Overall Educational Goal of Elective

The goal of this rotation is to enable students to better understand the risks and hazards of anesthesia, so that they can learn to safely prepare a patient physically and emotionally for the operating room. Students will also become familiar with problems specific to anesthesia, so that they will be able to consult with the anesthesiologist regarding medical problems that may affect the patient's response to anesthesia and surgery. In the process, students will learn what it means for a patient to be in the most optimal condition before proceeding to the operating room.

Objectives

- To give students an appreciation of the field of Anesthesiology
- To teach techniques of preoperative evaluation and the implications of concurrent medical conditions in the intraoperative period
- To teach the characteristics of commonly used anesthetic agents and techniques and their risks and complications
- To acquaint students with the principles and skills involved in airway management, intravenous line insertion, and the use of invasive and non-invasive monitoring

Brief Description of Activities

Students will participate in the induction of anesthesia and the maintenance of an airway by both mask and intubation; intraoperative management including the use of various anesthetic agents; various regional anesthetic techniques; pain management for acute and chronic conditions; the anesthetic management of the obstetrical, cardiac and pediatric patient; and anesthetic goals in an ambulatory setting.

Methods of Student Evaluation

Students will be assigned to an anesthesia attending and resident who will be responsible for evaluating their progress. Evaluation will be done by observing the students involvement in the intraoperative management of the patients that they are following and their ability to handle simple anesthetic techniques. Evaluation will also be based on their general medical knowledge and additional reading pertaining to anesthesia performed during their elective.

Third-Year Medical
Student Clerkship in Anesthesiology

The clerkship consists of a two-week rotation:

Goals:

1. To give you an appreciation of this field.

2. To teach techniques of preoperative evaluation: To recognize those patients and situations that pose an increased anesthetic risk, as well as optimal preoperative therapy for such patients to minimize this risk.

3. To teach you the characteristics of commonly used anesthetic agents and techniques and their risks and complications.

4. To acquaint you with the principles and skills involved in airway management, intraoperative fluid therapy and the proper use of intraoperative monitors.

While the clinical practice of anesthesia has had a long and interesting history, it is only in the last 50 years that the specialty of anesthesiology has become a fully recognized medical discipline.

It now requires of its practitioners a broad working knowledge of pharmacology, physiology, pulmonary medicine, cardiology, endocrinology, surgery, obstetrics, pediatrics and electronics.

In addition, the anesthesiologist must be skilled in airway maintenance, regional techniques and invasive monitoring.

Other than the management of the patient in the perioperative period, this specialty is strongly committed to:

1. The teaching of cardiopulmonary resuscitation

2. Critical Care Medicine

3. The treatment of acute and chronic pain

4. Research

Part I
The Preoperative Visit

Purpose:

1. To evaluate the medical and surgical problems and ensure that the patient is in optimal condition for surgery.

2. To establish rapport with the patient, discuss the types of anesthesia available for this particular surgical procedure, and, if needed, order premedications.

The information gathering should cover the following:

1. The proposed surgical procedure - What and why.

2. Medical History - Cardiovascular (congestive heart failure, angina, valvular disease, arrhythmias, previous MI, exercise tolerance); pulmonary (asthma, chronic obstructive pulmonary disease, upper or lower respiratory infection, cigarette smoking); renal (acute or chronic renal failure, specific defects); hepatic (hepatitis, cirrhosis); central nervous system (seizures, trauma, tumor, transient ischemic attacks); endocrine, metabolic (diabetes, obesity, thyroid); gastrointestinal (potential gastroesophageal reflux).

3. Medications - Name, amount taken, how often. Many drugs taken by the patient will interact with anesthetic agents or adjuvants. Therefore, some drugs will need to be continued up to the time of surgery and some should be discontinued.

4. Allergies - To what and with what manifestations.

5. Habits - Smoking, alcohol, drug abuse.

6. Physical Exam - Vital signs, physical habitus, upper airway and auscultation of the chest are normally included. Evaluation of specific pathologic conditions, for example: motion of the temporomandibular joint and neck. Sites for IVs and proposed regional block should be evaluated.

7. Laboratory Data - Depending on the patient's medical history and the procedure they are schedule for, various lab tests might be needed:

Test	Determination	Evaluates for
CBC	Hb/Hct WBC/diff	Anemia, O_2-carrying capacity Evidence of infection
Urinalysis	Glucose Acetone Sediment	Diabetes Diabetes, starvation Renal disease, infection
SMA-6	BUN K*/Na* Glucose CO_2	Hydration, screening for renal dysfunction Diabetes Acid-base status
Chest x-ray		Primarily screening or baseline. Important in patients with known cardiac or pulmonary disease
Electrocardiogram		Routine in patients aged 45 years or older. Poor predictor of ischemic heart disease or myocardial reserve.

After all this information has been gathered and evaluated, the patient is assigned to a physical status category.

Physical status:

1. Normal healthy patient

2. Patient with mild systemic disease

3. Patient with severe systemic disease that limits activity but is not incapacitating

4. Patient with incapacitating systemic disease that is a constant threat to life

5. Moribund patient, not expected to survive 24 hours with or without surgery

"E" added to the above if emergency.

Sometimes the anesthesiologist will request a consultation from an internist or cardiologist to help him with a specific problem of medical management or to see if this patient is in optimal condition and if not what can be done to achieve it.

Finally the anesthetic plan is discussed with the patient.

General Anesthesia

General anesthesia is a reversible state characterized by narcosis (sleep), analgesia (lack of pain), muscle relaxation, and loss of reflexes, which is also associated with reversible depression of organ function. It may be divided into three phases: induction, maintenance and emergence.

The induction period begins when anesthetic drugs are administered and continues until the patient has achieved a stable plane of surgical anesthesia. It is a period of high risk, because sudden alterations in respiratory and circulatory function may occur. Airway reflexes are lost and if there is risk of regurgitation or vomiting, aspiration should be prevented by isolating the

trachea. If required, endotracheal intubation is accomplished during this period. The laryngoscopy and insertion of an endotracheal tube can cause an intense sympathetic response (tachycardia, hypertension) as well as a parasympathetic (vagal) response (bradycardia). The vagal response can be prevented or treated with an anticholinergic agent (atropine) and the sympathetic stimulus can be obtunded by topical or intravenous lidocaine, beta-adrenergic blockade or deep anesthesia. The general anesthetics depress cardiovascular reflexes and some cause vasodilation which can lead to hypotension during changes in position or by lack of stimulation.

Maintenance is the period during which the surgery is performed. If the level of anesthesia is not quite deep enough the patient may respond to the incision with a slight increase in heart rate and increased respiratory rate and volume. After providing an adequate depth of anesthesia the anesthesiologist settles down to a routine monitoring of the patient who would usually cruise smoothly through this period.
Anticipated physiologic derangements are:

- Respiratory depression (by almost all anesthetic agents), there is also impairment of ciliary mobility so that secretions tend to pool in the lungs.

- Depression of myocardial conduction tissue leading to a slower sinus rhythm, nodal rhythm or a wandering pacemaker.

- Suppression of tear production (eyes should be protected by closing them and placing lubricant for long cases).

Emergence is the period after the anesthetic is discontinued. Changes that occur during this period are: blood vessels return to their normal state of constriction, which in certain circumstances may lead to fluid overload. Pain, shivering, hypothermia-induced vasoconstriction and the presence of an endotracheal tube may lead to hypertension and increased oxygen demand. Also, laryngospasm may occur while the patient moves from a surgical plane to being fully awake.

The goal during general anesthesia is to reach a level of anesthetic depth where there is analgesia, amnesia, loss of reflexes and, if need be, muscle relaxation with minimal depression of the various organs (heart, kidneys, liver) without long lasting side effects and ready reversibility. For this we need to measure anesthetic depth, so that the exact amount of anesthetic drug can be titrated against its effect. Physical signs such as pupillary size, respiration (type, rate and depth) reflex activity, and muscle tone were reliable signs in the days of diethyl ether but have become less useful now. Decrease in blood pressure correlates well with anesthetic depth when using inhalation agents (halothane, enflurane, isoflurane). Insufficient depth of anesthesia ("lightness") may manifest as movement when not paralyzed, tachycardia, hypertension, increased respiratory rate and depth, pupillary dilation, diaphoresis and lacrimation.

To evaluate and compare the potencies of the different inhalation agents the concept of MAC is used (minimum alveolar concentration). It is defined as the alveolar end tidal concentration of an anesthetic at which 50% of subjects do not move in response to a painful stimulus (skin incision). The more potent the agent, the lower the MAC.

A number of factors significantly alter MAC (> 10% change)

Increase MAC		Decrease MAC	
Physiological	**Pharmacological**	**Physiological**	**Pharmacological**
Youth	Ethanol (chronic)	(Old) age	Ethanol (acute)
Hyperthermia	Amphetamines (acute) Ephedrine	Hypothermia	Amphetamines (chronic)
		Pregnancy (hormonal)	Nitrous oxide
		$PaCO_2$ > 90 torr	Narcotics
		Life-threatening ↓ BP, hypoxemia	Thiopental
		Induced hypotension to 60% of control with nitroprusside or trimethaphan	Diazepam, hydroxyzine Lidocaine (intravenous) Marijuana (acute, high doses) Levodopa (acute) Alpha methyldopa Clonidine Reserpine

MAC is not affected by duration of anesthesia, hypertension, hypotension (MAP >60 torr), thyroid disease, anemia (Hct >10%), acidosis or alkalosis.

General Anesthetics

General anesthetics are a diverse group of drugs that produce unconsciousness, analgesia, depression of reflexes, and muscle relaxation. They are believed to act on membranes in the central nervous system; however, their exact mechanism of action is unknown.

The ideal agent would be one that is safe, nontoxic, inert, easy to administer, pleasant for the patient, nonflammable and nonexplosive, potent in 50% O_2 and has a low blood/gas solubility coefficient. Such an agent has not been found yet. Commonly used agents today are: nitrous oxide, halothane, enflurane, isoflurane, sevoflurane and desflurane. Inhalation agents are delivered from the anesthesia machine to the patient's lungs, taken up by the blood, and distributed to the body tissue. After an initial dilution of the agent in the circuit of the machine and in the functional residual capacity of the lung, the anesthetic enters the blood according to its partition coefficient between blood and gas. (Partition coefficient is the ratio of concentration of a substance between two phases, also called "solubility"). N_2O has a low partition coefficient (is less soluble in blood) and, therefore, its partial pressure in the lungs and then in the brain rises rapidly which explains its rapid onset of action. The other inhalation agents are more soluble and have a longer induction time.

Increasing alveolar ventilation increases the delivery of anesthetic agent to the lungs and, therefore, speeds up induction of anesthesia; increased shunt (perfusion of under or non-ventilated alveoli) delays induction.

Body tissues can be classified into three categories according to their blood flow:

1. The vessel rich group (VRG): heart, brain, liver and kidneys receive 75% of the cardiac output (CO) while they make up only 10% of body weight.

2. Muscle receives 20% of CO and constitutes 50% of the body by weight.

3. Fat receives 51% of CO and constitutes $\pm$ 20% of body weight in an individual of normal build.

The VRG equilibrates with anesthetic in 5 to 15 minutes because of its abundant blood flow. Equilibration with muscle and fat are much slower. As blood flows through the lungs anesthetic moves from the alveoli to blood. As long as cerebral blood flow remains constant, increasing cardiac output to other tissues will increase anesthetic gas removal from the lungs, thus slowing anesthetic delivery to the brain and delaying induction. Similarly, decreasing cardiac output to non-cerebral tissues will shorten induction time.

The short-acting barbiturates, which are used as induction agents, are administered intravenously and thus enter the bloodstream directly where an initial dilution occurs as it mixes with the blood volume. Because of its rapid flow, the drug is delivered first to the VRG where equilibration occurs within 1-2 minutes. If only a single dose of barbiturate is given, as during a typical induction, the concentration of drug in the VRG will fall as uptake by muscle and fat continues, reducing blood levels. In addition, a certain fraction of the drug is being metabolized by the liver, further lowering blood levels. The redistribution from VRG to other tissues accounts for the short duration of action seen clinically with single dose administration of the short acting barbiturates.

Elimination occurs by metabolism and excretion (lungs, kidneys) and is the mirror image of uptake. The insoluble agents N_2O have a shorter recovery time than the soluble ones (halogenated agents). Duration of exposure plays a role, for if fat has been allowed to "soak up" large quantities of anesthetic, recovery will be prolonged with all but the very insoluble agents.

Commonly Used Drugs

Barbiturates - Ultrashort acting are thiopental (Pentothal), thiamylal (Surital), and methohexital (Brevital). They belong to the hypnotics; given in a large dose they will produce sleep. They will also depress reflexes and are potent myocardial and respiratory depressants. They do not provide any analgesia.

Benzodiazepines - Tranquilizers - sedative, anxiolytic and amnestic properties. Diazepam (Valium) - drawbacks are: very long acting and irritating when injected intravenously. Midazolam (Versed) - water soluble and, therefore, nonirritating; much shorter half-life.

Propofol - a lipid soluble isopropylphenol that produces rapid induction of anesthesia followed by awakening in 4 to 8 minutes. The more rapid return to consciousness with minimal residual central nervous system effects is the most important advantage, especially for outpatient surgery or brief procedures. Propofol is a potent myocardial and respiratory depressant. Has an antiemetic effect. Pain on injection - give lidocaine with injection.

Ketamine - Structurally related to the veterinary anesthetic phencyclidine (Sernylan). It is a non-barbiturate intravenous general anesthetic, but differs from the barbiturates because it tends to support, rather than depress, the cardiovascular system. This is by sympathetic stimulation causing an increase in heart rate and hypertension. Other possible adverse effects are hallucinations and psychologic disturbances after recovery. Given in increments it will first produce a pharmacologic state in which the patient does not lose consciousness but is emotionally detached from and disinterested in the environment (called "dissociative anesthesia" with amnesia and analgesia), then in larger doses it will produce unconsciousness (general anesthesia).

Local Anesthetic (LA)

An agent which produces a transient and reversible loss of sensation in a circumscribed portion of the body. This primary effect of LAs is due to the decreased permeability of the nerve membrane to sodium ions, thereby preventing an action potential. The nerve membrane remains in a polarized state, and the block produced by LAs is therefore known as nondepolarizing nerve block. Modern LAs (all weak bases) are classified as either amides or esters depending on their chemical linkages. Most LAs are combined with an acid (usually hydrochloric) to form a salt which is stable and soluble in water. Esters such as procaine (Novocain) and tetracaine (Pontocaine) are mainly hydrolyzed in the plasma by esterases, whereas amides, such as lidocaine (Xylocaine) and bupivacaine (Marcaine) are metabolized in the liver. The toxicity of a LA is dependent on the plasma level of the drug. This, in turn, is influenced by the rate of absorption into the bloodstream, degree of plasma binding, rate of distribution to the tissues, and rate of removal via tissue metabolism and/or excretory pathways. Most LAs (except cocaine) have vasodilating properties, the clinical effects of which are to increase the rate of absorption of the drug in the blood, thereby increasing the anesthetic level in the blood and the potential for overdose. Absorption of the LA is also dependent on the injection site, the degree of vasodilation, the dose, and the presence of a vasoconstrictor in the solution. Vasoconstrictors, such as epinephrine, are frequently added to the LA solution (used for nerve block or infiltration) to prevent absorption of the drug, prolong its local pain control activity and reduce systemic reactions. Once the LAs are absorbed from the injection site, they can affect the cardiovascular system and central nervous system (CNS) (paradoxical excitation and then CNS depression and cardiac depression with increasing dose). Side effects, such as anxiety, tachycardia, and hypertension, may be related to the added epinephrine. In general, toxic reactions are related to overdosage or, rarely, to allergic manifestations. Lidocaine is also used intravenously for its antiarrhythmic affect.

Some facts about local anesthetics (Doses listed for adults)

Generic Name	Trade Name	Relative Potency	Latency	Duration (min)	Maximum (mg)	Dosage (mg/kg)	Comments
Esters							
Procaine	Novocaine	1	Slow	60-90	600-1000	8.5-14	-
Chloroprocaine	Nesacaine	1	Fast	30-60	800-1000	11-14	Transfer across placenta minimal
Tetracaine	Pontocaine	6	Slow	180-600	20	0.25	
Amides							
Mepivacaine	Carbocaine	2	Fast	120-240	300-400	4-5.5	
Prilocaine	Citanest	2	Fast	120-240	600	8	Methemoglobinemia
Lidocaine	Xylocaine	2	Fast	90-200	300-500	4-7	Sedation at toxic levels
Etidocaine	Duranest	6	Fast	180-600	300-400	4-5.5	Motor block greater than sensory block
Bupivacaine	Marcaine	8	Slow	180-600	75-150	1-2	Difficult resuscitation after overdose

Narcotics - (opioids) are potent analgesics and sedatives. Their main side effects are respiratory depression (all), histamine release (esp. morphine) causing hypotension and bronchoconstriction, nausea, vomiting, constipation and urinary retention. The most commonly used are morphine, meperidine (Demerol) and fentanyl (Sublimaze).

Naloxone (Narcan): A derivative of oxymorphone (Numorphan). Narcotic antagonist.

Neuromuscular blocking agents

Neuromuscular blocking agents are used clinically to provide muscle relaxation for surgery, facilitate endotracheal intubation, help overcome laryngospasm, and in some instances to weaken muscles and permit prolonged mechanical ventilation.

Muscle relaxants are traditionally classified into two groups: the depolarizing neuromuscular blocking agents and the nondepolarizing neuromuscular blocking agents.

Depolarizing Neuromuscular Blocking Agents

These drugs bind to the muscle endplate receptor and depolarize the membrane in a manner similar to acetylcholine. As long as they remain on the receptor they maintain the muscle in a depolarized state, and it cannot contract.

Clinical characteristics of depolarizing block include the following:

1. Fasciculations (contractions of small muscle fibers) may occur at the onset of the block.
2. Absence of tetanic fade during partial block.
3. Absence of post-tetanic potentiation during partial block.
4. No reversal of neuromuscular block by anticholinesterases.

Succinylcholine (Sch) is an example of a depolarizing neuromuscular blocking agent. In most people, the action of a single dose of Sch is transient (5 to 10 minutes) because it is hydrolyzed by plasma cholinesterase (pseudocholinesterase). Because of its short duration of action, Sch is widely used to facilitate endotracheal intubation.

Complications

Some complications and unwanted side effects of Sch include the following:

Fasciculations occur as motor units are depolarized, and lead to postoperative muscle pains. Fasciculations can be prevented by administering a small dose of nondepolarizing muscle relaxant (30 to 40 mg/kg d-tubocurarine or 10 to 15 μg/kg pancuronium) IV, 3 minutes before injecting Sch for intubation. The dose of Sch is then increased to 1.5 mg/kg. The onset of Sch block may be delayed and the duration of the block slightly prolonged. Although the small dose of nondepolarizing relaxant used is generally benign, some patients experience discomfort or even partial muscular paralysis; therefore, the patient's response must be observed carefully.

Large doses of Sch (>500 mg) or prolonged exposure (> 1 hour) of the endplate to Sch eventually will produce a nondepolarizing block (Phase II, "dual" block). The exact mechanism of Phase II block is unknown, but the postjunctional membrane becomes "desensitized" to acetylcholine. Phase II block is diagnosed by demonstrating the characteristics of a nondepolarizing block using a peripheral nerve stimulator.

Raised intraocular pressure occurs due to contraction of the extraocular muscles and contracture of the smooth muscles within the orbit.

Bradycardia may occur after a second dose of Sch, but can occur after the first dose in children. It is postulated that the presence of succinylmonocholine or choline (both metabolites of Sch) somehow sensitizes the myocardium to further doses of Sch. This complication is readily prevented or treated with atropine.

A transient ***increase in serum potassium*** (0.5 to 0.75 mEq/L), the result of muscle depolarization, normally occurs after the administration of Sch. However, dangerously high potassium levels can occur after Sch administration in patients with spinal cord transection, burns, crush injuries, or some central nervous system (CNS) lesions. Therefore, Sch is contraindicated in these situations.

Succinylcholine is a triggering agent of ***malignant hyperthermia***.

Nondepolarizing Neuromuscular Blocking Agents

These compounds are often described as competitive neuromuscular blocking agents. They combine with the acetylcholine receptors on the postjunctional membrane. In a graded fashion, nondepolarizing agents inhibit the interaction of the receptors with acetylcholine.

Characteristics of the block produced by nondepolarizing agents include the following:

1. ***Absence of fasciculations*** (because the endplate is not depolarized).

2. "***Fade***" of successive responses to both slow (twitch) and fast (tetanic) rates of nerve simulation during partial block. The amount of acetylcholine released by a nerve impulse is normally five times the amount needed to depolarize the motor endplate (the safety factor in neuromuscular transmission). At normal tetanic rates of stimulation (-50 Hz), the amount of acetylcholine released gradually declines. Because of the safety factor, the response of unmedicated persons to tetanic stimulation is not altered despite the decline in acetylcholine output. When molecules of nondepolarizing muscle relaxant occupy endplate receptors, excess acetylcholine must be present to compete successfully for the receptor sites. Thus, as the amount of acetylcholine decreases during tetanic stimulation, the response also decreases, producing tetanic fade.

3. The presence of ***post-tetanic potentiation.*** After tetanic stimulation, increased acetylcholine mobilization and synthesis in nerve terminals increases acetylcholine output with the next stimulus. In the presence of partial nondepolarizing block, this increase acetylcholine displaces more relaxant and allows more endplates to depolarize, resulting in a stronger twitch response - post-tetanic potentiation.

4. Reversal of the clinical paralysis as well as fade and post-tetanic potentiation by anticholinesterase drugs.

Nondepolarizing block is potentiated by respiratory acidosis, metabolic alkalosis, hypothermia and inhalation anesthesia (particularly those with an ether linkage, such as enflurane or

isoflurane). Hypokalemia may hyperpolarize (make more negative) the excitable membrane potentiating the effect of nondepolarizing muscle relaxants.

The parenteral or intraperitoneal administration of many antibiotics (e.g. neomycin, streptomycin, polymixin B) potentiates nondepolarizing muscle relaxants by decreasing acetylcholine release and decreasing the sensitivity of the postjunctional membrane to acetylcholine. This block can be partially reverse by CA^{2+}, but not by anticholinesterases.

The "ideal" muscle relaxant would be a nondepolarizing drug with a short latency and short duration of action. It should be free of cardiovascular effects and not cause histamine release. Termination of action should not depend on renal or hepatic function, and any metabolites should be inactive and nontoxic.

TABLE 1 - Autonomic Nervous System and Histamine Releasing Effects of Muscle Relaxants

Drug[a]	Nicotinic Receptors at Autonomic Ganglia	Cardiac Postganglionic Muscarinic Receptors	Histamine Release
Succinylcholine	Modest stimulation	Modest stimulation	Minimal
d-Tubocurarine	Moderate blockade [b]	None	Marked
Metocurine	Modest blockade[b]	None	Modest[b]
Gallamine	None	Moderate blockade	None
Pancuronium	None	Modest blockade	None
Pipecuronium	None	None	None
Doxacurium	None	None	None
Atracurium	None	None	Minimal[b]
Vecuronium	None	None	None
Mivacurium	None	None	Minimal[b]
Rocuronium	None	None (?)	None

[a] ED_{95} dose equivalent (See Tables 2 and 3)
[b] Occurs only with doses estimated to be two to three times the ED_{95}

TABLE 2 - Comparative Pharmacology of Long-Acting Nondepolarizing Muscle Relaxants

	d-Tubocurarine	Metocurine	Gallamine	Pancuronium	Pipecuronium	Doxacurium
ED_{95} ($mg \bullet kg^{-1}$)	0.51	0.28	1.0[a]	0.07	0.06	0.025
Onset of maximum twitch depression (min)	3-5	3-5	3-5	3-5	3-5	3-5
Recovery to 25% of control twitch height (min)	40-70	40-70	40-70	40-70	35-70	40-70
Renal excretion (% unchanged)	45	43	95	80	70	70
Biliary excretion (% unchanged)	10-40	<2	0	5-10	20	30[a]
Hepatic degradation (%)	Insignificant	Insignificant	Insignificant	10-40	10	Insignificant
Hydrolysis in plasma	No	No	No	No	No	No

[a] Estimate.

TABLE 3 - Comparative Pharmacology of Intermediate-Acting Nondepolarizing Muscle Relaxants

	Atracurium	Vecuronium	Rocuronium
ED_{95} ($mg \bullet kg^{-1}$)	0.20	0.05	0.3
Onset of maximum twitch depression (min)	3-5	3-5	1-2
Recovery to 25% of control twitch height (min)	20--35	20-35	20-35
Dose for tracheal intubation ($mg \bullet kg^{-1}$)	0.4-0.5	0.08-0.1	0.6-0.12
Dose for continuous infusion ($\mu g \bullet kg^{-1}$, min^{-1})	6-8	1	6-10
Renal excretion (% unchanged)	Insignificant	15-25	10-25
Biliary excretion (% unchanged)	Insignificant	40-60	50-70
Hepatic degradation (%)	?	20-30	10-20
Hydrolysis in plasma	Spontaneous Enzymatic		

TABLE 4 - Comparative Pharmacology of a Short-Acting Nondepolarizing Muscle Relaxant

	Mivacurium
ED_{95} ($mg \bullet kg^{-1}$)	0.07
Onset of maximum twitch depression (min)	2.5-4
Recovery to 25% of control twitch height (min)	12-20
Dose for tracheal intubation ($mg \bullet kg^{-1}$)	0.15-0.25
Dose for continuous infusion ($\mu g \bullet kg^{-1}$, min^{-1})	5-6
Renal excretion (%unchanged)[a]	Insignificant
Biliary excretion (% unchanged)	Insignificant
Hepatic degradation (%)	Insignificant
Hydrolysis in plasma[a]	Enzymatic

[a]Because plasma cholinesterase is decreased in patients with renal failure, an increased duration of action may occur.

Reversal of Nondepolarizing Neuromuscular Blockade with Anticholinesterases

Anticholinesterase drugs prevent the breakdown of acetylcholine, allowing it to accumulate. After the administration of anticholinesterases to reverse nondepolarizing neuromuscular block, accumulation of acetylcholine causes many unwanted side-effects. Acetylcholine affects not only the skeletal muscle, but also peripheral autonomic ganglia, smooth muscle, myocardium and secretory glands. In usual clinical practice, a dose of atropine or glycopyrrolate is administered with the anticholinesterase to oppose the muscarinic effects of acetylcholine.

Listed below are clinically important muscarinic and nicotinic effects of acetylcholine, and the doses and kinetics of the commonly used anticholinesterases.

Reversal of a nondepolarizing block is generally ineffective if total blockade exists (no twitches present in the train-of-four). At least some twitch should be noted after peripheral nerve stimulation. Alternatively, the patient should show some indication of clinical return of muscle contraction (e.g., breathing, movement).

Adequacy of the reversal of neuromuscular block is assessed by absence of tetanic fade or post-tetanic potentiation with a 30 to 50 Hz stimulus for 5 seconds, and T4:T1 ratio of 75% or greater.

If a peripheral nerve stimulator is not available, the anesthesiologist should test for vital capacity (>15 ml/kg) and inspiratory force (-25 cm H_20). The ability to lift the head 5 inches off the bed for 5 seconds usually correlates well with an adequate vital capacity.

When reversal is inadequate, additional anticholinesterase and atropine may be administered. In some instances, including respiratory acidosis or alkalosis, hypothermia, and concomitant use of antibiotics discussed above, it may be impossible to reverse the effects of nondepolarizing relaxants with anticholinesterases. In these instances, prolonged ventilatory support will be necessary.

Muscarinic Effects	**Nicotinic Effects**
Myocardium – bradycardia	Autonomic ganglia stimulated
Bowels – contracted	Skeletal muscle stimulated
Bronchioles – constricted	
Pupils – constricted	
Salivary glands – stimulated	
Sweat glands – stimulated	
Bladder – contracted	

Some pharmacologic properties of commonly used anticholinesterases

Drug	**Dose**	**Peak effect (min)**	**Duration of action**
Neostigmine (Prostigmin)	2.5-5 mg 20-30 μg/kg	8 - 12	45 min - 1 hr
Pyridostigmine (Mestinon) (Regonol)	5-10 mg 100-125 μg/kg	15 - 20	1 - 1-1/2 hr
Edrophonium (Tensilon)	35 - 70 mg 0.5-1.0 mg/kg	1 -5	30 - 45 min