CHAPTER 5

Anesthesia Pharmacology

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5.1 Pharmacology Pearls

The metabolic, cardiovascular, and pulmonary function differences between a patient with ideal body weight (IBW) and morbid obesity is clear. Because these differences affect the apparent volume of distribution of some drugs, there is increased risk of anesthesia in the morbidly obese. As drug dosages based on total body weight (TBW) can result in overdose, conversely, administration of drugs based on IBW can result in subtherapeutic doses.

Drugs That Need to Be Given in Ideal Body Weight

IBW is the difference between TBW and fat mass.

Propofol—induction dose

Rocuronium

Vecuronium

Remifentanil

Morphine

Alfentanil

Sufentanil—maintenance dose

Sugammadex (IBW + 40% excess weight)

Formula for IBW:

Males: 50 kg + 2.3 kg for each inch above 5 feet

Females: 45 kg + 2.3 kg for each inch above 5 feet

Drugs That Need to Be Given in Total Body Weight

TBW

Propofol—maintenance dose

Succinylcholine

Neostigmine

TIVA anesthetic

Midazolam

Atracurium

Cisatracurium

Fentanyl

Sufentanil—induction dose

Thiopental

5.2 Volatile Anesthetics

Inhalational agent pharmacokinetics is divided into four phases: absorption, distribution to the brain, metabolism, and excretion. The ultimate goal is to establish a particular partial pressure of an agent in the alveoli (P_A), which will equilibrate to attain a therapeutic tissue concentration with the brain to produce an anesthetized state.

Uptake and Distribution

Partial pressure of agent in alveoli (P_A) is determined by delivery minus loss. It is a reflection of partial pressure of agent in brain.

- Delivery affected by: inspired partial pressure, alveolar ventilation
- Uptake affected by: solubility, cardiac output, alveolar-to-venous partial pressure difference
- *The relative solubilities of anesthetic in air, blood, and tissues are expressed as partition coefficients. The greater*

TABLE 5-1 Alpha Beta Dopa Chart

Receptors	Tissue	Actions	Agonist	Antagonist
Alpha 1	Smooth muscle constriction: vascular, iris, uterus, bladder sphincters, heart Pupil Smooth muscle- gastrointestinal	α1: STIMULATORY RESPONSE *Vasoconstriction, inrecreased peripheral resistance *Increased BP *Inotrope (*activation increases intracellular calcium ion → concentration muscle contraction*) *Increase bladder sphincter *Decrease splanchnic flow *Mydrias is (dilates pupil) *Pancreas-insulin inhibited *Liver-hepatic glycogenesis * GI relaxation	Norepinephrine ++++ Epinephrine +++ Phenylephrine +++ Dopamine ++ Ephedrine ++	Treat HTN and BPH: **Selective antagonists:** Minipress Hytrin Cardura Flomax Prazosin **Nonselective antagonists:** Phentolamine = Phenoxybenzamine
Alpha 2	Platelets, Adrenergic & Cholinergic pathways, Vascular smooth muscle, Coronary arteries, Kidney, Brain, Fat cells	α2: INHIBITORY RESPONSE *alpha 2 *NEGATIVE FEEDBACK LOOP* — decr NE release & SNS outflow	Dexmedetomidine ++++	Yohimbe

		α2 presynaptic: inhibits NE *Coronary artery vasodilation *Centrally sedates; anxiolytic **α2 postsynaptic:** *Coronary artery constriction *Promote excretion of Na+ & H_2O *Insulin inhibited (↑ BG) *Platelet aggregation *Inhibition of lipolysis *Deer BP + catecholamine levels	(1600/1 of alpha2/alpha 1) Clonidine +++ (200/1 of alpha2/alpha1) Norepinephrine +++ Epinephrine + Dopamine +	
Beta 1	Myocardium, SA Node, Ventricular conduction, Coronary arteries	β1: STIMULATORY RESPONSE * *Cardiac:* positive inotrope (increases contraction) and BP *Chronotrope (increases HR) *Increase myocardial demand *Dilates coronary arteries *Renin release	Isoproterenol ++++ Dobutamine +++ Epinephrine +++ Norepinephrine ++ Ephedrine ++ Dopamine ++ Dopexamine +	Atenolol Metoprolol Esmolol

continues

Alpha Beta Dopa Chart, continued

Receptors	Tissue	Actions	Agonist	Antagonist
Beta 2	Myocardium, SA Node, Smooth muscle Myocardial, Bronchial, Uterine and Vascular smooth muscle, Skeletal muscle, Renal	β2: presynaptic NE release accelerated *positive inotrope; chronotrope; some constriction β2: postsynaptic Epi sensitive *Reduces diastolic blood flow *Relaxation of bronchial and vascular smooth muscle *Renal vessel relaxation	Isoproterenol ++++ Dopexamine +++ Epinephrine ++ Norepinephrine ++ Ephedrine ++ Dopamine + Dobutamine + Terbutaline	Propranolol Esmolol Timolol Nadolol Labetalol (*Increase airway constriction*)
Dopa 1	Blood vessels: renal, coronary, mesenteric	*Dilates blood vessels * Increased RBF, glomerular filtration, diuresis	Fenoldopam +++ Dopamine +++ Dopexamine ++ Metoclopromide +	Haloperidol Droperidol Phenothiazine
Dopa 2	Renal & mesenteric vessels, Sympathetic nerves	*Modulates transmitter release – inhibits by *NEGATIVE FEEDBACK LOOP* — decrease NE release & SNS outflow	Dopexamine ++++ Dopamine +++	Domperidone

the Blood:Gas (B:G) coefficient, the greater the anesthetic solubility—the drug more easily leaves the alveoli and goes out to blood (pulmonary circulation) causing the alveolar partial pressure to rise more slowly and leading to a prolonged induction and emergence.

- *Insoluble agents are taken up by blood less avidly than a soluble agent—the alveolar partial pressure rises more quickly and induction and emergence are faster.*
- ***What speeds induction:** less solubility of inspired gas, increased concentration of volatile agent, high flows, increased minute ventilation, decreased cardiac output (the faster the rate of rise of alveolar concentration).*
- ***What slows induction:** greater the solubility of inspired gas, increased cardiac output (slows the rate of rise of alveolar concentration).*

Fast Induction----------Slow Induction
Desflurane > Nitrous Oxide > Sevoflurane > Isoflurane > Enflurane > Halothane
Decreased Solubility----------Greater Solubility

Inhaled Anesthetics

Inhaled anesthetic agent: nitrous oxide

Inhaled halogenated agents: desflurane, halothane, isoflurane, enflurane, and sevoflurane

- produce immobility via actions on the spinal cord, enhance inhibitory channels, and attenuate excitatory channels (GABA, NMDA, glycine, acetylcholine, serotonin); supraspinal mechanisms produce sedation, hypnosis, and amnesia.

Metabolism of Volatiles: ventilation is most important factor in elimination of all inhaled anesthetics though small amounts of metabolism occur via the kidneys and the cytochrome P-450 system in the liver. Inducing enzyme systems in the liver are not associated with increased metabolism of volatile anesthetics.

TABLE 5-2 Volatile Chart

		H	I	E	S	D	N
Odor		—	+	—	—	++	—
MAC in O_2		0.75	1.17	1.63	1.8	6.6	104
MAC w 70% N_2O		0.29	0.56	0.57	0.66	2.4	—
MAC > 65 yrs old		0.64	1.0	1.55	1.45	5.17	—
Oil:Gas Coefficient	Potency	224	91	97	47	19	1.4
Blood:Gas Coefficient	Solubility	2.5	1.46	1.9	0.65	0.42	0.46
Vapor Pressure @ 20°C *-Directly proportional to temp*	VP	243	238	172	157	669	38,770
Vapor Pressure / total ambient pressure	VP/760	32	31	23	21	88	51.0
Metabolism (kidneys, liver)	Metab %	20	0.2	2–3	2–5	0.02	0.004

H: halothane I: isoflurane E: enflurane S: sevoflurane D: desflurane N: nitrous oxide

Measures of Anesthetic Potency: Minimum Alveolar Concentration (MAC)

MAC mirrors the brain partial pressure of an agent and is an indicator of gas potency.

MAC—1 MAC is the end-expiratory concentration at which 50% of patients will not show a motor response to surgical incision (ED_{50}).

MAC awake—volatile: 0.3–0.5; N_2O: 0.6

MAC 95%—1.3

MAC BAR (Block Autonomic Response to noxious stimuli)—**1.5**

Note: MAC need is highest in 6-month-old child.

N_2O and Diffusion Hypoxia: nitrous oxide is eliminated more rapidly than O_2 and CO_2—this results in the dilution of O_2 and CO_2 as N_2O is escaping, resulting in hypoxia. Give 100% O_2 for 5 minutes after N_2O is discontinued to prevent diffusion hypoxia.

5.3 Sedation, Anxiolytic, Amnestic

Benzodiazepines (BZD): produce effects by stimulating receptors in CNS enhancing inhibitory effects of GABA (gamma aminobutyric acid).

Pro: decrease CBF/ICP/O_2 consumption, potent antegrade amnesia, good preoperative anxiolytic, increases seizure threshold—anticonvulsant, unconsciousness at

TABLE 5-3 Influence on MAC

Factors That Increase MAC	Factors That Decrease MAC
Hyperthermia (> 42 degrees C)	Hypothermia (MAC decreases 7% for each degree decrease in Celsius temperature)
Hypernatremia	Hypotension
Incr. levels of CNS excitatory transmitters i.e. (cocaine, amphetamines) - drug that increases central catecholamines, i.e., MAO inhibitors; chronic alcohol abuse	Hypercarbia
	CNS depressants; drugs that decrease central catecholamines
Red hair, esp. females	Anemia (Hgb < 5 g/dL)
Infant	Acute alcohol intoxication
High cardiac output	Elderly (after age 40 yo, MAC decreases 6%/decade of age)
	Pregnancy
	Hypoxia (PaO_2 less than 40 mmHg)
	Hypotension
	Benzodiazepines, clonidine, narcotics, lithium, ketamine, lidocaine

TABLE 5-4 Volatile Agents and Physiologic Response

	Halothane	Isoflurane	Enflurane	Sevoflurane	Desflurane	Nitrous
Cerebral						
Cerebral blood flow (CBF)	↑↑	↑	↑	↑	↑	↑
Intracranial pressure (ICP)	↑↑	↑	1% 0 3% ↑↑	↑	↑	↑
Cerebral metabolic rate (CMR)	↓↓	↓↓↓	↓	↓↓	↓↓↓	↓or↑
Seizures or EEG changes	no	no	yes	no	no	no
Cardiovascular						
Contractility—myocardial depression	↓↓	↓	↓↓↓	↓	↓↓	s1. ↓
BP	↓↓	↓↓↓	↓↓↓	↓	↓↓	0
HR	0↓	↑	↑	0↓	↑ or sl. ↓	0
SVR	0	↓↓	↓	↓	↓↓	0
CO	↓↓	sl.↓	↓↓	↓	↓	0
Coronary vasodilator	yes	yes!	↑	sl. ↑	yes	yes
Respiratory						
Tidal volume	↓	↓	↓↓	↓	↓	↓

Respiratory rate	↑↑	↑	↑↑	↑	↑	↑
$PaCO_2$	↑↑	↑↑	↑↑	↑	↑↑	0
Apneic threshold	blunts	blunts	blunts	-	blunts	blunts!
Bronchodilator	yes	yes	yes	potent	no	-
Pulmonary vascular resistance	0	0	0	0	0	increase
NEUROMUSCULAR						
NDMRelaxant	potentiates	potentiates!	potentiates!	potentiates	potentiates!	sl. ↑
Skeletal muscle	relaxes	relaxes	relaxes	relaxes	varied	0
Renal						
Blood flow	↓	↓	↓↓	sl. ↓	↓	↓
GFR	↓	↓	↓↓	↓	sl. ↓	↓
Urinary output	↓	↓	↓↓	↓	↓	↓
Analgesia	0	0	0	0	0	mild
Malignant hyperthermia trigger	yes	yes	yes	yes	yes	no
"0"=no change; "-"=not known						

TABLE 5-5 Guedel Sleep Chart

Stage I	**Sedation stage** - getting sleepy. Will respond to verbal stimuli. Tolerates pain.	Respiratory: regular/voluntary Muscle tone: normal Eye movement: normal Pupil size: normal Eye and larynx reflexes: normal	 normal
Stage II	**Delirium stage** - want to get through this stage - patient can get agitated and can hurt self or others. Loss of consciousness.	Respiratory: irregular/ spontaneous Muscle tone: tense Eye movement: dysconjugate Pupil size: dilated/gets bigger Eye and larynx reflexes: tearing, swallowing, LARYNGOSPASM	 disconjugate dilated
Stage III	**Anesthesia stage** - desired depth for general anesthesia. "loss of lash"	Respiratory: regular/deep Muscle tone: Ø Eye movement: Ø Pupil size: constricted/ convergent Eye and larynx reflexes: Ø	 constricted
Stage IV	**Overdose** - decrease volatile agent dose.	Respiratory: apnea Muscle tone: flaccid Eye movement: Ø Pupil size: fixed/dilated Eye and larynx reflexes: Ø	 fixed/dilated

higher doses. Wide therapeutic index with a low incidence of toxicity. Not analgesics.

Con: no burst suppression, some circulatory depression and hypotension—can cause significant hypotension if patient hypovolemic, depresses ventilatory response to CO_2, small doses may cause apnea/respiratory arrest, produces upper airway reflex depression, nonanalgesic, no muscle relaxation.

Reversal: Flumazenil

TABLE 5-6 Benzodiazepines

	Diazepam (Valium)	**Midazolam** (Versed)	**Lorazepam** (Ativan)	**Remimazolam**
Dose	IM or IV: 2 to 5 mg or 5 to 10 mg × one dose	IV: 0.1–0.2 mg/kg or 1–3 mg at a time titrated	PO: 0.5–1 mg IV 0.1 mg/kg, Max 4 mg/dose	0.075 mg/kg
Onset / Elim ½-life	1–2 mins / 20 hrs LDOA	0.5–2 min / 1–4 hrs	PO 30–60 mins / 10-20 hrs IV 1–3 mins / 6-8 hrs LDOA	1–3 min / USDOA - shorter than midazolam
Metabolism Excretion	hepatic microsomal enzymes to *2 active metabolites:* desmethyldiazepam and oxazepam both with LDOA	liver hydroxylation; active metabolite. Excreted in urine.	Glucuronide to inactive metabolites	rapidly metabolized to an inactive metabolite by tissue esterases (organ independent)

continues

Benzodiazepines, continued				
	Diazepam (Valium)	**Midazolam** (Versed)	**Lorazepam** (Ativan)	**Remimazolam**
Notes	Burns on injection because it's mixed with propylene glycol	Water-soluble; does not cause pain on injection. 2–3× as potent as diazepam. Can have respiratory depression.	Strong amnestic, Anticonvulsant. Can have excessive sedation. 5–10× as potent as diazepam.	Combines properties of remifentanil and midazolam *In Phase III clinical trials; developed for procedural sedation & general anesthesia. Works on $GABA_{alpha}$ receptor; can be reversed with flumazenil. Higher clearance and smaller volume of distribution than midazolam.*

TABLE 5-7 Sedation–Other

	Droperidol (Inapsine)	Methohexital (Brevital)
Action	Dopamine antagonist	Barbiturate
Dose	0.6–2.5 mg Sedation up to 10 mg	2 mg/kg doses to effect; induction: 50–120 mg, 20–40 mg q4–7 mins Rectal suppository:
Onset / Duration	3 mins / 2–4 hrs – sedation up to 12 hours	IV: immediate; rectal: 5–11 mins / USDOA 5–10 mins
Metabolism Excretion	Liver and kidney	Liver, kidney, brain
Contraindicated	Parkinsonism, pheochromocytoma, head Injury, long QT on EKG. Give cautiously in patients with liver or kidney disease.	Acute intermittent porphyria (AIP), asthma, CV instability; caution with liver impairment.
Notes	Elongates QT with possible torsade de pointes, use as sedative, neuroleptic, antiemetic. Not amnestic.	Amnestic; 2–3× more potent with faster onset and recovery time as pentothal. See excitatory phenomenon. Can cause hypotension, seizures, vascular collapse.

5.4 Alpha 2 Agonists

Drug	Dose	Contraindication / Onset-DOA	Metabolism / Excretion	Notes
Dexmedetomidine (Precedex)	Oral, nasal, IV, IM, rectal routes. Oral: 2.6–4 mcg/kg 30–60 mins preop IN: 1–2 mcg/kg Load: 1 mcg/kg over 10 mins; maintenance: 0.2–0.7 mcg/kg/hr.	Do not give if patient bradycardic, hypotensive, or in 2nd or 3rd degree heart block. 7 min onset; elim half-life 2–3 hr.	Liver almost complete bio-transformation via glucuronidation and Cytochrome P450 Excrete in urine and feces.	Higher affinity for alpha2 receptors than clonidine; dose dependent sympatholytic effect-cause hypotension, bradycardia, cardio-depression; respiratory sparing. Abrupt discontinuation of prolonged infusions can cause hypertension. Decrease dose in renal or hepatic disease.
+ sedation	+ analgesia	+ hypnotic	+ anxiolysis	amnesia not predictable

Dexmedetomidine worksheet

Loading dose: 1 mcg/kg over 10 minutes

Example: formula to give 1 mcg/kg:

Pt weight in kg _____(#1) × **1 mcg/kg** = _____ (#2)

_____mcg (#2) ÷ 4 mcg/ mL = _____(#3)

_____mL (#3) × 6 _____ ml/hour (#4)

Set IV pump rate at #4 with volume limit at #3

Maintenance range: 0.2–0.7 mcg/kg/hr

0.4 mcg/kg (#5) × _____kg (#1) =

↕_____mcg (#6) + by 4 mcg/ml = ml/hr

or

weight in kg × 0.1 = _____ml/hr to run at 0.4 mcg/kg/hr

Clonidine (Catapres)	Premed: 5mcg/kg Oral 0.1 mg/hr until BP controlled, max 6 mg. Transdermal 0.1–0.3 mg/day Intrathecal 150–450 mcg Epidural 30 mcg/hr, max 40 mcg/hr	Can exacerbate bradyarrhythmias & hypotension; need dose adjustment with renal impairment. Caution in patients with CAD, PVD, or CVA. PO Onset 45 mins; IV Half-life 9–12 hr	Liver via Cytochrome P450. Excreted unchanged by kidney; 20% in feces	Used to decrease blood pressure, heart rate, and SVR; negative chronotropic effects. Decreases anesthetic requirements. Reduces postop shivering. Prolongs DOA with local anesthetic in intrathecal or epidural block. Stimulates gastric acid secretion by activation of histamine 2 receptors.
+ sedation	+ analgesia	+ hypnotic	+ anxiolysis	no amnesia

TABLE 5-8 Induction Agents

Induction drugs	Ketamine (Ketolar)	Propofol (Diprivan)	Etomidate (Amidate)	Pentothal (Thiopental)
Class	NMDA Antagonist; General Anesthetic, Sedation, Hallucinogenic	Increased affinity for GABA receptor; hypnotic	Increased affinity for GABA receptor; hypnotic	Barbiturate; acts on reticular activiating system
Dose	IV 1 mg/kg IM 10 mg/kg infusion: 0.1–0.5 mg/kg/hr	2 mg/kg IV/IM infusion: 100–250 mcg/kg/min	0.3 mg/kg IV bolus only	IV 4 mg/kg; infusion for incr ICP: 1.5–3.5 mg/kg
Onset	IV 1 min IM 3–4 mins	30 secs	30–60 sec	30 secs
Duration	12–25 mins	3–10 mins	3–7 mins	10–25 mins
Contraindicated	increased ICP, neuro surgery, heart disease, hypertension, aneurysms, angina, hyperthyroid	hypotension, shock states, EF < 50%	seizure disorder; avoid in pts with porphyria.	can precipitate Acute Intermittent Porphyria (AIP); asthma, COPD, shock, hypotension

Metabolism	phase I demethylation CYP450; metabolite to norketamine-1/4 as potent as ketamine	phase II glucuronide conjugates, excreted urine	microsomal enzymes in liver; plama esterases		redistributed
Notes	For shock states when cardiovascular depression must be avoided; give preop anticholinergic (glycopyrrolate) for antisialogogue; give benzodiazepines to help with psychomimetic effects.	↓ MAP, CO, CBF, ICP, CPP; children require higher dose due to incr. volume of disribution and clearance (opposite for elderly).	For hemodynamically unstable patients.		Highly liophilic and alkaline, can precipitate when injected in acidic fluid
Anlalgesia	yes	no	no	no	
Amnesia	yes	yes	no	yes	
Histamine	no	no	no	yes	

continues

Induction Agents, continued

Induction drugs	Ketamine (Ketolar)	Propofol (Diprivan)	Etomidate (Amidate)	Pentothal (Thiopental)
Pro	*Good with uncooperative patient; helps to preserve airway reflexes- potent bronchodilator; minimally depresses cardiorespiratory system. Stimulates SNS-increases BP and heart rate.*	*Antiemetic; bronchodilator; quick recovery; anticonvulsant; antipruritic, decreases intraocular pressure.*	*Least myocardial or pulmonary depression of any induction agent; good for unstable patients.*	*Anticonvulsant; used to decrease CMRO2 and ICP, CPP maintained, brain protection, and for burst suppression.*
Con	*Dissociates thalamus fom cerebrum –> dysphoria and hallucinations; increases ICP / cerebral blood flow and cerebral metabolism / intraocular pressure; increased CO/HR- negative effect on myocardial oxygen-demand ratio; ↑ airway secretions. If pt catecholamine depleted, ketamine can cause myocardial depression.*	*No analgesia. Pain on IV injection; respiratory (apnea) & myocardial depression (negative inotrope), decr. SVR; cross reativity in patients with egg allergy; supports bacterial growth.*	*No analgesia. pain on IV injection; myoclonus; adrenocortical suppresion; increased incidence nausea and vomiting; accelerates seizure foci / can lower seizure threshold.*	*No analgesia. + histamine; cardiopulmonary depressant, negative inotrope, vasoldilates; can cause laryngospasms / bronchospasm.*

5.6 Total Intravenous Anesthetic (TIVA)

No volatile (inhaled) anesthetics used. For a TIVA anesthetic, an IV-loading dose of the induction agent is given and a continuous infusion started immediately to maintain the desired plasma drug concentration—it must be reached quickly and maintained. A combination of IV infusions is required to provide complete anesthesia. A continuous infusion(s) requires less dose of each drug, creating synergy with less toxicity. TIVA achieves all 3 requirements for general anesthetic:

- Amnesia
- Analgesia
- Autonomic areflexia

*** TIVA does not allow for muscle relaxation*.

TIVA Medications

- Preoperative sedation recommended: Midazolam 1–5 mg IV
- Propofol is often the hypnotic drug of choice in TIVA. If using propofol, a narcotic infusion must be added. Propofol produces unconsciousness and amnesia but does not possess analgesia properties.
- Common Maintenance: propofol-opioid synergy.
  - Propofol: bolus: 0.25–1.5 mg/kg
  - Infusion: 100–200 mcg/kg/min
  - Stop infusion 5–8 minutes before extubation **with. . .**
  - Remifentanil drip **or**
  - Fentanyl drip
- Other induction drugs that can be used include: ketamine, etomidate, and methohexital.

TIVA is associated with better hemodynamic stability, earlier recovery, and less postoperative nausea and vomiting.

5.7 Narcotic Opioids

Analgesia produced by opioid receptor agonism in the brain (periaqueductal gray matter) and spinal cord (substantia gelatinosa); reduces MAC of volatile anesthetics.

Characteristics common to all opioids:

- Dose dependent ventilatory depression: decreased RR with increased VT; decreased response to increased carbon dioxide.
- Causes sedation but not unconsciousness in normal doses; primary effect is analgesia.
- May stimulate chemoreceptor trigger zone.
- Spasm of sphincter of Oddi in biliary tract: morphine more than other opioids, meperidine the least. Treat spasm with glucagon, atropine, narcan, or nitroglycerin.
- Increases ICP in head trauma patient.

Reversal: naloxone (Narcan)

Listed in order of potency: Sufentanil (750) > Remifentanil (250) > Fentanyl (100) > Alfentanil (10) > Hydromorphone (7) > Morphine (1) = Methadone (1) > Meperidine (0.1)

Volume of Distribution: a drug with a smaller volume of distribution has a quicker onset and shorter duration of action. Larger to smaller:

Meperidine > Fentanyl > Sufentanil > Morphine > Alfentanil > Remifentanil

Opioid drugs mimic endogenous opioids: dynorphins, enkephalins, endorphins, endomorphins, and nociceptin; receptors found distributed widely in the brain but are also found in the spinal cord and digestive tract.

TABLE 5-9 Sufentanil–Alfentanil

Narcotic / Opioid	Sufentanil (Sufenta)	Remifentanil (Ultiva)	Fentanyl (Sublimzte)	Alfentanil (Alfenta)
Dose	Sedation: 0.25–2 mcg/kg General: 8–10 mcg/kg Cardiac: 10–30 meg/kg Infusion: 0.5–1.5 mcg/kg/hr	Mix 1 mg:20 mL for 50 mcg/mL Load: 1 mcg/kg; Infusion: 0.1–1.0 mcg/kg/min; Postop: 0.025–0.3 mcg/kg/min	Give IV to Blunt DL: 25–50 mcg 3 min before induction. General: 1–5 mcg/kg; Cardiac: 50–100 mcg/kg Infusion: 2–10 mcg/kg/min Postop : 0.5–1.5 mcg/kg IV	IV Loading: 25-100 mcg/kg; Infusion: 0.5-2 mcg/kg min
Onset	1–3 min	1–3 min	Immediate onset	1 min (fastest onset of all opioids)
Duration	SDOA 20–40 min-duration related to dose	USDOA 3–8 min, plasma level decr 50% in 40 secs	30–60 min	SDOA <10 min
Metabolism Excretion	Hepatic metabolism; rapidly crosses blood brain barrier	Hydrolyzed by erythrocyte & tissue nonspecific esterases	Hepatic metabolism; metab to inactive norfentany. Renal excretion	Hepatic metabolism; metab to inactive noralfentanil

continues

Sufentanil–Alfentanil, continued

Narcotic / Opioid	**Sufentanil** (Sufenta)	**Remifentanil** (Ultiva)	**Fentanyl** (Sublimzte)	**Alfentanil** (Alfenta)
Notes	Most potent opioid – 1000x more potent than morphine with less resp depression. Causes muscle rigidity, bradycardia, hypotension, incr. ICP	Similar potency to fentanyl. Good to use as bolus for brief, intense stimulations, i.e., head pinning, retrobulbar block	80x more potent than morphine; causes nausea & vomiting, muscle rigidity, bradycardia. Releases histamine. Lipid soluble. Minimal CV depression. Good to blunt stimulation with laryngoscopy and incision Highly addictive	Causes profound bradycardia, increased nausea and vomiting, muscle rigidity. Onset 4x faster but 1/3 DOA than fentanyl; 10x more potent than morphine. Good to use as bolus for brief; intense stimulation, i.e., head pinning, Retrobulbar block

TABLE 5-10 Dilaudid–Demerol

	Hydromorphone (Dilaudid)	Morphine	Methadone (Dolophine)	Meperidine (Demerol)
Dose	IV 0.01–0.02 mg/kg	1–30 mg or 0.03–0.15 mg/kg IV; Infusion: 0.1 mg/kg	Single dose 20 mg, titrate for RR of 8, or 5 mg every 30–40min post-op	Postop: IV/IM 25–100 mg Shivering: 12.5–50 mg IV
Onset	1.5 min	5–10 min	1–24 min	1–5 min IM 10 mins
Duration	4–5 hr; peak effect in 20 mins	LDOA 4–5 hr slow peak time ~ 90 mins, prolonged analgesia into postop period	4–6 hrs	2–4 hr
Metabolism Excretion	Liver with 2 active metabolites; can accumulate with renal failure	Hepatic glucuronidation to active metabolites – morphine 3 & 6 glucuronide (6 is active analgesic), excreted renally	Liver to inactive form; cleared in bile and urine	90% liver — active metabolite — neurotoxic - Normeperidine lowers seizure threshold. Renally excreted

continues

Dilaudid–Demerol, continued

	Hydromorphone (Dilaudid)	Morphine	Methadone (Dolophine)	Meperidine (Demerol)
Notes	- histamine Nausea & vomiting, 5–10x as potent as morphine. Good drug for PCA pump postoperatively. Better tolerated in renal patients than morphine	+ histamine don't give with asthma patient. Stimulates nausea & vomiting; depresses ventilation. Bradycardia. Water soluble	+ histamine long-acting mu agonist. NMDA receptor antagonist properties. May be helpful with neuropathic pain. Primarily used in the prevention of opioid withdrawal symptoms and tx of chronic pain	+ histamine Avoid MAO inhibitors; structurally related to atropine-causes tachycardia. 1/10th potency of morphine. Chemically incompatible with barbiturates. Can be used to treat post-op shivering. Only opioid with local anesthetic properties

TABLE 5-11 Opioid Receptors

Opioid Receptor	Effect	Agonist	Antagonist
Mu-1	Analgesia: supraspinal/ spinal Euphoria Low abuse potential Miosis, bradycardia, hypothermia, urinary retention; slow GI peristalsis; pruritus, skeletal muscle rigidity	morphine meperidine hydromorphone methadone fentanyl sufentanil	Naloxone Nalbuphine (partial antagonist) Buprenorphine (partial antagonist)
Mu-2	Analgesia: primarily spinal Respiratory depression Physical dependence Marked constipation; bradycardia	morphine fentanyl	Naloxone
Kappa	Spinal analgesia Dysphoria, sedation Low abuse potential Anticonvulsant effects; neuroprotection Miosis	ketamine morphine fentanyl	Naloxone
Delta	Analgesia: supraspinal / mostly spinal Antidepressant effects Depression of ventilation Physical dependence Epileptogenic Constipation minimal	fentanyl	Naloxone
Sigma	A nonopioid receptor. Dysphoria, hallucinations, respiratory stimulation	Ketamine	Progesterone Haloperidol

5.8 Nonopioid Analgesics

Multimodal Approach (Preemptive Analgesia)

Multimodal approach—to minimize use of opioids. All of these agents have a ceiling effect in analgesia, and all have potential for serious adverse effects.

Include: nonsteroidal anti-inflammatory drugs (NSAIDs—COX inhibitors), acetaminophen, Pregabalin/gabapentin, ketamine, alpha 2 agonists, corticosteroids, and local anesthetics.

NSAIDS—Cyclooxygenase (COX) Inhibitors

Anti-inflammatory, analgesic, antipyretic.

Prostaglandins are produced by an enzyme in the cyclooxygenase pathway; they are a family of hormone-like substances that participate in a wide range of body functions: they promote inflammation needed in healing, fever, pain, support the blood clotting function of platelets, vasodilate and vasoconstrict, and protect the lining of the gastrointestinal tract. There are two COX enzymes: COX-1 and COX-2, which both produce prostaglandins. COX-1 specifically supports platelet function and protects the stomach. COX inhibitors work through inhibition of the production of prostaglandins.

All NSAIDs share the same significant adverse effects, though with differing frequency. These include effects in the following systems:

- Gastrointestinal: anorexia, nausea, pain, gastritis, ulcers, bleeding, and perforation. GI complications can often be offset by also taking a proton pump inhibitor: esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), or rabeprazole (Aciphex). These problems tend to emerge only after long-term or heavy use.
- Cardiovascular: including hypertension, myocardial infarction, stroke, and other thromboembolic events.

- Renal: sodium and water retention, decreased GFR, and renal failure (especially worrisome in patients with CHF, CRF, cirrhosis, HTN, or hypovolemia); kidney failure can occur; though it occurs rarely.
- Central nervous system: headache, dizziness, confusion, depression, reduced seizure threshold.
- Platelets: aspirin causes an irreversible inhibition of platelet aggregation. Platelet inhibition lasts 1 week (life of exposed platelets)

COX-2 is the enzyme produced in acute inflammation. COX-2 inhibitors were developed to relieve the pain but without all the gastrointestinal side effects. Only one COX-2 inhibitor, celecoxib (Celebrex), is still on the market. Other NSAID-type examples include:

- Aspirin (acetylsalicylic acid)
- Celecoxib 400 mg—contraindicated with Sulfa allergy.
- Ketorolac 30–60 mg IV; don't give greater than 5 days

Acetaminophen: acetaminophen eases pain and fever but does not affect inflammation. Excessive doses can cause serious, even fatal hepatic injury; reduced dose needed in renal impairment.

- PO max dose 4g/day (if < 50 kg—75 mg/kg/day); max safe dose: 3–4 grams per day, < 3 g/day for elderly or hepatic impairment.
- IV (Ofirmev) 1 gram over 15 mins

Anti-neuropathic/GABA Analog/Anticonvulsant

Used to treat certain types of nerve pain. Caution in patients with renal impairment (Creatinine > 1.5) or history of angioedema.

- **Pregabalin**: PO: 100 mg
- **Gabapentin** (Neurontin): PO: 100, 300 mg, 400 mg

Ketamine—see Section 5 Induction agents for more information

Works as sedative.

Alpha 2 agonists—see Section 5.4 Alpha 2 agonists

Centrally sedates, anxiolytic. Also, decreases blood pressure and catecholamine levels.

Analgesic, sedates, hypnotic, anxiolysis without amnesia, activates histamine release.

Corticosteroids—see Section 5.17 Corticosteroids

Anti-inflammatory effect.

Local Anesthetics—see Section 5.15 Local Anesthetics (LA)

Relieve pain by blocking the sodium channels from within the nerves, blocking the transmission of nociceptive impulses from reaching the dorsal horn of the spinothalamic tract.

5.9 Agonist–Antagonists (Partial Agonists)

Agonist–antagonists (Partial Agonists): drugs that possess properties of both full agonists and antagonists. Partial agonists bind to the receptors with varying affinity and activate these receptors, but not to the full degree. Because these drugs are partial agonists, higher doses can be given with fewer side effects than when high doses of full-agonist opioids are given. For example, low-dose buprenorphine is more potent than morphine but with less opioid-associated side effects such as respiratory depression, itching, constipation, etc. These drugs are less prone to abuse as they cause less euphoria.

When partial agonists are given at lower doses, in patients who are not opioid-dependent, effects are the same as if they've received a full agonist. As doses are increased, partial agonists produce increasing effects but only to a certain, maximum level even if doses continue to increase; thus, agonist–antagonists have a ceiling effect. At the highest doses, agonist–antagonists actually begin to act like partial or full antagonists—occupying

receptors but only partially, or not at all, activating them while preventing a full agonist from attaching to the receptor.

Of the agonist–antagonists, three of the most commonly given are:

Butorphanol (Stadol)

- Receptor: agonist at kappa, partial agonist of mu; partial agonist at sigma receptor, which is responsible for psychotomimetic effects
- Supplied: vial 1 mg/mL, 2 mg/mL; aerosol 10 mg/mL spray
- Dose 0.01–0.04 mg/kg or 1 mg IV q 3–4 hr PRN; 1–4 mg IM Q 3–4 hr PRN. Geriatric dosing should be decreased by 50%
  - Intranasal (IN): 1 mg spray in 1 nostril; may repeat after 60–90 mins up to 2 mg total dose.
  - Preop: 2 mg IM 60–90 minutes preoperatively
  - Anesthesia: 2 mg IV before induction and/or 0.5–1 mg increments during anesthesia (higher dose may be required, up to 0.06 mg/kg, or 4 mg/70 kg). Total cumulative dose varies; typically ranges between 4–12.5 mg (0.06–0.18 mg/kg)
- Onset: IV < 10 mins; IM 5–10 mins; IN < 15 mins
- DOA: 3 hrs IV/IM, 4–5 hrs IN
- Side effects: sedation, hypotension, nausea. In patients with cardiovascular disease, butorphanol causes increases in cardiac output and pulmonary artery pressures. Can cause acute biliary spasm.
- 2 mg of Stadol produces analgesia similar to 10 mg of morphine.
- Treats postoperative shivering more effectively than meperidine
- Can produce withdrawal in opioid-dependent patients

Nalbuphine (Nubain)

Semi-synthetic opioid used for moderate to severe pain. Can be used as treatment for morphine-induced pruritus.

- Receptor: agonist at kappa, partial agonist of mu and delta
- Supplied: 10 mg/mL
- Dose in opiate-naive patient: 0.1–0.3 mg/kg or 10 mg/70 kg IV/IM/SQ—up to 20mg/dose or 160 mg/day
- Dose in opioid-dependent patient: administer ¼ anticipated dose and observe for withdrawal symptoms.
- Anesthesia:
  - Induction: 0.3–3 mg/kg IV over 10–15 mins
  - Maintenance: 0.25–0.5 mg/kg in single IV administrations
- Onset: IV onset 2–3 mins, 15 mins IM
- DOA: 3–6 hrs
- Dosage adjustment: decrease dose for patients at high risk for respiratory depression. Use with caution in patients with liver or renal impairment.
- Side effects: sedation, vertigo, bradycardia, spasm sphincter of Oddi, hypertension, anaphylaxis
- Analgesia similar to morphine.
- **Giving IV can reverse the respiratory depressant effects of the narcotic but sustain the analgesia** (better to use than naloxone as it does not push opioid off the receptor)
- Also used to antagonize itching from epidural and intrathecal MSO4
- Can produce withdrawal in opioid-dependent patients and cause spasm of the sphincter of Oddi

Buprenorphine *(Buprenex, Suboxone)*

- Receptor: partial agonist at mu, antagonist at delta.
- Supplied: 0.3 mg/mL injection, 7.5—20 mcg/hr transdermal
- Dose: 0.3 mg deep IM or slow IV, may repeat after 45 mins. Max dose IM 0.6 mg or 0.3 mg IV. Dose of 0.3 mg = morphine 10 mg.
- At low doses, buprenorphine is many times more potent than morphine.

- Onset: 2 mins IV; 15 mins IM; peak effect 3 hours
- DOA: 6 hrs; 4-10 hrs with IM
- Dosage adjustment: decrease dose for patients at high risk for respiratory depression.
- Side effects: sedation, hypotension, dizziness, anaphylaxis
- Buprenorphine has a very slow dissociation from mu opioid receptors and resistant to reversal by naloxone.
- Some preparations of buprenorphine contain naloxone to deter intravenous injection.
- Can produce withdrawal in opioid-dependent patients

5.10 Antagonist Agents

Flumazenil (Romazicon)

Benzodiazepine (BZD) antagonist:

Vial: 0.1 mg/mL

Dose: 0.2 mg IV, repeat q1 min up to 1.0 mg. Last < 1hr

Onset: 1–3 mins, peak 6–10 mins

DOA: 1 hour to re-sedation (romazicon has very short half-life)—*the shortest half-life of a BZD is 2–3 hours and the half-life of Flumazenil is 1 hour. Patients should be closely monitored and repeated doses of Flumazenil may be necessary.*

Notes: Do not give to patient on BZD for life-threatening conditions (i.e., ICP, status epilepticus, cyclic antidepressant overdose).

Contraindicated: seizure disorder

Naloxone (Narcan)

Opioid antagonist: competes and displaces narcotics at mu receptor sites. Including analgesia, naloxone can reverse opioid-induced side effects (i.e., pruritus, biliary spasm, nausea and vomiting, etc.)

Vial: 0.4 mg/mL—dilute in 9 mL NS = 0.04 mg/mL.

** Giving a full undiluted ampule (1 mL = 0.4 mg/mL) of naloxone in a patient who has received opioids, but is not in respiratory arrest, may cause ischemia, heart attack, hypertension, stroke, heart failure, and/or pulmonary edema.*

Dose adults: 0.04–0.4 mg IV, repeat PRN up to 10 mg. Narcan can be administered IV, IM, SC, or intratracheally (ETT), with the most rapid onset of action achieved following IV administration

Onset: 2 mins (ETT 2–5 mins)

DOA: 20–60 mins (dose may need to be repeated if patient received narcotic with DOA > 1 hours.

Caution: in patients with known renal insufficiency as it may have a prolonged effect. When naloxone is given, there is a risk of acute withdrawal syndrome in opioid-habituated patients and infants of opioid-habituated mothers.

Patients with IV Access

Patients ≤ 20 kg: Dilute and give 0.02 mg (0.5 mL) IV every 3 minutes until desired respiratory rate is established NOT until return of desired sensorium.

Patients > 20 kg: Dilute and give 0.08 mg (2 mL) IV every 3 minutes until desired respiratory rate is established NOT until return of desired sensorium.

Patients without IV Access (IM, SC, ETT)

Patients ≤ 20 kg: Give undiluted (0.4 mg/mL) naloxone 0.01 mg/kg

SC/IM/ETT every 2 minutes until desired respiratory rate is established NOT until return of desired sensorium.

Patients > 20 kg: Give undiluted (0.4 mg/mL) naloxone at 0.2 mg (0.5 mL)

SC/IM/ETT every 2 minutes until desired respiratory rate is established NOT until return of desired sensorium.

Naltrexone

Used in alcoholics and opioid addicts, naltrexone is a mu, delta, and kappa opioid receptor antagonist. It is taken in oral form and is longer acting than naloxone.

5.11 Muscle Relaxants

TABLE 5-12 Succinylcholine Description

Depolarizing Muscle Relaxant	
Drug	**Succinylcholine** (Anectine)
Dose	Without pretx of defasciculating dose: 0.5–1 mg/kg With pretx: 1–2 mg/kg Infusion: 1 gram/500 mL, titrate to effect
Onset	30–60 seconds
Duration of Action	½ life: 47 seconds; USDOA < 10 mins
Metabolism	Succinylcholine diffuses away from the neuromuscular junction (NWJ) and is rapidly hydrolyzed by pseudocholinesterase into succinylmonocholine.
Don't Give With	Hyperkalemia, eye injury, increased intraocular pressure, burns and trauma > 24 hours old; known abnormal pseudocholinesterase levels. Should not be used routinely in children.
Notes	+ histamine Increased risk of problems with undiagnosed myopathies. Don't use routinely in pediatrics—can cause profound bradycardia; if have to give, administer atropine pre-Suxx in children.

Succinylcholine stimulates both muscarinic and nicotinic receptors.

Nicotinic effect: mimics action of acetylcholine at the neuromuscular junction on skeletal muscles.

Muscarinic effect: stimulation of the muscarinic receptors in the SA node of the heart produces bradycardia especially in patients (e.g., children) with a high vagal tone. Anticholinergic drugs (atropine) are effective in preventing or treating bradycardia.

Succinylcholine Depolarizing Blocks—2 Types Seen

Phase I block (depolarization block): produced by succinylcholine, often preceded by muscle fasciculation. *(Only depolarizing agent produces fasciculations before onset of paralysis.)* This is thought to be due to the prejunctional action of succinylcholine stimulating acetylcholine receptors on the motor nerve. Recovery from Phase 1 block occurs as succinylcholine quickly diffuses away from the NMJ.

- Does not exhibit fade during tetanus or TOF monitoring
- No post-tetanic potentiation

Phase II block: if enough succinylcholine is given (>4 mg/kg) or there is prolonged exposure (repeated boluses or continuous infusion) of the NMJ to succinylcholine, the quality of the block will change to resemble that of a nondepolarizing block.

- Fade of twitch response in TOF monitoring
- Has tetanic fade
- Has post-tetanic potentiation (enhancement of synaptic strength following tetanus)
- Acetylcholinesterase may reverse blockade but difficult to predict

TABLE 5-13 Succinylcholine Complications

Increased serum K+	Normal muscle releases enough potassium to increase normal serum potassium levels 0.5 mEq/L from succinylcholine-induced depolarization. Normally, this would not affect healthy patients with normal K+ levels, but in patients with pre-existing hyperkalemia, it can be deadly. Examples of diseases where receiving succinylcholine could elevate serum potassium levels: • burn injury • massive trauma • familial periodic paralysis • Guillain-Barré syndrome • muscular dystrophy (succinylcholine is a relative contraindication in children because of the potential for undiagnosed myopathies) • muscular denervation—hemiplegia/spinal cord injury • prolonged immobilization
Trigger for Malignant Hyperthermia	Along with volatiles.
Anaphylaxis	Succinylcholine accounts for ~50% of hypersensitivity reactions due to histamine release.
Increased intraocular pressure (IOP)	Normal IOP is 10–22 mmHg and generated by ocular muscle contraction. Succinylcholine increases IOP by 5–10 mmHg and this was thought to be due to increased muscle contractions, though this is not confirmed.
Increased intracranial pressure (ICP)	Muscle fasciculations can increase ICP but this effect can be offset with hyperventilation. In patients who already have an increased ICP, succinylcholine is NOT contraindicated because the harmful stimulation of intubation far outweighs any increase of ICP by the drug.

continues

Succinylcholine Complications, continued	
Increased intragastric pressure	Fasciculations may be responsible; however, there is a corresponding increase in lower esophageal sphincter pressure.
Muscle pain	Thought to be due to fasciculations but this relationship is inconsistent. No preventative measure is effective in all cases; however, a small dose of a nondepolarizing muscle relaxant ($1/10^{th}$ the intubating dose; i.e.: rocuronium 5 mg IV) given before the administration of succinylcholine can help to minimize this discomfort. This technique, however, reduces the potency of succinylcholine and a larger dose must be given to produce the same effect.
Abnormal plasma pseudocholinesterase levels	After giving succinylcholine, make sure twitches have returned (test with a peripheral nerve stimulator) before giving nondepolarizing muscle relaxants. Done to confirm patient does not have a prolonged succinylcholine block due to abnormal plasma pseudocholinesterase levels

Nondepolarizing Muscle Relaxants (NDMR)

Benzylisoquinolines NDMR

Drug names end in "urium"

e.g., atracurium, cisatracurium *(mivacurium no longer produced in United States)*

- metabolized by organ-independent degradation
- atracurium releases histamine (increased risk of bronchospasm), not cisatracurium
- lack any vagolytic effect

Aminosteroid NDMR

Drug names end in "onium":

e.g., vecuronium, rocuronium, pancuronium

- depend on organ function for metabolism and excretion (prolonged action in liver and renal disease)
- can have active metabolites
- tend not to release histamine

TABLE 5-14 NDMR Mivacurium–Vecuronium

	Mivacurium (Mivacron)	Rocuronium (Zemuron)	Vecuronium (Norcuron)
Dose	0.2 mg/kg Maint: 0.05 mg/kg	0.8 mg/kg Maint: 0.15 mg/kg Infusion: 9–12 mcg/kg/min	0.1 mg/kg; Maint: 0.12 mg/kg Infusion: 1–2 mcg/kg/min
Onset	1–3 min	1.5–3 min	3–4 min
Duration of Action	SDOA 15–20 min	IDOA 30–75 min	IDOA 40–90 min
Metabolism	Enzymes pseudocholinesterase	predominantly hepatobiliary—no active metabolite; excreted renally	Excretion-hepatobiliary 80%, Renal 10–20% Active metabolite: prolonged NMB—sometimes neuropathy develops; caution with IV infusion
Don't Give With	*No longer produced in U.S.*	Prolonged elimination in patients with hepatic disease & renal failure	Long acting in neonates & infants (due to immature liver). Prolonged elimination in patients with hepatic disease & renal failure
Notes	+ histamine Low risk for anaphylaxis	no histamine High risk for anaphylaxis	no histamine Reconstitute to 1–2 mg/mL. Women 30% more sensitive than men. Intermediate risk of anaphylaxis

TABLE 5-15 NDMR Atracurium–Pancuronium

	Atracurium (Tracrium)	Cisatracurium (Nimbex)	Pancuronium (Pavulon)
Dose	0.5 mg/kg; Maint: 0.1 mg/kg Infusion: 5–12 mcg/kg/min	0.2 mg/kg Maint: 0.02 mg/kg Infusion: 1–2 mcg/kg/min	0.1 mg/kg; Maint: 0.01 mg/kg
Onset	2–3 min	2–3 min	2–3 min
Duration of Action	IDOA 30–45 min	IDOA 40–75 min	LDOA 60–120 min
Metabolism	Hoffman Elimination (temp and pH dependent) to → Laudanosine (metabolite) can cause excitement and seizure activity.	Hoffman Elimination (temp and pH dependent)	15–20% biliary/hepatic 70–80% renal
Don't Give With	Histamine release may worsen cardiovascular disease, asthma.		Prolonged elimination in patients with renal and hepatic disease. May be dangerous with patients who have CAD, fixed outflow obstruction (aortic stenosis or HOCM); arrhythmogenic

NDMR Atracurium–Pancuronium, continued			
Notes	+ histamine Intermediate risk of anaphylaxis.	no histamine 4x more potent than Atracurium. Low risk for anaphylaxis.	no histamine Vagolytic: tachycardia – catecholamine release & decreased uptake. Intermediate risk of anaphylaxis.

TABLE 5-16 Conditions–Drugs Potentiate NMB

Conditions and Drugs That Potentiate Neuromuscular Blockade	• Aminoglycoside, gentamicin, streptomycin, clindamycin antibiotics • Volatile (inhaled) anesthetics • Magnesium • High doses of local anesthetics • Calcium channel blockers • Quinidine • Acid-base balance disturbances (respiratory acidosis potentiates blockade and antagonizes its reversal) • Trimethaphan, alpha blocker • Hypermagnesemia, hypokalemia, hypocalcemia • Elderly have decreased clearance and prolonged duration of neuromuscular block

TABLE 5-17 States That Reduce NMB Metabolism

States That Reduce Neuromuscular Block Metabolism and Prolong Effect	• Renal insufficiency — reduction in plasma clearance • Hepatic disease • Hypothermia • Volume status • Trimethaphan, alpha blocker

TABLE 5-18 Antagonists to NMB

Conditions and Drugs That Antagonize Nondepolarizing Blockade	• Some neuromuscular diseases: resistance to NDMR below the level of the lesion. • In hemiplegia, monitoring the paralyzed side has a less intense block and recovery is more rapid than on the unaffected side. • Debilitating muscle diseases or denervated muscle is resistant to nondepolarizing relaxants. • Chronic administration of drugs receptors such as Dilantin, Tegretol, antipsychotic medications (thorazine, etc.) cause up regulation of receptors • Calcium • Patients who take steroids • Cord transection • Stroke • Nerve damage • Thermal burn injuries: increased protein binding and up regulation of receptors • Chronic alcohol dependence • Hypermetabolic states

Obese patients: dosing with neuromuscular block: 20% more than lean body weight.

Onset to Maximum Block

Ultra-rapid (< 1 min) Succinylcholine

Rapid (1–2 mins) Rocuronium

Intermediate (2–4 mins) Atracurium, Mivacurium, Pancuronium, Vecuronium

Long (> 4 mins) Cisatracurium

Duration to ¼ TOF Recovery

Ultra-short (< 8 mins) Succinylcholine

Short (8–20 mins) Mivacurium

Intermediate (20–25 mins) Atracurium, Cisatracurium, Rocuronium, Vecuronium

Long (> 50 mins) Pancuronium

5.12 Anticholinesterase

(Cholinesterase inhibitor)

Anticholinesterase drugs reverse nondepolarizing muscle relaxation by inhibiting the destruction of acetylcholine by acetylcholinesterase. This leads to increased acetylcholine at neuromuscular junction overcoming the neuromuscular blocking effect at the nicotinic receptor.

The most prominent side effect of the anticholinesterase drugs, bradycardia, is due to muscarinic receptor activation, though salivation, increased bronchial secretions, and urinary and fecal incontinence also can occur. *See list of muscarinic side effects in "Anticholinergics."*

TABLE 5-19 Cholinesterase Inhibitors

Drug	Dose IV	Onset / Duration	Notes	TOF	Anticholinesterase Dose
Attempt at reversal should not be attempted until patient has at least 2 out of 4 TOF response and temperature > 35°C					
Neostigmine (Prostigmin) (Bloxiverz)	0.04–0.07 mg/kg max = 5 mg	*3–5 m / 1–3 hrs IDOA*	Most potent, most commonly given anticholinesterase; does not cross BBB	2	0.07 mg/kg
				3–4	0.05 mg/kg
				4	0.04 mg/kg
Edrophonium (Enlon); (Tensilon)	0.5–1.0 mg/kg over 30–45 sec Repeat q5–10 min max = 40 mg	*1– 2 min / 1–1.5 hrs fastest onset and SDOA*	Does not cross BBB. 10% as potent as *Neostigmine* BUT—½ anticholinergic effect as *Neostigmine*. Has less muscarinic effects, requires only ½ dose of atropine premedication. Less effective at antagonizing profound blockade and is not recommended for reversal of long-acting muscle relaxants.	2	1.0 mg/kg
				3–4	0.7 mg/kg
				4	0.5 mg/kg

Pyridostigmine (Mestinon)	0.1–0.3 mg/kg, max 2–4 mg/hr	*10–20 mins / 2–3 hr slowest onset, longest duration of action*	does not cross blood brain barrier. 20% as potent as *Neostigmine. Can be used to reverse CNS effects of anticholinergic*;	*2* *3–4* *4*	*0.3* mg/kg *0.25* mg/kg *0.2* mg/kg
Sugammadex (Bridion)	4–8 mg/kg single-bolus injection; 4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts (PTC) and there are no twitch responses to train-of-four (TOF) stimulation.	Readily recovers shallow or profound neuromuscular blockade consistently in 2–3 minutes	Recently approved by the FDA, Sugammadex is a modified gamma-cyclodextrin. Chemically, it has a hydrophilic periphery and a negatively charged lipophilic core that exerts its effects by forming tight water-soluble complexes in a 1:1 ratio with aminosteroid muscle relaxants (rocuronium > vecuronium >> pancuronium) preventing it from interacting with nicotinic receptors; "encapsulates and inactivates". Can see: anaphylaxis and/or marked bradycardia; vomiting, pain, nausea, hypotension, and headache.		Anticholinergics not needed with sugammadex. At 2 mg/kg, when given at TOF 2/4, will reliably produce TOF >0.9 in 2 minutes. 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation.

continues

Cholinesterase Inhibitors, continued

Drug	Dose IV	Onset / Duration	Notes	TOF	Anticholinesterase Dose
			Unlike other anticholinesterase drugs, Sugammadex has no action or effect at the neuromuscular junction. There is no biotransformation and elimination is by renal excretion only.		
Physostigmine	0.01–0.03 mg/kg	3–8 mins / 30 mins— 5 hrs	*Crosses blood brain barrier. Given for central overdose of atropine/scopolamine; reversal of CNS depression/delirium secondary to receiving benzodiazepines, postoperative shivering. Can see excessive salivation, convulsions.*		*Listed for information only. Not used to reverse muscle relaxants.*
Echothiophate			Anticholinesterase eye drops used in treatment of glaucoma.		*Listed for information only. Not used to reverse muscle relaxants.*

Factors That Confound Reversal

- Electrolyte disturbance: hypokalemia, hypocalcemia, hypermagnesemia
  - Alkalosis (hyperventilation)—can induce hypokalemia/hypocalcemia
- Hypothermia
- Blood flow to muscle: slow blood flow increases onset and duration of action
- Acidosis (potentiates effects of nondepolarizing block agents)

5.13 Anticholinergic

(Antimuscarinics or muscarinic antagonists)

Used in association with anticholinesterase agents (i.e., neostigmine) to prevent the side effects associated with their use

The chosen anticholinergic should be given at the same time, or immediately before, giving the reversal dose of anticholinesterase to prevent muscarinic side effects.

TABLE 5-20 Muscarinic Side Effects

Organ System	Muscarinic Side Effects
Cardiovascular	Bradycardia, bradyarrhythmias, hypotension
Pulmonary	Bronchospasm, bronchial secretions, hypoxia
Cerebral	Diffuse excitation (with physostigmine)
Ophthalmological	Pupillary constriction (miosis)
Gastrointestinal	Intestinal spasm, increased salivation
Genitourinary	Increased bladder tone

TABLE 5-21 Anticholinergics

Drug	Dose	Onset / Duration	Contraindications	S. E.
Glycopyrrolate (Robinul)	0.007 mg/kg or 0.2 mg for each 1 mg of Neostigmine	1–5 min / 2–7 hrs *Longer duration of action than atropine*	Narrow angle glaucoma, Prostatic hypertrophy, Myasthenia Gravis (anticholinesterase drugs used to treat myasthenia gravis), Paralytic ileus, Ulcerative colitis (severe)	Orthostatic hypotension, dry mouth, mydriasis, blurred vision, urinary retention, slows peristalsis in the intestine. No sedation, does not cross BBB.
Atropine	IV or IM 0.007–0.014 mg with edrophonium; up to usual adult dose 0.4–0.6 mg	1–4 min / 20 mins	Narrow angle glaucoma, Prostatic hypertrophy, bladder-neck obstruction. Reduces lower esophageal tone.	Constipation, dry mouth, mydriasis, blurred vision, urinary retention. Crosses the BBB, causes slight sedation, can cause delirium. *If dose too small, can cause bradycardia by acting directly on the SA Node or increasing vagal activity by affecting muscarinic receptors*. Cutaneous vessel dilation = Atropine Flush "red as a beet"; Inhibition of sweat glands lead to a rise in body temperature = Atropine Fever.
Scopolamine (Transderm Scop)	IV, IM 0.3–0.6 mg, SQ 0.6–1 mg, patch 1.5 mg	IV 30 mins before, IM 1 hr before, patch 4 hr before / long DOA	Urinary bladder obstruction, narrow angle glaucoma, intestinal obstruction, elderly patients, impaired liver or renal function	Crosses the BBB, causes sedation, poss. delirium. Best antisialagogue, + amnestic

TABLE 5-22 Common Combinations

Most common combinations-share speed of speed of onset and duration of action

Anticholinesterase	Dose	Anticholinergic	Dose
Neostigmine (Prostigmin, Bloxiverz)	0.04–0.07 mg/kg max = 5 mg	**Glycopyrrolate**	0.2 mg per 1 mg Neostigmine
Edrophonium (Enlon)	0.5–1.0 mg/kg max = 40 mg	**Atropine**	0.007–0.014 mg
Pyridostigmine (Mestinon)	0.1–0.3 mg/kg max 2–4 mg/hr	**Glycopyrrolate**	0.2 mg per 5 mg Pyridostigmine

TABLE 5-23 Compare Effects of Anticholinergics

	Glycopyrrolate	Atropine	Scopolamine
Antisialagogue	moderate	mild	large
Sedation/amnesia	none	mild	large
CNS effect	none	mild	moderate
Heart rate	mild increase	moderate increase	no to mild increase
Bronchodilator	moderate	large	moderate
Pupil dilation (mydriasis)	mild	moderate	large
Lower esophageal sphincter relaxation	moderate	moderate	moderate
PONV prophylaxis	—	—	large

Choosing which anticholinergic to give with a specific anticholinesterase is done based on equivalent onset and duration of action. For example, the reason to use atropine, and not glycopyrrolate, in conjunction with edrophonium to reverse nondepolarizing muscle relaxants: atropine has an onset time more similar to edrophonium; otherwise, the muscarinic effects of edrophonium occur before glycopyrrolate can block them.

5.14 Antiemetics—Receptor Specific and Adjunct

See Chapter 1, Section 1.3, Postoperative Nausea and Vomiting (PONV) or Postoperative Vomiting (POV) for more information.

Even patients with zero known risk factors, and considered low risk for postoperative nausea and vomiting (PONV), carry a 10% risk of PONV and may benefit from prophylactic antiemetic therapy. Some providers believe, though, that not all patients should receive PONV prophylaxis.

Adults at moderate risk for PONV should receive combination therapy with one or two prophylactic drugs from different classes. In general, combination therapy has superior efficacy compared with monotherapy for PONV prophylaxis because drugs with different mechanisms of action optimize efficacy.

Combination drug antiemetic therapy of greater than 2 antiemetics is recommended for patients at high risk for PONV.

All drugs given below in BOLD are listed in charts

Serotonin (5-HT3) receptor antagonists *(cheat: drug names end in "tron")*—more effective in preventing emesis than nausea.

- **ondansetron** (Zofran)—DO NOT give to pediatric patients < 1 month.

- **dolasetron** (Anzemet)—prolongs QT interval the most; single dose only.
- **granisetron** (Kytril)
- **tropisetron** (Navoban)
- palonosetron (Aloxi)—long acting

Dopamine 2 receptor antagonist

- **Metoclopramide (Reglan)**
  - Increases LES tone and intestinal motility; promotes gastric emptying, thus reducing gastric volume; "prokinetic."
  - Can cause extrapyramidal symptoms, manifested primarily as acute dystonic reactions.
  - GI motility effects antagonized by anticholinergics (glycopyrrolate) and narcotics.
  - Check with surgeon before giving for **ANY** GI case.
  - Can cause methemoglobinemia; treat methemoglobinemia with methylene blue 1–2 mg/kg IV.
    - Contraindications
      - Bowel obstruction
      - Pheochromocytoma: metoclopramide stimulates secretion of catecholamines from pheochromocytoma causing hypertensive crisis
      - QT prolongation—can worsen prolongations and cause Torsades de pointes
      - Parkinson's disease: may experience exacerbation of parkinsonian symptoms
      - Patients on antipsychotics
- **Butyrophenone—**Black box warning: can increase QT prolongation, which can lead to Torsades de pointes
  - **droperidol (Inapsine, Innovar)**
    - Antiarrhythmic properties at higher doses
    - Higher doses are used for sedation
  - **haloperidol (Haldol)**
    - Don't use with Parkinson's patients

- **Phenothiazine—**very sedating
  - **prochlorperazine (Compazine)—**weak antihistamine, potent antidopaminergic, and antimuscarinic (anticholinergic) agent
  - **promethazine (Phenergan)**

AChM$_1$ Acetylcholine-muscarinic receptor antagonist

Scopolamine (Transderm Scop, Scopace)-predominantly motion sickness; long onset of action, not effective for rescue therapy

Adjunctive Antiemetics

Benzodiazepines: midazolam (Versed)

Corticosteroid: dexamethasone (Decadron)

Antihistamine and Anticholinergic (acetylcholine receptor):

dimenhydrinate (Dramamine)—motion sickness

Antihistamine H_1 blockers: diphenhydramine (Benadryl)

Antihistamine H_2 blockers—partial inhibition of enterochromaffin-like cells of gastric antrum—reversible inhibition of H_2 receptor-mediated secretion of acidic gastric fluid; increases gastric pH.

Famotidine, Cimetidine, Nizatidine, Ranitidine

ANTACIDS—Must be nonparticulate
Sodium Citrate (Bicitra): 15–30 mL PO 30 minutes before induction

NK-1 receptor—Substance-P antagonists
aprepitant (Emend): long onset of action, not effective for rescue therapy. Usually given before chemotherapy treatment. Given in combination with corticosteroid and 5-HT3 antagonist.

Note: These recommendations are evidence-based and not all the drugs have an FDA indication to treat PONV.

TABLE 5-24 Doses and Timing in Adults

Drug	Class	Dose and Route	Dose Timing
ONDANSETRON (Zofran)	5-HT3 receptor antagonist	4–8 mg IV	30 mins before EOC
DOLASETRON (Anzemet)	5-HT3 receptor antagonist	12.5 mg IV	15 mins before EOC
GRANISETRON (Kytril)	5-HT3 receptor antagonist	0.35–1.5 mg IV	Just after induction
TROPISETRON (Navoban)	5-HT3 receptor antagonist	2 mg IV	30 mins before EOC
METOCLOPRAMIDE (Reglan)	dopamine antagonist	10 mg IV	
DROPERIDOL (Inapsine)	dopamine antagonist - Butyrophenone	0.625–1.25 mg IV	30 mins before EOC

continues

Doses and Timing in Adults, continued

Drug	Class	Dose and Route	Dose Timing
HALOPERIDOL (Haldol)	dopamine antagonist - Butyrophenone	0.5–2 mg IM/IV	*unknown*
PROCHLORPERAZINE (Compazine)	dopamine antagonist Phenothiazine	5–25 mg IM/IV/rectal	30 mins before EOC
PROMETHAZINE (Phenergan)	dopamine antagonist Phenothiazine	6.25 mg IM	Just after induction
PROMETHAZINE		12.5–25 mg IV/rectal	
SCOPOLAMINE	M1- Anticholinergic-muscarinic receptor antagonist	1.5 mg transdermal patch	4 hr before surgery is ideal

TABLE 5-25 Antiemetic Adjunctive

MIDAZOLAM (Versed)	Benzodiazepine	1-2 mg IV	After combination therapy given and patient nauseous postoperatively
DEXAMETHASONE (Decadron)	Corticosteroid	4–5 mg IV	Just after induction
DIMENHYDRINATE (Dramamine)	Antihistamine and Anticholinergic	1 mg/kg IV	*unknown*
DIPHENHYDRAMINE (Benadryl)	Antihistamine H_1 blockers	25-50 mg IV	Just after induction
FAMOTADINE (Pepcid)	Antihistamine H_2 blocker	20 mg IV	Pre-induction
APREPITANT (Emend)	NK-1 receptor - Substance-P antagonists	115–150 mg over 30 mins IV	Give PO 1 hour or IV 30 minutes prior to chemotherapy

Pharmacologic Combination Therapy

Because the effects of interventions from different drug classes are additive, combining interventions has an additive effect in risk reduction.

Combinations in Adults

- droperidol (max dose 1 mg IV) + dexamethasone
- 5-HT3 receptor antagonist + dexamethasone
- 5-HT3 receptor antagonist + droperidol
- 5-HT3 receptor antagonist + dexamethasone + droperidol
- 5-HT3 antagonist + promethazine + dexamethasone
- 5-HT3 antagonist + dexamethasone + scopolamine patch + IM promethazine

Combination Therapy Pearls

Corticosteroids given in combination with a serotonin receptor antagonist yield the greatest antiemetic protection.

The 5-HT3 antagonists, which have strong antivomiting efficacy (but have headache as a common side effect), can be used in combination with droperidol, which works against nausea and helps to fight headache (droperidol IM is used to treat migraine headaches).

When used in combination with another drug, ondansetron doses in adults typically should not exceed 4 mg and can be much lower.

5.15 Local Anesthetics (LA)

Provide anesthesia and analgesia by blocking voltage-gated sodium channels, disrupting the conduction of impulses along nerve fibers.

- Potency related to lipid solubility
- Speed of onset related to pKa (degree of ionization)
- Duration of action related to protein binding

Lidocaine, prilocaine, or benzocaine/cetacaine local anesthetics may cause methemoglobinemia (Hgb can carry oxygen but can't release it effectively); treat methemoglobinemia with methylene blue 1–2 mg/kg IV.

Ester LA

cheat: have one "i" in their name

General: metabolized by pseudocholinesterase into "paba"; increased allergy risk—if there is an existing allergy to an Ester LA, choose an Amide LA instead.

- **Procaine** (Novocaine)—0.5–1 %
  Max dose 12mg/kg
  Fast onset, short duration (<1hr)
  Used for spinal, infiltration, PNBs
- **Chloroprocaine**—1–3 %
  Max dose 12mg/kg
  Very quickly metabolized so very high doses can be used to speed onset
  Fastest onset, short duration (<1hr)
  Used to convert labor epidurals to surgical blocks for STAT cesarean, PNBs
- **Tetracaine** (Pontocaine)—0.5–1 %
  Max dose 3mg/kg
  Slow onset, long duration (2–6hrs)
  Used for very long-acting spinals, topical
  Motor blockade may be denser than sensory block
- **Cocaine—**blocks NE reuptake vasoconstrictor, topical use only, significant systemic absorption occurs. Solution 4% (40 mg/mL) available, max dose 1.5 mg/kg. Often used in awake airway management for local anesthetic and to decrease bleeding; can produce cardiovascular toxicity. Do not give to patients with cardiovascular disease, severe HTN, or if taking MAO inhibitor.
- **Benzocaine** (Hurricaine/Cetacaine)—spray formulations for topical anesthesia

Max dose—not available. *Cetacaine is a combination of tetracaine & benzocaine.*

Amide LA

cheat: have at least two "i's" in their name

General: metabolized by amidases in liver—CP450 system; may be safely used in patients with Ester LA allergy

- **Lidocaine** (Xylocaine)—0.5–5 %
  Max dose—4.5 mg/kg, 7 mg/kg with epi
  Fast onset, short duration (0.5–2hrs)
  Used for IV induction, IV regional, infiltration, PNB, epidural anesthesia
  Can be used as a continuous intravenous analgesic
- **Mepivacaine**—1–2 %
  Max dose—4.5 mg/kg, 7 mg/kg with epi
  Fast onset, moderate duration (2–4hrs)
  Used for infiltration, PNB, epidural
- **Bupivacaine** (Marcaine, Sensorcaine)—0.5–0.75 %
  Max dose—3mg/kg (Levobupivacaine is less cardiotoxic, but not avail in United States)
  Less motor than sensory block
  Slow onset, long duration, high cardiac toxicity
  Used for PNBs, epidural, spinal, infiltration
- **Prilocaine** 4%—used for dental nerve block
- **Ropivacaine**—0.2–1 %
  Max dose—3mg/kg
  Similar to bupivacaine with less cardiac toxicity
- **Dibucaine**—used to diagnose atypical plasmacholinesterase. Dibucaine will depress the activity of normal pseudocholinesterase by 80%; Heterozygous 60–80%; homozygous 20%.

Local Anesthetics—Absorption Rate Related to Tissue Vascularity

Affected by presence of use of a vasoconstrictor with local anesthetic

Highest absorption to lowest: *IV > tracheal > intercostal > paracervical > caudal > lumbar epidural > brachial plexus > sciatic > (topical) > subcutaneous*

Plasma Concentration of Local Anesthetic and Effects

- 1–5 mcg/mL: analgesia
- 5–10: lightheaded, tongue numb, tinnitus, muscle twitch
- 10–15: seizures, unconscious
- 15–25: coma, respiratory arrest
- >25: CV depression

Excitatory precedes depression: signs/symptoms (s/s)

Asleep patient: first s/s heart arrhythmia and collapse

Awake patient: central nervous system s/s

LA Toxicity

Avoid intravascular injection, prevention is paramount (aspirate prior to injection, small test dose), use appropriate monitoring.

- Treatment if signs of toxicity occur:
  - Stop local anesthetic
  - Begin supportive care—ACLS: CPR, meds (may need decreased dose of epi), airway management as appropriate
- Initiate early Intralipid (IL) therapy
  - Bolus IL 20% 1.5 ml/kg over 1 minute
  - Follow by infusion of 0.25 ml/kg
  - May repeat boluses q3–5 min
  - Total dose 12 ml/kg
  - Consider early initiation of cardiopulmonary bypass

5.16 Antibiotics

Antibiotic therapy should be given within 60 minutes prior to surgical incision for adequate serum drug tissue levels at

incision. Exceptions to this include: 1) Vancomycin should be started 2 hours prior to incision; and 2) if a proximal (to incision) tourniquet is used, the entire antibiotic dose should be administered before the tourniquet is inflated. Considerations:

- Obesity has been linked to an increased risk for surgical-site infection and dosage adjustments may be warranted.

To be given via slow infusion

- Vancomycin (Red Man Syndrome)—over 30–60 mins
- Gentamicin (ototoxicity/nephrotoxicity)—over 30–60 min due to potential risk of oto-nephrotoxicity.
- Metronidazole (low pH of 4.8–5.2)—over 60 mins
- Ciprofloxacin (contains lactic acid)—over 60 mins to reduce risk of venous irritation.
- Clindamycin (potential QT prolongation)—infusion rates should not exceed 30 mg/min

Adult Dosing *See your specific institution recommendations regarding dose and redose timing.*

TABLE 5-26 Common Prophylactic Antibiotics

Antibiotic	Brand Name	Normal Dose
Ampicillin	Omnipen	2 g
Ampicillin-Sulbactam	Unasyn	3 g
Cefazolin	Ancef	1 g < 80 kg
		2 g 80–120 kg
		3 g > 120 kg
Cefotaxime	Claforan	1 g
Cefoxitin	Mefoxin	2 g
Ceftriaxone	Rocephin	2 g
Cefuroxime	Ceftin, Zinacef	1.5 g

Common Prophylactic Antibiotics, continued		
Ciprofloxacin	Cipro	400 mg
Clindamycin	Cleocin	900 mg
Ertapenem	Invanz	1 g
Fluconazole	Diflucan	400 mg
Gentamicin	Garamycin	5 mg/kg
Levofloxacin	Levaquin	500 mg
Metronidozole	Flagyl	500 mg
Piperacillin-Tazobactam	Zosyn	3.375 g
Vancomycin	Vancocin	15 mg/kg
Adjust for renal insufficiency except for ceftriaxone and clindamycin		

It is recommended that the antibiotic be redosed when two ½-lives have elapsed during a long surgical procedure.

5.17 Corticosteroids

Common IV Glucocorticoids include

- dexamethasone (Decadron): long-acting anti-inflammatory
- hydrocortisone (Cortisone, Solu-Cortef): short-acting anti-inflammatory
- methylprednisolone (Solu-Medrol): intermediate-acting anti-inflammatory

Produced by the adrenal cortex, corticosteroids work at the cellular level to decrease the inflammatory response

by inhibiting phospholipase (preventing the formation of arachidonic acid), lymphocyte alterations, cytokine expression; sodium ion channel blockade, and stabilization of the cell membrane with decreased capillary permeability. Steroids are used as an antiemetic and believed to decrease edema, blood loss, and the formation of postoperative fibrosis and scarring.

Antiemetic: **Dexamethasone (Decadron) at doses of 4 mg**, max dose 8 mg—is an effective antiemetic. It is believed to modulate the release of endorphins or inhibit prostaglandin synthesis. It has a delayed onset of action and should be given immediately after induction; it can cause genital burning in some awake patients. Caution in patients with an active infection, CHF, diabetes, or renal impairment.

Stress-dose steroids: Normal daily production of cortisol is 20 mg, but under stress the body will produce 300 mg. Perioperative stress is related to the degree of trauma and the depth of anesthetic. If patient on steroids for longer than 1 week in the last 6 months, cover with a stress dose of **Hydrocortisone 100 mg IV**. This stress dose potentiates catecholamines, epinephrine and norepinephrine, stabilizing hemodynamics. Acute adrenal insufficiency rarely occurs, but it can be life threatening and giving steroid coverage with hydrocortisone has little risk.

5.18 Drugs to Affect Heart Rate

These are agents that can be used specifically to increase heart rate and a few others that are common drugs that have the side effect of an increased heart rate.

To Increase

Anticholinergics

- glycopyrrolate (Robinul)
- Atropine

Sympathomimetic/catecholamine

- epinephrine (Adrenalin)
- isoproterenol (Isuprel)

Dopamine

Dopexamine

Ephedrine

Alpha blockers

Cardiac pacing

To Decrease

- beta-blockers
- calcium-channel blockers
- cardiac glycoside: digoxin (Lanoxin)

5.19 Beta-Blockers

Beta-Blockers: block effect of endogenous catecholamines, norepinephrine, and epinephrine at Beta receptors

First generation B-blockers were non-selective:

B1 increases HR & BP, Beta blocking will decrease HR, contraction, and BP

B2 bronchodilates, Beta blocking will constrict bronchioles

Second generation are relatively selective and more cardioselective for Beta 1 adrenoceptors.

B-Blocker Advantages: decrease HR and BP, decrease ventricular contractility heart rate (increasing diastolic time for coronary artery perfusion), MVO_2; opposes effect of endogenous catecholamines at Beta receptors.

B-Blocker Disadvantages/Contraindications: bronchospasm risk, asthma, cardiac failure, 2° and 3° heart block, severe bradycardia

TABLE 5-27 Atenolol–Labetalol

	Atenolol (Tenormin)	Brevibloc (Esmolol)	Labetalol (Trandate, Normodyne)
Receptors	B1	B1	B1 and B2, alphI
Action	Cardioselective B1 blocker	Cardioselective B blocker - short acting. **SA** node blocker	Nonselective B-blocker selective alphI blocker
Dose	1.25–5 mg	Bolus: 10–30 mg IV or 0.25–0.5 mg/kg; Infusion: 25–200 mcg/kg/min	IV bolus: 2.5–10 mg/2 min repeat q10 mins until target BP reached, max 30 mg Infusion: 500 mg/250 mL in D5W: 0.5–2 mg/min
Onset / Duration	5 mins / 6–7 hrs	1–5 min / 10-20 mins;	2 mins / 5 hrs
Used for	HTN, tachycardia	HTN, tachycardia, SVT, intra/post op HTN	HTN, tachycardia, eclampsia, aortic aneurysm or dissection; decr peripheral resistance
Side Effects	Agranulocytosis, fever, mental depression/disorientation, arterial thrombosis, bronchoconstriction	decreases CO, hypotension, negative inotrope	seizure, headache, coma, bradycardia, hypotension, CHF, bradycardia, (delta) MS, bronchospasm, fatigue, urinary retention, hypo- and hyperglycemia

Atenolol–Labetalol, continued			
Notes	Dosage decreased in renal disease; short-term management	Increase **SA** node recovery time, least likely to cause broncho-constriction. Most rapid elimination of all B-blockers-degraded by esterases	Rapidly drops BP with minimal change in HR. Alpha:Beta 1:7 IV (1:3 PO)—helps to maintain myocardial oxygen supply/demand ratio

TABLE 5-28 Lopressor–Propranolol

	Lopressor (Metoprolol)	**Propranolol** (Inderal)
Receptors	B1 blocker ++ B2 blocker +	Prototype B1 and B2 blocker
Action	Cardioselective B1 blocker	Nonselective B-blocker
Dose	IV 1.25–5 mg increments	IV 0.5–1 mg q5 mins, max 5 mg
Onset / Duration	20 mins / 3–5 hrs	2 mins / 3–6 hrs
Used for	HTN, tachycardia	Angina, arrhythmias, AMI, aortic stenosis, pheochromocytoma
Side Effects	bronchoconstriction	Opposes effect of endog-enous catecholamines at beta receptors

continues

Lopressor–Propranolol, continued		
	Lopressor (Metoprolol)	**Propranolol** (Inderal)
Notes		Preferred B-blocker with thyrotoxicosis (blocks adrenergic effect & peripheral deiodination of T4) and Pheochromocytoma. High first pass metabolism in liver, only 25% reaches systemic circulation. Highly protein bound

AME—Atenolol Metoprolol Esmolol—B1 cardio selective. . .cheat: "AME for the heart"

Continue preoperative beta-blocker if already taking. Discontinuation can lead to paradoxical hypertension, tachycardia, and angina pectoris secondary to receptor up regulation.

5.20 Angiotensin Inhibitors (Ace inhibitors; ACEi; ARB)

Renin-Angiotensin System (RAS)

↓ *renal blood flow (low BP) causes* ***renin*** *to be released*

renin converts

Angiotensinogen

to

Angiotensin I

Angiotensin I is then converted to Angiotensin II by

Angiotensin-Converting Enzyme

Figure 5-1 Angiotensinogen Renin Pathway

Cheat: generic name ends in "pril"

Angiotensin II is the active hormone. It has two main effects:

- potent vasoconstrictor
- releases aldosterone from adrenal cortex causing water reabsorption by the kidneys

Used to: treat congestive heart failure, essential and malignant HTN, kidney complications from diabetes mellitus, and for treatment after myocardial infarction.

Action:

- inhibit angiotensin converting enzyme (ACE), preventing angiotensin I from becoming angiotensin II in the lung
- decrease blood pressure by relaxing blood vessels, decreasing myocardial oxygen demand
- decreases peripheral vascular resistance
- decreases aldosterone secretion and decreases Na+ and water retention by reducing water reabsorbed by the kidneys, lowering blood volume (helps with CHF)
- decreases potassium loss; ACEi should not be given with potassium-sparing diuretic.

ACEi Advantages: highly effective in renovascular hypertension

ACEi Disadvantages and Side Effects: cough, angioedema, hyperkalemia,

ACEi Precautions: aortic stenosis, hypovolemia

Notes:

Dosages of all ACE inhibitors (except fosinopril) should be reduced with renal dysfunction as ACEi's can decrease glomerular filtration rate. Fosinopril has substantial biliary excretion, and renal insufficiency does not alter its metabolism.

TABLE 5-29 ACEi Name and Dose

Generic Name	Brand Name	Dose IV	Dose PO
benazepril	Lotensin	—	10 mg/day
captopril	Capoten	—	6.25 to 25 mg 2–3 x/day
enalapril	Vasotec	1.25 mg IV slowly every 6 hours (max 5 mg IV q 6 hrs)	start 2.5 to 5 mg/day
fosinopril	Monopril	—	10 to max 80 mg/day
lisinopril	Prinivil, Zestril	—	10 to max 80 mg
moexipril	Univasc	—	7.5 mg to max 30 mg
perindopril	Aceon	—	4 to 8 mg/day
quinapril	Accupril	—	5–10 to max 80 mg/day
ramipril	Altace	—	2.5 to max 20 mg/day
trandolopril	Mavik	—	1 to max 8 mg/day

Angiotensin-Receptor Blockers (ARBs): also modify the renin–angiotensin system by directly inhibiting the effects of angiotensin II, but they do not inhibit the breakdown of bradykinin and patients do not have the associated dry cough, angioedema, and renal complications that can occur with ACEi's. Used to treat the same conditions as ACEi.

Examples of ARBs: irbesartan (Avapro), losartan (Cozaar), olmesartan (Benicar), telmisartan (Micardis), valsartan (Diovan)

5.21 Calcium Channel Blockers (CCB)

Inhibits Ca++ ion influx across heart and smooth muscle cells.

General Advantages: decreasing myocardial contractility and oxygen demand; dilates coronary arteries, peripheral vasodilation with decreased afterload, decreased BP. Good with asthmatics, instead of B-blockers.

Disadvantages: severe bradycardia, heart failure, peripheral edema

Decrease dosing with myocardial ischemia or instability.

Should be continued throughout the preoperative period for patients going for surgery.

TABLE 5-30 CCB-Clevidipine–Diltiazem

	Clevidipine (Cleviprex)	Diltiazem (Cardizem)
Mix	Provided in 50 or 100 mL vials, 0.5 mg/mL; do not dilute.	125 mg/100 mL D5W, NS
Dose	Infusion only: 1–2 mg/hr, adjust dose q 5–10 mins; max dose 16 mg/hr	Loading Dose: 0.25 mg/kg IVP over 2 minutes; may repeat bolus in 15 minutes if necessary with 0.35 mg/kg over 2 minutes. Infusion: 5–15 mg/hr
Onset/ Duration	2–4 mins / end of infusion	2–5 mins / 3–5 hrs
Used for	HTN	HTN, rapid ventricular response with A Fib. or A Flutter; PSVT

continues

CCB-Clevidipine–Diltiazem, continued

	Clevidipine (Cleviprex)	Diltiazem (Cardizem)
Contraindications	Allergy to soy or eggs, severe aortic stenosis	sick sinus syndrome, VT, second- or third-degree heat block, WPW, hypotension, shock, concurrent use with IV beta-blocker
Notes	Does not protect against effects of abrupt B-blocker withdrawal.	IV diltiazem has less negative inotropic action than verapamil and preferred CCB in patients with LV failure
Negative inotrope	+	0
Negative chronotrope	+	0
Coronary vasodilator	+	+++
Systemic vasodilator	+	++

TABLE 5-31 CCB-Nicardipine–Verapamil

	Nicardipine (Cardene)	Nifedipine (Procardia)	Verapamil (Calan, Isoptin)
Mix	25 mg/240 mL D5W, NS	—	—
Dose	Initiate: 5 mg/hr (50 mL/hr). Incr. by 2.5 mg/hr (25 mL/hr) q5–15 mins to max of 15 mg/hr (150 mL/hr)	10–30 mg PO or sublingual, Max 180 mg/day *not given IV*	IV: 2.5–10 mg over 2 mins, 2nd dose 5–10 mg after 30 mins; max total dose 20 mg
Onset/ Duration	5–15 mins / 50 hrs	5–10 min / 6–8 hrs	1–5 min / 3 hrs

Pharm

CCB-Nicardipine–Verapamil, continued			
Used for	HTN; arterial vasodilator, antianginal, significantly decr. SVR.	HTN, antianginal, direct vascular smooth muscle relaxation; coronary vasodilator; used for rate control in SVT.	SVT (antiarrhythmic), HTN, antianginal, increase CO, decrease SVR; no increase in ICP. Diltiazem preferred in patients with severe LV dysfunction.
Contraindications	Severe aortic stenosis, sick sinus syndrome, second- or third-degree heart block Not compatible with NaHCO3 (5%) or lactated ringers. Dose adjustment in renal or hepatic impairment	Sick sinus syndrome, second- or third-degree heart block. dose adjustment in renal or hepatic impairment, porphyria. Can cause ventricular arrhythmias.	Sick sinus syndrome, second- or third-degree heart block. Dose adjustment in hepatic impairment. Can cause ventricular arrhythmias.
Negative inotrope	0	0	+
Negative chronotrope	+	0	0
Coronary vasodilator	+	++++	++
Systemic vasodilator	+	++++	++

5.22 Vasopressors–Inotropes

All vasoconstrictors can cause tissue necrosis with extravasation

TABLE 5-32 Dobutamine-Ephedrine

	Dobutamine (Dobutrex)	**Dopamine** (Intropin)	**Dopexamine** (Dopacard)	**Ephedrine**
Receptors	Direct acting synthetic catecholamine—strong beta 1, weak beta 2 agonists	Endogenous sympathetic catecholamine. Direct & indirect agonists mod A1, B1, D1;	Potent agonists B2 & D2, weak B1, moderate D1; no effect on alpha receptors.	Noncatecholamine sympathomimetic, stimulates NE Direct and indirect agonists Alpha 1, B1-2
Action	Inotrope	Inotrope, vasoconstrictor	Cardiac stimulant	Inotrope, chronotrope
Mix	500 mg/250 mL D5W or NS	400 mg/250 mL NS, LR or D5W	Mix in D5W or NS to 800 mcg/mL	50 mg in 250 mL NS or D5W
Concentr.	2000 mcg/mL	1600 mcg/mL		0.2 mg/mL

Dose	2–20 mcg/kg/min; Max 40 mcg/kg	**dopa1 (inodilator):** 0.5–3 mcg/kg/min **beta1** 3-10 mcg/kg/min **alpha1 (inoconstrictor):** 10–20 mcg/kg min	*POSSIBLE APPROVAL IN USA SOON*. IV infusion 0.5–1 mcg/kg/min Max 6 mcg/kg/min	Bolus: 2.5–10 mg Infusion: 2–20 mcg/min; max 150 mg/24 hrs
Onset / Duration	1–4 mins / 10–20 mins	2–3 mins / 10–15 mins	unknown / 11 mins	Immediate / 10–60 mins
Used for	To incr CO without much incr. in HR; heart failure, low cardiac output states	Hypotension, low CO; to incr renal & mesenteric blood flow, shock	Mild inotrope & chronotrope; arterial vasodilation to decr SVR and pulmonary vasc resistance	Increase CO, myocardial contractility, give if hypotensive with slow HR
Side Effects	HTN, arrhythmias, tachycardia, coronary artery vasodilator, hypokalemia, improved urinary output	Angina, arrhythmias, increases PAP	Causes nausea and vomiting, arrhythmias, angina	HTN, tachycardia, bronchodilator

continues

Dobutamine-Ephedrine, continued

	Dobutamine (Dobutrex)	**Dopamine** (Intropin)	**Dopexamine** (Dopacard)	**Ephedrine**
Notes	Contraindicated in idiopathic hypertrophic subaortic stenosis. Does not cause release endogenous norepinephrine	Contraindicated in pheochromocytoma, tachyarrhythmias; induces release of stored norepinephrine; Use with MAO inhibitors may cause HTN crisis	Contraindications: thrombocytopenia, aortic stenosis, HOCM, pheochromocytoma. Dopaminergic agonist—has advantages over dopamine -less arrhythmogenic & alpha vasoconstrictor effects	No effect on uterine blood flow. Don't give in patients with hypersensitivities to other sympathomimetics; angle-closure glaucoma, thyrotoxicosis
HR	minimal	increase	increase	increase
BP	minimal increase	increase	slight decrease	increase
SVR	decreased	no effect to increased	decrease	decrease
PVR	decreased	no effect to increased	no effect	increase

TABLE 5-33 Epinephrine–Norepi

	Epinephrine (Adrenalin)	Isoproterenol (Isuprel)	Norepinephrine (Levophed)
Receptors	Endogenous sympathetic catecholamine. Direct acting agonists, Alpha 1, beta 1–2	Synthetic catecholamine pure Beta 1 & 2 agonists	Endogenous sympathetic catecholamine. Direct acting, potent alpha 1, moderate B 1 & 2 agonists
Action	Inotrope, vasoconstrictor	Chemical pacemaker, has inotropic & chronotropic properties	Inotrope, vasoconstrictor
Mix	4 mg/250 mL NS or D5W	2 mg / 250 mL D5W or NS	4 mg/250 mL D5W or D5NS
Concentr.	16 mcg/mL	8 mcg/mL	16 mcg/mL
Dose	ACLS IV push: 1 mg q 3 mins **Beta2:** 1–2 mcg/min; **Beta 1:** 2-5 mcg/min **Alpha 1:** 5–10 mcg/min **Alpha & Beta:** 10–20 mcg/min or 0.01–0.2 mcg/kg/min	Bolus IV: dilute 0.2 mg Isuprel in 9 mL of NS - 0.02–0.06 mg IV infusion 0.5–5 mcg/min	Initial infusion: 0.5–1 mcg/min Maint infusion; 2–12 mcg/min or 0.01–0.2 mcg/kg/min
Onset / Duration	30 secs / 20–30 mins	Immediate / < 1 hr	30 secs / 3 mins
Used for	To increase CO & increase BP; bradycardia, for bronchospasm, asthma, shock	Use with CHF with bradycardia; drug of choice for treatment of bradycardia in patient with complete heart block. Asthma or pulmonary HTN	Refractory hypotension, shock; increases SVR

continues

Epinephrine–Norepi, continued

	Epinephrine (Adrenalin)	Isoproterenol (Isuprel)	Norepinephrine (Levophed)
Side Effects	Vent. ectopy, HTN, angina, bronchodilation. hyperglycemia due to anti-insulin effect. SVR may be decreased, maintained, or increased depending on dose	Increased contractility & CO, bronchodilator, hypotension, myocardial ischemia, supraventricular arrhythmias	Variable CO, decr renal blood flow, hyperglycemia; angina, tachyarrhythmias
Notes	Significant increase in myocardial oxygen demand. Prototype adrenergic agonist; activated via adrenal medulla Use with MAO inhibitors may cause HTN	Increases myocardial demand with increased heart rate. Do not use as a vasopressor	Increases myocardial oxygen demand. Intense constriction in all vasc beds; give through central line if possible. Avoid MAO inhibitors
HR	increase	increase	reflex brady
BP	increase	sl. incr or no effect	increase
SVR	increase	decrease	increase
PVR	increase	decrease	increase

TABLE 5-34 Phenylephrine–Vasopressin

Phenylephrine (Neosynephrine)	Vasopressin (Pitressin)
Direct acting, Alpha 1 agonist	endogenous antidiuretic hormone; V1: blood vessels; V2: collecting tubule in kidney
Direct vasoconstrictor	direct arterial, mesenteric vasoconstriction through activation of smooth muscle receptors
20 mg/250 mL D5W or NS	40 u in 100 mL
80 mcg/mL	0.4 u/mL
Bolus: 40–160 mcg infusion: 10–200 mcg/min or 0.01–0.2 mcg/kg/min	IV bolus: 40 u Infusion: 0.20.4 u/min to max 0.9 u/min
Immediate / 5–15 mins	1–3 mins / 45 mins
Use in vasodilated state with tachycardia, to slow HR in SVT with hypotension; low SVR	Alternative to epinephrine in treating countershock-refractory vent fibrillation (VF), maintaining adequate SVR sepsis. Diabetes insipidus insufficient ADH.
Arrhythmias, HTN	Avoid with vascular disease; H_2O reabsorption in renal tubules; decr urine, decr in splanchnic blood flow & in platelet concentration
No effect on myocardial oxygen demand. Decr renal, splanchnic & cutaneous flow, decr coronary flow. Avoid MAO inhibitors.	no actions on β-adrenergic receptors, so it may produce less tachycardia than epinephrine; metabolic acidosis
reflex brady	no change
increase	increase
marked increase	marked increase
minimal increase	unknown

5.23 Vasodilators

Vasodilator-Alpha Blockers

Beta-blockade may be instituted when alpha blockers are initiated to attenuate tachycardia.

TABLE 5-35 Phentolamine

Alpha Blockers	Phentolamine (Regitine)
Class	Competitive antagonist at alpha$_{1\text{-}2}$, histamine and serotonin receptors
Action	Primarily arterial vasodilation with little venodilation.
Mix	10 mg in 500 mL D5W
Concentr.	20 mcg/mL
Dose	Bolus: 1 to 5 mg or 30–70 mcg/kg IV infusion: 1 to 20 µg/kg/min or 0.5–1 mg/min
Onset / Duration	Immediate / 10–30 mins
Used for	Good for high norepinephrine states, i.e., pheochromocytoma or clonidine withdrawal
Side effects	Hypoglycemia, hypotension, AMI, arrhythmias, histamine release, increased gastric acid, cerebrovascular spasm
Notes	α2 stimulation decreases NE release. Used if vasopressors infiltrated into tissue from peripheral IV. See unopposed beta effects.
HR	reflex increase
Contractility	increased
BP	decreased
SVR	large decrease
PVR	decreased slightly
Preload	decreased

Vasodilator-Ganglionic Blocker

TABLE 5-36 Ganglionic Blocker

Ganglionic Blocker	Trimethaphan (Arfonad)
Used for	HTN emergencies
Action	Peripheral vasodilation, reflexive tachycardia, competes with nicotinic acetylcholine transmission
Dose	10–20 mcg/kg/min
Side effects	prolonged neuromuscular blockade and potentiation of neuromuscular blocking agents, hypotension, urinary retention; pupillary mydriasis, histamine release; rapid onset tachyphylaxis
Notes	Ganglionic blockers interfere with neurotransmission at ANS ganglia without inducing nicotinic neuromuscular blockade

Vasodilator-Phosphodiesterase Inhibitors

Do not stimulate either alpha or beta receptors; they act as an inotrope and vasodilator by inhibiting phosphodiesterase. Blocking the phosphodiesterase enzyme prevents the breakdown of cAMP and cGMP (intracellular second messengers), which can have many effects, including smooth muscle relaxation. These drugs are also used to inhibit platelet aggregation.

TABLE 5-37 Phosphodiesterase Inhibitors

	Enoximone (Perfan)	Inocor (Amrinone or Inamrinone)	Milrinone (Primacor)
Class	imidazole phosphodiesterase inhibitor	Pyridine phosphodiesterase inhibitors	
Action	vasodilator, weak inotrope & chronotrope.	Inotrope, vasodilator; does not act via beta receptors	
Mix	Unknown, new to U.S.	400 mg in 250 mL in 0.9% NS Do not mix in dextrose solutions	50 mg/200 mL in D5W or NS
Concentr		1.6 mg/mL	200 mcg/mL
Dose	Loading: 0.25–1 mg/kg slow IV Infusion: 1.25–7.5 mcg/kg/min; max 24 mg/kg/24 hrs	0.75 mg/kg over 2–3 mins, repeat in 30 mins if needed. Infusion: 5–20 mcg/kg/min, max 10 mg/kg daily	Load: 50 mcg/kg over 10 mins Infusion: 0.375–0.75 mcg/kg min
Onset / Duration	Rapid onset / elim half-life is about 3–4 hours in normal subjects but about 7 hours in patients with cardiac failure	2–5 mins / 0.5–2 hrs	5–15 mins / 3–6 hrs
Used for	CHF	Treats decreased CO and CHF; to decrease SVR/preload; pulmonary HTN	Treats decreased CO and CHF, pulmonary HTN, RV failure; given to decrease SVR/preload

Phosphodiesterase Inhibitors, continued			
Side Effects	Decreases CO and reduces ventricular preload in cardiogenic shock	Decreases preload; hypotension, decreases SVR and PVR	
	Does not increase myocardial oxygen consumption	Tachycardia at higher dosing, arrhythmias, hepatotoxicity	Tachyarrhythmias (SVT), ventricular arrhythmias, hypotension, angina, hypokalemia, thrombocytopenia
Notes	abnormal LFTs, thrombocytopenia. 1/10th as potent as milrinone		Dose adjustment needed in renal disease

Natural Vasodilators: bradykinin, histamine, serotonin, prostaglandins, ↑ K, ↑ H, ↑ CO_2, ↑ Mg, ↑ Na

In treating hypertension, before vasoactive medications are given, other pharmacologic interventions include giving or increasing: volatile anesthetics, opioids, propofol, etc.

Controlled Hypotensive Technique

General antihypertensives include: alpha and beta blockers, calcium channel blockers, angiotensin II antagonist, ace inhibitors, phosphodiesterase inhibitors, ganglionic blockers; diuretics.

Pharmacologically lowering blood pressure can be done to a predetermined level to minimize blood

loss, improve surgical visibility, and decrease transfusion requirements. Done in all types of surgical cases but especially neurosurgery, orthopedics, and in patients who choose not to receive blood products (Jehovah's Witness) or who may be difficult to cross-match. Use caution in patients with cardiac/renal/cerebrovascular/peripheral vascular disease, chronic hypertension, fixed cardiac output, and/or anemia. Meticulous attention to mean blood pressure is important, especially in cases where the patient is in the prone or sitting (beach-chair) positions.

Correlating to lower limit of cerebral perfusion pressure (CPP) will help to maintain adequate perfusion to vital organs. CPP = MAP—CVP (or ICP).

A gradual decrease in BP is much preferred to a rapid decrease.

Complications Related to Reduced Tissue Perfusion: delayed recovery, renal disturbances, reflex tachycardia, cerebral thrombosis, hepatic necrosis, MI and/or cardiac arrest, blindness

TABLE 5-38 Fenoldopam–Nisiritide

	Fenoldopam (Corlopam)	Hydralazine (Apresoline)	Nisiritide (Natrcor)
Action	Vasodilator- D1 agonist—stimulates cAMP	Direct arterial vasodilator	B-type natriuretic peptide (BNP)—venous & arterial vasodilator
Mix	20 mg/500 mL 1.5NS or D5W	—	1.5 mg in 250 mL D5W, NS
Concentr.	40 mcg/mL	20 mg/mL	6 mcg/mL

Fenoldopam–Nisiritide, continued			
Dose	Start infusion at 0.01 mcg/kg/min, double dose at 5–10 min intervals until BP controlled—max dose of 1.6 mcg/kg/min.	2.5–40 mg, dose over 1 min, repeat as needed.	Bolus: 2 mcg/kg IV; Infusion: 0.01 mcg/kg/min Max dose 0.03 mcg/kg/min
Onset / Duration	< 2 mins / 1–4 hrs	5–20 mins / 2–6 hrs	15 mins / > 60 mins
Used for	Rapid decr in BP. Good in management of perioperative hypertension or in patients with renal dysfunction-decr renal vasc resistance & stimulates diuresis.	HTN with slow heart rate, CHF unresponsive to digoxin and diuretics	CHF with dyspnea at rest, Decreases R atrial pressure, PCWP, SVR; improves CO
Side Effects	Hypokalemia, hypotension, tachycardia, peripheral edema	Sodium retention, can increase CO	Hypotension, fever, lethargy, syncope, chest pain; renal dysfunction
Notes	Use < 48 hours. Has no alpha or beta activity with no effect on HR or contractility	Smooth muscle relaxation; use cautiously in CV or cerebrovascular disease	Endogenous hormone released by ventricles in volume overload. Do not shake vial of drug, rock gently. Caution in renal dysfunction

continues

Fenoldopam–Nisiritide, continued

	Fenoldopam (Corlopam)	Hydralazine (Apresoline)	Nisiritide (Natrcor)
HR	reflex tachycardia	can cause tachycardia	0
BP	decrease	decrease	decrease
SVR	decrease	decrease	decrease
PVR	0	0	decrease

TABLE 5-39 Nitroglycerin–Nitroprusside

Nitroglycerin (Tridil)	Sodium Nitroprusside (SNP, Nipride)
Vasodilator: venous > arterial; decreases preload	Release of nitric oxide causing vasodilation: arterial > venous; decreases preload & afterload
50/250 premix	100 mg/250 mL D5W
200 mcg/mL	400 mcg/mL
5–400 mcg/min 1 mL/hr = 3 mcg/min, max 200 mcg/min or 0.2–4 mcg/kg/min	Infusion: 10–280 mcg/min or 2–4 mcg/kg/min Max: 10 mcg/kg/min
1–2 mins / 3–5 mins	30 secs / 1–10 mins
Angina, coronary artery spasm, acute MI, increased preload; to decrease preload/CVP, CHF; decr LVEDP & LVEDV, decr myocardial O2 consumption	Rapid decr in BP; HTN, to decrease SVR (afterload), aortic dissection, LV dysfunction

Nitroglycerin–Nitroprusside , continued	
Hypotension, increased cerebral blood flow; headaches, methemoglobinemia	Hypotension, palpitations, increased cerebral blood flow, methemoglobinemia
Marked reduction in preload, some reduction in afterload; can cause methemoglobinemia. Increases cerebral blood flow. Use glass bottle and special tubing for infusion	Can cause cyanide and thiocyanate toxicity. Contraindicated in pregnancy and renal disease. Degraded by light; cover infusion bag
reflex tachycardia	increase
decrease	decrease
decrease	decrease
decrease	decrease

5.24 Antiarrhythmic IV Agents

All antiarrhythmic drugs are used cautiously in patients with renal or hepatic disease. When renal or hepatic dysfunction is present, a dosage reduction may be necessary.

TABLE 5-40 Adenosine–Diltiazem

	Adenosine (Adenocard)	Amiodarone (Cordarone)	Bretylium (Bretylol)	Diltiazem (Cardizem)
Mix	not diluted	900 mg in 500 mL D5W only	2 Gm in 500 mL in D5W premix	125 mg in 125 mL NS or D5W
Concentration	3 mg/mL	1800 mcg/mL	4 mg/mL	1 mg/mL
Dose	6 mg by rapid IV bolus, if no results, repeat 1–2 min later with 12 mg rapid bolus.	Infusion only, give med thru filter: Load 150 mg in 100 mL over 10 mins, then, 1 mg/min (360 mg) over next 6 hours, then decrease to 0.5 mg/min (540 mg) over next 18 hrs	IV bolus: 5 mg/kg over 15–30 sec, repeat as necessary to max 30 mg/kg in 24 hrs. Infusion: 1–2 mg/min	0.25 mg/kg over 2 mins, may repeat in 15 mins with 0.35 mg/kg. May follow with infusion at 5–15 mg/hr for up to 24 hrs.
Action Use	Converts PSVT to N SR—interrupts re-entrant pathway in AV Node	Suppression of VFib, pulseless VTach. Prolongs action potential and refractory period	Treat VTach & other ventricular arrhythmias resistant to lidocaine, prophylaxis against VFib	Antianginals, antiarrhythmic (SVT, rapid ventricular AFib or Aflutter), antihypertensive (calcium channel blocker)

Onset / Duration	Immediate / 1–2 mins	2 hrs / peak 3–7 hrs / unknown duration	5–10 mins / 6–24 hrs	2–5 min / peak 2–4 hrs / duration unknown
Side Effects	Flushing, asthma, chest discomfort	Hypotension, CHF, ARDS, pulmonary fibrosis, pulmonary toxicity, increases PR and QT intervals, decreases pulmonary vascular resistance	Hypotension, angina, bradycardia	Hives, flushing, AV block, arrhythmias, CHF, hypotension, Stevens-Johnson syndrome
Contraindication	Contraindicated in SSS or second- or third-degree AV block	Contraindicated in cardiogenic shock, second- or third-degree AV block, SSS	No specific contraindications	Contraindicated in SSS or second- or third-degree AV block, recent MI, systolic BP < 90 mmHg
Notes		Decrease FIO2 to < 80% when on Cordarone	Dose timing increased with renal insufficiency	

TABLE 5-41 Ibutilide-Quinidine

	Ibutilide (Corvert)	**Lidocaine** (Xylocaine)	**Procainamide** (Pronestyl)	**Quinidine** (Quinidex)
Mix	Undiluted: 0.1 mg/mL Give 1 mL/min	2 gm in 250 mL D5W	2 g/250 mL of 0.9% NS	800 mg quinidine (10 mL) in 50 mL D5W
Concentration	0.1 mg/mL	8. mg/mL	8 mg/mL	16 mg/mL
Dose	> 60 kg: 1 mg over 10 mins, may be repeated 10 mins after end of dose < 60 kg: 0.01 mg/kg over 10 mins, may be repeated 10 mins after end of dose	IV push: 1–1.5 mg/kg; may repeat doses of 0.5–0.75 mg/kg q 5–10 min up to a total dose of 3 mg/kg; may then start continuous fusion of 1–4 mg/min.	IV push: 10 to 50 mg/min (or 100 mg every 2–5 mins) up to 17 mg/kg or until arrhythmia suppressed, hypotension or QRS widened > 50%. If arrhythmia disappears, start IV infusion: 1–4 mg/min	200–400 mg at rate ≤ 10 mg/min until arrhythmia suppressed, hypotension, bradycardia or QRS complex widened
Action Use	Conversion recent onset AFib/Aflutter to NSR	VTach, VFib, stable wide complex vent ectopy	Ventricular and atrial arrhythmias, decreased CO, maintenance of NSR after conversion from AFib/AFlutter	AFib/AFlutter, prevention of recurrent ventricular arrhythmias, decrease myocardial excitability, slow conduction velocity

Onset / Duration	45 mins / ≤ 24 hrs	immediate / 10–20 min	immediate / 3–4 hrs	1–5 min / 6–8 hrs
Side Effects	arrhythmias	Seizures, cardiac arrest, anaphylaxis, CNS depression, AV block, hypotension, paresthesia	Seizures, asystole, heart block, ventricular arrhythmias, cardiac arrest, hypotension, agranulocytosis, Rapid IVpush can cause VFib or asystole.	Hypotension, torsades de pointes, agranulocytosis
Contraindication	hypersensitivity	Third-degree heart block	AV block, myasthenia gravis	Conduction defects (in the absence of a pacemaker), myasthenia gravis
Notes	Activates slow inward current of sodium in cardiac tissue, resulting in delayed repolarization, prolonged action potential duration	Caution with liver disease and all heart blocks	Dose adjustment in renal or cardiac disease	Decrease myocardial excitability, slows conduction velocity

5.25 Herbals

All herbal supplements should be discontinued 2 weeks before surgery.

TABLE 5-42 Herbals

Risk with anesthesia / surgery	Herbal	Used for:
Increased bleeding risk	Black cohosh	Used to decrease BP; can cause bleeding
	Gingko biloba	Taken to improve memory, enhances antiplatelet and anti-thrombotic; can cause bleeding
	Garlic	Used to lower BP and cholesterol, inhibits platelet aggregation. Can increase effects of blood thinners with increased bleeding
	Ginseng	Inhibits clotting; interferes with warfarin
	Ginger	Increased risk of bleeding, esp. if taken with aspirin and ginkgo
	Fish oil	Promotes blood thinning; can increase bleeding
	Dong quai	Used for menopausal/menstrual symptoms, shown to affect estrogen and other hormones; might slow blood clotting
	Feverfew	Used to treat migraine headaches, arthritis, menstrual cramps, to reduce inflammation
	Hoodia	Appetite suppressant; can increase bleeding

Herbals, continued		
Cardiovascular risk	Ephedra (ma-huang)	Used for weight loss and asthma. Can cause HTN, tachycardia, arrhythmias, and stroke
	Garlic	Can drop BP
	Ginseng	Energy boost; can cause HTN and tachycardia
	Hoodia	Can increase or decrease BP depending on other meds patient taking
	Guarana	Caffeine active ingredient; can increase BP, cause cerebral vasoconstriction
Sedating risk	Kava	Decreases anxiety, CNS depress/sedative—potentiate barbiturates/benzodiazepines/muscle relaxants
	St. John's wort	Relieves depression and anxiety; can cause sedation. Inhibit serotonin neurotransmitters reuptake (similar to SSRI Prozac)
	Valerian	Relieves anxiety; can cause sedation. May increase GABA levels
	Gingko biloba	Improves memory; can cause increased sedation
	Ginger	Antiemetic, anti-inflammatory; can increase sedation

continues

Herbals, continued

Risk with anesthesia / surgery	Herbal	Used for:
Interact with other medications	Echinacea	Increase immunity to fight colds, infections; can lead to liver inflammation/damage with anesthesia. Contraindicated in autoimmune diseases
	Kava	Calms anxiety; can cause liver damage
	Licorice	Used to treat heartburn; can cause hypokalemia; can cause excess mineralocorticoid activity manifested by sodium/water retention, hypervolemia, HTN, and edema
	St. John's wort	Alters metabolisms of other drugs (cyclosporine, warfarin, steroids)
	Valerian	Relieves anxiety; can cause irregular heart rhythm
	Hoodia	Appetite suppressant; can injure liver cells
Photosensitivity (skin laser procedure)	St. John's wart	Photosensitivity rarely occurs with very high doses
	Dong quai	Increased photosensitivity
Hypoglycemia	Ginseng	Energy boost; can lower blood sugar
	Hoodia	Shown to affect hormones; can make brain see blood glucose levels greater than they really are