PRIMER

Rapid-sequence intubation and the role of the emergency department pharmacist

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Purpose. The pharmacology, pharmacokinetics, safety, and dosing of medications used during the pretreatment and paralysis with induction steps of rapid-sequence intubation (RSI) and the role of the pharmacist in RSI are reviewed.

Summary. RSI is a process involving the administration of a sedative induction agent and a paralytic agent to facilitate endotracheal intubation. This is a procedure in which the emergency department (ED) pharmacist can play an integral role, especially in the steps of pretreatment, paralysis with induction, and postintubation management. The pretreatment phase occurs three minutes before administration of induction and neuromuscular blockers. The purpose of pretreatment is to attenuate the pathophysiologic response to laryngoscopy and intubation. Three minutes after the pretreatment agents have been administered, paralysis with induction will begin. The purpose of induction is to produce a state of general anesthesia, allowing for the administration of paralytics and facilitation of ideal intubating conditions. It is advisable for the ED pharmacist to be familiar with the steps and medications involved with RSI so that appropriate interventions may be made, facilitating both the successful intubation and the safety of the patient. The relative chaos that may occur during emergent RSI requires the ED pharmacist to have a clearly defined primary plan as well as contingency plans to deal with potential complications. Commonly used medications during intubation include lidocaine, fentanyl, etomidate, midazolam, thiopental, ketamine, succinylcholine, and rocuronium.

Conclusion. The selection of an appropriate sedative and neuromuscular blocker during the pretreatment and paralysis with induction steps of RSI can be facilitated by an ED pharmacist.

Index terms: Anesthesia; Anesthetics, local; Anesthetics; Anxiolytics, sedatives and hypnotics; Dosage; Etomidate; Fentanyl; Hospitals; Intubation; Ketamine; Lidocaine; Midazolam; Neuromuscular blocking agents; Opiates; Pharmaceutical services; Pharmacists, hospital; Rocuronium; Succinylcholine; Thiopental; Toxicity

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While the practice of emergency pharmacy is not new, it is becoming more common to find an emergency department (ED) pharmacist practicing in the ED,[1] and an expanded role of ED pharmacists has been supported by the Institute of Medicine.[2] Pharmacists can play an integral role in the ED, contributing to patient care during trauma, medical resuscitation, cardiac arrest, supraventricular tachycardia, procedural sedation, and rapid-sequence intubation (RSI), to name only a few examples. Since increasing numbers of EDs are adding a pharmacy specialist, it is worth reviewing one of the more frequently encountered procedures in which these pharmacists are involved: RSI.

An audio interview with the author, which supplements the information in this article, is available on *AJHP*'s website at www.ajhp.org/site/misc/podcasts.xhtml.

This article reviews RSI and the indications, contraindications, dosages, and adverse effects of medications used throughout the procedure. The article focuses on pretreatment and paralysis with induction during RSI, as well as the role of the ED pharmacist.

Overview

In RSI, a sedative and a neuromuscular blocker are administered to facilitate the process of endotracheal intubation.[3]

RSI may be thought of as a series of seven discrete steps, often referred

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to as the "seven p's": (1) preparation, (2) preoxygenation, (3) pretreatment, (4) paralysis with induction, (5) protection and positioning, (6) placement of the tube in the trachea, and (7) postintubation management.[4] The ED pharmacist has the opportunity to play a large role in pretreatment (identify patients requiring pretreatment, appropriate agents, and doses), paralysis with induction (select appropriate induction and paralytic agents and doses), and postintubation management (select appropriate agents and doses, help maintain sedation and analgesia). For the sake of brevity, this article focuses on the steps of pretreatment and paralysis with induction, though Figure 1 describes the timing of each of the seven steps.

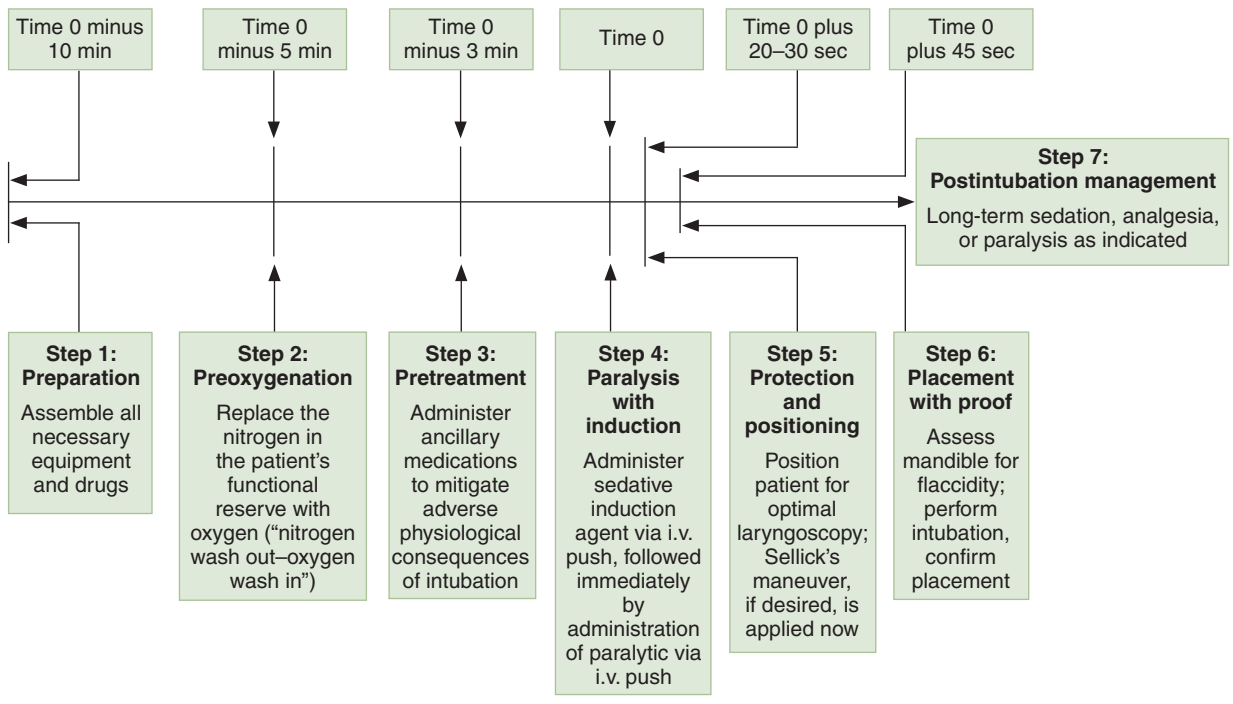
Pretreatment

Pretreatment occurs three minutes before the administration of induction agents and neuromuscular blockers. The purpose of pretreatment is to attenuate the pathophysiologic response to laryngoscopy and intubation.[5] During intubation, sympathetic and parasympathetic nerves, which innervate the airway, are stimulated. This results in a release of systemic catecholamines, leading to an increase in mean heart rate of approximately 30 beats/min, an increase in mean arterial blood pressure of approximately 20–25 mm Hg, and an increase in arterial wall shear stress.[6] Placement of the endotracheal tube also stimulates upper-airway reflexes, precipitating cough, laryngospasm, and lower-airway bronchospasm.[7]

Historically, the pretreatment mnemonic *LOAD* was used to cue the use of lidocaine, opioids (specifically fentanyl), atropine, and defasciculating dosages of neuromuscular blockers. Based on current evidence, only lidocaine and fentanyl can be recommended for pretreatment, though atropine may be used in patients younger than one year old.[6] Defasciculation is no longer recommended as a routine part of emergency RSI.[6,8-10]

Lidocaine. Lidocaine, an amide anesthetic, is a class 1B antiarrhythmic that blocks sodium channels in neurons, eliminating their ability to depolarize and carry signals.[11,12] When given intravenously, lidocaine has an onset of action of approximately 45–90 seconds and a duration of action of 10–20 minutes after the administration of a single dose. However, since lidocaine is mainly metabolized by the liver (90%), the half-life may double in patients with hepatic dysfunction.[11] The typical dose used in RSI is 1.5 mg/kg i.v. administered three minutes before intubation.[6] Lidocaine is absolutely contraindicated in patients with an amide anesthetic allergy, who are severely bradycardic, or who have severe heart block (unless the patient has a functioning pacemaker).[11] Severe drug interactions have been identified in patients concurrently receiving lidocaine and dofetilide,

Figure 1. Timeline of rapid-sequence intubation.[4]



monoamine oxidase inhibitors, or amiodarone.[13]

Lidocaine's ability to suppress the cough reflex may play a role in mitigating intracranial pressure (ICP) elevation during RSI. Intubation involves the introduction of a noxious stimulus (endotracheal tube) into the trachea, which activates the cough reflex. Coughing increases ICP and may increase the risk of hemorrhagic stroke or herniation in a patient whose ICP is already elevated.[14] Patients with head trauma (e.g., closed head injury, traumatic brain injury) are at greatest risk of complications from ICP elevation.[15] While lidocaine's ability to suppress the cough reflex has been demonstrated,[16-24] data regarding its ability to blunt ICP elevation are conflicting, and there have been no studies in emergency RSI evaluating ICP as a primary end point.[25] The use of lidocaine to blunt the cough reflex with the goal of mitigating ICP elevation has been found to be safe when appropriately dosed. Thus, the use of lidocaine as a pretreatment for this indication is recommended until more robust data are produced.[5]

Lidocaine also has the purported benefit of inhibiting bronchospasm in patients who have reactive airway disease.[26,27] It is believed that when the airway is stimulated in asthmatic patients, the vagus nerve mediates a bronchospastic response, resulting in respiratory distress and decreased airflow immediately after intubation.[28] The results of studies evaluating the ability of lidocaine to inhibit bronchospasm are conflicting,[29-31] though use of the drug for this indication is currently recommended.[32]

Fentanyl. Fentanyl is an opioid-receptor agonist that selectively activates the μ-receptor, thus precipitating analgesia. The onset of action is almost immediate, and the duration of action is approximately one hour.[33] The typical fentanyl dose used for pretreatment in RSI is 1–3 μg/kg i.v. administered three minutes before intubation.[6] This dose should be administered over 30–60 seconds to avoid precipitous respiratory depression.

The rationale for using fentanyl as pretreatment lies in its ability to blunt the release of catecholamines secondary to airway manipulation, thereby limiting postintubation increases in blood pressure.[34-36] Patients undergoing intubation who would be adversely affected by a systemic release of catecholamines and the subsequent increases in blood pressure, heart rate, and the force of cardiac contraction should receive pretreatment with fentanyl. Patients thought to be at greatest risk include those with increased ICP, ischemic heart disease, intracranial hemorrhage, cerebral or aortic aneurysm (known or suspected), or major vessel dissection.[6] Pretreatment with fentanyl should be avoided in patients who are dependent on sympathetic drive to maintain blood pressure and cardiac output (i.e., patients in decompensated shock or who are hemodynamically unstable).

Chest wall rigidity secondary to fentanyl administration has been reported but not when used for RSI pretreatment. Muscle rigidity is thought to be related to the dose and speed of opioid administration and is usually seen in fentanyl doses exceeding 100 μg/kg. Most cases of rigidity associated with fentanyl have resulted from its use as an induction agent for cardiac surgery.[37]

Atropine. In the past, atropine was recommended as a routine pretreatment agent for intubation of pediatric patients when succinylcholine was used for paralysis. Since succinylcholine stimulates muscarinic receptors, bradycardia is a possible response to succinylcholine administration. Although the incidence and severity of bradycardia are greater in pediatric patients,[38] no compelling data support the use of atropine as a pretreatment agent, and it is not currently recommended for routine use. Atropine should be kept on hand during intubation and may be used if bradycardia does occur in both pediatric and adult patients.

Paralysis with induction

Three minutes after the pretreatment agents have been administered, paralysis with induction begins. In order to remain consistent with the seven p's, paralysis is listed first in the step, but it should be noted that *induction should always precede paralysis* due to the risk of inadequate sedation. If a paralytic agent is administered before sedation, the possibility exists that sedation will be inadequate, leaving the patient fully aware of the procedure yet unable to give any indication that he or she is still conscious and alert, thereby increasing the risk of posttraumatic stress disorder. This is an important area for pharmacy intervention, especially if working with new practitioners who may be unaware of the proper order of administration.

Induction

The purpose of induction is to produce a state of general anesthesia, allowing for the administration of paralytics and facilitating conditions for ideal intubation. Agents approved for induction in RSI include ultra-short-acting barbiturates (thiopental and methohexital), benzodiazepines (midazolam), and miscellaneous agents, including etomidate, ketamine, and propofol.

Ultra-short-acting barbiturates. Thiopental and methohexital are ultra-short-acting central nervous system (CNS) depressants, which mediate sedation but not analgesia. Both have a rapid onset of action (less than 30 seconds) and an approximate duration of 5–10 minutes.[39,40] Previously, these agents were widely used for induction in RSI but have largely been replaced by other agents, particularly etomidate. Methohexital is rarely used for induction in RSI and will not be discussed further in this article.

Many patients undergoing RSI are hemodynamically unstable, and thiopental is not an ideal agent for sedative induction in these patients. Thiopental has negative cardiovascular effects mediated via myocardial depression and peripheral vasodilation,[39] making it unattractive for use in the hemodynamically unstable patient. However, thiopental will decrease cerebral blood flow, decrease the metabolic demand of the brain, and inhibit or terminate seizures, making it a reasonable option for use in patients with an already-elevated ICP secondary to head injury or in patients in status epilepticus.[3,39] It should be noted, however, that with lower thiopental doses, airway manipulation may lead to catecholamine release, causing intracranial hypertension, laryngospasm, cough, and bronchospasm, especially in patients with asthma.[3] In order to mitigate these effects, it has been recommended to coadminister fentanyl, especially in patients who have suffered a head injury.[37]

The recommended intubating dose of thiopental sodium is 3–5 mg/kg i.v., but this dose must be adjusted based on the patient's hemodynamic and cardiovascular status (e.g., lower doses for hypotensive patients).[41] Other agents are available that confer more hemodynamic stability, which is why thiopental is rarely used for induction in RSI.

Benzodiazepines. Benzodiazepines exert their pharmacologic activity via modulation of γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter. They may be beneficial for use in RSI secondary to their amnestic, anxiolytic, central muscle relaxant, sedative, anticonvulsant, and hypnotic effects.[3] As a class, benzodiazepines share similar pharmacologic profiles but differ in selectivity, lipophilicity, and onset and duration of action. High lipophilicity is appealing since increasing lipophilicity equates to a more rapid rate of onset due to the brain's high lipid content. Of the available benzodiazepines, midazolam is the most lipophilic and the only agent arguably suitable for induction in RSI. However, the appropriate doses of midazolam required for intubation are rarely used. In 2003, Sagarin and colleagues[42] conducted a substudy of the National Emergency Airway Registry project and found that most induction doses of midazolam were vastly subtherapeutic, typically 0.03–0.04 mg/kg. This is problematic for two reasons: (1) inadequate patient sedation may result in his or her awareness of the intubation procedure and (2) subtherapeutic doses of an induction agent may worsen the laryngoscopic view and decrease the likelihood of successful early intubation. The recommended dose of midazolam for induction is 0.2–0.3 mg/kg and has a mean time of onset of 60–90 seconds.[41,43] In an emergency care setting, this delayed onset is less than ideal, making midazolam a suboptimal agent for routine use in RSI, especially since superior agents with a more rapid and reliable onset of action are available. While midazolam is commonly used to manage postintubation sedation, it should not routinely be used for the purpose of induction for intubation.

Etomidate. Etomidate is the gold standard for induction in RSI. It is a sedative–hypnotic with a very stable hemodynamic profile and a reliably rapid onset of action (10–15 seconds) and duration of action (4–10 minutes) at a dose of 0.3 mg/kg i.v.[44] It exerts its effect by enhancing the effect of GABA, thereby inhibiting excitatory stimuli. Etomidate also decreases cerebral blood flow and cerebral metabolic rate while conferring hemodynamic stability, resulting in the attenuation of elevated ICP.[3] While it is not the most cerebroprotective of the induction agents (barbiturates hold this title), etomidate does possess reliable pharmacokinetic parameters and provides hemodynamic stability and CNS inhibition, making it an extremely attractive agent for routine use in RSI.

Although widely used as an induction agent in RSI, etomidate is not devoid of controversy. Etomidate transiently inhibits the conversion of cholesterol to cortisol via the inhibition of 11-β-hydroxylase, which has been associated with adrenal suppression for as long as 48 hours.[45-53] While it is likely that the accompanying adrenal suppression is clinically insignificant in otherwise healthy patients, the possibility exists that a more-pronounced effect may be seen in patients already in septic shock. The use of etomidate in this population remains controversial. Patients with evolving septic shock are often unstable and may require emergent intubation, forcing the provider to consider the benefits of etomidate (reliable pharmacokinetic profile, hemodynamic stability) versus the risk of delayed and transient adrenal suppression, which some practitioners still perceive as hypothetical.[54] Two recent systematic reviews have addressed the use of etomidate in patients who were critically ill[55] or had suspected sepsis.[56] Both reviews noted a definite association between etomidate and transient adrenal suppression, but the significance of this association was unclear, as neither review reported a significant effect on mortality when compared with other induction agents. A recently published prospective, double-blind, randomized study compared the effects of single-dose etomidate versus midazolam when used for RSI in patients with suspected sepsis.[57] In this study, 122 patients were randomized to receive either etomidate 0.3 mg/kg ($n = 63$) or midazolam 0.1 mg/kg ($n = 59$). The primary outcome was length of hospital stay, and the study was adequately powered to detect a three-day difference in length of stay. Secondary outcomes included length of intensive care unit stay, days of ventilator use, and inhospital mortal-

ity. The results did not demonstrate a significant difference between etomidate and midazolam in any of the outcomes, though the study may have been inadequately powered to detect a significant difference in secondary outcomes.

In the absence of more-compelling evidence, there are three potential options when considering using etomidate in patients with septic shock.

1. *Do not use etomidate.* Advocates of this approach state that etomidate should not be used in patients with septic shock. However, no convincing data exist to support this practice. Ketamine may be considered a reasonable alternative for induction in hypotensive patients, but practitioners tend to be less familiar with this agent versus etomidate.
2. *Use corticosteroids before etomidate.* Those who recommend the routine administration of corticosteroids before etomidate administration argue that this practice may mitigate the adrenal suppression caused by etomidate.[58] The basis of this recommendation stems from a study conducted in 2002.[59] In this study, the ability of corticosteroids to reduce 28-day mortality in patients with early septic shock who were nonresponders to a standard corticotropin stimulation test was evaluated. However, 21 months into the trial, the protocol was amended to exclude patients who had received etomidate for induction in RSI, since 68 (94%) of 72 patients in this group were nonresponders. The investigators felt that this high nonresponse rate in patients receiving etomidate would undermine the study's ability to determine the general prevalence and severity of adrenal insufficiency in early septic shock. Interestingly, a post hoc analysis found that the mortality rate in the etomidate group was 54.8% when corticosteroids were administered and 75.7% when they were not.[60] Since the post hoc analysis was not designed to specifically examine corticosteroid supplementation in patients receiving etomidate, it is difficult to draw a meaningful conclusions regarding the role of prophylactic corticosteroid administration.
3. *Use etomidate and inform subsequent health care providers.* Alerting subsequent providers that etomidate was used will help them formulate continuing plans of care. Considering the benefits of using etomidate (e.g., hemodynamic stability, reliability) and the lack of convincing evidence to recommend otherwise, this is likely the most reasonable option.

Etomidate has been associated with an increase in electroencephalogram (EEG) activity as well as a lowered seizure threshold for focal seizures,[61-66] though it may raise the seizure threshold for generalized seizures.[65,67] Considering the potential for an increase in EEG activity in the seizing patient, it may be prudent to consider an alternative agent for induction, unless the patient is hypotensive.

Ketamine. Ketamine is a nonbarbiturate, phencyclidine derivative that rapidly produces a state of anesthesia characterized by profound analgesia, normal pharyngeal–laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, and cardiovascular and respiratory stimulation.[68] Ketamine also produces dose-related amnesia, though the effects are not as pronounced as those produced by benzodiazepines.[69] Clinically, the patient will remain in a cataleptic state, characterized by open eyes and a slow nystagmic gaze.[70] Anesthetic and analgesic effects are thought to be partly due to noncompetitive antagonism of the *N*-methyl-D-aspartate receptor, subsequently inhibiting the release of the excitatory neurotransmitter glutamate.[71]

Numerous mechanisms have been proposed to explain the analgesic action of ketamine. Some researchers have suggested that it produces a selective depressant effect on the medial thalamic nuclei, blocking the afferent signals associated with the affective–emotional components of pain perception while maintaining the conduction of signals related to localization of somatic stimuli.[70,72-74] Others have theorized that the analgesic action may be related to lamina-specific suppression of spinal cord activity,[75,76] while others have attributed its analgesic properties to an interaction with μ-, δ-, and κ-opioid receptors.[71] Irrespective of the mechanism, ketamine is unique in that it is the only induction agent for use in RSI that possesses both sedative and analgesic properties.

In patients who are not catecholamine depleted, ketamine will produce a dose-related rise in the heart rate–systolic blood pressure product, leading to a transient rise in the cardiac index but no significant change in the stroke index.[70,77] Patients who are catecholamine depleted and lack autonomic control will experience direct myocardial depressant effects, leading to dose-dependent negative inotropic and chronotropic effects.[70,78,79]

A byproduct of the ketamine-associated elevation in the rate–pressure product is a catecholamine-mediated increase in cardiac work and a subsequent increase in myocardial oxygen demand.[41,70] The increase in myocardial oxygen demand makes ketamine a suboptimal agent for normotensive or hypertensive patients with ischemic heart disease. It also increases salivary and tracheal–bronchial secretions and, in rare circumstances, may precipitate laryngospasm. This effect may be problematic for awake intubation but is typically of little consequence during RSI.[41,70]

In addition to the effects listed above, ketamine directly relaxes bronchial smooth muscle, antagonizes the spasmogenic effects of histamine, and potentiates the bronchodilatory effects of epinephrine,[70,80] all of which may be beneficial in patients with reactive airway disease.

Based on its mechanism of action and safety profile, ketamine

may be considered the induction agent of choice in patients with reactive airway disease.[81] It may also be a good choice for patients who are hypotensive, volume depleted, or hemodynamically unstable secondary to sepsis.

Avoidance of ketamine in patients with elevated ICP has been routinely advised after early studies found increased cerebral oxygen consumption, increased cerebral blood flow, and increased ICP after the drug's administration.[82,83] Recently, however, doubt has been raised regarding the clinical significance of these effects. Several studies have indicated that while ketamine will increase cerebral blood flow and cerebral metabolism in spontaneously breathing patients, it does not appear to increase ICP in patients undergoing controlled ventilation and sedation.[84-90] In fact, mean arterial pressure is maintained, vasopressor use is decreased, and cerebral perfusion pressure remains stable when ketamine is used for analgesia and sedation in intubated, head-injured patients compared with benzodiazepine and opioid combinations.[87-89] This stabilization of cerebral perfusion pressure may be of benefit in hypotensive patients with severe, blunt head trauma. Hypotension in the presence of blunt head trauma has been associated with increased mortality, meaning every effort should be made to maintain a systolic blood pressure above 90 mm Hg.[86] Ketamine may be a reasonable induction choice in this setting.

The usual induction dose of ketamine in RSI is 1.5 mg/kg i.v.[41] In catecholamine-depleted patients, it is not recommended to exceed a dose of 1.5 mg/kg. If being used for prolonged postintubation sedation and analgesia, ketamine should be initiated at 10% of the induction dose, repeated as needed and titrated to effect. Alternatively, an infusion of 0.1–0.5 mg/min may be initiated to maintain postintubation sedation.[68]

Propofol. Propofol is an alkylphenol derivative with hypnotic properties and is highly lipid soluble. Like all general anesthetics, its mechanism of action is not fully understood, but propofol is thought to elicit its effect via the enhancement of GABA activity at the GABA-receptor complex.[91] Propofol has been shown to decrease blood pressure via a reduction in preload,[81] afterload,[93-95] and decreased cardiac contractility.[96-98] These negative cardiovascular effects may lead to myocardial depression and a potential detrimental reduction in cerebral perfusion pressure, especially in hemodynamically unstable patients. Propofol does, however, decrease cerebral oxygen consumption and ICP, which makes it a valid option in the hemodynamically stable patient with elevated ICP.[91] In addition to a basal infusion, some practitioners may administer bolus doses in an attempt to mitigate postintubation agitation and facilitate a deeper level of sedation. Because negative cardiovascular effects are more pronounced in patients who are elderly, are debilitated, or have American Society of Anesthesiologists class III/IV physical status[91,99] (multiple systemic diseases, moderately controlled systemic diseases, or poorly controlled systemic disease), the practice of administering postintubation bolus doses of propofol should be discouraged in these patients. If the decision is made to administer a bolus dose of propofol, the dose should be administered in 20-mg increments over 10 seconds in order to reduce the risk of hypotension.[91]

Propofol will cause bronchodilation when used for induction,[100] making it a reasonable choice when intubating patients with reactive airway disease, but with an adverse-event profile that includes myocardial depression, hypotension, and a reduction in cerebral perfusion pressure, propofol's role as an induction agent for RSI is limited.

The induction dose of propofol is 1.5–2.5 mg/kg i.v. in a normotensive, euvolemic patient.[41,91] Hemodynamically unstable patients should receive smaller induction doses to lessen the corresponding myocardial depression.

The only true contraindication to the use of propofol is a history of hypersensitivity to propofol or soy allergy. Propofol will also cause pain on injection, which may be lessened by either administering it in a rapidly running i.v. in a large vein or administering lidocaine in the same syringe as propofol, mixed in a 10:1 ratio (10 mL propofol:1 mL 1% lidocaine hydrochloride).[91]

Neuromuscular blocking agents

Neuromuscular blocking agents (NMBAs) paralyze skeletal muscle by blocking impulse transmission at the neuromuscular junction. They are used to facilitate ideal conditions for rapid endotracheal intubation while minimizing the risk of aspiration.

There are some key factors to consider when administering NMBAs for RSI. First, NMBAs do not possess any sedative, amnestic, or analgesic properties and should be coadministered with a sedative. Patients receiving an NMBA alone will remain fully aware of their surroundings and will retain all sensory perception (including painful stimuli). Inadequate sedation before attempting intubation may increase the likelihood of negative physiological responses (e.g., elevated ICP, hypertension, tachycardia) to airway manipulation.

When an NMBA is administered, the practitioner must be prepared for a difficult or failed airway. Depending on the agent used, the patient may remain paralyzed for up to 60 minutes and unable to breathe independently, making it necessary to provide bag-valve mask ventilation in the event of a failed airway. If this approach is unsuccessful and the patient with a failed airway cannot be adequately oxygenated, acquisition of a surgical airway will become necessary.

The two primary groups of NMBAs used in emergency medicine are the depolarizing and nondepolarizing neuromuscular blockers. Depolarizing agents mimic the action of acetylcholine at the neuromuscular junction, leading to sustained depolarization of the junction and thus preventing muscle contraction.[3] Nondepolarizing agents competitively inhibit receptors in the neuromuscular junction, resulting in the prevention of acetylcholine binding and subsequent muscle contraction. According to the National Emergency Airway Registry project, the most frequently utilized NMBA for RSI is the depolarizing agent succinylcholine (82%), followed by the nondepolarizing agents rocuronium (12%) and vecuronium (5%).[101]

Depolarizing NMBAs. Long considered the gold standard for neuromuscular blockade, succinylcholine is the most widely used NMBA for RSI and is the only depolarizing agent currently available in the United States. Succinylcholine stimulates both autonomic ganglia and muscarinic receptors of the sympathetic and parasympathetic nervous systems, not just those at the neuromuscular junction.[102] While succinylcholine does not have a direct effect on the myocardium, stimulation of muscarinic receptors may precipitate bradycardia, especially when repeated doses are administered. Like acetylcholine, it depolarizes the postsynaptic membrane, producing repetitive excitation of the motor end plate. The resulting clinical effect is transient muscle fasciculation followed by full paralysis. Due to rapid hydrolysis by plasma cholinesterase, only a small fraction of the administered i.v. dose of succinylcholine reaches the neuromuscular junction. In diseases such as myasthenia gravis, this may be problematic, as even less succinylcholine will reach its intended destination.[103] In these patients, the dose must be empirically increased so that enough will make it to the neuromuscular junction to produce paralysis.

Succinylcholine remains the NMBA of choice in emergency RSI due to its rapid onset of action and its relatively short duration of action. Succinylcholine is contraindicated in patients with a personal or family history of malignant hyperthermia.[104] Dantrolene should be administered as soon as a diagnosis of malignant hyperthermia is seriously considered.[105]

Succinylcholine also should not be given to patients with hyperkalemia. Serum potassium has been shown to increase, on average, up to 0.5 meq/L after the administration of succinylcholine.[106,107] This occurs secondarily to the depolarization of myocytes, leading to the release of potassium, and will occur even in normal, healthy patients. This mild rise is of little clinical significance except in patients with a predisposition to hyperkalemia, whose serum potassium may rise by as much as 5–10 meq/L, resulting in serious dysrhythmias or cardiac arrest.[104,108] In the case of burn injury, crush injury, denervation injury, or severe infection, the increased risk of hyperkalemia does not manifest until approximately five days after the injury or infection occurred.

Finally, concern has been raised regarding the use of succinylcholine in penetrating eye injuries, as the agent has been linked to increases in intraocular pressure.[102,109] To date, no cases of vitreous extrusion after the use of succinylcholine in patients with a penetrating or an open globe injury have been reported.[37] Use of a defasciculating dose of a nondepolarizing NMBA may be considered in patients with an open globe injury, though there is not a body of supporting evidence behind this recommendation.[110]

The normal dose of succinylcholine chloride for RSI is 1.5 mg/kg i.v., providing an onset of action within 45 seconds and paralysis lasting approximately 10 minutes.[104] The dose should be based on the patient's actual body weight, even if he or she is morbidly obese. If the patient's weight is unknown before intubation, the practitioner should overestimate rather than underestimate the weight-based dose to increase the likelihood of obtaining optimal intubating conditions. Overestimating the dose is supported by evidence noting that as the dose of succinylcholine decreases, intubating conditions worsen,[111-115] and the margin of safety in dosing succinylcholine chloride has been demonstrated up to a cumulative dose of 6 mg/kg.[116]

Occasionally, intravenous access may be lost or unobtainable. During a life-threatening circumstance in which emergent RSI is indicated, succinylcholine chloride may be administered intramuscularly at a dose of 4 mg/kg, though the total dose should not exceed 150 mg.[102] If administered intramuscularly, the absorption and onset of action will be dependent on the patient's circulatory status. The mean time to onset of action after intramuscular administration is five to six minutes, but effects may be seen in as few as two to three minutes.[102,117] The greatest risk of intramuscular administration of succinylcholine relates to the delayed onset of action. Since the onset of paralysis is delayed and gradual, the possibility exists that the patient's respirations will be compromised but relaxation will be insufficient to facilitate intubation. Bag-valve mask ventilation will likely be required to maintain the patient's oxygen saturation during this period.

Nondepolarizing NMBAs. Nondepolarizing NMBAs compete with and block the action of acetylcholine at the postjunctional cholinergic nicotinic receptors in the neuromuscular junction. This results in the inhibition of muscle contraction without the fasciculations seen with succinylcholine. In addition to the difference in receptor blockade, nondepolarizing agents differ

from depolarizing agents in their pharmacokinetic profiles. As a class, the nondepolarizing NMBAs have a slower onset of action and a greatly lengthened duration of action. The nondepolarizing NMBA with the closest profile to succinylcholine is rocuronium. When dosed at 1 mg/kg, rocuronium bromide has a rapid onset of action (approximately 60 seconds) but a long duration of action (approximately 40–60 minutes).[118] Since nondepolarizing NMBAs have a lengthened duration of action compared to succinylcholine, it is very important to anticipate a difficult airway. Being prepared for a difficult airway involves the preparation and possible execution of a contingency plan to manage a failed airway. Such plans will include maintaining patient ventilation via bag-valve mask ventilation or the acquisition of a surgical airway.

The nondepolarizing NMBAs are divided into two groups: the benzylisoquinolinium compounds (tubocurarine, atracurium, and mivacurium) and the aminosteroid compounds (rocuronium, vecuronium, and pancuronium). The aminosteroids are the only agents used for emergency RSI, and only rocuronium is recommended for use in this setting. The primary differences among the aminosteroid nondepolarizing agents are their time to onset and duration of effect.

Vecuronium, the most potent of the aminosteroid NMBAs (one third more potent than pancuronium), has a slow onset of paralysis (2–3 minutes) and a duration of effect of approximately 45–65 minutes.[119] The slow onset limits its utility in emergency RSI, but vecuronium may be used for maintenance of paralysis in the postintubation period (i.e., sustained paralysis for ventilator dyssynchrony). If a nondepolarizing agent is indicated and rocuronium is not available, vecuronium bromide may be given using a modified priming regimen consisting of an initial priming dose of 0.01 mg/kg followed in 3 minutes by an intubating dose of 0.15 mg/kg administered either immediately before or after administration of the sedative or induction agent.[120]

Pancuronium has an onset of action of approximately 3–4 minutes and a duration of effect of 60–100 minutes.[121] Its slow onset makes pancuronium a poor choice for emergency RSI, especially since faster-acting agents are available. Pancuronium also produces a sympathomimetic effect, leading to an increase in heart rate, mean arterial pressure, and cardiac output.[121] Due to the increased risk of myocardial ischemia, pancuronium is not recommended for use in patients with coronary artery disease.

Rocuronium bromide has a duration of effect of 40–60 minutes when given in doses of 0.6–1.2 mg/kg i.v., respectively. While it has been studied in the context of intubation, rocuronium has not been extensively studied in the setting of emergent RSI. A recent critical appraisal by Mallon and colleagues[122] evaluated three prospective studies[123-125] and one Cochrane review[126] of rocuronium versus succinylcholine for intubation. Of the three prospective studies, one focused specifically on ED patients and RSI.[125] All three studies found that succinylcholine yielded better intubating conditions more expeditiously compared with rocuronium. Although rocuronium may not produce intubating conditions identical to those seen with succinylcholine, it does not appear that intubation success rates decline with rocuronium use. Based on the results of these studies, succinylcholine remains the drug of choice for RSI, but rocuronium may be substituted in cases where a contraindication to succinylcholine exists.

Suggested intubating doses of rocuronium bromide range from 0.6 to 1.2 mg/kg, but a study performed by Kirkegaard-Nielson et al.[127] found that the ideal dose for balancing a rapid onset of action with an intermediate duration of action is 1 mg/kg i.v. At this dose, intubating conditions are achieved within approximately one minute, making rocuronium very similar to succinylcholine.

There are no known absolute contraindications to nondepolarizing NMBAs, though caution should be exercised when considering their use in patients with myasthenia gravis. The use of nondepolarizing agents in RSI is indicated only when a contraindication to the use of succinylcholine exists, such as a history of malignant hyperthermia or a condition that may precipitate hyperkalemia.

Role of the pharmacist

Emergency RSI is an area where the ED pharmacist has a unique opportunity to become intimately involved with patient care. Emergent RSI often may be chaotic and fast paced. The emergency physician will be focused on preparing for intubation, evaluating the patient, and ensuring that tools are available for a surgical airway, making it easy, for example, to overlook contraindications to using the gold standard of succinylcholine or etomidate. Here, the ED pharmacist will be able to more-thoroughly evaluate the patient's medical history, ensuring that appropriate agents and doses are selected. A few questions the ED pharmacist should attempt to answer before intubation include

- What is the reason for intubation?
- What is the patient's past medical history?
- Are there any contraindications to the use of succinylcholine?
- Does the patient have a history of renal failure or hyperkalemia?
- Does the patient have reactive airway disease?
- Does the patient look like he or she will have a difficult airway?
- What is the patient's Mallampati score (degree to which posterior oropha-

ryngeal structures are visible, which may lead to complication?
- Is there an airway obstruction present?
- Is the patient morbidly obese?
- Does the patient have decreased neck mobility?
- Will the patient require pretreatment?
- Did the patient suffer head trauma?
- Does the patient have asthma or cardiovascular disease?
- What are the patient's current hemodynamic parameters?
- What is the patient's weight, and what dose of the selected medications will be used?
- What are the ideal agents for postintubation sedation and analgesia?
- Is the patient hypertensive?
- Will the patient need to be frequently awakened to assess neurologic status?
- Does the patient have a history of alcohol or benzodiazepine dependence?
- How many i.v. lines are available?

As the ED pharmacist is considering these questions, he or she should gather the appropriate medications required for induction, paralysis, and postintubation management and prepare them in the appropriate doses. The relative chaos that may occur during emergent RSI requires the ED pharmacist to have a clearly defined primary plan in mind as well as contingency plans to deal with potential complications.

In addition to working with the physician to determine the appropriate pharmacologic management for RSI, the ED pharmacist should work closely with the nursing staff throughout the procedure to help ensure the proper order of administration. Other areas in which the ED pharmacist may be heavily involved include protocol development, education, management of drug shortages, handoff information, and medication storage (i.e., RSI kit management).

Although the process was not defined in this article, the ED pharmacist should also develop a plan and prepare agents needed for postintubation management. Appropriate agents for prolonged sedation and analgesia should be obtained (e.g., propofol, midazolam, fentanyl, morphine, hydromorphone) and should be ready for administration as soon as the patient is successfully intubated, if clinically indicated.

Conclusion

The selection of an appropriate sedative and neuromuscular blocker during the pretreatment and paralysis with induction steps of RSI can be facilitated by an ED pharmacist.

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