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Rapid Sequence Intubation Medication Therapies
A Review in Light of Recent Drug Shortages

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ABSTRACT
Rapid sequence intubation is a stepwise process developed to assist health care providers in placing emergent artificial airways for patients requiring assisted ventilation. This practice includes routine administration of sedative and neuromuscular blocking agent (NMBA) medications for patient comfort during endotracheal tube placement. Members of the multidisciplinary team should be well educated about the various medications used during this process to ensure safe medication practices in an emergent situation. Recent drug shortages have forced many health care professionals to use alternative medications with which they are less familiar. The intent of this review is to familiarize health care providers with the pharmacology and adverse effect profiles of alternative sedative and NMBA medications used in emergent airway placement in light of recent drug shortages. **Key words:** endotracheal intubation, neuromuscular blocking agent, rapid sequence intubation, sedation, sedative

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AIRWAY MANAGEMENT is one of the primary roles of emergency personnel when critically ill patients present to the emergency department (ED). One way to ensure appropriate airway management in these patients is to place an endotracheal tube or other artificial airway to assist with ventilation. Indications for endotracheal intubation may include airway protection for patients with an inability to maintain airway patency, respiratory distress, undergoing sedation for medical and surgical procedures, trauma, and neuromuscular

paralysis (Neumar et al., 2010). Rapid sequence intubation (RSI) is a streamlined, six-step process developed and used in most EDs to ensure each patient receives rapid airway placement in a universally concise and consistent manner (Reynolds & Heffner, 2005). These steps also allow for any patient requiring advanced airway protection to be intubated with a decreased risk of vomiting and aspiration regardless of their preparation prior to the procedure. The role of medication therapy in RSI procedures is to provide adequate sedation and paralysis in order to assist with endotracheal tube placement. If done appropriately, RSI results in a success rate of more than 98.5% (Reynolds & Heffner, 2005).

Health care institutions have faced challenges in recent years due to expected, and unexpected, drug shortages resulting in alternative drug utilization and changes to their RSI medication boxes to accommodate these changes. Health care professionals may be less familiar with these alternative therapies in terms of their pharmacology and adverse effect profiles. It is imperative for pharmacists and other health care professionals to understand the dosing, onset of action, duration of action, and potential adverse effects of these medications to ensure continued safe practices in these critically ill patients. The intent of this article is to provide a brief background review on the step-wise fashion of RSI and to review the pharmacology of RSI medications to assist emergency care providers in selecting and dosing appropriate agents and recognizing potential adverse effects.

STEPS IN RAPID SEQUENCE INTUBATION

Rapid sequence intubation is usually performed in six concise steps that are often referred to as the "6 Ps" of endotracheal intubation (Mace, 2008; Reynolds & Heffner, 2005). First, a team of multidisciplinary health care professionals *prepares* for RSI by assessing patients for potentially difficult airways that may require advanced techniques for successful intubation. The *preparation* step also gives the team time to ensure the appropriate equipment is readily available at bedside, the patient is connected to necessary monitoring devices, and all essential intravenous lines are in place (Walls, 2012). At this time, the pharmacist or nurse responsible for medication therapy can verify which medications the intubator wishes to use for the procedure, ensure appropriate dosing of the medications based on patient-specific factors, and prepare them at the bedside. Once the preparation step is complete, the team will work to *preoxygenate* the patient with a tight-fitting, nonrebreather oxygen mask for 3–5 min to achieve optimal oxygen stores. Bag mask ventilation should be reserved for patients who are not breathing spontaneously, because it may lead to gastric insufflation, vomiting, and aspiration. Following *pre-oxygenation*, the team is ready for intubation. The next step is to administer *pretreatment*, if applicable, and *paralytic with induction* medications (Caro & Bush, 2012; Caro & Laurin, 2012; Caro & Tyler, 2012). At an appropriate interval after medication administration, the intubator will *place* the endotracheal tube, connect the tube to the ventilator, and check for appropriate placement (listen for gastric and breath sounds, watch for chest rise and fall, check for end-tidal CO_2 via color change detector or waveform capnography, obtain a chest x-ray, etc.). The multidisciplinary team will then work together to provide *postintubation* management, which includes inflating the cuff, securing the tube, establishing waveform capnography monitoring (if not already done), and continued pain and sedation therapy to assist with mechanical ventilation (Walls, 2012). See Table 1 for a summary of these six steps and their associated processes.

As outlined earlier, the purpose of RSI is to ensure concise and consistent management for all patients requiring endotracheal intubation. It requires a multidisciplinary team that may consist of a lead physician, potentially a resident physician, an intubator, nursing staff, paramedics, a clinical pharmacist, and respiratory therapist to achieve this goal. The clinical pharmacist or nurse is usually responsible for medication preparation and

Table 1. Six "Ps" of RSI procedures

Step	Examples
Preparation	Assess for difficult airway
	Obtain appropriate equipment (ET tube, ventilator, etc.)
	Place appropriate monitoring devices at the bedside
	Place all necessary intravenous lines
	Obtain and prepare appropriate RSI medications
Preoxygenation	Build up oxygen stores with tight-fitting, nonbreather oxygen mask for 3–5 min prior to the procedure
Pretreatment	Administer any necessary pretreatment medications (e.g., fentanyl, lidocaine)
Paralytic (with sedative prior to administration)	Administer sedative medication, followed by NMBA
Placement	Check for appropriate placement of ET tube
	Listen for gastric and breath sounds
	Watch for chest rise and fall
	Check for end-tidal CO_2 via color change or waveform capnography
	Obtain a chest x-ray
Postintubation management	Inflate and secure ET cuff after confirmation of appropriate ET tube placement
	Establish continuous waveform capnography (if not already done)
	Administer appropriate pain, sedation, and NMBA medications (e.g., boluses or continuous infusions)

Note. CO_2 = carbon dioxide; ET = endotracheal tube; NMBA = neuromuscular blocking agent; RSI = rapid sequence intubation. Information from Caro & Bush, 2012; Caro & Laurin, 2012; Caro & Tyler, 2012; Reynolds & Heffner, 2005; Walls, 2012.

administration. It is important for these individuals to be aware of the indications for each medication based on patient-specific factors. Patient-specific factors that should be considered to ensure optimal therapy is administered include weight, medical history, and the patient's current clinical picture including vital signs.

ROLE OF MEDICATIONS IN RAPID SEQUENCE INTUBATION

Patients requiring endotracheal intubation should be evaluated for appropriate RSI medication therapy on the basis of their current clinical status. Preinduction medications may be given to control the physiological catecholamine release associated with airway stimulation by the laryngoscope in select patients (Reynolds & Heffner, 2005). This may include tachycardia from β-receptor activation and hypertension from α-receptor activation in adult patients or bradycardia due to vagal nerve stimulation in pediatric patients. After reviewing the need for preinduction therapy, the multidisciplinary team should select appropriate sedatives and neuromuscular blocking agents (NMBAs) based on several patient-specific factors. The onset of therapy should ideally be rapid to facilitate endotracheal tube placement, and the duration of action should also ideally be short to avoid prolonged paralysis. Depending on the duration of action of the sedative and NMBA medications selected for RSI, it is possible the patient may experience prolonged paralysis after the sedation medication wears off. This is potentially more likely because drug shortages of shorter acting NMBAs may result in the use of longer acting NMBAs. Because of this, postintubation management with continuous pain and sedation medications is even more imperative and should start immediately after endotracheal intubation. See Table 2 for a summary of dosing, onset of action, duration of action, and common adverse effects seen

Table 2. Pharmacology for rapid sequence intubation medications

Medication	Dosing	Onset of action	Duration of action	Adverse effects	Reversal agent
Preinduction agents					
Atropine	0.02 mg/kg (min: 0.1 mg; max: 0.5 mg)	1 min	30–60 min	Dry mouth Tachycardia Hypertension Pupil dilation	None
Fentanyl	2–3 mcg/kg (max: 100 mcg)	Immediate	30–60 min	Minimal	Naloxone 0.4–2 mg (adults) 0.1 mg/kg (pediatrics)
Lidocaine	1.5 mg/kg (max: 100 mg)	45–90 s	10–20 min	Cardiac dysrhythmias	None
Low-dose ND NMBAs: rocuronium, vecuronium	0.01 mg/kg	2–4 min	30–90 min (rocuronium) 30–45 min (vecuronium)	Bronchospasm Respiratory depression	None
Sedative agents					
Etomidate	IV: 0.3 mg/kg (max: 40 mg)	10–20 s	4–10 min	Adrenal suppression	None
Midazolam	IV and IM: 0.1–0.2 mg/kg	2–5 min	30–80 min	Hypotension Respiratory depression	Flumazenil 0.2 mg (adults) 0.01 mg/kg (pediatrics)
Ketamine	IV: 1–2 mg/kg IM: 4–10 mg/kg	IV: 30–40 s IM: 3–4 min	IV: 5–10 min IM: 12–25 min	Hypertension Cardiac dysrhythmias Increased ICP Emergence phenomenon Laryngeal spasm	None
Propofol	IV: 1–2 mg/kg	10–50 s	3–10 min	Hypotension Cardiac dysrhythmias Bronchospasm	None
Neuromuscular blocking agents					
Succiny-choline	IV: 1.5 mg/kg	IV: 30–60 s	IV: 5–15 min	Muscle fasciculations	None
	IM: 3–4 mg/kg (max: 150 mg)	IM: 1–4 min	IM: 15–20 min	Increased ICP Hyperkalemia Respiratory depression	

(*continues*)

Table 2. Pharmacology for rapid sequence intubation medications (*Continued*)

Medication	Dosing	Onset of action	Duration of action	Adverse effects	Reversal agent
Rocuronium	IV: 0.6–1.2 mg/kg	1–2 min	30–90 min	Respiratory depression	None
Vecuronium	IV: 0.1–0.2 mg/kg	2–4 min	30–45 min	Bronchospasm Respiratory depression	None

Note. ICP = intracranial pressure; IM = intramuscular; IV = intravenous; ND NMBAs = nondepolarizing neuromuscular blocking agents (e.g., rocuronium, vecuronium). Information from Caro & Bush, 2012, Caro & Laurin, 2012; Caro & Tyler, 2012; Chameides, Samson, Schexnayder, & Hazinski, 2011; Reynolds & Heffner, 2005.

with the medications listed in the following section that are commonly used during RSI procedures.

PREINDUCTION MEDICATIONS

Atropine

Atropine may be used for pediatric patients who experience bradycardia associated with vagal nerve stimulation during the passing of the laryngoscope or bradycardia induced by succinylcholine administration (Reynolds & Heffner, 2005). This reaction is more common in pediatric patients than in adult patients because of the differences in their oropharynx and neck anatomy that allows for easier stimulation of the vagal nerve in children. Atropine also decreases oral secretions that may provide easier viewing for endotracheal tube placement. The American Heart Association recommends the use of atropine with RSI in all patients younger than 1 year, patients 1–5 years of age receiving succinylcholine, and pediatric patient older than 5 years who receive subsequent doses of succinylcholine (Chameides, Samson, Schexnayder, & Hazinski, 2011). In these settings, atropine is dosed at 0.02 mg/kg (minimum dose of 0.1 mg, maximum dose of 0.5 mg). Common adverse effects associated with the use of atropine include dry mouth, tachycardia, hypertension, and pupil dilation (Chameides et al., 2011).

Fentanyl

Fentanyl is used as a premedication in RSI to blunt the catecholamine response associated with α-receptor stimulation (Reynolds & Heffner, 2005). α-receptor stimulation results in hypertension that can be problematic in patients with cardiac disease. Fentanyl acts to help decrease hypertension secondary to RSI and has a lesser effect on heart rate or tachycardia (Caro & Bush, 2012). Patients to consider for premedication with fentanyl in RSI include those with suspected intracranial hypertension, hypertensive emergency, and myocardial ischemia. When used as a preinduction agent, fentanyl is usually dosed at 2–3 mcg/kg (maximum dose of 100 mcg) initially, but doses may be repeated to achieve goal response (Caro & Bush, 2012).

Lidocaine

Lidocaine can be given as a premedication for RSI in patients with traumatic brain injuries (TBIs) or reactive airway disease (Reynolds & Heffner, 2005). Elevated intracranial pressure (ICP) is a concern in TBI patients, and this can be exacerbated with endotracheal suctioning as well as RSI because of catecholamine release. The use of lidocaine is postulated to help blunt these effects and prevent further elevations in ICP during RSI (Caro & Bush, 2012). It also acts to reduce airway reactivity and suppress a patient's cough reflex to assist with endotracheal tube placement.

Despite its presumed role based on the pathophysiology of patients presenting to the ED requiring RSI, there is no evidence-based literature that supports the role of lidocaine in improving neurological outcomes. Three studies looked at the use of lidocaine prior to intubation in neurosurgical patients requiring nonemergent elective procedures with no definitive answer regarding the ability of lidocaine to blunt increases in ICP during intubation (Bedford, Winn, & Tyson, 1980; Hamill, Bedford, Weaver, & Colohan, 1981; Samaha, Ravussin, Claquin, & Ecoffey, 1996). One study looked at the use of either endotracheal or intravenous lidocaine in patients with severe head injuries, but it is unclear whether intubation took place emergently in the ED or intensive care unit. Neither study group proved the ability of lidocaine to lower ICPs in this setting (Yano et al., 1986). No studies looked directly at trauma patients presenting to the ED who required RSI. Because of this, it is not always recommended, or used, in ED settings because of lack of evidence in this specific patient population. The premedication dose of lidocaine for RSI is 1.5 mg/kg (maximum dose of 100 mg), and it should be given 3 min prior to RSI for full effect (Caro & Bush, 2012). The major adverse effect to consider with lidocaine use is cardiac dysrhythmias (Reynolds & Heffner, 2005).

Low-Dose Nondepolarizing Neuromuscular Blocking Agents

Succinylcholine, a depolarizing NMBA commonly used as a paralytic agent in RSI, can cause fasciculations, which are postulated to increase ICPs, in some patients (Reynolds & Heffner, 2005). This is of particular concern in patients who present with TBI. Most of the studies analyzing the incidence of increased ICP associated with the use of succinylcholine were done in neurosurgical patients requiring elective procedures and not in the setting of RSI in patients with TBI (Brown, Parr, & Manara, 1996; Kovarik, Mayberg, Lam, Mathisen, & Winn, 1994; Lam, Nicholas, & Manninen, 1984; Marsh, Dunlop, & Shapiro, 1980; McLesky, Cullen, Kennedy, & Galindo, 1974). Because of the lack of data in this patient population, a defasiculating dose of a non-depolarizing NMBA is not always recommended or used in the ED setting. If implemented as part of the RSI procedure, a nondepolarizing NMBA such as rocuronium or vecuronium at one tenth of the intubation dose is administered 1–2 min prior to RSI (Reynolds & Heffner, 2005).

SEDATIVE MEDICATIONS

Etomidate

Etomidate is a short-acting sedative hypnotic with γ-aminobutyric acid (GABA)-like effects that lead to sedation. Its pharmacokinetic and adverse effect profiles explain its popularity because it is estimated to be used in 70%–80% of emergent RSI procedures (Bergen & Smith, 1997; Sagarin, Barton, Chng, & Walls, 2005). Etomidate has a quick onset of action (5–15 s) and moderate duration of action (5–15 min) that is well suited for successful intubation. It has a hemodynamically neutral adverse effect profile, with a lack of cardiac and respiratory adverse effects compared with similar agents. Etomidate also has neuroprotective effects in trauma patients that result in a decreased cerebral metabolic rate and decreased ICP (Caro & Tyler, 2012). Some health care professionals question the use of etomidate for RSI in certain patient populations (e.g., sepsis) because of its risk for adrenal suppression (Dmello, Taylor, O'Brien, & Matuschak, 2010; Edwin & Walker, 2010; Tekwani, Watts, Sweis, Rzechula, & Kulstad, 2010). This concern stems from the fact that etomidate blocks 11-β-hydroxylase, an enzyme responsible for in vivo stress steroid production, potentially resulting in decreased cortisol levels and diminishing a septic patient's ability to respond to hemodynamic changes and infection. Despite this mechanism, studies to date have failed to determine a definitive conclusion to this hypothesis due in part to the various study designs and the emergent nature of its utilization (e.g., study consent, enrollment,

randomization). Health care professionals must use clinical judgment in deciding whether to use etomidate as the sedative agent for RSI in septic patients and other patients at risk of adverse effects with induced adrenal suppression. Doses of etomidate at 0.3 mg/kg are sufficient to induce sedation in the setting of RSI (Caro & Tyler, 2012).

Midazolam

Midazolam is a schedule IV benzodiazepine that also exhibits GABA-like effects for sedation without causing adrenal suppression compared to etomidate (Reynolds & Heffner, 2005). In addition, it has amnestic properties that may further assist in making the procedure more comfortable for the patient and anticonvulsant properties for patients with seizure activity. Midazolam is a preferred sedative choice for patients without intravenous access because it can be administered intramuscularly as well as intravenously. Major adverse effects with midazolam therapy include hypotension, with decreases in mean arterial pressure by as much as 10% compared with etomidate, and respiratory depression when combined with other central nervous system (CNS) depressing medications (Bergen & Smith, 1997). It may also be a less desirable choice in patients who may have tolerance due to chronic benzodiazepine use. However, it may be advantageous in those who present with seizure activity secondary to benzodiazepine or alcohol withdrawal, although higher doses may need to be used in these situations. The dose for RSI ranges from 0.1 to 0.2 mg/kg (Reynolds & Heffner, 2005). In clinical practice, this dose typically does not exceed 10 mg but special considerations should be based on each patient's response.

Ketamine

Ketamine is a schedule III general anesthetic that blocks *N*-methyl-d-aspartate receptors that elicit excitatory responses in the CNS (Miller, 2000). Recent shortages of benzodiazepines and etomidate have resulted in the increased use of ketamine for sedation during RSI. Like most sedatives in this setting, it has a rather quick onset of action (30–60 s). Furthermore, it can be administered both intramuscularly and intravenously. It is less favorable as a sedating agent for RSI than etomidate and midazolam because of its adverse effect profile (Sih, Campbell, Tallon, Magee, & Zed, 2011). It is not recommended for use in cardiac patients because of its risk of developing hypertension and arrhythmias, and it should also be used with caution in TBI patients because of its potential ability to increase ICP. Caution regarding its use in TBI patients stems from small sample size trials conducted in the 1970s that demonstrated variable effects on ICP with ketamine administration. Increased ICPs were observed in patients with abnormal cerebrospinal fluid pathways (e.g., hydrocephalus, shunts; List, Crumrine, Cascorbi, & Weiss, 1972; Shapiro, Wyte, & Harris, 1972); however, ICPs remained within normal range in healthy individuals (Gardner, Olson, & Lichtiger, 1971; Gibbs, 1972). None of these studies were conducted in actual trauma patients. Studies conducted in TBI patients using continuous infusions of ketamine found no significant changes in ICP between the study groups (Bourgoin et al., 2003, 2005; Kolenda, Gremmelt, Rading, Braun, & Markakis, 1996; Schmittner et al., 2007). These studies, however, have limited applicability to those receiving single doses of ketamine for RSI. Ketamine has been shown to produce nystagmus as well as emergence phenomena in adult and pediatric patients. During emergence phenomena, patients experience visual hallucinations, which may be pleasant (more common in pediatrics) or unpleasant (more common in adults). To help counteract this reaction, small doses of benzodiazepines (e.g., midazolam 2 mg) may be administered with ketamine. When used for RSI, ketamine can be administered at doses of 1–2 mg/kg intravenously or 4–10 mg/kg intramuscularly (Caro & Tyler, 2012).

Propofol

Propofol is a short-acting hypnotic with several proposed mechanisms of action. It stimulates GABA receptors similar to etomidate and midazolam to produce sedation but also blocks sodium channels (Reynolds & Heffner,

2005). This sedative has an extremely short duration of action that may require repeated doses during RSI to maintain sedation during the procedure (Caro & Tyler, 2012). Because of this, and an increased incidence of hypotension associated with repeat boluses, it is not routinely used for RSI. The use of propofol, however, may be beneficial in TBI patients because of its ability to decrease ICP, but it may also be detrimental in terms of its ability to enhance hypotension by decreasing mean arterial pressures by as much as 10% in hemodynamically unstable patients (Bergen & Smith, 1997; Ludbrook, Visco, & Lam, 2002). Common doses seen for RSI procedures range from 1 to 2 mg/kg (Caro & Tyler, 2012).

NEUROMUSCULAR BLOCKING AGENTS

Succinylcholine

Succinylcholine is a depolarizing NMBA that acts on acetylcholine receptors to depolarize the endplate membrane resulting in skeletal muscle paralysis (Caro & Laurin, 2012). Some health care providers prefer succinylcholine to the nondepolarizing NMBAs because of its faster onset (30–60 s) and shorter duration of action (5–20 min, based on the route of administration). Common and clinically relevant adverse effects include a potential for increased ICP resulting from muscle fasciculations, hyperkalemia, rhabdomyolysis, and malignant hyperthermia (Caro & Laurin, 2012). It is the only NMBA that can be administered intramuscularly if an intravenous line cannot be placed. Succinylcholine is the preferred NMBA in patients who are actively seizing during RSI because of its short duration of action, thus avoiding the inadvertent masking of symptoms of seizure activity. It is not recommended for patients with end-stage renal disease and patients with burns after 24 hr postinjury because of the risk of developing hyperkalemia. The administration of succinylcholine in patients with end-stage renal disease can increase a patient's potassium concentration by as much as 0.5 mEq/L, resulting in an increased risk of developing cardiac arrhythmias and cardiac arrest (Powell & Miller, 1975). In patients without end-stage renal disease, the increase in potassium is typically transient and less likely to cause cardiac arrhythmias. It should also be used with caution in trauma patients because of its ability to increase ICP. The usual doses of succinylcholine are 1.5 mg/kg intravenously or 3–4 mg/kg intramuscularly for RSI (Caro & Laurin, 2012).

Nondepolarizing Neuromuscular Blocking Agents

Neuromuscular blocking agents such as rocuronium and vecuronium act to induce paralysis by competitively acting with acetylcholine to bind to the motor endplate (Reynolds & Heffner, 2005). Rocuronium and vecuronium have fewer adverse effects than succinylcholine, but they consistently have a longer duration of action (40–75 min), resulting in prolonged paralysis for a rapid procedure (Caro & Laurin, 2012). Adverse effects are minimal but include potential hemodynamic changes (hyper/hypotension and tachycardia). It is imperative to administer additional sedation until NMBA effects wear off to prevent unnecessary stress with known paralysis. Methods for sedation may include boluses or continuous infusions based on the physician's preference and long-term intubation plan. RSI dosing ranges for rocuronium and vecuronium are 0.6–1.2 mg/kg and 0.1–0.2 mg/kg, respectively (Caro & Laurin, 2012).

ADMINISTRATION AND MONITORING

Table 2 summarizes important pharmacological parameters for each RSI medication discussed earlier. The multidisciplinary team should take into consideration the onset of action of each medication to take advantage of its full effects during RSI. Patient comfort is also critical in proper administration of RSI medications. To avoid patient awareness of paralysis, it is imperative to always administer the sedating agent 1–2 min before the NMBA.

This will ensure appropriate onset of action with sedation prior to administration of the NMBA. All RSI medications can be administered via rapid intravenous push. The intravenous line used for administration of the RSI medications should be flushed with normal saline between medications to prevent compatibility issues.

Patients should be monitored for cardiac rhythm and vital sign changes. Awareness of adverse effect profiles is important prior to medication selection to assist in avoiding exacerbating underlying medical conditions and diagnosing adverse effects should they arise. Because of the nature of the medications selected for RSI procedures and their quick onset and duration of action profiles, it should be rare that any of the medications administered require reversal due to adverse effects with or without higher doses. If needed, however, reversal agents are available for fentanyl and midazolam (see Table 2). Naloxone can be given to reverse the effects of fentanyl and other opioid agonists at an initial dose of 0.4–2 mg (0.1 mg/kg in pediatric patients) rapid intravenous push. Flumazenil is used only in cases where the adverse effects of midazolam are considered clinically significant because there is a risk of seizures associated with the use of this antidote. When administered, the dose of flumazenil is 0.2 mg (0.01 mg/kg in pediatric patients) rapid intravenous push.

CONCLUSION

In patients requiring RSI in the ED, it is important to consider patient-specific factors when selecting preinduction, sedative, and NMBA medications. Recent drug shortages have limited medication selection and have forced many institutions to use RSI agents with less familiar pharmacology and adverse effect profiles. It is important for health care professionals to be educated and comfortable with all potential RSI medications because most drug shortages are unexpected and unannounced. This process will ensure health care institutions continue to provide safe and effective medication practices in emergency situations.

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