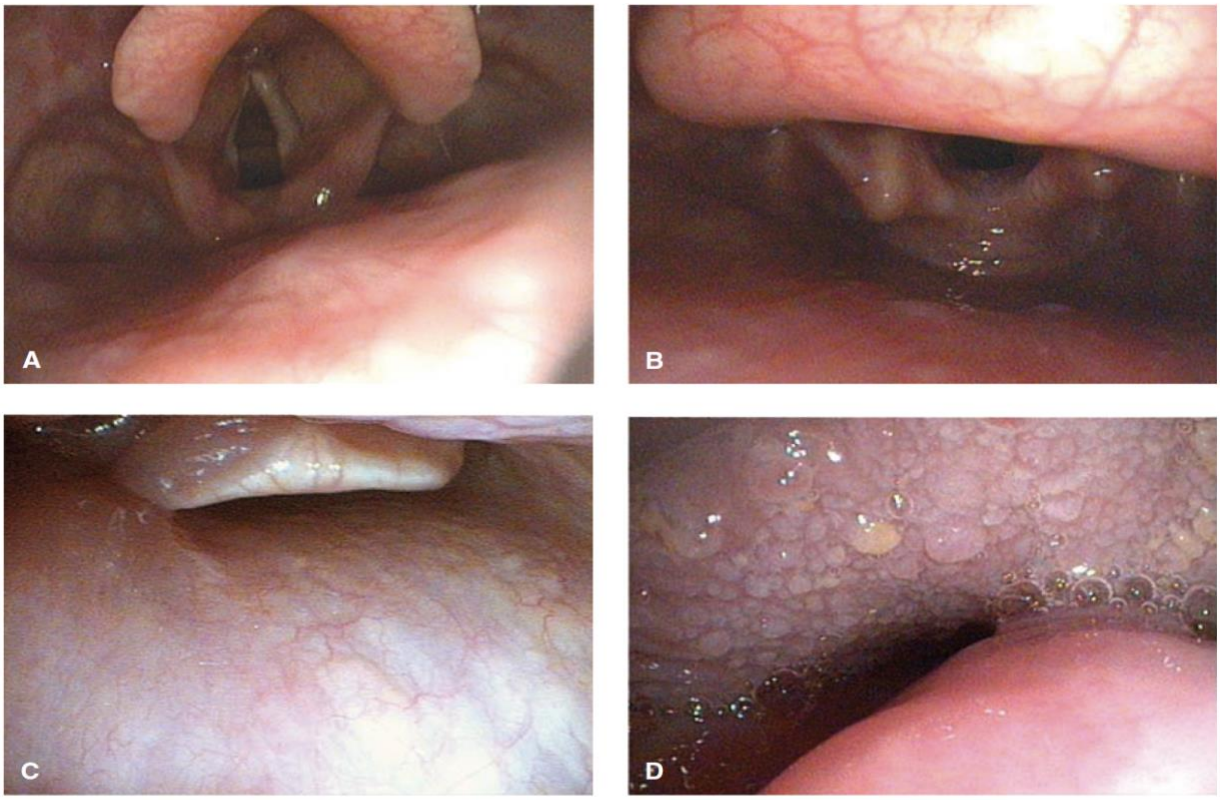


Figure 20-4 The Cormack-Lehane laryngeal view scoring system: grade 1 (**A**), grade 2 (**B**), grade 3 (**C**), and grade 4 (**D**). (From Rosenblatt WH, Sukhupragarn W. Airway management. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. *Clinical Anesthesia.* 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:777, with permission.)

❖ **Airway Anatomy**

- ❖ Human airway extends from nares to alveoli
- ❖ **Upper airways** - pharynx, nose, mouth, larynx, trachea and main-stem bronchi.
- ❖ **Cricothyroid membrane** is an important externally identifiable structure, in adulty typically about 1 to 1.5 fingerbreadth below the thyroid notch.
- ❖ Due to the size and less acute angle of divergence from the main bronchus, aspirated object s or deeply inserted ET tubes tend to get stuck **in the right primary bronchus.**

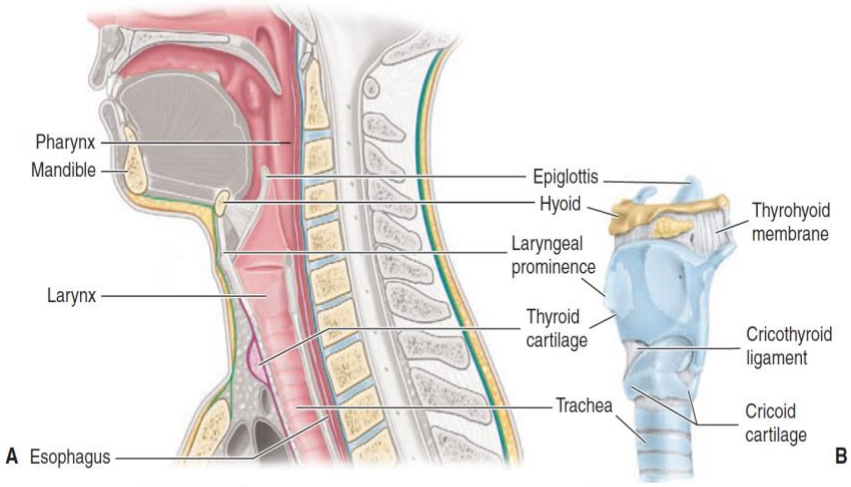


Figure 20-1 Sagittal view of upper airway anatomy (**A**) and lateral view of laryngeal skeleton (**B**). (From Moore KL, Agur AMR, Dalley AF. *Clinically Oriented Anatomy.* 7th ed. Philadelphia: Wolters Kluwer Health; 2013, with permission.)

- **Airway Exam**
  - All patients must be evaluated for the need to intubate and mechanically ventilate. Successful ventilation (with or without intubation) is the primary goal of airway assessment.
    - All levels of sedation, GA or regional pose risks of airway compromise as anesthetics have respiratory side effects.
    - Majority of respiratory injures are due to inadequate ventilation, esophageal intubation and difficult tracheal intubation.
      - Question people's prior Anesthetics
  - Performing various maneuvers will help us estimate the difficulty of endotracheal intubation. If anticipating difficulty, prepare advanced airway equipment. Factors affecting mask ventilation (presence of beard, BMI > 26 KG/M2, missing teeth, Age > 55, History of snoring)
    - Mouth opening: Incisor distance of 3 cm or greater
    - Upper lip bite test: lower teeth are brought in front of upper teeth. This estimates the ROM of the temporomandibular joint
    - Dentition – presence of loose teeth, dentures, crowns or masses.
  - Cardiopulmonary Exam
    - Cardiac and Pulmonary Exams (pulses, respiratory effort, baseline pulse oximetry saturation)
    - Need for further cardiac testing (stress test) or intervention (Catherization or CT surgery)
      - Determine patient's metabolic functional activity.
  - GI Exam – increased potential for aspiration if suffering from GI illnesses. Screen for GI illness/symptoms like GERD, gastric ulcers, ascites, abdominal distension, guarding
  - MSK – Neck ROM, preexisting nerve injuries

Anesthetic Plan

- With the history and physical exam gathered, patient is standardized into a physical status classification determined by ASA (American Society of Anesthesiologists)

  This is a tool used by Anesthesiologist to risk stratify patients based on their acuity of their disease burden and establish a standardized way of classifying patients prior to various surgeries.

- Each Anesthetic plan takes the individual patient into consideration. For instance, does the patient need general anesthesia or MAC (monitored anesthetic care) vs. Regional vs Local? Is awake intubation required, how difficulty is the patient to mask ventilate? Need for arterial or Central line to monitor blood pressure or hemodynamic status? How much analgesia does the patient require? What kind of surgery, surgeon and OR staff is on staff today? Is PACU familiar with managing this type of patient? Do they need to remain intubated and head to ICU post-op?

ASA PS Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

**The addition of "E" denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)*

Table 8.6 Formulation an anesthetic plan based on patient history

Patient history	Area to evaluate	Anesthetic considerations
Airway perceived as difficult to intubate or ventilate	Head, eyes, ears, nose, throat: airway; prior anesthesia outcomes	Obtain fiberoptic equipment; obtain skilled help
Asthma	Pulmonary disease	Optimize therapy; use bronchodilators; consider extubating during deep anesthesia
Diabetes, insulin-dependent	Endocrine, metabolic, diabetes	Discuss insulin management with patient and primary care doctor; monitor blood glucose intraoperatively; determine presence of autonomic neuropathy and plan management appropriately, such as administration of metoclopramide and PACU or ICU stay
Drug abuse	Social history	Consider HIV and Hepatitis testing; prescribe medications to avoid withdrawal symptoms in perioperative period
Gastroesophageal reflux or hiatus hernia	Gastrointestinal disease: hiatus hernia	Administer H_2 antagonists or oral antacids and consider rapid-sequence induction of anesthesia; or use awake intubation techniques and obtain appropriate equipment
Heart disease: valve disease, risk of subacute bacterial endocarditis	Cardiac history and exam, imaging studies	Consider antibiotic prophylaxis. Arrange for antibiotic administration 1 h prior to surgery
Personal malignant hyperthermia history, family history, or suspected potential history	Prior anesthetic/surgical history	Obtain clean anesthesia machine (new CO_2 absorbent, remove vaporizers, flush circuit with 10 L/min for 10 min); use appropriate technique and precautions; have agents to treat malignant hyperthermia available
Monoamine oxidase inhibitors	CNS: psychiatric/medication	Discontinue therapy preoperatively if patient is not suicidal; plan for perioperative pain therapy
Pacemaker or automatic implantable cardiac defibrillator	Cardiovascular disease: electrocardiogram	Evaluate cause of pacemaker implementation; obtain repolarizing equipment or magnet; use electrocautery with Bovie pad placed appropriately (monopolar); use bipolar electrocautery if possible
Peripheral motor neuropathy	CNS disease: neurologic deficit	Avoid depolarizing muscle relaxants; adjust dose of non-depolarizing muscle relaxants appropriately
Pregnancy or uncertain pregnancy status	Genitourinary: pregnancy	Monitor fetal heart rate; use oral antacids; adjust induction of anesthesia; determine status of pregnancy
Pulmonary tuberculosis	Pulmonary disease: tuberculosis	Use disposable breathing circuit or clean equipment; ensure adequate treatment of patient prior to surgery
Renal insufficiency	Genitourinary disease	Monitor fluid status intraoperatively

Adapted from Fischer et al. [11]
CNS **central nervous system,** ***HIV*** **human immunodeficiency virus,** ***ICU*** **intensive care unit,** ***PACU*** **postanesthetic care unit**

❖ Informed Consent

- Walk the patient through the possible risks and complications of undergoing Anesthesia and Surgery.
- Some of the risks include
  - Infection and bleeding
  - Post-operative nausea and vomiting (PONV)
  - Awareness under anesthesia
  - Need for post-operative mechanical ventilation (failing to meet extubation criteria)
  - Dental Injury
  - Risk of HIV and viral transmission from blood transfusion despite minimal risk

Box 16.2 Complications of Endotracheal Intubation

During Direct Laryngoscopy and Endotracheal Intubation
Dental and oral soft tissue trauma
Systemic hypertension and tachycardia
Cardiac dysrhythmias
Myocardial ischemia
Inhalation (aspiration) of gastric contents

While the Endotracheal Tube Is in Place
Endotracheal tube obstruction
Endobronchial intubation
Esophageal intubation
Endotracheal tube cuff leak
Pulmonary barotrauma
Nasogastric distention
Accidental disconnection from the anesthesia breathing circuit
Tracheal mucosa ischemia
Accidental extubation

Complications After Endotracheal Extubation
Laryngospasm
Inhalation (aspiration) of gastric contents
Pharyngitis (sore throat)
Laryngitis
Laryngeal or subglottic edema
Laryngeal ulceration with or without granuloma formation
Tracheitis
Tracheal stenosis
Vocal cord paralysis
Arytenoid cartilage dislocation

Room Set up and Monitors (MS MAIDS)

ASA standards for Basic Anesthesia Monitoring

Standard 1 – "qualified anesthesia personal shall be present in the room throughout the conduct of all general anesthetics, regional anesthetics and monitored anesthesia care.

Standard 2 – "During all anesthetics, the patient's oxygenation, ventilation, circulation and temperature shall be continually evaluated."

Oxygenation – FiO_2 analyzer + O_2 concentration alarm. Blood oxygenation – pulse oximetry
Ventilation – continuous capnography (expired Tidal Volume)
Circulation – EKG (minimum 3 leads, consider 5 for cardiac concerns), BP – minim q5 minutes
Temperature – some form of temperature probe

MS MAIDS - Machine, Suction, Monitors, Airway, IV, Drugs, Special (4T's and Seat)

Machine – assure adequate source of gases from the wall, ensure alternative source of oxygen (E-cylinder), fail-safe alarms are working, check levels of volatile agent in the machine vaporizer, perform high pressure test, perform low pressure test, make sure ventilator bellows are working

Suction – important to have a powerful enough suction that can remove any secretion in the oropharynx present during induction. This should be established prior to bringing patient to the room

Monitors – minimal required monitoring: pulse oximetry, blood pressure, ECG, Capnography and temperature probe.

Airway – important equipment for maintaining airway, i.e. having back up set of equipment if first pass induction/intubation fails. Minimum airway set up – working laryngoscope (2 types and sizes of blades), endotracheal tubes of right size, with tested and working endotracheal cuff.

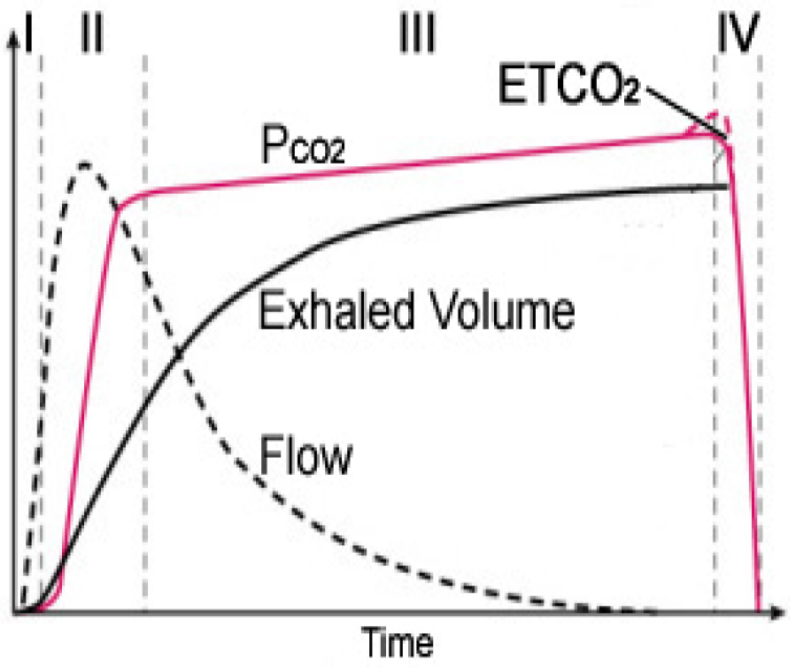
IV– preparing a full IV set up just in case another access is needed in case of blood loss or increase in intraoperative fluid requirement. Along with this: *fluid warmers, pressure bags, rapid infusers, Central line access equipment.*

Drugs – adequate supply of medication to induce, maintain and assist with emergency of the patient. An anesthesia provider ought to remain by the patient throughout the case. Typically, emergency drugs *succinylcholine, atropine, ephedrine, and phenylephrine* are drawn up and available in addition to induction agents (Propofol, fentanyl, Rocuronium)

Special equipment – catch all terms for the additional equipment (4 T's – temperature, twitch monitor, teeth (bite guard),), OG/NG tube, fluid warmer, hugger blanket, Foley, Transesophageal echo

❖ Capnograph

- Measures exhaled CO2 (other gases as well)
- Distal to Y-piece increases dead space
- Number and tracing provide much physiologic information

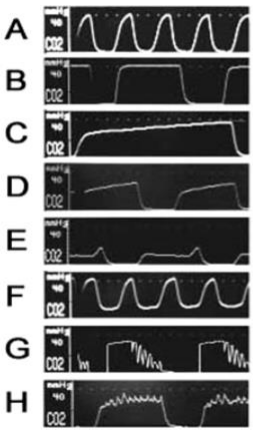


Capnogram Phases

I. Dead space gas exhaled
II. Transition between airway and alveolar gas
III. Alveolar plateau
IV. Inspiration

- **Bronchospasm** - upsloping trace
- **Inadequate circulation** resulting from **hypotension** indicating BP is too low for pt - number decreasing
- **Pulmonary embolism** - decreasing number and increased gradient between ETCO2 and PaCO2
- **Esophageal intubation**, **circuit disconnect** - no ETCO2 tracing
- **Exhausted CO2 absorbent** - ETO2 does not return to 0-5)
- **Clinical pearl:** when apneic – ETCO2 to increase by 6 after 1 minute, and to increase by 3 every minute thereafter

Capnography



Example Traces

A. Spontaneous ventilation
B. Mechanical ventilation
C. Prolonged exhalation (spontaneous)
D. Emphysema
E. Sample line leak
F. Exhausted CO_2 absorbant
G. Cardiogenic oscillations
H. Electrical noise

For more example tracings visit:
http://www.capnography.com/find.htm

❖ EKG

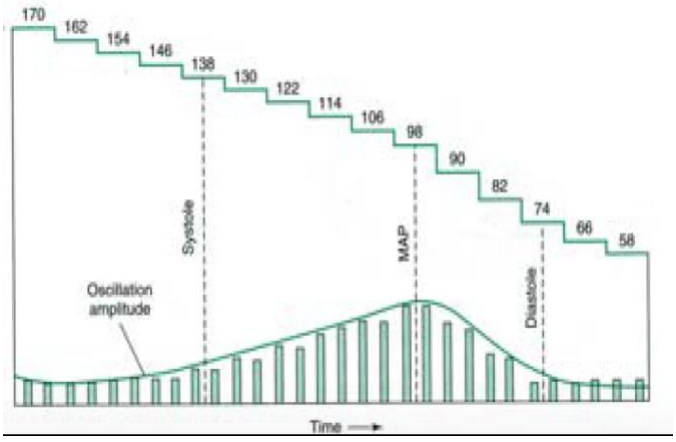
- Continuous cardiac monitoring for rate and rhythm is standard of care in Anesthesia
- Most arrhythmias can be detected by standard 3 lead but cardiac ischemia is best detected by five lead (displaying both leads II and V). Can detect 80% of ischemic event.
  - Possible to have normal appearing ECG with no cardiac output or BP (PEA – pulseless electrical activity)

❖ Pulse oximetry

- The probe emits light at 660 nm (red, for Hb) and 940 nm (infrared, for 02Hb)
- Sensors detect light absorbed to each wavelength
  - **Photo-plethysmography** – identifies arterial flow (alternating current = AC) and cancels out the absorption during non-pulsatile flow (direct current = DC), the patient is their own control
  - Pulse Ox not connected to a patient often reads 85%.
  - **Falsely High SpO_2** – Carboxyhemoglobin (COHb) – similar absorbance to O_2Hb. At 50% COHb, SaO2 = 50% on ABG, but SpO2 may be 95%
  - **Falsely Low SpO2** - dye (methylene blue), blue nail polish, shivering, ambient light, lower perfusion (low cardiac output, profound anemia, hypothermia, elevated SVR), malposition

❖ Blood pressure

- NIBP – non-invasive blood pressure measurement, automated interpretation of oscillations.
  - **MAP = (SBP +2 DBP) / 3]**
  - Cuff too small – **Falsely High BP**
  - Cuff too big – **Falsely Low BP**
  - MAP is the primary measurement
  - More distal sites have higher BP
    - Radial SBP > Aortic SBP
  - Position matters – consider the height of interposed column of water



❖ Intubation

- **Mask Ventilation**: The most basic airway management but probably the first and most critical skill any anesthesiologist must master.
  - **3 goals**
    1- Optimal seal must be made between the mask and the patient's face
    2- Patient's oropharynx must be open by anterior displacement of the mandible (Jaw thrust)
    3- Sufficient positive pressure must be generated to overcome the resistance of the patient upper airway, chest wall and diaphragm to effect efficient gas exchange at the alveoli.

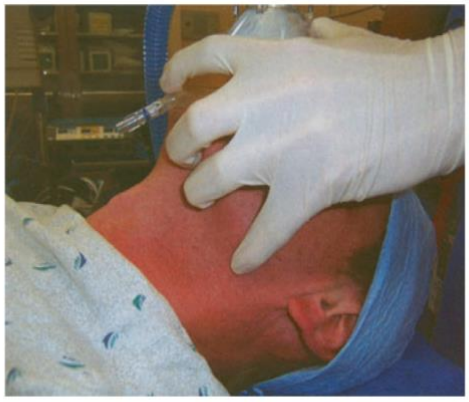


Figure 9.3 Optimal facemask ventilation

➢ LMA, DL, Preoxygenation

- LMA are used in patents who are receiving general anesthesia but don't require intubation with ET tube.
- The lubricated device is inserted blindly into the patient's mouth along the hard palate, past the tongue, just the tip of the hypopharynx
  - The cuff is inflated and to occlude the GI tract, however pulmonary aspiration isn't fully prevented

- **Relative** LMA Contraindication
  - Increased risk for pulmonary aspiration
  - Requiring positive pressure ventilation
  - Lengthy procedure
  - Utilizing other procedures outside of supine

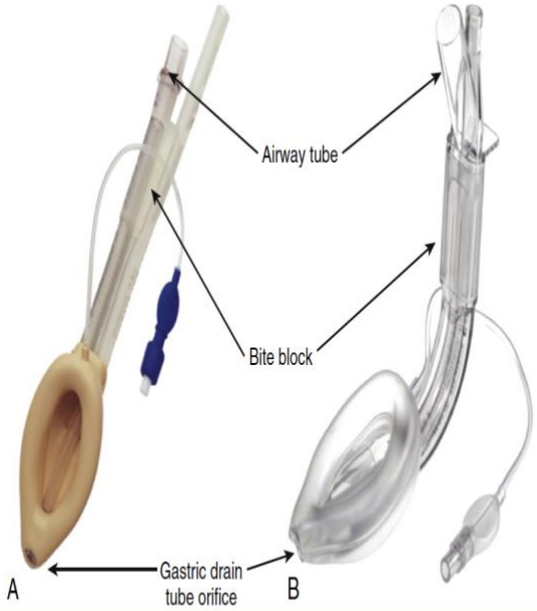


Fig. 16.10 (A) The reusable laryngeal mask airway (LMA) ProSeal. (B) The single-use LMA Supreme. These modifications of the LMA Classic have a gastric drain, built-in bite block, and modified cuffs for improved airway seals. (Images courtesy of Teleflex, Morrisville, NC, modified with permission.)

➢ Direct Laryngoscopy

- Most common way of achieving endotracheal intubation.
- The process involves visualizing the patient's glottis through the **sniffing position** (cervical flexion and atlanto-occipital extension) aligning the **oral cavity, the pharynx, and the larynx**
  - Hold the Laryngoscope with your left hand (irrespective of hand dominance)
  - Open patient's mouth with either **head tilt** or **fingers using scissoring motion**.
  - Insert the Laryngoscope carefully, sweeping the tongue from right to left and advancing further until you can visualize the epiglottis. Aiming to wedge into the vallecula
  - Using your upper arm (**NO WRIST MOTION**), lift the laryngoscope toward the opposite wall and ceiling. **No ROTATIONAL** Movement
  - Once positioned, remove the laryngoscope, hold the ET tube in position, remove the stylet and inflate the cuff balloon
  - Ensure proper tube placement
    - ♦ Listen for bilateral breath sounds
    - ♦ Check end tidal CO2
    - ♦ Misting of the ET tube
- Make sure the ET tube is securely taped, place on ventilator and set gas flow

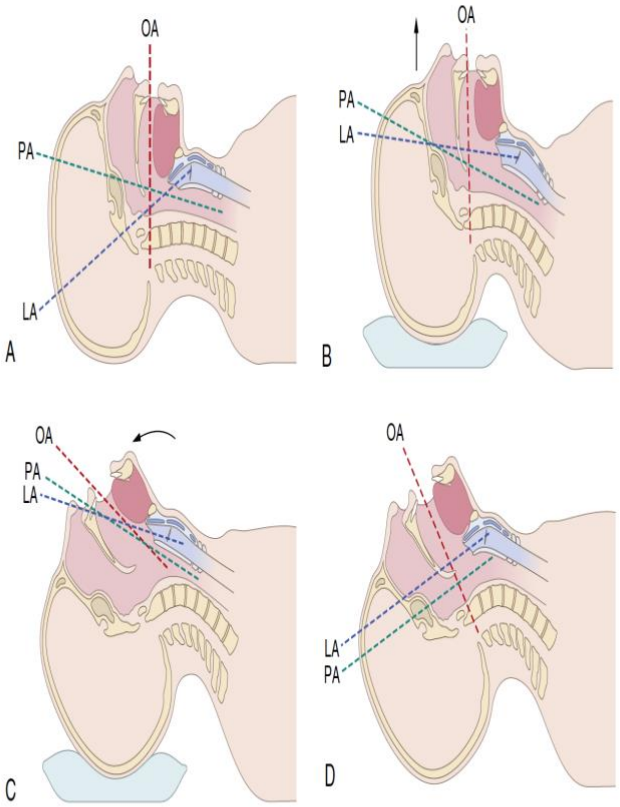


Fig. 16.7 Schematic diagram showing alignment of the oral axis (OA), pharyngeal axis (PA), and laryngeal axis (LA) in four different head positions. Each head position is accompanied by an inset that magnifies the upper airway (the oral cavity, pharynx, and larynx) and superimposes, as a variously bent bold dotted line, the continuity of these three axes with the upper airway. (A) The head is in a neutral position with a marked degree of nonalignment of the OA, PA, and LA. (B) The head is resting on a large pad that flexes the neck on the chest and the LA with the PA. (C) The head is resting on a pad (which flexes the neck on the chest) with concomitant extension of the head on the neck, which brings all three axes into alignment (sniffing position). (D) Extension of the head on the neck without concomitant elevation of the head.

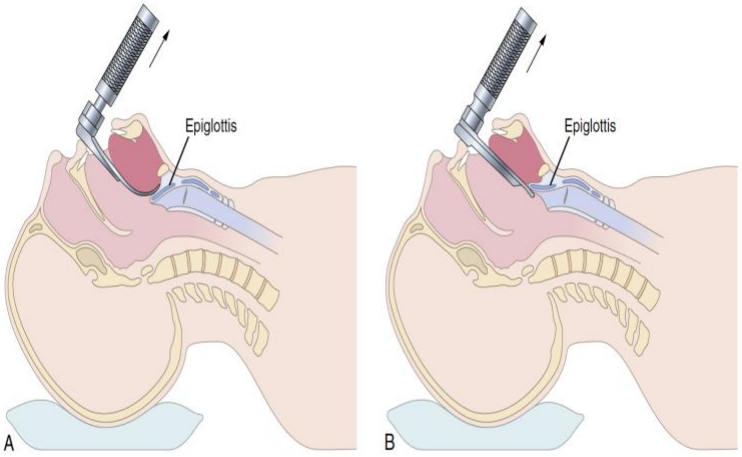


Fig. 16.13 Schematic diagram depicting the proper position of the laryngoscope blade for exposure of the glottic opening. (A) The distal end of the curved blade is advanced into the space between the base of the tongue and the pharyngeal surface of the epiglottis. (B) The distal end of the straight blade is advanced beneath the laryngeal surface of the epiglottis. Regardless of blade design, forward and upward movement exerted along the axis of the laryngoscope handle, as denoted by the arrows, serves to elevate the epiglottis and expose the glottic opening.

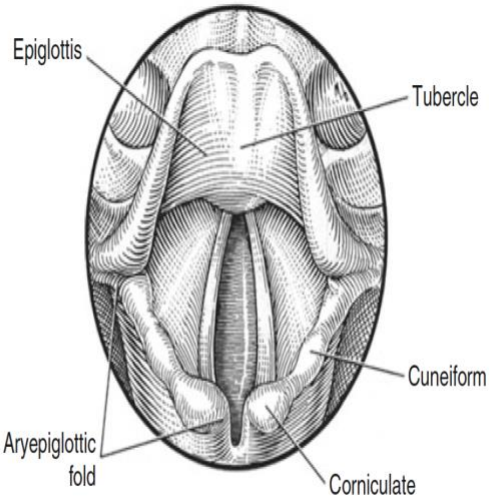


Figure 9.1 The glottis and epiglottis (Reproduced with permission from Finucane and Santora [7])

❖ **Preoxygenation**

- 100% of O_2 is delivered through facemask. The goal being to achieve end-tidal oxygen concentration of greater than 80%. Good seal in mask ventilation will optimize preoxygenation.
- The first part of induction should be preoxygenation which will allow for longer times of apnea (by increasing oxygen reserves through denitrogenating) thereby optimizing time for securing an airway or problem solving an unanticipated difficulty airway.
    - When apneic, a normal person uses approximately of 250 – 300 mL of oxygen each minute and can desaturate in as little as 30 – 60 seconds.
    - FRC – fractional residual capacity – approximately 3 L in normal person, contains mainly nitrogen. With 100% oxygen this is effectively replaced.
    - This pre-oxygenation can provide 3 – 6 additional minutes of apnea before significant O2 desaturation occurs.
- A healthy adult, who is not obese, can be apneic for approximately 9 minutes before significant desaturation occurs. This time is primarily dependent on oxygen consumption and the FRC.
    - Obesity, pregnancy, and other conditions that significantly decrease FRC or factors that increase oxygen consumption decrease the time to
    - Preoxygenation in a 25-degree head-up position in obese patients can increase the time to desaturation by decreasing atelectasis and improving ventilation/perfusion matching

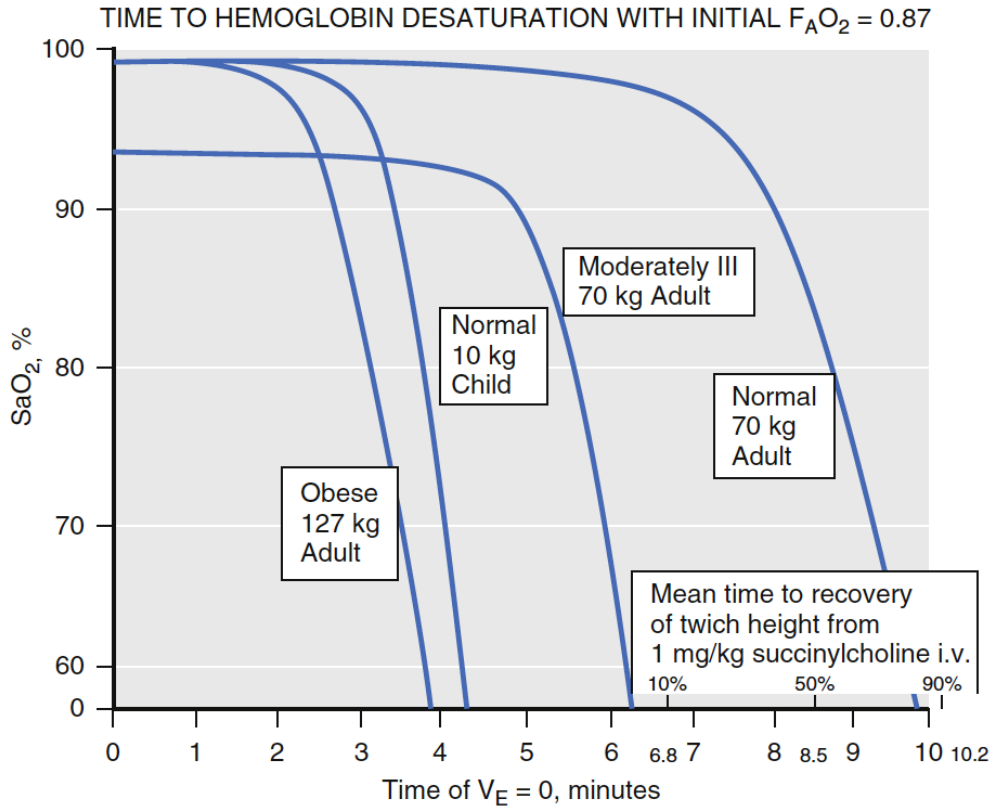


Fig. 16.8 The oxygen saturation (SaO_2) versus time of apnea of various types of patients. The time to reach an oxygen saturation of 80% was 8.7 minutes in a healthy 70-kg adult, but was 3.1 minutes in an obese patient. F_AO_2, alveolar fraction of oxygen; V_E, minute ventilation. (From Benumof JL, Dagg R, Benumof R. Critical hemoglobin desaturation will occur before return to an unparalyzed state following 1 mg/kg intravenous succinylcholine. *Anesthesiology.* 1997;87(4):979-982.)

Fundamental of Pharmacology

❖ Pharmacology

▪ Basic Pharmacology Principals

- **Pharmacokinetics** – often times thought of how the body processes the drugs. Key components include Administration (absorption), Distribution, and drug metabolism and excretion.
- **Pharmacodynamics** - Is often thought of how a drug causes physiological and pharmacological reactions with in the body. Reponses on receptors at the cellular level.

➢ **Absorption**: process by which drugs moves from site of administration into the blood stream.

♦ **Routes**: there are various ways of administering drugs transdermal, transmucosal, subcutaneous, intramuscular and intravenous. *Most anesthetic drugs use intravenous or inhaled routes.*

➢ **First pass metabolism:** Drugs passing through the GI system will also pass through the portal venous system before entering systemic circulation. Consequently, there is extensive metabolism by liver. Unlike IV administration where it's 100% bioavailable, there is a higher dose requirement for enteric administration of drugs

➢ **Ionization:** generally speaking nonionized parts of a drug are absorbed easily through the gastric mucosa. The acidity of the stomach can affect drug absorption. Weak bases (opioids) have a hard time with absorption while weak acids (barbiturates) can cross easily.

➢ **Distribution –** systemic circulation to target organs. Affected by free fraction and protein binding, volume of distribution (Vd) and Redistribution, Storage

- **Free fraction and protein binding:** most drugs are protein bound making them therapeutically inactive, the free portions, about 10%, are active. When plasma proteins are decreased there will be freer drug and more activity. Hepatic and renal conditions will decrease plasm protein concentrations., increasing free fraction and hence drug activity
- **Vd –** total dose of drug given divided by plasma concentration. Lipophilic drugs will have low plasma concertation and consequently high volume of distribution while hydrophilic/protein bound drugs will have Vd that is close to plasma volume.
- **Redistribution:** some drugs will quickly distribute into certain parts of the body (brain and heart) and slowly into adipose tissue. Once more and more distribution occur into adipose tissue however, equilibrium will force them out of brain and heart, leading to less therapeutic effect.
- **Storage:** lipid soluble drugs that store into adipose tissue will eventually reach saturation, leading to a pharmacodynamics that is mediated by metabolism and excretion of such drugs. These processes however are slower than redistribution.

➢ **Metabolism and Excretion** – most excretion occurs through liver, kidney and lungs. Liver end products are often polar and water soluble and excreted through kidney. Lungs are the primary site of inhalational anesthetics.

- **Zero-order kinetic –** drugs is metabolized at a fixed rate, regardless of concentration

- **First-order kinetic –** most drugs are metabolized through this process, where rate of metabolism is proportional to concentration. Drugs half time – where 50% of drug is eliminated. 5 half-times is equivalent to 96.9% of drug elimination
- **Clearance** – theoretic volume of blood that is cleared of drugs per unit time.
  - Different pathways of clearance are addictive. If there is a decrease in a pathway (hepatic failure) will prolong the effect of the drug
- **Context-Sensitive half-time** – some drugs are eliminated from plasma by redistribution to adipose tissue. Phenomenon of context-sensitive half times where 50% reduction in drug concentration increases with increasing total doses of drug or duration of infusion. Drugs that are highly redistributed but metabolized slowly will be affected.

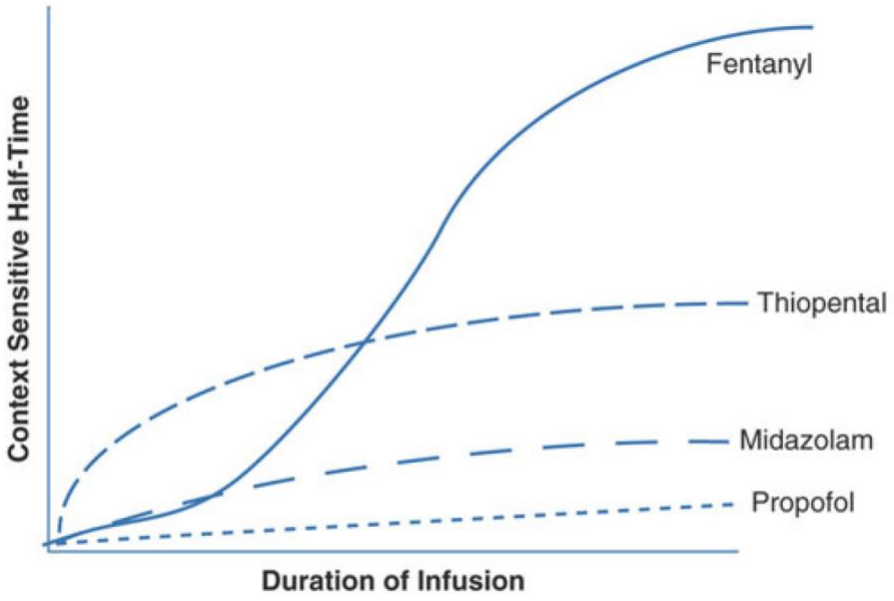


Figure 3.2 Context sensitive half times as a function of duration of infusion (Image Courtesy J. Ehrenfeld)

Pharmacodynamics

- **Potency**: refers to the dose of the drug required to achieve a therapeutic effect. A smaller dose of a more potent drug will achieve the same effect as a larger dose of a less potent drug
- **Efficacy**: refers to the maximum effect achievable with the drug. Once a drug's maximum effect has been reached, giving more will not result in increased effects.
- **Toxicity**: Drug toxicity occurs when undesirable side- effects of its administration occur.
- **Therapeutic index**: is the ratio of the dose producing a toxic effect to that producing a therapeutic effect. A drug with a high therapeutic index requires a much higher dose to do harm than to achieve a desired effect, giving a relatively high margin of safety.

Commonly Used Medications

Induction Agents

- Induction is the process of starting a general anesthetic, where the patient is put to sleep. Ideal goal for an induction agent is to act quickly, but also short-acting. The reason being that if something goes wrong during induction, there is always the option of waking up the patient.

- Benzos and Opioids through Intravenous administration could be considered induction agents. IV induction however runs the risk of unpredictable onset time and longer duration of action.

- ### IV Anesthetic

  IV Anesthetics used for Induction:

  - Commonly used – Propofol, etomidate, ketamine, thiopental (Barbiturate)
  - The primary mechanism for most IV anesthetics is inhibition of GABA receptors. GABA is the primary inhibitory neurotransmitter in the CNS. Increased chloride conductance across membrane and into postsynaptic neuron promotes hyperpolarization, thus inhibiting neuronal signaling. This has a sedative and hypnotic effect on the individuals.
  - Other IV anesthetic mechanisms - Ketamine (exerts effect through NMDA receptor) and Dexmedetomidine (Alpha-2-receptor activation)
  - Benzos – increase the efficiency of GABA-receptor and Chloride ion channel coupling. While Propofol and Barbiturates decrease the rate of dissociation of GABA and its receptors

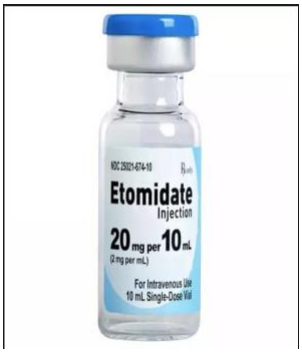
- **Propofol (Diprivan)**
    - Induction Dose: **1.5– 2.5 mg/Kg**
        - Children require higher doses – larger Vd and clearance
        - Elderly require lower doses – lower Vd and clearance
    - Infusion dose – 100 – 200 mcg/kg/min
  - Increases binding affinity of GABA with $GABA_A$ receptor.
  - Produced in an 1% egg lecithin emulsion, glycerol and soybean oil (relevant to patient allergies to egg white – not contraindicated with egg allergy).
  - Formulation can support bacterial growth – need for good sterile technique
  - Highly lipid soluble – only administered intravenously
    - **Half-life of 2 – 8 minutes**
  - Rapid hepatic metabolism to water soluble compound and removed by kidneys
  - Potent cardiovascular and respiratory depressant
  - Decreases BP by decreasing cardiac contractility, SVR and preload (inhibition of sympathetic tone and direct vascular smooth muscle effect).
  - **The most profound cardio depressant** of all induction agents.
    - Avoid in cases where spontaneous ventilation is required, patient is hypotensive already or unable to maintain hemodynamic stability.
  - **In 2/3 of patient is there also pain on injection**. Co-administration of 1% lidocaine can lessen the pain.
  - Has **antipruritic** and **antiemetic properties** – used in TIVA (total intravenous anesthesia) and as background infusion to prevent PONV (post op nausea & vomiting)

Barbiturates (Thiopental)

- Most commonly used are thiobarbiturates (thiopental, thiamylal and oxybarbiturate methohexital)
    - Induction Dose: **3 – 5 mg/kg adults**
        - 5-6 mg/kg in children
        - 6-8 mg/kg in infants
  - Thiopental no longer produced in US, unlikely used
  - **Depress the reticular activating system in the brainstem**
  - Enhance $GABA_A$ receptor transmission
  - Leads to prolonged cognitive effects compared to Propofol: it decreases cerebral metabolic rate of oxygen (CMRO2), Cerebral blood flow (CBF) and intracranial pressure (ICP).
  - **Thiopental possible cerebro-protective** – was commonly used in neurosurgery cases.
  - Highly alkaline
  - Should NOT be mixed with acidic solution such as paralytic agents, since it will precipitate and occlude IV catheters.
  - Undergo terminal elimination via hepatic metabolism.
  - Should not be used in patient with porphyria – will stimulate porphyrin formation and lead to acute crisis.

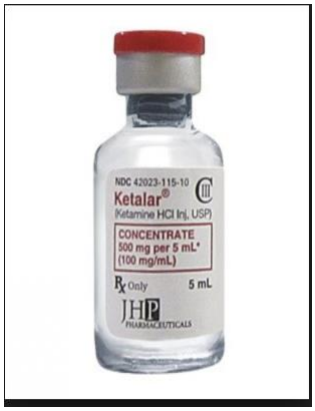
Etomidate

- Structurally unrelated to other anesthetic agent - has an imidazole ring, making it lipid soluble.
    - Induction dose: **0.2 – 0.3 mg/kg**
- Injectable solution mixed with propylene glycol which can cause irritation on injection.
    - Lidocaine pre-administration will help.
- **Rapid onset** due to high lipid solubility and large non-ionized fraction
- Acts through binding to GABAA receptors
- decreases CMRO2, CBF and ICP while maintaining good CPP.
- **PONV is more common with Etomidate than with Propofol or thiopental**.
- Transiently inhibits 11-B-hyroxlase, an enzyme involved with production of steroids – **can cause adrenal suppression**.
- Inhibition lasts for 4 – 8 hours, worse with infusions
- **No analgesic effect** – doesn't inhibit the sympathetic response to laryngoscopy and intubation, as such should be accompanied with neuromuscular blocker.



Ketamine (Ketalar)

- is highly lipid-soluble phencyclidine derivative
- In US, sold as racemic mixture
    - Dose: ***
    - Several routes of administration: IV, IM, Oral, Rectal, epidural and intrathecal
- Mechanism through NMDA (N-Methyl-D-aspartate) receptor antagonism.
- NMDA receptor is an excitatory receptor found throughout CNS, and some areas of spinal cord
- **Causes analgesia** by blocking pain signals at spinal cord but also disassociating the signal between thalamus and limbic system.
- **Dissociative amnesia** – patient appear conscious (eye open, staring) but unresponsive to sensory input (pain, verbal, stimulus)
    - Unique property compared to other IV anesthetics
- Can causes **unpleasant emergence reactions** with hallucination, out of body experiences and fear.
- Stimulates sympathetic nervous system
- **Has minimal respiratory depression**
    - Causes potent bronchodilation
- Increases CBF, CMRO2, ICP. Normocapnia counteracts increased CBF
- Direct myocardial depressant but indirectly increases catecholamines resulting in increased blood pressure, heart rate and cardiac output.
- Relative contraindication in patients with space-occupying CNS lesions
- Preferred in **uncooperative and Pediatric patients**



Dexmedetomidine (Precedex)

- **Highly selective alpha-2 adrenergic agonist**
- **Sedation** and **analgesia** without much respiratory depression
- Alpha 2 receptors located presysnaptically and in locus ceruleus
- Decreases activation of downstream neuron
  - Half-life of 2 hrs.
    - Dose:
    - Loading dose: **0.5 – 1 mcg/kg over 10 minutes**
    - infusion dose: **0.2 – 0.7 mcg/kg**
- Sedation for awake fiberoptic intubation, regional anesthesia or as an adjunct to general anesthesia. In ICU, to wean patients off ventilator
- Pre-existing opioid tolerance or patient with OSA
- Good for PONV

- **Benzodiazepines**
  - Commonly used benzos are: **Midazolam** (Versed), **Diazepam** (Valium) and **Lorazepam** (Ativan)
  - All benzos have **anxiolytic, amnestic, sedative, hypnotic, anticonvulsant** properties. **NOT analgesic.**
  - Bind to same GABAa receptors as barbiturates but at different site on receptor
    - Similar to Propofol and barbiturates – decrease CMRO2, CBF, ICP.
    - Produce respiratory, cardiovascular and upper airway reflex depression
  - Usually given as premedication for sedation and anxiolysis before GA (general anesthesia). Also used for MAC – Monitored anesthesia care. Half-life of 3 hrs
  - Dose
    - Versed:
      - Premedication: **0.04 – 0.08 mg/kg IV (1-2 mg)**
      - Induction dose **0.1 – 0.2 mg/kg IV**
      - Infusion rate of **0.25 to 1 mcg/kg**
  - Unlike Propofol and barbiturates, sedation can be reversed by administration of flumazenil – specific competitive antagonist with high affinity for benzo receptors
    - Dose: 0.5 – 1 mg IV
    - Short acting than benzos – consider re-sedation

Drug	Induction 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-dependent respiratory depression (apnea in 25-35% of patients)	-Pain on injection (32-67%) -can be attenuated with lidocaine and with injection into larger veins -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-dependent 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	-Analgesic effects -Intrinsic myocardial depressant effects which may be unmasked with depleted catecholamines

Table 4.4 Cardiovascular effects of IV induction agents

Drug	Mean arterial pressure	Systemic vascular resistance	Cardiac output	Contractility	Heart rate	Intracranial pressure
Propofol	↓↓	↓↓	↓↓	↓↓	↓↓	↓
Thiopental	↓		↓	↓	↑	↓
Etomidate	–	–	–	–	–	↓
Ketamine	↑	↑	–	–	↑	↑

Table 4.3 Recommended drug dosages for common IV agents[a]

Benzodiazepines[b]	Induction agents
Midazolam 1–4 mg	Propofol 2–2.5 mg/kg (induction), 25–200 mcg/kg/min (infusion)
Diazepam 2.5–10 mg	Thiopental 3–5 mg/kg
Lorazepam 1–4 mg	Etomidate 0.2–0.5 mg/kg
Opioids (Bolus)[b]	Ketamine 1–2 mg/kg IV, 3–4 mg/kg IM (induction or bolus),
Morphine 1–5 mg	1–2 mg/kg/h infusion
Hydromorphone 0.2–0.5 mg	*Neuromusclular blockers*[c]
Fentanyl 25–100 mcg	Succinylcholine 1–2 mg/kg, 20 mg bolus for laryngospasm
Meperidine 25–50 mg	Rocuronium 0.6 mg/kg
	Vecuronium 0.1 mg/kg
	Cisatracurium 0.15 mg/kg
	Pancuronium 0.1 mg/kg

[a]Adult dosages: always start at low end of range and titrate up
[b]Titration ranges for premedication or intraop/post op bolus dosing
[c]Intubating dosages: divide by 3 for ED95, divide by 5 for maintenance bolus dosing

Maintenance

- Inhalational Anesthetic Agents – inhaled gases as pain relievers have been around since 1840s. Nitrous oxide was used for analgesia and sedation while diethyl ether was used for general anesthesia. Volatile anesthetics (vaporized liquids prepared to be inhaled) are synthesized and serve as current mode of inhalational anesthetic

- Mechanism of action is complex with multiple membrane protein and ion channels. Shown to affect GABA, NMDA, glycine receptor subunits
    - Benefits:
        - ♦ Rapid induction of anesthesia, rapid titratability and rapid emergence
        - ♦ Reliable amnesia, immobility and modest degree of muscle relaxation and blunting of adrenergic response to surgical stimulation

- Partial pressure of gas in the alveolus which will equilibrate with concentration in the brain is the most important factor
    - At higher altitudes with lower barometric pressure, the partial pressure in the alveolus will decrease, leading to decreased effect of inhalational anesthetics
    - Alveolar partial pressure is determined by input minus output at he alveoli.
        - ♦ Input – Inspired pressure, alveolar ventilation and anesthetic breathing circuit (short circuit, smaller loss through circuit absorption)
        - ♦ Solubility, cardiac output, alveolar to venous partial pressure difference
            - ➢ High soluble gasses = more gas in blood before CNS
            - ➢ High CO = larger tank before getting to CNS
- The most commonly used inhalational agents (**nitrous oxide, isoflurane, sevoflurane, and desflurane**)
    - **All are bronchodilators** (except for desflurane – irritating and might cause bronchospasm)
    - All agents cause **dose-dependent myocardial depression**, but offset by sympathetic nervous system activation
    - All agents cause **dose related decrease in blood pressure** by decreasing SVR (but maintain CO)
    - Dose-dependent depression of ventilatory response to hypercarbia and hypoxia
    - Preserved minute ventilation
    - Except of halothane, inhaled **anesthetics are not metabolized by body and eliminated by ventilation**
    - All but nitrous oxide can cause Malignant Hyperthermia
    - Currently most are used during maintenance phase but can be used during induction in pediatric cases since IV placement might not be possible with children.

MAC - minimum alveolar concentration – is commonly used to describe the dose of inhalational anesthetics. It is the alveolar concentration at 1 atm at steady-state concentration at which 50% of subjects do not respond to surgical incision.

- ➢ It provides a standard way of estimating anesthetic depth and comparing one agent to another.
- ➢ Mac of 1 = equivalent to ED50 – is a population average
- ➢ Mac normalizes different potencies of volatile agents
    - MAC values are additive between different inhalational agents
    - It is inversely proportional to potency (lipid solubility).

- MAC 0.3 – 0.4 = MAC-awake = awakening form anesthesia in absence of other agents
- MAC 1.3 = ED95 = blunting of response in 95% of patients
- MAC 1.5 = MAC_{BAR} Blocking of adrenergic response to surgical stimulus

MAC values can be increased or decreased for various factors.

Table 5.2 Minimum alveolar concentration (MAC) values

Agent	MAC (%)
Desflurane	6.0
Sevoflurane	2.05
Isoflurane	1.15
Halothane	0.75
Nitrous oxide	105

Table 5.3 Factors affecting MAC

Increased MAC	Decreased MAC
Children (from infancy to adolescence)	Premature infants and the elderly
Hypernatremia	Hypothermia
Cocaine or amphetamine intoxication	Pregnancy
Chronic alcohol use	Acute alcohol intoxication
MAO inhibitors	Opiates, benzodiazepines, barbiturates, clonidine, dexmedetomidine
Tricyclic antidepressants	

Volatile Anesthetics (Isoflurane, Sevoflurane, Desflurane): share many similar characteristics and side-effects:

- **Cardiovascular**: Depress myocardial contractility and cause peripheral vasodilation. Arterial BP is decreased in dose dependent form
- **Respiratory**: Tidal volume is decrease by volatile anesthetics. RR increases leading to stabilization for minute ventilation. Volatile anesthetics also produce bronchodilation
- **Cerebral** effects: reduce cerebral oxygen consumption. Hyperventilation reverses the cerebral vasodilation seen with these agents
- **MSK effects**: NMS blockers are potentiated
- **OB**: dose-dependent reduction in uterine smooth muscle contractility
- **PONV**: known to cause nausea and vomiting

- **Nitrous Oxide**: Commonly used as an adjuvant anesthetic
  - *Advantages*: Very cheap, Not a trigger for MH, insoluble in blood (rapid uptake and elimination)
  - *Disadvantages*: Can diffuse into air filled cavities and may cause air expansion (thorax, bowl, middle ear, ET tube balloons, Pulmonary blebs)

- **Isoflurane**: Highly pungent, 2nd most potent of clinically used agents (MAC 1.2%) vasodilation
  - *Advantage*: preserves flow-metabolism in the brain (CMO2 to CBF)
  - *Disadvantage*: Coronary steal – dilation of normal coronary arteries

- **Sevoflurane**: Half as potent as isoflurane (MAC 2.15%), potent bronchodilator,
  - *Advantage*: rapid uptake and elimination, sweet smelling,
  - *Disadvantage*: can cause fires, can form Carbon monoxide in esiccated CO2 absorbent. Can degrade in the presence of soda lime to produce Compound A – a nephrotoxin. Fresh gas flow should be maintained at least 1L/min.

- **Desflurane**: lowest blood: gas solubility coefficient (lower than Nitrous oxide), low potency (MAC 6.6%)
  - *Advantage*: Very fast uptake and elimination

- *Disadvantage*: Very pungent – can be very irritating to awake patient through the breathing mask. High vapor pressure, close to atmospheric pressure, making boil at room temperature. As a result, vaporizer is constructed differently.

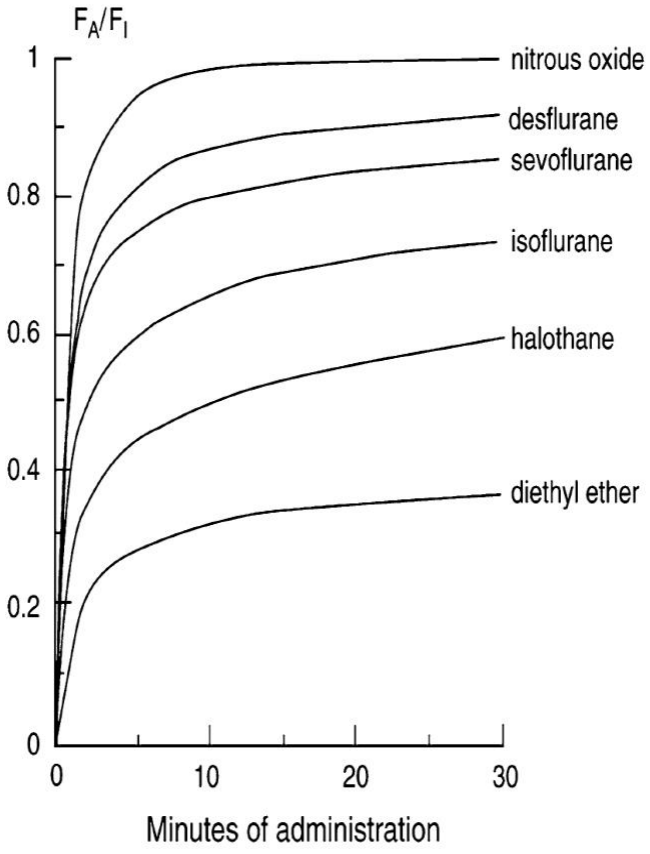


Figure 5.1 Ratio of concentration of anesthetic in alveolar gas to inspired gas. Graph shows how the ratio between the inspired (FI) and alveolar (FA) concentrations of inhalational anesthetics changes with time of administration. The least soluble drugs approach equilibrium (FA/FI) the fastest (From Modern Anesthetics: Handbook of Experimental Pharmacology, by Helmut Schwilden, Springer 2008. Used with Permission)

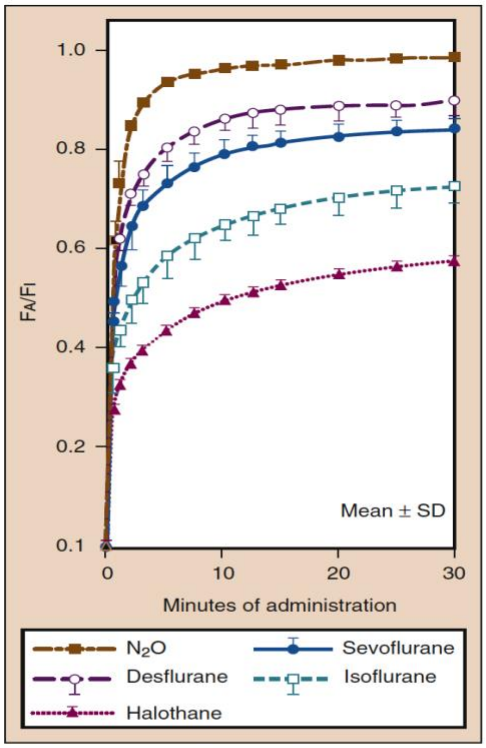


Fig. 7.5 The blood-gas partition coefficient is the principal determinant of the rate at which the alveolar concentration (FA) increases toward a constant inspired concentration (FI). The rate of induction of anesthesia is paralleled by the rate of increase in the FA. Despite similar blood solubility (see Table 7.1), the rate of increase of FA is more rapid for nitrous oxide (*dashed brownish-gold line*) than for desflurane (*dashed purple line*) or sevoflurane (*solid blue line*), reflecting the impact of the concentration effect on nitrous oxide (see Fig. 7.4). Greater tissue solubility of desflurane and sevoflurane may also contribute to a slower rate of increase in the FA of these drugs compared with nitrous oxide. *SD*, Standard deviation. (From Yasuda N, Lockhart SH, Eger EI II, et al. Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesth Analg*. 1991;72:316-324, used with permission.)

Know these numbers!

Gas	Vapor Pressure (mmHg)	Blood gas solb coef	MAC %
N2O	38,770	0.47	105
Desflurane	669	0.42	6.0
Sevoflurane	157	0.65	2.0
Isoflurane	238	1.4	1.2
Halothane	243	2.4	0.75
Enflurane	172	1.9	1.68

OPIOIDS

- Commonly used **morphine**, **hydromorphone** (Dilaudid), **fentanyl** and its derivates and **meperidine** (Demerol)

- **Mechanism of Action**
  - Analgesia is produced by Mu opioid receptor agonism in the brain at the periaqueductal gray matter and spinal cord (substantia gelatinosa) via Mu, Kappa and Delta receptors.
    - Lead to neurotransmitter inhibition vis inhibition of ACH and substance P release.
    - Endogenous endorphins normally bind to these receptors to provide pain relief

- IV Opioids are important means of pain control in surgical patients intraoperatively. There is an increased effort of multi-modal pain control to reduce reliance on opioids and derivatives.
    - Short acting opioids such as fentanyl used for pain control intraoperatively
    - Longer acting opioids such as morphine and hydromorphone used for postoperative pain

Table 4.2 Dose, time to peak effect, and duration of analgesia for commonly used perioperative opioids

Opioid	Dose[a] (mg)	Peak (min)	Duration (h)
Morphine	10	20–30	3–4
Meperidine	80	5–7	2–3
Hydromorphone	1.5	15–30	2–3
Fentanyl	0.1	3–5	0.5–1
Sufentanil	0.01	3–5	0.5–1
Alfentanil	0.75	1.5–2	0.2–0.3
Remifentanil	0.1	1.5–2	0.1–0.2

[a]Approximately equianalgesic dosages

Morphine – Least lipid-soluble opioid, long onset to peak time, providing prolonged analgesia. Used for post-op pain control, not used in acute surgical setting

- Can cause histamine release and bradycardia

Hydromorphone – Post -op pain control due to longer duration of action, used towards the end of a case for smoother wakeup. Peak effect in 15 minutes, used for cases with constant surgical stimulation. Titratable like fentanyl.

- No histamine release

Meperidine (Demerol) – reserved to treat shivering upon emergence. Structurally similar to atropine. Commonly in younger patients

- Anticholinergic side effects: tachycardia, causes histamine release, has euphoric effect with less respiratory depression than other opioids
- Avoid in patients on MAO inhibitors – hyperthermia, seizures

Fentanyl – rapid-acting synthetic opioid – 100 x more potent than morphine. Frequently used during induction to blunt sympathetic response to laryngoscopy. Cheap and easily titratable.

- **Sulfentanil and Alfentanil** – both analogues of fentanyl, used during significant intraoperative stimulation (i.e. Mayfield head pins, rigid bronchoscopy)
  - Sulfentail is 5-10 times more potent than fentanyl.
  - Alfentanil is ultra-short-acting duration (5-10 min) and onset (fastest acting opioid) with 25% potency of fentanyl.

Remifentanil – commonly used for infusion when significant intra-op stimulation but minimal post-op pain is expected. Similar potency as fentanyl.

- No context sensitivity of half-life, broken down by plasma esterases
- Does not accumulate and only lasts 5-10 minutes irrespective of infusion duration.
- Infusion rate: **0.05 – 0.1 mck/kg/min**

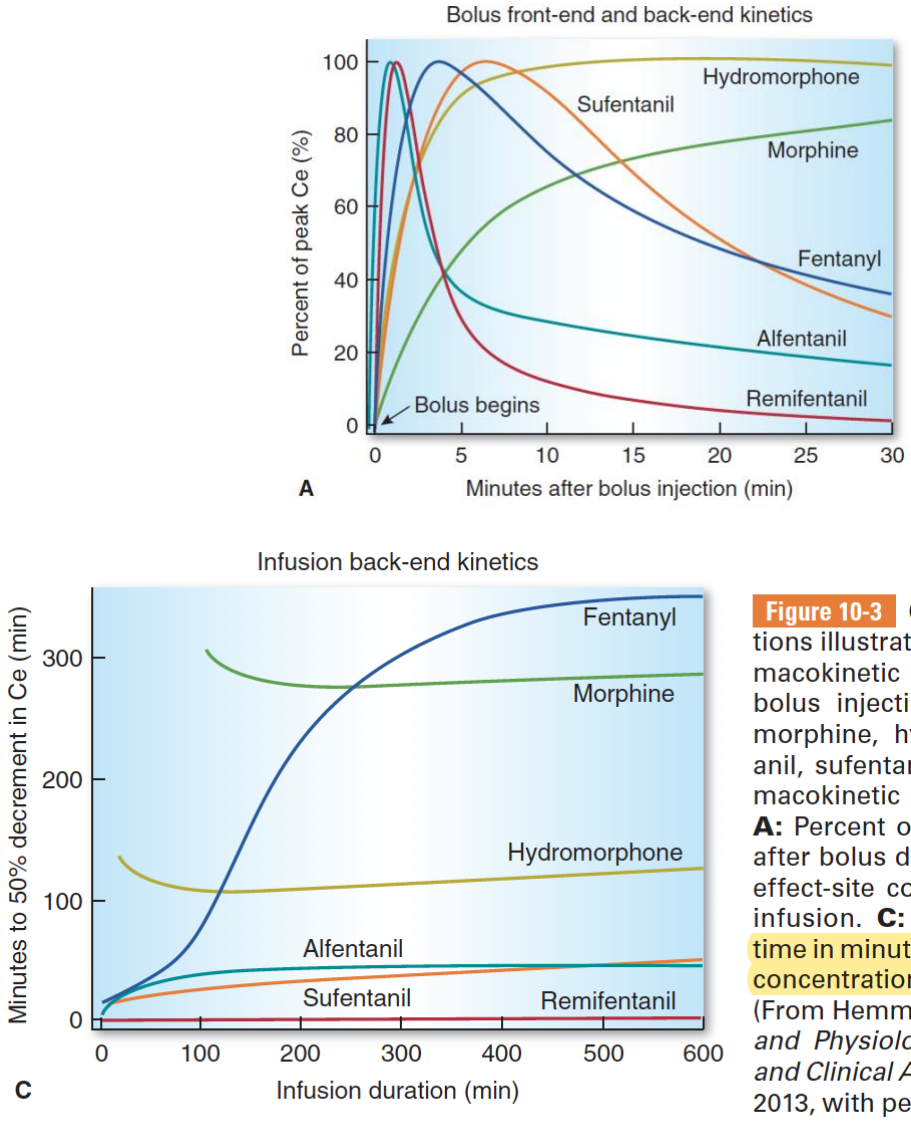


Figure 10-3 Opioid pharmacokinetics. Simulations illustrating front-end and back-end pharmacokinetic behavior after administration by bolus injection or continuous infusions for morphine, hydromorphone, fentanyl, alfentanil, sufentanil, and remifentanil using pharmacokinetic parameters from the literature. **A:** Percent of peak effect-site concentrations after bolus dosing. **B:** Percent of steady-state effect-site concentrations after beginning an infusion. **C:** Context-sensitive half-time, or time in minutes to a 50% decrease in effect-site concentrations after an infusion is stopped. (From Hemmings HC, Egan TD. *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application*. Philadelphia: Elsevier; 2013, with permission.)

Side effect profile

- Sedation – respiratory depression
  - Major Side-effect – naloxone (Narcan) at the ready (0.04 – 0.4 mg every 2 minute)
  - Decrease hypoxic drive to breath and increase apneic threshold (CO_2 level)
- Ileus – peripheral opioid receptors in the GI tract
  - Methylnaltrexone – peripheral opioid receptor antagonism
- Itching, nausea, urinary retention
- Bradycardia, hypotension – when given with other anesthetics (Hemodynamically stable when given alone)
- Miosis (pin point pupils)
- Chest wall rigidity – mainly fentanyl

Local Anesthetics

- Cell membrane of nerves contain sodium and potassium channels that help with the propagation of electric signals. Local anesthetics exert effect by preventing the activation of voltage gated sodium channels, inhibiting membrane depolarization.
  - Local anesthetics preferentially bind to sodium channels in the **open** or **inactivated state**.
  - Fiber size and type: Peripheral nerves contain myelinated A and Ba fibers and unmyelinated C fibers.
  - Differential conduction blockage

    - Sympathetic fibers > Pain/Temp fibers > Motor/pressure/ Proprioceptive fibers.

    - Patients might have incomplete blockage of motor and pressure despite sympathectomy and blockage of pain sensation
    - At physiological PH, local anesthetics are at equilibrium lipid soluble, (neutral form) and charged form (water soluble)
      - Neutral form – cross neuronal membrane
      - Ionized form – binds to alpha subunit of sodium channels

- Factors that affect mechanism
  - **PH** – most local anesthetics are weak bases.
    - pKa closer to physiologic PH – **Faster Onset**
      - Implies greater concentration of neutral, lipid soluble form, able to cross neuronal membrane
    - Necrotic tissue, with local acidosis – **Slower onset**
      - pKa further from physiologic PH, more ionized form, slower onset and less sensitive to local anesthetic action
  - **Epinephrine** – formulated in lower pH (4-5) SINCE IT IS INSTABIE IN ALAKLINE environments
    - Low pH slows onset of local anesthetic action
    - Causes local vasoconstriction and slows absorption – affects mostly shorter-acting locals (lidocaine) and not long acting (bupivacaine and ropivacaine)

- **Dived into 2 structural categories**
  - **Amides** – (lidocaine, mepivacaine, prilocaine, ropivacaine, bupivacaine) metabolized by cytochromes in the liver

- **Esters** – (procaine, tetracaine, cocaine, 2-chlorprocaine) metabolized by pseudocholinesterase in plasma (except for cocaine, partially metabolized by liver)

- Systemic absorption depends on administration dose and rate of absorption.
  - IV > tracheal > intercostal > caudal > epidural > brachial plexus > sciatic > subcutaneous injections
  -

Local Anesthetic side effects/toxicity

- **CNS** – First sign of local anesthetic toxicity – lightheadedness, perioral or tongue numbness or metabolic taste –> CNS excitation (block inhibitory pathways) – CNS depression, Seizure - Coma
- **Cardiovascular** – if high concentration, can bind to myocardial sodium channels. – cardiac arrhythmias, depressed contractility, and cardiac arrest. Bupivacaine is more cardiotoxic (High potency agents have greater cardiotoxicity than lower potency agents)
- **Neurotoxicity**
- **Hypersensitivity/Allergy** – true allergy is exceedingly rare. Sensitivity to metabolize – PABA – para-aminobenzoidc acid – often as a result of esters. If so, switch to amides

Treatment of Local Anesthetic Toxicity –

- Stop local anesthetic
- Given benzos for seizure
- Begin ACLS, CPR, secure airways
- Avoid vasopressin, Ca channel blocker, beta blockers
- Start early infusion of 20% lipid emulsion solution (Intralipid) reported to be effective in reversing symptoms. Local anesthetic will be sequestered in the lipid emulsion and removed.
  - 20% 1.5 ml/kg, followed by 0.25 ml/kg/min (up to 60 min)

Table 6.2 Properties of common local anesthetic agents

	Agent	Onset of action	pK_a (36 °C)	Max dose (mg/kg)[a]	Duration of action (h)
Amides	Lidocaine	Rapid	7.8	4.5 (7 with epi)	1–2
	Mepivacaine	Moderate	7.7	5 (7 with epi)	1.5–3
	Prilocaine	Slow	8.0	6 (9 with epi)	1–2
	Ropivacaine	Slow	8.1	2.5 (3 with epi)	4–8
	Bupivacaine	Slow	8.1	2.5 (3 with epi)	4–8
Esters	2-Chloroprocaine	Very Rapid	9.1	9 (15 with epi)	0.5–1
	Procaine	Rapid	8.9	7 (10 with epi)	0.75–1
	Tetracaine	Slow	8.4	1.5(2.5 with epi)	3
	Cocaine	Rapid	8.7	1.5	0.5

[a]Maximum dose for a single subcutaneous injection

Neuromuscular Blocking Drugs

- Muscle relaxants are used during general anesthetic to provide improved surgical and anesthetic environments. Example – help with tracheal intubation, allow for abdominal closure and help with decreasing movement during Neurosurgery. There are two classes of paralytics to based on mechanism of action at the neuromuscular junction.

Agent	ED95 (mg/kg)	Intubating Dose (mg/kg)	Onset (min)	Duration to 25% recovery (min)	Intra-op Mainenance	Metabolism / Excretion
Succinylcholine	0.3	1	1-1.5	6-8	Rarely done	plasma cholin-esterase
Rocuronium	0.3	0.6	1.5-2	30-40	0.1 -0.2 mg/kg prn	Liver
		RSI 1.2	1	>60 min		Bile + Urine
Vecuronium	0.05	0.1 -0.2	3-4	35-45	0.01 -0.02 mg/kg prn	Liver
						Bile + Urine
Cisatracurium	0.05	0.15-0.2	5-7	35-45	0.3 mg/kg q20min prn	Hoffman elimination

Adopted from Table 20-2, Ch 20, Barash Clincial Anesthesia 6th edition

- **Depolarizing**: Succinylcholine is the only available depolarizing NMB on market. It's a two ACH molecule joined by methyl group that works as ACh receptor agonist a neuromuscular junction. This causes depolarizing and prevention of junctional repolarization since the drug isn't metabolized by native acetylcholinesterases, prolonging depolarization.
  - Dose
    - Intubating dose**: 1-1.5 mg/kg**
      - Onset: **30 – 60 sec**
      - Duration: **10 min** (often used in rapid sequence induction and intubation)
  - Metabolized by pseudocholinesterase after diffusing away to the extracellular fluid
  - 1:3000 patients have a homozygous abnormal plasma cholinesterase, which can predispose patients to a prolonged paralysis, lasting 3 – 8 hours

Contraindication – Hyperkalemia (since induction causes an increase in K+), upregulated junctional and extra junctional cholinergic receptors (burn injury, muscular dystrophy, myotonia, crush injury), history of malignant hyperthermia. Increased potassium can lead to fatal arrhythmias

- cannot be reversed by acetylcholinesterase inhibitors.

Table 4.5 Contraindications to succinylcholine use
Elevated serum potassium levels (>5.5 meq/L)
History of burn injury
History of denervation injury
Known or suspected myopathy
Known or suspected risk for malignant hyperthermia
Known pseudocholinesterase deficiency

❖ Non-Depolarizing:

- Four most commonly used with intermediate duration are (rocuronium, vecuronium, cistracurium)
- competitively inhibiting ACh from binding to **postsynaptic nicotinic receptors**. This results in inhibition of junctional depolarization
- NMBs are commonly used to maintain muscle relaxation during surgery due to their longer duration of action.
  - Rocuronium<vecuronium<cistaracurium<pancuronium = onset time/duration

➢ **Pancuronium** – on of the oldest non-depolarizing muscle blocker (NMBAs) – has Vagolytic effects as well as direct sympathomimetic effects – blocking norepinephrine presynaptic reuptake. High potency with slow onset of blockage. – mostly obsolete due to risk of postop residual weakness.

➢ **Vecuronium** – intermediate duration NMBA – devoid of cardiovascular effect – more potent than rocuronium – onset is slower – No longer used for Rapid sequence intubation – RSI since rocuronium

➢ **Rocuronium** – low potency, high plasma concentration after bolus administration, duration of action is shorter, low risk of accumulation with renal and hepatic metabolism, more hemodynamically stable, no histamine release and rare allergic reactions. In high doses (1.2 mg/kg) can be used for RSI.

➢ **Cisatracurium** – developed to reduce histamine release.

Reversal of NMBs is accomplished by administration of acetylcholinesterase inhibitor (neostigmine), preventing the breakdown of ACh at the NMJ. The increase concentration of ACh is then able to out-compete the paralytics.

- Anticholinergics such as **glycopyrrolate** must be co-administered to prevent excess activation of parasympathetic leading to bradycardia, asystole, or bronchospasm.

❖ Cisatracurium is degraded in plasma unlike other NMBs (**Hoffman elimination**), which are rely on biliary and renal excretion. Commonly used in patients with hepatic or renal failure.

- Twitch monitors, electrodes placed at the ulnar or facial nerve, help give us feedback on the response to Non-depolarizing agents. Different patient will have wide range of responses. Furthermore, twitch monitors are used to assess the degree of muscle paralysis or reversal of paralysis towards the end of surgical procedure. Response is assess with sight and feel often times (or recording – more accurate)
  - NMBA Monitoring
    - **TOF Ratio** – train of four ratio between 4th and 1st twitch – high-voltage stimulation pulse (2 Hz) spread over 2 seconds – most commonly used. Only four twitches used since ACh will be successively depleted. TOF = 0.9 is considered fully strong. TOF = 0.5 – indicates partial blockade.
    - **Tetanic** – rapid continuous stimulation at 50 Hz (or 100 Hz) pulses for 5 seconds -
    - **Double burst**
    - **Single Twitch**

Depolarizing vs Nondepolarizing NMBA Monitoring

Normal Stimulus	Depolarizing Block		Nondepolarizing Block
	Phase I	Phase II	
Train-of-four	Constant but diminished	Fade	Fade
Tetany	Constant but diminished	Fade	Fade
Double-burst (DBS)	Constant but diminished	Fade	Fade
Posttetanic potentiation	Absent	Present	Present

An aside about sux:

Phase I block is typical for a single bolus of sux.

Sux can cause a **Phase II** block at high or repeated doses and with with prolonged infusions.

N.B. Neostigmine will potentiate a phase I block but will reverse a phase II block if there is a low enough concentration of sux left.

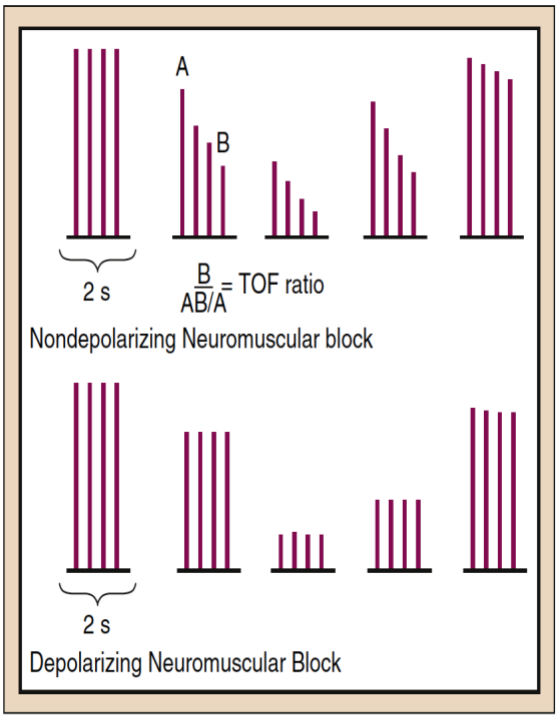


Fig. 11.8 Schematic illustration of the mechanically evoked response to train-of-four (TOF) electrical stimulation of the nerve after injection of a nondepolarizing neuromuscular blocking drug (upper panel) or a depolarizing (succinylcholine) neuromuscular blocking drug (lower panel). The TOF ratio, given by the relation of the first response (upper panel) to the fourth (lower panel), is less than 1 (fades) only in the presence of (upper panel) effects at the neuromuscular junction produced by a nondepolarizing neuromuscular blocking drug. (Modified from Viby-Mogensen J. Clinical assessment of neuromuscular transmission. *Br J Anaesth.* 1982;54:209-223, used with permission.)

Agent	ED95 (mg/kg)	Intubating Dose (mg/kg)	Onset (min)	Duration to 25% recovery (min)	Intra-op Mainenance	Metabolism / Excretion
Succinylcholine	0.3	1	1-1.5	6-8	Rarely done	plasma cholin-esterase
Rocuronium	0.3	0.6	1.5-2	30-40	0.1 -0.2 mg/kg prn	Liver
		RSI 1.2	1	>60 min		Bile + Urine
Vecuronium	0.05	0.1 -0.2	3-4	35-45	0.01 -0.02 mg/kg prn	Liver / Bile + Urine
Cisatracurium	0.05	0.15-0.2	5-7	35-45	0.3 mg/kg q20min prn	Hoffman elimination

Adopted from Table 20-2, Ch 20, Barash Clincial Anesthesia 6th edition

Table 4.6 Neuromuscular blocking drugs

Drug	Onset	Duration (min)	Mode of elimination	Important notes/ side effects
Succinylcholine	30–45 s	5	Plasma cholinesterase	Increased duration in pts with pseudocho-linesterase
Cisatracurium	2–4 min	30–40	Hoffman degradation	Deficiency
Vecuronium	2–4 min	30–40	Liver/renal	Few side effects
Pancuronium	4–6 min	120–180	Liver/renal	Can cause tachycardia & hypertension
Rocuronium	1–2 min	30–40	Liver/renal	May be used for rapid sequence induction if succinylcholine contraindicated

❖ **Acetylcholinesterase inhibitors** - Neostigmine and Edrophonium
Reversal of neuromuscular blockade
Prevent breakdown of ACh at NMJ

❖ **Cholinergic crisis** – overdose of acetylcholinesterase inhibitors – bradycardia, bronchospasm, vomiting, miosis and muscle weakness.

SLUD CB2:

- Salivation
- Lacrimation,
- Urination,
- Diarrhea
- Ciliary constriction (miosis)
- Bronchospasm, Bradycardia.

❖ **Anticholinergics** – Atropine and Glycopyrrolate

- Used to counteract the sideffects of paralytic reversal agents – mainly brachycardia and bronchospasm.
- Based on comparable duration of action, these combinations are used.
  - Neostigmine and glycopyrrolate are paired for slower onset and longer acting
  - Edrophonium and atropine (quicker onset, shorter acting).
- Atropine unlike glycopyrrolate, can cross the blood brain barrier and can cause central anticholinergic syndrome. Symptoms include delirium, excitation fever, flushing, and tachycardia.
  - Counteract with Physostigmine (CNS acting acetylcholinesterase inhibitor) – increase ACH in the CNS, restoring blockage of cholinergic activity in the CNS.

Central Anticholinergic Syndrome:

- Blind as a bat (Blurred vision)
- Red as a beet (Flushing)
- Dry as a bone (Anhydrosis)
- Fast as a hare (Tachycardia)
- Mad as a hatter (Delerium)

❖ Pharmacology of Adjunct Agents (Ephedrine, Phenylephrine, Norepinephrine, Dopamine)

Table 7.1 Actions of vasoactive receptor sites

Receptor	Receptor site action
α-1	Glycogenolysis, gluconeogenesis, constricts vascular smooth muscle, relaxes GI tract
α-2	Constricts vascular smooth muscle, decreases insulin secretion and norepinephrine release
β-1	Increases heart rate and contractility, secretion of renin
β-2	Glycogenolysis, gluconeogenesis, relaxes vascular smooth muscle and bronchioles
Δ-1	Increases renin release, dilates vascular smooth muscle
Δ-2	Constricts smooth muscle, inhibits norepinephrine release

Table 7.2 Receptor actions of commonly used vasopressors

Drug	Direct	Indirect	Site of action
Ephedrine	+	++	α, β
Phenylephrine	+		α
Norepinephrine	+		α, β
Dopamine	++	+	α, β, D (dopamine receptor)

Table. 7.3 Vasopressor dosing

Ephedrine	2.5–10 mg IV bolus
Phenylephrine	40–100 mcg IV bolus or 20–150 mcg/min infusion
Norepinephrine	0.01–0.1 mcg/kg/min infusion
Dopamine	2–20 mcg/kg/min infusion

- Antiemetics

Table 7.4 Commonly used antiemetics[a]

Ondansetron (Zofran)	4 mg IV, may repeat × 1 (0.1 mg/kg up to 4 mg in children)
Dolasetron (Anzemet)	12.5 mg IV, may repeat × 1
Granisetron (Kytril)	0.5–1 mg IV
Promethazine (Phenergan)	12.5–25 mg IV, may repeat × 1
Dexamethasone (Decadron)	4–8 mg IV, best given early during intraoperative period
Droperidol (Inapsine)[b]	0.625 mg IV, may repeat q 10 min × 3

[a]All dosages for adults unless noted
[b]Must monitor ECG for 2 h post administration

- Basics of Residency and beyond
  - What anesthesiologist do
    - OR, ICU, Outpatient surgery, (MRI, Cardiac Catch, GI labs), Pain clinic
    - General Anesthesia, Regional (epidural, nerve blocks), PACU, ICU
    - Anesthesiology training
      - CA-3 = PGY-4
      - Advanced (less common) vs Categorical programs vs combined programs (Ans-peds, Ans-Med)
      - Exams: ITE (In-Training Exam), ABA
      - Board exam: Part 1 taken after completion of CA-1-year, graduate from residency – take part 2 of written exam, first available oral exam (April or October)
      - ACGME approved fellowships (cardiac, cortical care, OB, pain, Pediatric – pediatric sub specialty – cardiac, pain/palliative care, regional, research); Non-ACGME – Regional, Liver, Research, Informatics

Intravenous Anesthetics

Intravenous Anesthetics	Onset	Elimination	Pharmacokinetics	Advantages/ Use	Disadvantages
Barbituates (H&A) -Thiopental -Methohexital -Thiamylal	30-40 sec	 -10-12 hrs - 3-6 hrs	Redistribution	Rapid onset Fast recovery Anesthesia for short procedures.	No analgesia Alkaline/Tissue Irritant. Resp & CV depression Low TI OD risk
Benzodiazepines (H&A) -Diazepam -Midazolam -Lorazepam	3-5 min	 -20-40 hrs -2-6 hrs	Demethelated in the Liver. (prolonged t1/2 with cirrosis, etc)	Relative rapid onset Minimal resp and CV depression Preanesthetic	Not a good analgesic Can't produce surgical analgesia
Dissociative (H&A) -Ketamine		-2-3 hrs		Intense analgesia and amnesia Radiological procedures in children, Bronchodilator	Dissociative anesthesia (II) unpleasant recovery w/ hallucinations and nightmares
Miscellaneous (H&A) -Etomidate -Propofol	 ≈1 min 40-50 sec	 4-8hrs 3-6hrs	 Large volume of distribution, highly lipophilic	 Prevents N/V, quick recovery	 Hypotension, cv depression, requires mechanical ventilation, discoloration of urine (green)
Opioids **(A)** -Morphine -Fentanyl -Meperidine (Demerol) -Sufentanyl		 2-7 hrs 3-4 hrs 2-4 hrs		Minimal CV effects at normal dosages	Dose related cardiac depression. Meperidine-cardiac depression

Pharm Charts

Inhalational Anesthetics

Inhalation Anesthetics	Major Advantages	Primary Use	Toxicity/concerns
Nitrous Oxide	No odor Fast induction and recovery Minimal cardiopulmonary depression Good analgesic	Minor surgery Used in combination with general anesthetics for general anesthesia	Acute-N/V Chronic-inhibition of B12 metabolism and induction of B12 DEFICIENCY
***H*alothane**	Pleasant odor Slower induction and recovery	Most widely used pedi anesthetic world wide. Asthma patients (no bronchoconstriction)	Slow induction/recovery Sensitizes myocardium to catecholamines→Vent. Arrythmias ***H***epatotoxicity
Enflurane	Pleasant odor Less S.E. than Halothane	Adults	Hypotension Seizures @ high [ ] Nephrotoxicity
Isoflurane	Stable cardiac rhythm Rapid onset/recovery Minimal metabolism→low tox potential Excellent Muscle relaxant	Most widely used anesthetic in adults.	Pungent odor (not great for kids) Broncho-irritant
Desflurane	Rapid onset/recovery High potency (least soluble) Even less metabolism	Ambulatory surgery (for rapid recovery)	Very pungent Irritating to airways LARYNGOSPASM Expensive$$$
Sevoflurane	Fast induction/recovery High potency (least soluble) Nonirritating vapor	Outpatient anesthesia Inhalation Induction (especially children)	
Methoxyflurane			Renal Toxicity