Chapter 4. Pharmacology of Intubation

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4.1 Physiology of Tracheal Intubation

4.1.1 What Are the Physiological Responses to Tracheal Intubation?

The goal of tracheal intubation is to provide a secure, definitive airway. Unfortunately, laryngoscopy and intubation can result in a cascade of physiological and pathophysiological reflex responses. These responses are initiated by stimulation of afferent receptors in the posterior pharynx supplied by the glossopharyngeal and vagus nerves. The central nervous system (CNS), cardiovascular system, and respiratory system all respond predictably to these afferent stimuli, and in selected patients the resultant physiologic manifestations may adversely affect the patients' outcome. Though no data exist to suggest that patient outcomes are altered by attenuating the increases in intracranial pressure (ICP), stimulation of the autonomic nervous system with increases in the heart rate and blood pressure, and stimulation of the upper and lower respiratory tract resulting in increases in airway resistance, in light of the possible adverse effects in a compromised patient, it seems both reasonable and logical to attempt to attenuate these responses.

The CNS responds to airway manipulation by increasing cerebral metabolic oxygen demand ($CMRO_2$) and cerebral blood flow (CBF). If the intracranial compliance is decreased (tight brain), the increase in CBF may increase the ICP further. This response is important in situations in which there is a loss of autoregulation such that blood flow to the brain, or regions of the brain, becomes pressure-passive (ie, increases in blood pressure result in increases in ICP).

Laryngoscopy stimulates protective reflexes and predictably leads to cardiovascular and respiratory system responses mediated by the sympathetic nervous system. In children, this process is believed to be primarily a monosynaptic reflex promoting vagal stimulation of the sinoatrial node, resulting in bradycardia. In adults, a polysynaptic event predominates whereby impulses travel afferently via the 9th and 10th cranial nerves to the brain stem and spinal cord. An efferent sympathetic response results in norepinephrine release from adrenergic nerve terminals, epinephrine release from the adrenal glands, and activation of the renin–angiotensin system leading to tachycardia and hypertension. These responses may be detrimental in patients with myocardial ischemia (tight heart), known intracerebral or aortic aneurysms, major vessel dissection, or those with major vascular injuries. Hypertension may also lead to significant increases in ICP if autoregulation has been lost (eg, acute severe head injury or intracranial hemorrhage).

The respiratory system may respond in three important ways to laryngoscopy and intubation: activation of the upper airway reflexes leading to laryngospasm; coughing; and bronchospasm (tight lungs). Laryngospasm, a forceful involuntary spasm of the laryngeal musculature, may produce difficulty with intubation as well as ventilation. Persistent and life-threatening laryngospasm is treated with a gentle continuous positive airway pressure with 100% oxygen, intravenous lidocaine (1.5 $mg \cdot kg^{-1}$), or if persistent, neuromuscular blockade (eg, succinylcholine at 10% of the intubating dose). Negative intrathoracic pressure created by inspiration attempts against a closed glottis (laryngospasm) may result in negative pressure pulmonary edema (see Chapter 58).

Coughing may produce significant adverse effects in patients with increased ICP, unstable cervical spine injury, or penetrating eye injuries.

Activation of the lower airway reflexes leads to an increase in airway resistance. This reaction is most often manifested by bronchospasm brought about by reflexes, irritants, or antigens, and may be mitigated in adults by the intravenous administration of lidocaine 1.5 $mg \cdot kg^{-1}$.

Whether mitigation of these reflexes improves patient outcome is not known. However, it is known that specific prelaryngoscopy therapy is capable of mitigating these potentially harmful physiologic effects. The useful agents are most easily remembered by the mnemonic *LOAD*, which stands for *L*idocaine, *O*pioid, *A*tropine, and *D*efasciculating agent. Current evidence is most compelling for the use of lidocaine and opioids, and much less so for atropine and defasciculating doses of nondepolarizing agents.

This chapter provides a general discussion of the appropriate pharmacological agents used in airway management and their relevant properties. It should be emphasized that the goal of this chapter is not to discuss the rationale of using a specific sedative or muscle relaxant in an anticipated difficult airway. Rather, this discussion will center on the use of drugs to facilitate tracheal intubation and mitigate adverse physiological consequences.

4.2 Pretreatment Agents Using the *LOAD* Approach

4.2.1 What Is the LOAD Approach and Why Do We Use It?

Prelaryngoscopy agents, also known as "pretreatment agents," are used to attenuate the adverse physiologic responses to laryngoscopy and intubation. LOAD is a mnemonic that might be used to enhance recall of the commonly used pretreatment medications: *L*idocaine, *O*pioids, *A*tropine, and *D*efasciculating agents. Ideally, all pretreatment agents should be administered shortly before (typically about 3 minutes) induction to synchronize the onset of peak drug effects of all drugs administered in the airway management sequence.

While short-acting beta blockers, such as esmolol, have been shown to be beneficial in attenuating the sympathetic response to laryngoscopy,[1] they are not effective in attenuating to any extent a rise in ICP. They potentially increase airway resistance, especially in patients with reactive airways disease. Furthermore, beta blockers are also negative inotropes and in some clinical situations, particularly emergencies in which maximum cardiac reserve should be preserved, the combination of beta blockers and the negative

cardiovascular effects of most induction agents could be catastrophic.

4.2.2 What Is the Rationale of Using Lidocaine for Tracheal Intubation?

Local anesthetics bind to closed, inactivated sodium channels and prevent subsequent channel activation. Sodium channels in the closed inactivated state are not permeable to sodium and therefore action potentials cannot be generated. Local anesthetic agents are a combination of a lipophilic benzene ring and a hydrophilic amine either linked by an amide or an ester bridge. Lidocaine is a low-potency, rapid-onset, and intermediate-acting amide local anesthetic. The literature is replete with articles that offer varying conclusions as to the efficacy of lidocaine when used in the pretreatment phase of tracheal intubation to attenuate various adverse effects of laryngoscopy and intubation.

Attenuation of the elevation of ICP related to airway manipulation is ascribed to lidocaine's ability to increase the depth of anesthesia, decrease $CMRO_2$ demand globally, decrease CBF, and increase cerebrovascular resistance. Patients with intracranial pathology may have an abnormal intracranial pressure–volume relationship which can predispose them to abrupt, extreme, and prolonged elevations of ICP. Such increases can contribute to secondary injury of the brain, such as herniation of the brain and impaired perfusion leading to ischemia. Indirect evidence exists that lidocaine can attenuate the intracranial hypertensive response to laryngoscopy and intubation. For instance, intracranial hypertension associated with endotracheal suctioning is suppressed by intravenous lidocaine.[2-5] Intratracheal lidocaine is equally effective.[4] Lidocaine (1.5 $mg \cdot kg^{-1}$) administered 3 minutes before intubation suppresses the cough reflex and attenuates the increase in airway resistance resulting from laryngoscopy and endotracheal intubation.

Lidocaine's effect on antigenic-mediated bronchospasm is more controversial. Lidocaine and other local anesthetics may lead to bronchoconstriction in patients with reactive airway disease when given via the inhalational route[6] (see Chapter 3 for a full discussion of this evidence). In normal individuals, lidocaine does not alter airways resistance, and has been shown to produce mild bronchodilation.[7] Groeben et al[8-10] in three similar trials showed that intravenous lidocaine attenuated the response to an inhalational histamine challenge in patients with mild asthma. The inhalational administration of lidocaine to such patients, however, was met with short-lived initial increases in airway resistance.[10] Intravenous lidocaine but not inhalational lidocaine seems appropriate for the attenuation of the bronchoconstrictive response to upper airway manipulation and tracheal intubation. Lidocaine (1.5 $mg \cdot kg^{-1}$) 3 minutes before induction is advocated for patients with reactive airway disease (ie, tight lungs) or elevated ICP (ie, tight brains). Lidocaine has a wide safety margin, particularly at a dose of 1.5 $mg.kg^{-1}$. The primary toxic effect is the development of seizures, which usually occurs at much higher doses.

4.2.3 Why Do We Use Opioids Prior to Tracheal Intubation?

Opium, derived from the seeds of the poppy (*Papaver somniferum*), is composed of more than 20 alkaloids, some of which serve as the foundation molecules for modern opioids. A German pharmacist isolated the first alkaloid from opium in 1806 and named it morphine after the Greek god of dreams, Morpheus.[11] A broad

definition of the term "opioid" includes all drugs, synthetic and natural, which interact with opioid receptors, whether endogenous, exogenous, agonist, or antagonists. Opioids are routinely employed during an anesthetic induction and with the advent of newer, more rapid-acting agents, such as remifentanil, they continue to play a role in airway management.

Opioids act throughout the nervous system, including the dorsal horn of the spinal cord (substantia gelatinosa), periaqueductal gray matter, and in the periphery. They inhibit presynaptic release and postsynaptic response to excitatory neurotransmitters such as acetylcholine (ACh) and substance P by altering the potassium and calcium conductance.[11] As such, they are useful in attenuating adverse responses to airway manipulation in patients with *tight brains* and *tight hearts*.

Although highly selective, opioid effects typically involve complex interactions among various receptor sites. The list of opioid receptors continues to expand. Mu (μ), kappa (κ), and delta (δ) receptor classes and their subtypes have been firmly established.[12] Most clinically useful opioids are highly selective μ agonists, which are responsible for the bulk of supraspinal and spinal analgesia.

Opioids are typically of low molecular weight but vary widely in their lipid solubility, percent of ionization, and degree of binding to proteins (Table 4-1). Commonly used opioids for induction (fentanyl, sufentanil, and remifentanil) are more lipid soluble, which accounts for their speed of onset of action. Redistribution is responsible for the termination of their CNS drug action. Metabolism of most opioids occurs through a two-stage hepatic process that generally results in an inactive metabolite. The exception is remifentanil, which contains an ester linkage and is rapidly hydrolyzed by nonspecific esterases in the blood and tissue.

Table 4-1 Pharmacokinetics of Opioids in Clinical Use

	MORPHINE	FENTANYL	SUFENTANIL	REMIFENTANIL
pK_a	7.9	8.4	8	7.2
% Ionization	23	8.5	20	58
% Protein bound	35	84	90	66
Rapid Redistribution-$t_{½\pi}$ (min)		1.2-1.9	1.4	0.4-0.5
Redistribution-$t_{½\alpha}$ (min)	1.5-4.4	9.2-19	17	2-3.7
Elimination-$t_{½\beta}$ (h)	1.7-3.3	3.6-6.6	2.2-4.1	0.17-0.33

See reference 11.

Physiologically, opioids exert their effect on all organ systems. Venodilation and depressed sympathetic reflexes typically result in a decrease in heart rate and blood pressure. Unlike some opioids (most notably morphine) fentanyl, sufentanil, and remifentanil do not release histamine. This is partly why they cause less hypotension than morphine. All opioids depress ventilation by blunting the carbon dioxide response at the respiratory center, raising the apneic threshold and depressing the slope of the CO_2 response curve.

The primary reason to include an opioid in the intubation sequence is their ability to significantly attenuate the sympathetic response that occurs with manipulation of the airway. Unfortunately, the rapid administration of

fentanyl and its derivatives has been associated with brief episodes of coughing and chest wall rigidity.[13-15] Large induction doses of an opioid can decrease pulmonary compliance in 50% to 86% of patients and potentially induce glottic closure interfering with ventilation of the patient.[13-16] Doses of this magnitude are seldom if ever employed in emergency airway management, in or out of the operating room (OR).

4.2.4 What Types of Opioids Are Commonly Used for Tracheal Intubation?

The hemodynamic and intracranial responses to tracheal intubation are usually short lived. Therefore, the *ideal* choice of an opioid for tracheal intubation should be based on its pharmacokinetic and pharmacodynamic characteristics, namely, a rapid onset and a brief duration of drug effect. While there are currently many opioids available, the following discussion will be restricted to only those opioids with a rapid onset and short duration of drug effect.

4.2.4.1 Fentanyl

Like meperidine, fentanyl is a phenylpiperidine-derived synthetic opioid agonist. It is roughly 100 times more potent than morphine. Fentanyl in large doses (10-30 $\mu g \cdot kg^{-1}$) causes chest wall rigidity in 35% to 85% of patients.[13,15,17] This side effect is present in all age groups.[18] Rigidity is a unique and idiosyncratic response to opioids and is probably related to the dose and speed of administration. Although the exact mechanism is unknown, an animal study demonstrated opioid-induced muscle rigidity coincident with activation of central μ-receptors.[19] Others have suggested mechanisms involving the cerulospinal noradrenergic system[20,21] and the neurochemical system affected in Parkinson disease.[22]

Tagaito et al[23] found that increasing doses of fentanyl reduced the incidence of respiratory and laryngeal responses to laryngeal irritation under propofol anesthesia. Fentanyl is a short-acting opioid owing to redistribution of the drug, although accumulation with repeated dosing can limit its use. Peak drug effect occurs 3 to 5 minutes following intravenous administration with an equilibration half-time between the plasma and brain of 5 minutes.[24] Doses recommended for attenuating the adverse effects of airway manipulation range from 1 to 4 $\mu g \cdot kg^{-1}$. One must be prepared to treat dose-related hypotension and respiratory depression that may occur with fentanyl administration.

4.2.4.2 Sufentanil

A thienyl derivative of fentanyl, sufentanil is 10 to 15 times more potent than fentanyl. Sufentanil is a highly specific μ agonist with similar pharmacokinetic properties as fentanyl. It is extremely lipophilic, permitting rapid penetration of the blood–brain barrier and onset of CNS effects. Sufentanil 0.3 to 1 $\mu g \cdot kg^{-1}$, administered 1 to 3 minutes prior to intubation, will blunt the response to laryngoscopy. Rigidity has been reported with larger doses.[17] The difficult ventilation associated with opioid rigidity may be due in part to vocal cord closure.[14,16]

4.2.4.3 Remifentanil

Remifentanil is a structurally unique opioid. It is a piperdine analog with a methyl ester side chain. The ester linkage renders it susceptible to cleavage by nonspecific plasma and tissue esterases.[25] The rapid metabolism of remifentanil, rather than redistribution, is responsible for its ultrashort duration of action; and with limited redistribution, there is no accumulation. It is rapidly cleared from the plasma (3 $L \cdot min^{-1}$).[17] Remifentanil is not, however, a substrate for pseudocholinesterase and therefore it is unaffected by pseudocholinesterase deficiency.

Remifentanil is a potent μ receptor agonist with a similar potency to fentanyl. Doses of 0.25 to 3 $\mu g \cdot kg^{-1}$ have successfully attenuated the response to laryngoscopy.[26-31] At higher doses, centrally mediated depression of sympathetic tone and vagally induced bradycardia may occur. This bradycardia can be attenuated by the prior administration of glycopyrrolate or other antimuscarinics.[11] Peak respiratory depression occurs 5 minutes after bolus dosing, and lasts 10 minutes after 1.5 $\mu g \cdot kg^{-1}$ and 20 minutes after 2 $\mu g \cdot kg^{-1}$.[32] Remifentanil, like other opioids, may cause chest wall rigidity depending on the dose and speed of administration.[33]

The clinical utility of remifentanil is reflected in its distinctive pharmacokinetic characteristics. Its rapid onset, brief duration, and easily titratable nature have enhanced its profile for airway management, particularly in emergency settings, and for short surgical procedures. A small dose of remifentanil (0.25 $\mu g \cdot kg^{-1}$) can provide excellent conditions for laryngeal mask airway insertion with minimal hemodynamic disturbance.[34] The trachea may be successfully intubated without muscle relaxants with the combination of remifentanil and an induction agent. Remifentanil, 2 to 4 $\mu g \cdot kg^{-1}$, in this setting, provides good to excellent intubating conditions.[28,35-37]

Suppression of airway reflexes while maintaining patient comfort without compromising spontaneous ventilation for awake tracheal intubation is possible with remifentanil via continuous infusion (0.07-0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$).[38-40] Puchner et al[41] successfully used remifentanil, 0.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$, for procedural sedation in a case of severe neck swelling in a morbidly obese patient with no alternative to awake bronchoscopic intubation. Similarly, in cases of head and neck surgery where a tenuous airway needs to be maintained, remifentanil allows a high degree of titratability with high rates of success.[42]

4.2.5 What Is the Role of Atropine (or Other Antimuscarinic) Administration Prior to Tracheal Intubation?

Vagally mediated, succinylcholine-induced bradycardia may be seen in children. Bradycardia can be attenuated or abolished by administering atropine 0.02 $mg \cdot kg^{-1}$ or glycopyrrolate 0.01 $mg \cdot kg^{-1}$[43] as pretreatment before administering succinylcholine. However, there is no evidence that pretreatment with an antimuscarinic in children is any more effective than responsive therapy in the event bradycardia occurs. The age after which this response to succinylcholine disappears is unknown. Regardless of the age, *repeated doses* of succinylcholine may produce vagally mediated bradycardia, necessitating the administration of an

antimuscarinic.

Unlike the natural derivatives of *Atropa belladonna*, atropine and scopolamine, glycopyrrolate is a synthetic, quaternary ammonium antimuscarinic agent. Because of its polar nature, glycopyrrolate is unable to cross the blood–brain barrier, and so is devoid of CNS activity. It is a potent antisialagogue with minimal sedating properties, which makes glycopyrrolate a useful pretreatment medication. Glycopyrrolate increases the heart rate in a manner similar to atropine with an onset of effect in 2 minutes, lasting 30 to 60 minutes.[44] Typically, increases in the heart rate following glycopyrrolate administration are more gradual than those with atropine, thereby avoiding a rapid tachycardia that may be a particular concern in patients with cardiovascular disease.

4.2.6 Why Do We Use Defasciculating Agents for Tracheal Intubation?

Fasciculations are involuntary muscle contractions. Practically, all patients who receive succinylcholine will experience fasciculations. Fasciculations have been associated with an increase in catecholamine release and elevations of ICP. Small doses of nondepolarizing muscle relaxants (NDMRs), such as vecuronium, rocuronium, and pancuronium, when administered prior to succinylcholine have been clearly shown to decrease the incidence of succinylcholine-induced fasciculations.[45-50]

Arguably, their greatest benefit is in mitigating the increase in ICP caused by succinylcholine. The appropriate defasciculating dose for any of the NDMRs is 10% of their ED_{95}. Typically, the suggested intubating dose is twice the ED_{95}. Therefore, the defasciculating dose would be approximately 5% of the intubating dose of the NDMRs. The use of higher doses will increase the incidence of muscle weakness and apnea prior to the induction of anesthesia. When used as a defasciculating agent, rocuronium 0.06 $mg \cdot kg^{-1}$ should be administered 1.5 to 3 minutes prior to succinylcholine.[51]

4.3 Induction Agents

The ideal induction agent would quickly render the patient unconscious, unresponsive, and amnesic in one arm/heart/brain circulation time. Such an agent would also provide analgesia, maintain stable cerebral perfusion pressure (CPP) and cardiovascular hemodynamics, be immediately reversible, and have few, if any, adverse side effects. Unfortunately, such an induction agent does not exist.

Most induction agents are highly lipophilic, and therefore have a rapid onset of effect within 30 to 45 seconds of intravenous administration. Their clinical effect is likewise terminated quickly as the drug rapidly redistributes from the CNS to less well-perfused tissues. All induction agents have the potential to cause myocardial depression and hypotension. These effects depend on the particular drug and the patient's underlying physiologic condition. The faster the drug is administered, the larger the amount of the drug that will be delivered to those organs with the greatest blood flow (such as the brain and heart) and the more pronounced the effect. The choice of drug and the dose must be individualized to each patient to capitalize on desired effects, while minimizing adverse effects.

Anesthetic induction is intended to rapidly render the patient unable to appreciate, respond to, or recall noxious

stimuli. It is at one end of a spectrum that runs from awake, alert, and oriented at one end to deep anesthesia and death on the other.

The induction agents include short-acting barbiturates: thiopental and methohexital; benzodiazepines: principally midazolam; and miscellaneous agents: etomidate, ketamine, and propofol. Opioids can function as anesthetic induction agents when used in very large doses (eg, fentanyl 30 $\mu g \cdot kg^{-1}$) but are rarely, if ever, used for that purpose during routine or emergency intubation, so will not be discussed in this chapter.

All of the induction agents discussed in this chapter share similar pharmacokinetic characteristics. As mentioned previously, they are highly lipophilic, and therefore a standard induction dose of an induction agent administered to a euvolemic, normotensive patient will take effect within 30 seconds. The duration of observed clinical effect of each drug is measured in minutes and is due to the redistribution of the drug from the central circulation (brain) to larger, but less well-perfused tissues, for example, fat and muscle. The elimination half-life ($t_{1/2\beta}$, usually measured in hours) is characterized by each drug's reentry from fat and lean muscle into plasma down a concentration gradient followed by hepatic metabolism which precedes renal excretion. Generally it requires four to five elimination half-lives to clear the drug completely from the body.

Because the target organ is the brain, and the desired effect is produced rapidly following bolus injection of the drug, dosing of induction agents in normal-sized and obese adults should be based on ideal body weight in kilograms. Hypovolemia results in the patient having a contracted central compartment; therefore, lower doses of induction agents are necessary to achieve adequate levels at the target organ (brain). Aging affects the pharmacokinetics of induction agents. In older adults, lean body mass and total body water decrease while total body fat increases, resulting in an increased volume of distribution, an increase in $t_{1/2\beta}$, and an increased duration of drug effect. Older adults are also much more sensitive to the hemodynamic and respiratory depressant effects of these agents, and consequently, most induction doses should be reduced.

4.3.1 Barbiturates

4.3.1.1 Discuss the Different Types of Barbiturate Induction Agents

Barbiturates are derived from barbituric acid, a cyclic compound obtained by the combination of urea and malonic acid. They are prepared as water-soluble, alkaline (2.5% solution with pH >10) sodium salts that are dissolved in isotonic saline or water. These agents act at the barbiturate receptor, which forms part of the GABA-receptor complex to enhance and mimic the action of GABA. Thiopental decreases GABA dissociation from its receptor, which enhances GABA's neuroinhibitory activity, directly opens the chloride channel, and, at higher drug concentrations, causes hyper-polarization of this chloride channel resulting in global depression of neuronal excitation and subsequent unconsciousness. The most commonly used barbiturates are thiopental and methohexital.

Thiopental is the prototypical barbiturate. It is highly lipid soluble and highly protein bound. Thiopental undergoes hepatic oxidation to hydroxythiopental and carboxylic acid derivatives, which are water soluble and excreted via the kidney. Methohexital shares similar clinical pharmacologic properties with thiopental although it is significantly less lipid soluble and is two to three times more potent than thiopental. The

elimination of methohexital is three to four times faster than thiopental.[52]

4.3.1.2 What Are the Indications and Contraindications of Barbiturate Induction Agents?

Barbiturates are primarily used as an induction agent for patients suspected of having increased ICP. Their ability to decrease ICP stems from the cerebral vasoconstriction and subsequent decrease in CBF. The decreased systemic vascular resistance is not matched by the decreased CBF and so cerebral perfusion pressure (CPP) is maintained and possibly increased.[53] Barbiturates remain a mainstay of intravenous cerebroprotective measures despite limited outcome data.[54-57]

Barbiturates have significant anticonvulsant activities in addition to their cerebroprotective properties.[58] Methohexital is often used in those patients undergoing electroconvulsive therapy (ECT) because of its desirable rapid onset of amnesia and short duration of action. While methohexital is often preferred over thiopental for ECT because of longer seizure activities, the clinical efficacy of ECT does not appear to correlate with the duration of seizure activity.[59] Thiopental and other barbiturates are absolutely contraindicated in patients with acute intermittent porphyria, or variegate porphyria, as they can activate the enzyme responsible for precipitating an acute attack, which can be life threatening.

4.3.1.3 What Are the Clinical Doses of Barbiturate Induction Agents?

The dosing of thiopental depends on the hemodynamic status of the patient and the concomitant use of other agents. Apart from stimulating the release of histamine from mast cells, thiopental is a potent venodilator and myocardial depressant.[60,61] Consequently, the dose must be decreased in patients with decreased intravascular volume, those with compromised myocardial function, elderly adults, and whenever thiopental is used with other drugs that affect sympathetic tone or cardiovascular function. In euvolemic, normotensive adults, a recommended induction dose of thiopental is 3 to 5 $mg \cdot kg^{-1}$. For most emergency intubations, the lower dose of this range (3 $mg \cdot kg^{-1}$) achieves excellent sedation and intubating conditions with fewer tendencies to cause hypotension that often occurs with the 5 $mg \cdot kg^{-1}$ dose. Thiopental should be avoided entirely in severely hypotensive patients for whom other drugs, especially etomidate or ketamine, may preserve greater hemodynamic stability. The onset of methohexital is more rapid and the duration of action shorter than it is with thiopental. The recommended induction dose of methohexital in the euvolemic, normotensive patient is 1.5 $mg \cdot kg^{-1}$.

4.3.1.4 What Are the Common Side Effects of Barbiturates?

The chief side effects of thiopental include central respiratory depression, venodilation, and myocardial depression. These last two may produce hypotension that tends to be greater in treated, and untreated, hypertensive patients compared with normotensive patients. Both of these effects may be detrimental in patients where optimal preload is required to maintain cardiac output and prevent organ ischemia. Thiopental causes a dose-related release of histamine (anaphylactoid response) which in most situations is not clinically

significant, but may exacerbate hypotension or bronchospasm in patients with reactive airways disease.[61] Although barbiturates produce dose-dependent depression of ventilation centers, they do not completely blunt airway reflexes.[62]

There is a 10% to 20% incidence of nausea and vomiting that occurs during recovery from a barbiturate induction. Two to five percent of patients will experience pain on injection of thiopental or methohexital, especially if small veins are used. Inadvertent intra-arterial injection or subcutaneous extravasation of thiopental can result in chemical endarteritis and distal thrombosis, ischemia, and tissue necrosis. Methohexital has a greater incidence than thiopental of twitching and hiccups (excitatory phenomena) that may be misdiagnosed as seizures.[63]

4.3.2 Benzodiazepines

4.3.2.1 Discuss the Clinical Pharmacology of Benzodiazepines

Although chemically distinct from the barbiturates, the benzodiazepines also exert their effects via the GABA-receptor complex. Benzodiazepines specifically facilitate the binding of GABA to the benzodiazepine receptor, which in turn modulates chloride conduction, inhibiting neuronal function. The benzodiazepines provide amnesia, anxiolysis, sedation, anticonvulsant effects, and hypnosis (sleep). This potent, dose-related amnesic property is perhaps their greatest asset.

Benzodiazepines generally contain a benzene and diazepine ring. All have similar pharmacologic profiles, though various substitutions in the ring structures make each agent pharmacologically unique and their clinical usefulness variable. The lipophilicity of the benzodiazepines varies widely. Greater lipid solubility confers a more rapid onset of action because of the brain's high lipid content. The two benzodiazepines most clinically used during airway manipulation are midazolam and diazepam. Of the two, midazolam is the most lipid soluble. Although midazolam is prepared as a water-soluble agent in acidic aqueous medium, the imdazole ring structure closes at physiological pH greatly increasing the lipid solubility. Many studies have shown that the onset of effect is slower for midazolam than diazepam.[64] Regardless, the time to clinical effectiveness of benzodiazepines is longer than any of the other induction agents, which hinders their role in emergency airway management. The termination of action of midazolam and diazepam is due to redistribution and subsequent hepatic metabolism via cytochrome P450 to 3A4 microsomal oxidation. The innate structure of each parent compound determines the precise mechanism of hepatic degradation, and the production of active or inactive metabolites, both of which will dictate the eventual elimination half-life ($t_{1/2\beta}$) of each drug. Midazolam has one insignificant active metabolite and a $t_{1/2elim}$ of 2 to 4 hours. Diazepam has two active metabolites, both of which can prolong its sedative effect but more importantly are metabolized and excreted more slowly than diazepam and account for its prolonged $t_{1/2\beta}$ of 20 to 40 hours. The benzodiazepines do not release histamine, and allergic reactions are very rare.

4.3.2.2 What Are the Clinical Uses and Adverse Effects of Benzodiazepines?

The primary indications for benzodiazepines are anxiolysis, amnesia, and sedation. In this regard, the

benzodiazepines are unparalleled. Midazolam is primarily used for procedural sedation, anxiolysis, and seizure management. Because of their dose-related reduction in systemic vascular resistance and direct myocardial depression, dosage must be adjusted in volume-depleted or hemodynamically compromised patients. Unlike the other induction agents, including those that cause hypotension, midazolam is generally underdosed during emergency induction. It is postulated that this is due to the clinicians' familiarity with sedating doses of midazolam employed during procedural sedation and lack of familiarity with the dosing and pharmacokinetics of midazolam as an induction agent.

The dose of midazolam for induction of anesthesia is 0.1 to 0.3 $mg \cdot kg^{-1}$. Berggren and Eriksson[65] prospectively demonstrated that midazolam 0.4 $mg \cdot kg^{-1}$ provided anesthetic depth similar to that of thiopental 6 $mg \cdot kg^{-1}$ in 60 female patients undergoing induction for elective abortion. Driessen et al[66] found that 0.2 $mg \cdot kg^{-1}$ midazolam and 5 $mg \cdot kg^{-1}$ thiopental provided similar depth of anesthesia in 40 women undergoing outpatient anesthesia. Jensen et al[67] found similar results using 0.2 $mg \cdot kg^{-1}$ midazolam versus 3 $mg \cdot kg^{-1}$ of thiopental for 40 orthopedic surgeries and Izuora et al[68] found 0.15 to 0.2 $mg \cdot kg^{-1}$ midazolam comparable to thiopental 4 to 6 $mg \cdot kg^{-1}$ in 145 patients undergoing surgical procedures. Interestingly, Sagarin et al[69] recently demonstrated that most emergency intubations are performed using midazolam doses in the range of 0.03 to 0.04 $mg \cdot kg^{-1}$. The lower dosing appears to be due to the inexperience with the larger doses of midazolam used for induction or the concern that hypotension may ensue. Other induction agents, including thiopental and etomidate, were used in recommended doses.[69]

Except for midazolam, the benzodiazepines are insoluble in water and are usually supplied in a propylene glycol solution. Unless injected into a large vein, pain and venous irritation on injection can be significant.

4.3.3 Etomidate

4.3.3.1 Discuss the Clinical Pharmacology of Etomidate

Etomidate is a carboxylated imidazole derivative that is primarily an intravenous hypnotic agent used for the rapid induction of anesthesia. It is available in a 0.2% solution dissolved in 35% propylene glycol. It inhibits the reticular activating system, mimicking GABA at the GABA-receptor complex. Etomidate owes its rapid onset to its high lipid solubility and large nonionized portion at physiological pH ($pK_a = 4.2$).[17] Its rapid redistribution leads to prompt awaking following administration. The elimination half-life of etomidate is 2 to 5 hours. It is rapidly hydrolyzed by hepatic metabolism and plasma esterases to water-soluble inactive metabolites excreted primarily by the kidneys.

Etomidate is a potent direct cerebral vasoconstrictor.[70] It attenuates underlying elevated ICP by decreasing CBF and $CMRO_2$. Its hemodynamic stability preserves CPP. The use of etomidate in patients with seizure disorders ought to be limited to the induction of anesthesia and not its maintenance. Etomidate has been shown to increase electroencephalographic activity in certain leads[71] and is less effective than other agents in

attenuating the motor activity associated with seizures.[72]

The respiratory system may be centrally stimulated by etomidate, so administration is not usually associated with apnea unless opioids are coadministered.[17,73] Etomidate lacks any direct bronchodilatory properties. Eames et al[62] prospectively demonstrated that 2.5 mg·kg^{-1} of propofol was superior to either 0.4 mg·kg^{-1} etomidate or 5 mg·kg^{-1} thiopental in decreasing mean airway pressure during bronchoscopy in 75 patients.

Etomidate is touted as *the* most hemodynamically stable induction agent.[74-76] It mildly decreases the systemic vascular resistance but appears to have no direct effect on cardiac output or contractility. Gauss et al[77] conducted an echocardiographic assessment of the hemodynamics of various induction agents and showed that etomidate produced no changes in the hemodynamic variables measured.

4.3.3.2 What Is the Role of Etomidate as an Induction Agent for Tracheal Intubation?

Etomidate is becoming the induction agent of choice for most emergency rapid-sequence inductions (RSI) because of its rapid onset, its profound hemodynamic stability, its positive CNS profile, and its rapid recovery. As with any induction agent, dosage must be adjusted in hemodynamically compromised patients. The use of etomidate to facilitate airway management in the patient with status epilepticus is not contraindicated, as it does depress the level of consciousness, and long-term medication with benzodiazepines or propofol ordinarily follows the intubation.

In euvolemic and hemodynamically stable patients, the normal induction dose of etomidate is 0.2 to 0.4 mg·kg^{-1}. In compromised patients, the induction dose should be reduced commensurate with the patient's clinical status. Etomidate has no analgesic properties.

4.3.3.3 What Are the Adverse Effects of Etomidate?

Etomidate is associated with nausea and vomiting during recovery in 30% to 40% of patients undergoing general anesthesia. Pain on injection is common because of the propylene glycol solvent. The incidence can be as high as 80%.[78] Myoclonic movements due to an imbalance of inhibition and excitation in the thalamocortical tract are common and have been confused with seizure activity.[71] It is of no clinical consequence and generally terminates promptly. The occurrence of hiccups, usually during awakening, is highly variable, ranging between 0% and 70%.[79]

The most significant and controversial side effect of etomidate is its reversible blockade of 11-beta-hydroxylase. Etomidate causes reversible adrenocortical suppression by interfering with 11-beta-hydroxylation of 11-deoxycortisol, which prevents its conversion to cortisol. It decreases both serum cortisol and aldosterone levels. Single bolus induction doses of etomidate have transiently inhibited cortisol and aldosterone synthesis.[80-82] The possible long-term adrenocortical suppression has limited the use of etomidate as a sedative for intensive care management and total intravenous anesthesia.

4.3.4 Ketamine

4.3.4.1 Discuss the Clinical Pharmacology of Ketamine

Ketamine, an arylcyclohexylamine, is a structural analog of phencyclidine, which may account for the psychomimetic side effects such as hallucinations and nightmares. The compound has a chiral center producing stereoisomers and is commercially available as a racemic mixture. It is fairly lipid soluble and minimally protein bound accounting for its rapid onset (45-60 second). Ketamine is extensively taken up by the liver and metabolized by the cytochrome P-450 biotransformation system. The primary metabolite, norketamine, has roughly one-fifth the potency of the parent molecule. Its high lipid solubility produces rapid redistribution and short duration of effect. Rapid hepatic metabolism is responsible for the short elimination half-life of 2 to 3 hours. Ketamine has been touted as a "complete" anesthetic by many, as it provides analgesia, amnesia, and hypnosis (unconsciousness). Besides blocking polysynaptic spinal cord reflexes, ketamine is a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors at the GABA-receptor complex, promoting the inhibition of excitatory neurotransmitters in selected areas of the brain. An interaction between ketamine and a number of the opioid receptors may be partially responsible for its analgesic properties. Ketamine produces dissociative anesthesia by electrophysiologically separating the thalamus from the limbic system. Patients may appear conscious but are unable to respond to stimuli. Ketamine centrally stimulates the sympathetic nervous system, which in turn releases catecholamines, augmenting the heart rate and blood pressure in those patients who are not catecholamine depleted secondary to the demands of their underlying disease. Similar to most other anesthetics, however, ketamine in the face of catecholamine depletion causes dose-dependent myocardial depression.

Traditionally, ketamine's direct stimulation of the CNS is thought to increase cerebral metabolism, $CMRO_2$, and CBF, thus potentially increasing ICP in patients with CNS injury. These generalizations may not be valid. Pfenninger et al[83] investigated the effect of 2 $mg \cdot kg^{-1}$ of ketamine on the ICP and CPP of ventilated pigs. There was no increase in ICP in normal pigs with induced intracranial hypertension. Likewise, in ventilated goats, ketamine significantly decreased the $CMRO_2$, while the ICP did not increase.[84] Albanese et al[85] studied the effects of ketamine (5 $mg \cdot kg^{-1}$) in eight patients with traumatic brain injury who were ventilated and sedated with propofol. There was a significant decrease in the ICP, while the CPP and middle cerebral artery blood flow velocity were unchanged. Mayberg et al[86] found similar results with a cohort of patients presenting for a craniotomy anesthetized with isoflurane and nitrous oxide who received 1 $mg \cdot kg^{-1}$ of ketamine. The mean arterial blood pressure, CPP, and arterial carbon dioxide did not change, while the ICP significantly decreased. There is emerging evidence that the antagonist behavior of ketamine at NMDA receptors may have a neuroprotective benefit.[87] Unfortunately, the evidence with respect to the use of ketamine for induction of anesthesia specifically in the patient with intracranial hypertension is lacking. However, it can be said that ketamine may be used in the sedated, mechanically ventilated patient with little concern for worsening intracranial hypertension. Ketamine's long-term exclusion from the induction of patients with decreased intracranial compliance may be an overgeneralization.

A key feature of ketamine is its effects on the respiratory system. Despite inducing a profound anesthesia,

upper airway reflexes and central respiratory drive are preserved to a degree following ketamine administration, although with high doses, hypoventilation and apnea will occur. In addition, ketamine directly relaxes bronchial smooth muscle, producing bronchodilation. Ketamine has been successfully used to treat status asthmaticus and less severe bronchospasm.[88-92] Hemmingsen et al[89] in a placebo-controlled trial showed that ketamine (1 $mg \cdot kg^{-1}$) successfully relieved bronchospasm in ventilated subjects.

4.3.4.2 with Its Unique Characteristics, What Is the Role of Ketamine as an Induction Agent in Management of the Airway?

Ketamine is the traditional induction agent for patients with reactive airways disease who require tracheal intubation. Because of its unique pharmacologic profile, ketamine may also be considered for induction in patients who are hypovolemic and for patients with hemodynamic instability due to cardiac tamponade or distributive shock. In normotensive or hypertensive patients with ischemic heart disease, catecholamine release may adversely increase myocardial oxygen demand, but it is not known whether this effect is clinically significant. Ketamine's preservation of central respiratory drive makes it appealing for awake upper airway evaluation in the difficult airway patient. On the basis of the previous discussion, the use of ketamine in patients with elevated ICP remains controversial. Traditional teaching would have us avoid ketamine despite there being little to no evidence to support such a practice.

4.3.4.3 Discuss the Clinical Use and Adverse Effects of Ketamine

The induction dose of ketamine is 1 to 2 $mg \cdot kg^{-1}$. This dose needs to be adjusted for hypovolemic and/or hypotensive patients. Ketamine may be mixed with propofol as a 50:50 mixture (5 $mg \cdot mL^{-1}$ of each), "ketofol," a combination that produces less hypotension and respiratory depression than propofol alone. Because of its stimulating effects, ketamine enhances laryngeal reflexes and increases pharyngeal and bronchial secretions. These secretions may precipitate laryngospasm and be bothersome during upper airway examination in the difficult airway patient or during procedural sedation. An antimuscarinic agent, such as glycopyrrolate, may be administered in conjunction with ketamine to promote a drying effect. The maintenance of airway reflexes does not negate the need for intubation and airway protection when faced with patients at risk for aspiration.

Five to thirty percent of patients will experience hallucinations or dreams on emergence from ketamine. They are more common in the adult than in the child and can be eliminated by the concomitant or subsequent administration of a benzodiazepine.[93] This is less of an issue in emergency airway management, in which often the patient is sedated with benzodiazepines for prolonged periods.

4.3.5 Propofol

4.3.5.1 Discuss the Clinical Pharmacology of Propofol

Propofol (2,6-diisopropylphenol) is an alkylphenol derivative with hypnotic properties. Propofol is supplied in

an emulsion of 10% soybean oil, 2.25% glycerol, and 1.2% egg lecithin.[94] It is highly lipid soluble and hence rapidly acting. The initial redistribution half-life is 2 to 8 minutes. It is rapidly metabolized to inactive, water-soluble metabolites.

Propofol enhances GABA activity at the GABA-receptor complex. It decreases $CMRO_2$ and ICP.[95-97] Propofol causes a direct reduction in blood pressure through vasodilation and direct myocardial depression, resulting in a decrease in CPP, which may be detrimental in a compromised patient.[98] Propofol has profound anticonvulsant properties.[99] It is a potent depressor of ventilation inhibiting hypoxic and hypercarbic ventilatory drive.

4.3.5.2 What Is the Role of Propofol as an Induction Agent for Tracheal Intubation?

Propofol is an excellent induction agent in hemodynamically stable patients. Its potential for hypotension and reduction in CPP may reduce its role as an induction agent for rapid-sequence intubation/induction (RSI). However, it remains a commonly used agent in this setting as the adverse hemodynamic changes and other pharmacological effects of propofol are very predictable. Altered dosing for the unstable patients or using it in conjunction with ketamine, *ketofol*, helps to attenuate the undesirable hemodynamic effects. Apart from avoiding the use of propofol in patients with known egg allergy (egg lecithin emulsion), there are no absolute contraindications to the use of propofol.

The induction dose of propofol is 1 to 2 $mg \cdot kg^{-1}$ in a euvolemic, normotensive patient. Because of its predictable tendency to reduce mean arterial blood pressure, smaller doses are generally used when propofol is given as an induction agent for emergency induction. Young adults and children may require 2 to 3 $mg \cdot kg^{-1}$.

The pain associated with the injection of propofol is comparable to that of methohexital, less than etomidate, and more than thiopental.[11] This effect can be attenuated by injecting the medication through a rapidly running intravenous infusion in a large vein. Alternatively, pretreatment with a small dose of 1% lidocaine (4 mL)[100] or mixing the propofol with a small amount of 1% lidocaine (2-4 mL) prior to injection[101] have both been shown to minimize the discomfort. Propofol can cause mild clonus but to a lesser degree than thiopental, etomidate, or methohexital.[71]

4.3.6 Inhalational Agents

4.3.6.1 What Is the Role of Inhalational Anesthetics as Sedating/Induction Agents in Management of the Airway?

From the beginnings of anesthesia, volatile anesthetics have been an integral part of anesthesia induction. This technique is more commonly used in pediatrics than in adults. In the early days of ether anesthesia, inductions were stormy affairs. With the advent of newer volatile agents that are potent, less pungent, and poorly soluble (leading to rapid onset), a smooth inhalational induction can be easily accomplished.[102]

The major advantage of an inhalational induction is that spontaneous ventilation can be preserved and patients can regulate their own depth of anesthesia. The technique of inhalational induction in pediatric epiglottitis is well established. The safety of extending this practice to other causes of upper airway obstruction, and in adults with upper airway obstruction of any cause, has yet to be conclusively established. However, some have reported that tracheal intubation can be successfully carried out using this technique while maintaining spontaneous ventilation in an uncooperative patient with a difficult airway.[103-105] While halothane mask induction had played a major role in inducing pediatric patients in the past, most practitioners currently favor sevoflurane. Theoretically, the addition of nitrous oxide may speed the onset of anesthesia. However, unconsciousness can be accomplished in less than 60 seconds with sevoflurane and oxygen when using a primed circuit with 8% sevoflurane and fresh gas flow of 8 $L \cdot min^{-1}$.[105,106] Although, intravenous induction seems to be the preferred induction technique, inhalational means of induction will remain a core anesthetic skill for the foreseeable future.

4.4 Neuromuscular Blocking Agents

Neuromuscular blocking agents are the cornerstone of emergency airway management and are used to obtain total control of the patient to facilitate rapid endotracheal intubation while minimizing the risks of aspiration or other adverse physiologic events. Neuromuscular blocking agents do not provide analgesia, sedation, or amnesia, and an induction or sedative agent must be used during RSI in patients who are not completely unresponsive. Similarly, appropriate sedation is essential when neuromuscular blockade is maintained for controlled mechanical ventilation following intubation.

4.4.1 Discuss the Clinical Pharmacology of Neuro-Muscular Blocking Agents

In order to understand the pharmacology of neuromuscular blocking agents, it is important to understand their effects at the postjunctional, cholinergic, nicotinic receptors at the neuromuscular junction. Under normal circumstances, the neuron synthesizes acetylcholine (ACh) from choline and acetate and packages it in vesicles. Each vesicle contains 5,000 to 10,000 ACh molecules. Calcium enters the nerve through channels that open in response to the action potential propagating the length of the nerve. Calcium permits the binding of specific proteins to the vesicles necessary for them to bind to the nerve end membrane. Binding produces fusion and the release of ACh. The ACh migrates across the synaptic cleft and attaches to nicotinic ACh receptors, promoting muscle fiber depolarization producing muscle contraction. ACh then detaches from the receptor to be eligible for reuptake into the nerve terminal or hydrolysis by acetylcholinesterase, which also resides in the cleft.

Neuromuscular blocking agents are either ACh agonists (depolarizers of the motor end plate) or antagonists (nondepolarizers of the motor end plate). The antagonists attach to the receptors and competitively block ACh from accessing ACh receptors. Because they are in competition with ACh for the motor end plate, they can be displaced from the end plate by increasing concentrations of ACh, the end result of reversal agents (the cholinesterase inhibitors), such as neostigmine and edrophonium, which inhibit acetylcholinesterase and allow ACh accumulation and the return of neuromuscular function.

In clinical practice, there are two classes of neuromuscular blocking agents: the noncompetitive or

depolarizing neuromuscular blocking agents, of which succinylcholine is the prototype and the only one in common clinical use. The competitive or nondepolarizing agents are divided into two main classes: the benzylisoquinolinium compounds and the aminosteroid compounds. The benzylisoquinolines, *d*-tubocurarine, metocurine, atracurium, cisatracurium, and mivacurium share common properties. The aminosteroids, vecuronium, pancuronium, rapacuronium, and rocuronium also share common attributes that are distinct from those of the benzylisoquinolines.

The ideal muscle relaxant to facilitate tracheal intubation would have a rapid onset, a short duration of action, no significant adverse side effects, and metabolism and excretion independent of liver and kidney function. Unfortunately, such an agent does not exist. Succinylcholine comes closest to meeting all these desirable goals. Despite the historic and well-known adverse effects of succinylcholine and the continuous advent of new competitive neuromuscular blocking agents, succinylcholine remains an essential drug in facilitating tracheal intubation.

4.4.2 Depolarizing Neuromuscular Blocking Agent

4.4.2.1 What Are the Clinical Pharmacological Characteristics of Succinylcholine that Make It a Unique Neuromuscular Blocking Agent?

Succinylcholine is chemically similar to ACh. It consists of two molecules of ACh linked by an ester bridge and, as does ACh, succinylcholine stimulates the nicotinic and muscarinic cholinergic receptors of the sympathetic and parasympathetic nervous systems. Once succinylcholine reaches the neuromuscular junction, it binds tightly to the ACh receptors. ACh receptors related to neuromuscular transmission are located in three areas:

- The presynaptic receptors, responsible for regulation of ACh vesicles release, generate an action potential along the neuron.
- The postsynaptic receptors: the principle paralyzing component of succinylcholine occurs at the postsynaptic receptor. The resultant depolarization and subsequent desensitization to further stimulation produced by succinylcholine occurs because unlike ACh, succinylcholine is not rapidly hydrolyzed by acetylcholinesterase. Succinylcholine is resistant to degradation by cleft acetylcholinesterase and is susceptible to rapid hydrolysis by pseudocholinesterase, an enzyme of the liver and plasma not present at the neuromuscular junction. Therefore, diffusion away from the neuromuscular junction motor end plate and back into the vascular compartment is ultimately responsible for succinylcholine metabolism. This also explains why only a fraction of the initial intravenous dose of succinylcholine ever reaches the motor end plate to promote paralysis.
- Extrajunctional receptors, although numerous, are generally not of clinical significance. In pathological states such as denervation injuries or severe muscle crush injury, these receptors become unregulated and proliferate. The depolarization of the extrajunctional receptors in large numbers can result in clinically significant hyperkalemia.

Succinylmonocholine, the initial metabolite of succinylcholine, sensitizes the cardiac muscarinic receptors in the sinus node to repeat doses of succinylcholine, which may then lead to atropine responsive bradycardia.

4.4.2.2 What Are the Indications and Contraindications for Succinylcholine?

Succinylcholine remains the neuromuscular blocking agent of choice for emergency RSI because of its rapid onset and relatively brief duration of action. A personal or family history of malignant hyperthermia (MH) is an absolute contraindication to the use of succinylcholine. Patients judged to be at risk for succinylcholine-related hyperkalemia also represent absolute contraindications to its use. Under these circumstances, to facilitate tracheal intubation rapidly, a large dose of a competitive, nondepolarizing neuromuscular blocking agent should be used.[107] Relative contraindications to the use of succinylcholine are dependent on the skill and proficiency of the airway practitioner and individual patient's clinical circumstance (ie, "context sensitive"; see Chapter 6). A patient who is felt to represent a difficult intubation, and in whom bag-mask-ventilation is also felt to be difficult or impossible, should not receive any neuromuscular blocking agents except as part of a planned approach to the difficult airway.

4.4.2.3 How Can Succinylcholine Be Used Safely?

In the normal-sized adult patient, the recommended dose of succinylcholine for intubation is 1 to 2 $mg \cdot kg^{-1}$. In a rare, life-threatening circumstance when succinylcholine must be given IM because of inability to secure venous access, a dose of 3 to 4 $mg \cdot kg^{-1}$ IM may be used.

The intubating dose is typically felt to be two to three times the dose that produces on average 95% decrease in twitch height of the adductor pollicis muscle (effective dose or ED_{95}). The ED_{95} of succinylcholine is 0.3 to 0.6 $mg \cdot kg^{-1}$ in adults,[108,109] 0.5 $mg \cdot kg^{-1}$ in children, and 0.7 $mg \cdot kg^{-1}$ in infants and neonates.[110] Therefore, an appropriate intubating dose of succinylcholine for a normal-sized adult is 1 $mg \cdot kg^{-1}$. For obese patients dosing would appear to be more successful if the total body weight is used rather than ideal body weight.[111] The average onset time is 1 to 1.5 minutes. Defasciculation with a nondepolarizing muscle relaxant will decrease the potency of succinylcholine by half. Therefore, if one intends to pretreat the fasciculations with a nondepolarizing agent, a succinylcholine dose of 1.5 to 2 $mg \cdot kg^{-1}$ is required for intubation.[109]

Succinylcholine is rapidly cleared by plasma pseudocholinesterase which is an enzyme manufactured in the liver. Once succinylcholine diffuses out of the synaptic cleft it is hydrolyzed to succinylmonocholine and then to succinic acid. The mean elimination half-life of succinylcholine is 43 seconds.[112] The rate of metabolism determines the duration of action. A normal adult has a theoretical 8-minute apneic reserve of oxygen. The mean time to return of spontaneous ventilation after an intubating dose of succinylcholine (1 $mg \cdot kg^{-1}$) is approximately 5 to 8 minutes.[113] Hayes et al[113] did however have 10% of their patients desaturate before the return of spontaneous ventilation. The airway practitioner still has to provide mechanical ventilation until the function of the respiratory muscles returns. Doses less than 1 $mg \cdot kg^{-1}$ may not compromise the intubation nor do they shorten the apneic period.[114]

4.4.2.4 What Are the Adverse Effects of Succinylcholine and How Can We Minimize These Side Effects?

The recognized side effects of succinylcholine include fasciculations, hyperkalemia, bradycardia, asystole, prolonged neuromuscular blockade, MH, and masseter muscle spasm. Each of these will be discussed separately.

Fasciculations. Fasciculations are involuntary, unsynchronized muscle contractions caused by depolarization of ACh receptors. Fasciculations cause muscle damage that manifests itself as myalgias, increased creatinine kinase, myoglobinemia, and an increase in catecholamines leading to increases in heart rate and blood pressure. These uncontrolled muscle contractions increase oxygen consumption and carbon dioxide production, and can lead to increased cardiac output, and potentially CBF and ICP. In an animal study, the increase in ICP was found to be secondary to the increase in muscle spindle activation caused by succinylcholine-induced spindle depolarization.[115] Lastly, fasciculations tend to increase intragastric pressure, though this is not clinically significant as it is offset by an increase in lower esophageal sphincter tone.

Virtually all patients receiving succinylcholine will experience fasciculations. The same cannot be said for postoperative myalgias which occur following the administration of succinylcholine at a rate 1.5% to 89%.[116] However, 15% to 20% subjects undergoing surgery without being exposed to succinylcholine will suffer from postoperative myalgias.[117] Not only is the link between fasciculations and myalgias controversial, there is no evidence that the severity of fasciculations corresponds with more severe myalgias[116], nor does it appear to be a dose-related side effect. In fact, McLoughlin et al[118] suggest that increasing the dose of succinylcholine may decrease the incidence of myalgias, suggesting that the larger dose leads to a more synchronous contraction and a reduction in shearing forces.

Small doses of NDMRs given prior to succinylcholine have clearly been shown to decrease the incidence and intensity of fasciculations[45-50], but their ability to effectively relieve postoperative myalgias is not quite as clear.[46-48] A meta-analysis did determine that atracurium, *d*-tubocurarine, galamine, and pancuronium can decrease the frequency of fasciculations and myalgias.[50] Traditionally, 10% of the intubating dose of an NDMR has been given to pretreat for fasciculations. However, at this dose, a significant number of patients experience weakness. While a dose of 0.06 $mg \cdot kg^{-1}$ of rocuronium has been shown to decrease the incidence of fasciculations, it does not decrease the incidence of myalgias.[47-49,119] Harvey et al[46] showed that rocuronium at doses 0.03 and 0.05 $mg \cdot kg^{-1}$ was equally effective in decreasing the incidence of fasciculations. The timing of rocuronium administration (3 vs 1.5 minutes) prior to the succinylcholine does not seem to affect it effectiveness.[49]

Lidocaine is an alternative to nondepolarizing muscle relaxants for defasciculation. At doses of 1.5 $mg \cdot kg^{-1}$, lidocaine effectively decreases the incidence of fasciculation and myalgias following the administration of succinylcholine.[50,116] Lidocaine appears to work by preventing ionic exchange across the sodium channels.

Hyperkalemia. Under normal circumstances, serum potassium increases minimally when succinylcholine is administered (0-0.5 $mEq \cdot L^{-1}$) due to depolarization of the myocytes. A pathological response to succinylcholine can occur, however, resulting in rapid and dramatic increases in serum potassium. These

pathologic hyperkalemic responses occur by two distinct mechanisms: receptor upregulation and rhabdomyolysis. In either situation, potassium increase may approach four times the normal efflux of potassium, resulting in hyperkalemic dysrhythmias, or cardiac arrest.[120] Two forms of postjunctional ACh receptors exist, mature (junctional) and immature (extrajunctional). Each ACh receptor is composed of five proteins arranged in circular fashion around a common channel. Both types of receptors contain two alpha subunits. ACh must attach to both alpha subunits to open the channel and effect depolarization and muscle contraction. When receptor upregulation occurs, the mature receptors at and around the motor end plate are gradually converted over a 4 to 5-day period to immature receptors that propagate throughout the entire muscle membrane. Upregulated receptors are characterized by low conductance and prolonged channel-opening times, resulting in increasing levels of potassium, clinically significant dysrhythmias, and cardiac arrest.[119] Most of the entities associated with hyperkalemia during emergency RSI are the result of receptor upregulation. Interestingly, these same extrajunctional nicotinic receptors are relatively refractory to nondepolarizing agents, so larger doses of vecuronium, pancuronium, or rocuronium will be required to produce paralysis.

Rhabdomyolysis is the other mechanism by which hyperkalemia may occur. It is most often associated with myopathies. In cardiac arrest situations related to rhabdomyolysis and continued loss of potassium, resuscitation seems to be less successful than in receptor upregulation. Gronert[120] reviewed 129 cases of cardiac arrest from hyperkalemia; 57 were due to rhabdomyolysis and 78 due to upregulation. The mortality was higher in those cases of rhabdomyolysis (30%) compared to cases of upregulation (11%). Succinylcholine is a toxin to unstable membranes in any patient with a myopathy and should be avoided.

Receptor upregulation occurs in burn victims, patients that suffer denervation injury, and in patients with sepsis or widespread inflammation. In burn victims, extrajunctional receptor sensitization becomes clinically significant at 4 to 5 days postburn. It lasts an indefinite period of time, although the *at risk* period is deemed to have passed at the point healing of the burned area is complete. It is prudent not to administer succinylcholine to postburn patients if any question exists regarding the status of their burn. The percent of body surface area burned does not determine the magnitude of hyperkalemia; significant hyperkalemia has been reported in patients with as little as 8% total body surface area burn.[121] Most emergency intubations for burns are performed well within the safe 4-day window after the burn occurs. There have been no reports of hyperkalemia in the first 24 hours postburn. It seems rational to avoid the administration of succinylcholine until the burn has completely healed.

The patient who suffers a denervation event secondary to a lower motor neuron or upper motor neuron injury is at risk for hyperkalemia. Following lower motor neuron denervation injuries, patients exhibit a sensitivity to succinylcholine, which begins 3 to 4 days postinjury[119] and patients suffering from severe polyneuropathies display increased potassium release following the administration of succinylcholine.[122,123] Upper motor neuron lesions, such as stroke and traumatic closed head injuries, display a similar sensitivity to succinylcholine, usually 3 to 5 days after the event.[119] As long as any neuromuscular disease is active, one ought to expect that there will be augmentation of the extrajunctional receptors and risk for hyperkalemia with the use of succinylcholine. Congenital upper motor neuron and lower motor neuron lesions, such as cerebral palsy and myelomeningocele, do not exhibit an altered response to succinylcholine.[124,125] The duration of the upregulation and altered response to succinylcholine in neuromuscular disorders is not clear. Upregulation

has been observed 3 years following an injury and may last even longer in progressive disease types.[119] Unlike fasciculations, the hyperkalemic response cannot be attenuated by administering defasciculating doses of NDMRs, and therefore, these specific clinical situations should be considered absolute contraindications to succinylcholine during the specified time periods.

Infection or inflammation can alter the neuromuscular junction response to muscle relaxants.[119] This situation is complicated by the intensive care unit environment where total body disuse atrophy and chemical denervation of the ACh receptors can occur if muscle relaxants are chronically infused. Exaggerated hyperkalemic responses to succinylcholine have been observed in patients with life-threatening infections.[126,127] The at-risk time period appears to be 5 days after the illness has begun and continues indefinitely as long as the disease process is present.

Succinylcholine is absolutely contraindicated in patients with inherited myopathies such as Duschene and Becker muscular dystrophies. The combination of the succinylcholine-induced contractures and the fragile muscle membrane of the myopathic patients predisposes them to rhabdomyolysis.[51] In children up to 10 years of age, an elevated creatine kinase is a highly sensitive indicator of muscular dystrophy.[128] Myopathic rhabdomyolysis and hyperkalemia-induced cardiac arrest is associated with a significant degree of mortality. The hyperkalemic efflux can be four times the expected normal response. Any inappropriate response by young males following the use of succinylcholine should alert the practitioner to the possibility of undiagnosed Duschene muscular dystrophy.[129]

There is a paucity of evidence supporting the notion that chronic renal failure patients with normal levels of serum potassium present a risk of an exaggerated hyperkalemic response with the administration of succinylcholine. Indeed, the majority of renal failure patients are successfully intubated using succinylcholine without adverse cardiovascular complications. A review of the literature by Thapa et al[130] concluded that there was insufficient evidence to support a recommendation to avoid succinylcholine in patients with renal failure.

Patients with hyperkalemia may be different. Despite succinylcholine being used successfully in patients with hyperkalemia[131] without any adverse events, succinylcholine still cannot be recommended for such patients. Even the normal 0.5 $mEq.L^{-1}$ efflux of potassium could be lethal in a patient with preexisting significant hyperkalemia and acidosis.

Bradycardia. Bradycardia following the administration of succinylcholine is seen most commonly in children because of their heightened vagotonic state. This is especially so as the sympathetic nervous system does not mature until 4 to 6 months of age. Bradycardia is attenuated or abolished by administering atropine 0.02 $mg \cdot kg^{-1}$ or glycopyrrolate 0.01 $mg \cdot kg^{-1}$[43] as pretreatment before administering succinylcholine. The age above which prophylactic atropine is no longer needed is unknown. McAuliffe et al[132] have shown that the incidence of bradycardia following succinylcholine in children 1 to 12 years of age is lower than previously thought, stating that atropine pretreatment may not be necessary. Expert opinion has gravitated to this same recommendation: treat bradycardia if it preexists or occurs following succinylcholine administration rather

than employing routine pretreatment. Regardless of the age, repeated doses of succinylcholine may produce the profound vagally mediated bradycardia requiring the administration of antimuscarinics.

Prolonged Neuromuscular Blockade. Prolonged neuromuscular blockade may result from an acquired reduction in pseudocholinesterase concentration, a congenital absence of pseudo- cholinesterase, or the presence of an atypical form of pseudocholinesterase, all of which will delay the degradation of succinylcholine and prolong paralysis. Reduced concentrations of pseudocholinesterase may be a result of liver disease, pregnancy, burns, oral contraceptives, uremia, drug abuse, or plasmapheresis. This quantitative loss of pseudocholinesterase is rarely clinically significant. Atypical or abnormal genetic variants of pseudocholinesterase can be uncovered by testing. The patient who is a homozygous for atypical pseudocholinesterase (1:1500) may have paralysis for 3 to 6 hours after a single dose of succinylcholine.

Increase in Intraocular Pressure. Elevated intraocular pressure results from muscle contractures of the orbital muscles that occur following stimulation of the postsynaptic ACh receptors. Although succinylcholine can increase the intraocular pressure by 6 to 8 mm Hg,[133] there have been no reported cases of vitreous extrusion in the presence of an opened globe injury related to the administration of succinylcholine or during intubation. The use of succinylcholine has been advocated in patients for whom the prompt securing of the airway is indicated in the face of open globe injuries.[134] The more pressing concern should be protection and the prevention of the deleterious side effects of intubation, such as hypoxia and coughing.

Malignant Hyperthermia. A personal or family history of MH is an absolute contraindication to the use of succinylcholine. MH is an acute hypermetabolic disorder of skeletal muscle. The incidence of MH ranges from 1:50000 to 1:4000.[135] It is an inherited syndrome typified by alteration of the Ry1 ryanodine receptor which modulates calcium release from the sarcoplasmic reticulum. It can be triggered by halogenated anesthetics and succinylcholine. Following the initiating event, its onset can be acute and progressive or delayed for hours. Generalized awareness of MH, earlier diagnosis, and the availability of dantrolene have decreased the mortality to approximately 10%.[136]

MH is characterized by an acute loss of intracellular calcium control. This results in a cascade of rapidly progressive events manifested primarily by increased metabolism (increased oxygen consumption and carbon dioxide production) as well as muscular rigidity, autonomic instability, hypoxia, hypotension, severe lactic acidosis, hyperkalemia, and myoglobinemia. An elevation in temperature is a highly variable manifestation. The treatment for MH consists of discontinuing the known or suspected precipitant and the immediate administration of dantrolene. Dantrolene is essential to successful resuscitation and should be given as soon as the diagnosis is seriously entertained. Dantrolene is a hydantoin derivative that acts directly on skeletal muscle to prevent calcium release from the sarcoplasmic reticulum without affecting calcium reuptake. The initial dose is 2.5 $mg \cdot kg^{-1}$ and is repeated every 5 minutes until muscle relaxation occurs or the maximum dose of 10 $mg \cdot kg^{-1}$ is administered. Dantrolene is free of any serious side effects. Additionally, measures to control body temperature, manage hyperkalemia, maintain acid–base balance, and enhance urinary output to preserve renal function must be instituted as soon as possible.

All cases of MH require constant monitoring of pH, arterial blood gases, and serum potassium. Immediate and aggressive management of hyperkalemia with the administration of calcium gluconate, glucose, insulin, and

sodium bicarbonate may be necessary. Following an acute MH crisis, intensive care monitoring is recommended for 24 to 36 hours. Arterial pH, myoglobinemia, and creatine kinase should be serially monitored. Recrudescence occurs in 25% of MH cases.[135] Patients should be maintained on dantrolene (1 $mg \cdot kg^{-1}$ every 6-8 hours) for the first 24 hours after a crisis.

Masseter Muscle Rigidity. Masseter muscle rigidity (MMR) is defined as the transient inability to distract the mandible from the maxilla such that the mouth cannot be opened or opened only with force.[137] The incidence of MMR following succinylcholine is 0.3% to 1%.[138] Pretreatment with defasciculating doses of nondepolarizing NMBAs will not prevent masseter rigidity. MMR typically subsides in 2 to 3 minutes. More than 50% of patients with MMR are susceptible to MH based on caffeine–halothane contracture studies.[139] In the setting of the OR where an operation is contemplated, continuance of a nontriggering anesthetic following tracheal intubation is reasonable if proper monitoring is available (end-tidal carbon dioxide, temperature, creatine kinase, and myoglobin) and the anesthesia practitioner is comfortable treating MH,[138] otherwise the anesthetic should be discontinued and patient monitored for signs of MH.

4.4.3 Nondepolarizing (Competitive) Neuromuscular Blocking Agents

4.4.3.1 Discuss the Clinical Pharmacology of Nondepolarizing Neuromuscular Blocking Agents

Nondepolarizing muscle relaxants (NDMRs) competitively antagonize the action of ACh transmission at the postjunctional, cholinergic, nicotinic receptors at the neuromuscular junction. They are incapable of inducing the conformational change necessary to initiate the depolarization of the neuromuscular junction. NDMRs prevent ACh access to both alpha subunits of the nicotinic receptor, which is required for muscle contraction. This competitive blockade is characterized by the absence of fasciculations and the reversal of paralysis by acetylcholinesterase inhibitors that prevent metabolism of ACh to allow its reaccumulation and the potential for retransmission at the motor end plate, promoting a muscle contraction. Metabolism and elimination of NDMRs occur through a variety of biochemical pathways involving the liver, kidney, and Hofmann degradation. Hofmann degradation, a nonenzymatic degradation, is largely responsible for the metabolism of cisatracurium and atracurium.

Mivacurium is a benzylisoquinoline derivative that unlike the rest of the NDMRs is metabolized by pseudocholinesterase. Intubating doses range from 0.15 to 0.2 $mg \cdot kg^{-1}$ with a short onset time and brief duration. Mivacurium duration will be prolonged in patients with atypical pseudocholinesterase. As well, mivacurium releases histamine that can induce hypotension.

Cisatracurium, as previously mentioned, undergoes Hofmann degradation and elimination, rendering it virtually independent of liver and renal function. It is devoid of autonomic side effects. Cisatracurium has a relatively long onset time and intermediate duration.

Rocuronium, an aminosteroid, is eliminated primarily by the liver. It has an ED_{95} of 0.3 $mg \cdot kg^{-1}$. A dose of 0.6 $mg \cdot kg^{-1}$ can provide good intubating conditions in 90 seconds. In order to provide good intubating

conditions in 60 seconds, similar to that of succinylcholine, a larger dose (1-1.2 $mg \cdot kg^{-1}$) is commonly required for an RSI.[107] However, it has an intermediate duration of action.

Rapacuronium, a newer rapid-onset aminosteroid NDMR, provides good intubating conditions in doses of 1.5 $mg \cdot kg^{-1}$ and has a short duration of action (17 minutes).[140] Unfortunately, rapacuronium has caused life-threatening bronchospasm and as a result its sale has been suspended.[141]

4.4.3.2 What Are the Indications and Contraindications of NDMRs?

The NDMRs serve a multipurpose role in emergency airway management (Table 4-2). They can be used as pretreatment agents to attenuate the many undesirable side effects associated with muscle fasciculations (eg, myalgia and the increase in ICP, IOP, etc) following the use of succinylcholine. They can also serve as the muscle relaxant of choice if succinylcholine is contraindicated or unavailable, or to maintain postintubation paralysis. NDMRs are contraindicated in the face of difficult ventilation/intubation and/or an inexperienced airway practitioner.

Table 4-2 Commonly Used NDMRs, Their Therapeutic Intubating Doses, Pretreatment Doses for Preventing Fasciculation and Myalgias, and Their Basic Pharmacokinetics

	INTUBATING DOSE ($mg \cdot kg^{-1}$)	PRETREATMENT ($mg \cdot kg^{-1}$)	ONSET (s)	DURATION (min)
Rocuronium	0.6-1.2	0.03-.06	60-90	45
Vecuronium	0.15	0.005-.01	300	45
Cisatracurium	0.15	0.005	300	45
Mivacurium	0.2	0.01	120-180	30

See reference 11.

4.4.3.3 How Can We Use NDMRs Effectively?

Defasciculation prior to the administration of succinylcholine is used in patients to minimize myalgias and the elevation of ICP secondary to the increased CBF associated with the increase of carbon dioxide production from the fasciculations and muscle spindle activation. The appropriate dose is 10% of the ED_{95} of any of the nondepolarizing agents. Presently, rocuronium appears to be the most commonly used NDMR to abate fasciculations[51] and it can be given 1.5 to 3 minutes prior to the induction of anesthesia.[49]

NDMRs are the only option for rapid-sequence induction when succinylcholine is contraindicated or not available. In these situations, NDMRs can be used for emergency RSI. The drug of choice is rocuronium 1 to 1.2 $mg \cdot kg^{-1}$ based on its time to onset. If rocuronium is not available, vecuronium 0.15 $mg \cdot kg^{-1}$ is a reasonable alternative (Table 4-2).

4.4.4 How Do We Decide When to Use a Nondepolarizing Muscle Relaxant versus Succinylcholine for Tracheal Intubation?

The use of neuromuscular blocking agents to facilitate endotracheal intubation results in an increased success rate and fewer complications.[107,142-144] Whether succinylcholine or an NDMR is used to accomplish the task is a hotly debated topic. Succinylcholine is superior to the slower onset NDMRs such as pancuronium, atracurium, and vecuronium.[145] The most commonly used muscle relaxants in a rapid-sequence induction/intubation are succinylcholine and rocuronium based on their pharmacokinetic and pharmacodynamic profiles. For each drug, the dosage is critical to their success of intubation. The most appropriate dose of succinylcholine is 1 to 2 $mg \cdot kg^{-1}$.[108,109,114] Doses of 1 to 1.2 $mg \cdot kg^{-1}$ of rocuronium provide better intubating conditions within 60 to 90 seconds than the lower dose of 0.6 $mg \cdot kg^{-1}$.[107,146,147] In the emergency department and the OR, succinylcholine (1-2 $mg \cdot kg^{-1}$) and rocuronium (1-1.2 $mg \cdot kg^{-1}$) in the appropriate doses have been used safely and efficaciously with unparalleled success.[143,144,147,148] However, one must always be wary of the potentially difficult intubation, and in those cases, the selection of rocuronium would be unwise.

4.4.5 Are There Any New Muscle Relaxants or Adjuncts with a Better Pharmacodynamic Profile?

The next generation of neuromuscular blocking drugs aims for a rapid onset with a short duration of action, mimicking succinylcholine, but with minimal side effects. The ideal NDMR was thought to be rapacuronium, a newer rapid-onset aminosteroid NDMR. It provided good intubating conditions with a short duration of action.[140] However, after widespread usage of rapacuronium, it became evident that it can cause severe bronchospasm associated with arterial desaturation and difficult ventilation.[140,141,146] As a result of its life-threatening bronchospasm, rapacuronium was withdrawn from the market in 2001.

Another new generation muscle relaxant candidate is an asymmetrical mixed tetrahydroisoquinolinium chlorofumarate, Gantacurium (GW280430A). It is an NDMR with an ultrashort duration of action, developed to replace succinylcholine. Belmont[149] has estimated the ED_{95} to be 0.19 $mg \cdot kg^{-1}$. The onset of action at doses 2.5 to 3 times the ED_{95} was within 90 seconds with transient cardiovascular adverse effects suggestive of histamine release.[149] Spontaneous recovery to a train-of-four of 0.9 was evident 12 to 15 minutes after large doses ($3 \times ED_{95}$).[150] Gantacurium's metabolism is nonenzymatic; partially due to rapid formation of an inactive cysteine product; the other portion undergoes ester hydrolysis to inactive metabolites.[150] The early studies indicate no significant adverse cardiovascular or respiratory side effects in humans.[141] A phase-2 trial in adults has been completed (*http://clinicaltrials.gov/show/NCT00235976*), but no results have yet been published.

The most promising new agent is not a muscle relaxant but a new reversal agent for muscle relaxants. Sugammadex is a modified γ-cyclodextrin. Cyclodextrins are cyclic oligosaccharides, whose 3D structures

resemble a hollow, truncated cone or doughnut.[151] They have a hydrophobic interior and hydrophilic exterior, the hydrophobic portion traps drugs within the cyclodextrin cavity. Sugammadex is a muscle relaxant-binding agent; it does not interact with nicotinic receptors or with acetylcholinesterases, and acts independently of the degree of neuromuscular blockade. Sugammadex encapsulates and inactivates rocuronium and vecuronium; the resultant complex is excreted in the urine.[152] Sugammadex does not appear to have any significant hemodynamic or respiratory consequences.

Sugammadex may enable the rapid reversal of a profound nondepolarizing block in cases of difficult laryngoscopy and potentially eliminate succinylcholine from the standard anesthetic drug cart, cost notwithstanding. Reversal of profound rocuronium blockade (1.2 $mg \cdot kg^{-1}$) with sugammadex (16 $mg \cdot kg^{-1}$) was significantly faster than spontaneous recovery from succinylcholine (1 $mg \cdot kg^{-1}$).[153] Jones et al[154] administered either sugammadex (4 $mg \cdot kg^{-1}$) or neostigmine and glycopyrrolate to reverse a profound rocuronium neuromuscular block. The drugs were administered at the reappearance of 1 to 2 post-tetanic counts; sugammadex reversed the neuromuscular block significantly faster than the traditional reversal agents.

Rocuronium binds tightly to sugammadex rendering recurarisation as unlikely. However, if an inadequate dose of sugammadex is administered, unbound rocuronium redistributed from peripheral compartments may hinder the efficacy of sugammadex.[155] Because of its renal clearance, more study is required on its use in individuals with renal disease and other comorbidities. Although sugammadex is a useful addition to the armamentarium of airway practitioners, the intelligent use of muscle relaxants ought to limit the need for such an agent in difficult and failed airway management.

4.5 Summary

Tracheal intubation and manipulation of the airway are associated with significant physiological changes. Although it is unknown if pharmacological attenuation of these responses improves outcomes, it seems both reasonable and logical to minimize these responses, particularly in compromised patients: *tight heart*, *tight brain*, and *tight lungs*. This chapter provides a general discussion of the appropriate pharmacological agents and their relevant properties. Successful and safe use of these drugs requires a clear understanding of patient's physiology, the pharmacokinetic and pharmacodynamic properties of the drugs, as well as the associated side effects.

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