Induction agents for rapid sequence intubation in adults for emergency medicine and critical care

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INTRODUCTION

The first task of any clinician managing an acutely unstable patient is to secure the airway. In most circumstances, emergency clinicians use rapid sequence intubation (RSI) to accomplish this task. RSI incorporates a rapidly acting sedative (ie, induction) agent, in addition to a neuromuscular blocking (ie, paralytic) agent, to create optimal intubating conditions. Selection of the sedative agent and dose most appropriate for the clinical scenario is an important component of RSI.

The pharmacology and selection of induction agents for use in emergency RSI outside of the operating theater will be reviewed here. The techniques and other medications used in the performance of RSI, as well as other aspects of airway management, are discussed separately. (See "Rapid sequence intubation in adults for emergency medicine and critical care" and "Rapid sequence intubation (RSI) in children for emergency medicine: Approach" and "Neuromuscular blocking agents (NMBAs) for rapid sequence intubation in adults for emergency medicine and critical care" and "Pretreatment medications for rapid sequence intubation in adults for emergency medicine and critical care".)

RAPID SEQUENCE INTUBATION

Rapid sequence intubation (RSI) is the standard of care in emergency airway management for intubations not anticipated to be difficult [1-4]. RSI is the virtually simultaneous administration of a sedative and a neuromuscular blocking agent to render a patient rapidly unconscious and flaccid in order to facilitate emergency endotracheal intubation and to minimize the risk of aspiration. Multiple studies confirm the high-success rate of RSI using the combination of a sedative and a paralytic drug [2-4]. (See "Rapid sequence intubation in adults for emergency medicine and critical care" and "Neuromuscular blocking agents (NMBAs) for rapid sequence intubation in adults for emergency medicine and critical care" and "Rapid sequence intubation (RSI) in children for emergency medicine: Approach".)

INDUCTION AGENTS

Overview — Induction agents (sedatives) are integral to the performance of rapid sequence intubation (RSI) [5]. They provide amnesia, blunt sympathetic responses, and can improve intubating conditions.

When a paralytic agent is used for intubation without sedation, the patient may be fully aware of their environment, including pain, but unable to respond [6-9]. In addition to its inhumanity, this circumstance allows for potentially adverse physiologic responses to airway manipulation, including tachycardia, hypertension, and elevated intracranial pressure (ICP) [10]. Sedative use prevents or minimizes these effects. Furthermore, clinicians can sometimes select an induction agent that both facilitates RSI and ameliorates the patient's underlying condition. As an example, ketamine can be used in severe asthma to reduce bronchospasm [11].

Use of sedatives may also improve the laryngoscopic view obtained during RSI [5,12,13]. During RSI, the clinician must perform laryngoscopy during the earliest phase of neuromuscular paralysis. Sedatives improve laryngoscopy in part by supplementing the yet incomplete relaxation provided by the paralytic. Even in the presence of a full neuromuscular blocking dose of a paralytic, the addition of a sedative improves intubating conditions during RSI [5].

Each of the major induction agents in common use is discussed below (table 1).

Etomidate

General use — Etomidate is an imidazole-derived, sedative-hypnotic agent that is frequently used for RSI. Etomidate acts directly on the gamma-amino butyric acid (GABA) receptor complex, blocking neuroexcitation and producing anesthesia. For RSI, etomidate is given by intravenous (IV) push in a dose of 0.3 mg/kg, with a time to effect of 15 to 45 seconds and a duration of action of 3 to 12 minutes [14]. It is hemodynamically neutral and does not stimulate histamine release [15-22].

Etomidate provides no analgesic effect, so it does not blunt the noxious stimulation of the upper airway during laryngoscopy and intubation. For patients in whom this is a concern (eg, patients with cardiovascular disease or elevated intracranial pressure), an opioid analgesic, such as fentanyl, is often given during the pretreatment phase of RSI [23,24]. (See "Pretreatment medications for rapid sequence intubation in adults for emergency medicine and critical care".)

Etomidate causes a mild increase in airway resistance but may be used in patients with bronchospasm [25].

The relative hemodynamic stability associated with etomidate makes it a particularly useful medication for the intubation of hypotensive patients, as well as for patients with intracranial pathology, when hypotension must be avoided [15-19,21,26]. However, all sedative agents, including etomidate, have been associated with postintubation hypotension, especially in patients who exhibit hemodynamic instability at presentation prior to RSI [27-31]. This highlights the importance of preintubation resuscitation. (See "The physiologically difficult airway: Optimization of airway management in adults at risk of decompensation for emergency medicine and critical care".)

Concerns with etomidate include adrenal suppression, myoclonus, and evidence of regional cerebral excitation (determined by electroencephalogram) after intubation [18,32,33]. Myoclonus has been misidentified as seizure activity, leading to incorrect recommendations that etomidate be avoided in patients with seizure disorders. Etomidate is safe to use for the induction of patients with seizures or even refractory status epilepticus [34]. Myoclonus during RSI is brief and minimal, because of the concomitant administration of a paralytic agent, and of no clinical significance. Etomidate decreases cerebral blood flow and cerebral metabolic oxygen demand while preserving cerebral perfusion pressure [21]. Postintubation sedation with propofol or a benzodiazepine helps to prevent neuroexcitation.

Adrenocortical suppression — The major controversy surrounding etomidate stems from the reversible adrenocortical suppression associated with its use. The evidence surrounding this issue is reviewed separately. (See "General anesthesia: Intravenous induction agents", section on 'Etomidate'.)

Etomidate is a reversible inhibitor of 11-beta-hydroxylase, which converts 11-deoxycortisol to cortisol (figure 1). (See "Adrenal steroid biosynthesis".)

A single dose of etomidate causes a transient but measurable decrease in the level of circulating cortisol that occurs in response to the administration of exogenous adrenocorticotropic hormone (ACTH), although cortisol levels do not fall below the normal physiologic range. This effect does not persist beyond 12 to 24 hours.

We recognize the critical importance of maintaining adequate blood pressure early in the treatment of sepsis. Although controversy persists regarding the use of etomidate in septic patients, no definitive studies have shown an increase in long-term mortality with etomidate use in this setting [35,36]. Pending more definitive studies, we believe that etomidate is an acceptable induction agent for patients with severe sepsis. Etomidate has the advantages of hemodynamic stability when compared with most other sedative or induction agents, and familiarity because of its widespread use for RSI outside the operating room. When intubating the critically ill patient with possible adrenal insufficiency, the clinician must weigh the theoretical risk of cortisol suppression against the hemodynamic instability that may be caused by alternative induction agents.

Etomidate should **NOT** be used as an infusion or in repeated bolus doses for maintenance of sedation after intubation. Emergency clinicians should inform the physicians assuming care for the patient in the intensive care unit or operating suite if etomidate has been used for induction. If ACTH stimulation testing is being considered, clinicians should be aware that the results may be affected by prior administration of etomidate. (See "Evaluation and management of suspected sepsis and septic shock in adults".)

Some authors recommend the use of empiric glucocorticoids for the first 24 hours after a dose of etomidate in patients with sepsis, but this approach lacks support from outcome studies [37,38]. We suggest that patients with sepsis who receive etomidate for RSI also receive a single dose of glucocorticoid (eg, hydrocortisone 100 mg IV) **only** if they manifest hypotension that is refractory to treatment with aggressive fluid resuscitation and a vasopressor. This approach is consistent with that used for patients who do not receive etomidate. A discussion of the role of glucocorticoids in septic shock is discussed separately. (See "Corticosteroid therapy for refractory septic shock in adults".)

Benzodiazepines — Benzodiazepines cause sedation and amnesia through their effects on the GABA receptor complex. Midazolam is the most rapidly acting benzodiazepine commonly used for RSI [39,40]. The induction dose for midazolam is 0.1 to 0.3 mg/kg IV push, with a time to effect of approximately 30 to 60 seconds, and a duration of action of 15 to 30 minutes [39,40].

Like all benzodiazepines, midazolam does not provide analgesia but does possess antiseizure effects, making it an effective agent for RSI in patients with status epilepticus [34,41].

The routine induction dose of midazolam for RSI is 0.2 mg/kg. In this dose, midazolam causes moderate hypotension, with an average drop in mean arterial blood pressure in healthy patients of 10 to 25 percent [39,40]. This tendency to induce hypotension limits midazolam's usefulness in the setting of hypovolemia or shock. If midazolam must be used in such patients, we suggest a dose of 0.1 mg/kg, which will somewhat delay the speed of onset and decrease the depth of sedation achieved, but should not severely compromise intubating conditions. For patients in shock, we suggest etomidate or ketamine because of their superior hemodynamic profiles. (See 'Etomidate' above and 'Ketamine' below.)

Midazolam is frequently underdosed (common dose 0.05 mg/kg) when used for emergency department RSI [42]. Midazolam is often used for procedural sedation in much smaller doses than are required for RSI, which may contribute to underdosing [40].

Midazolam can be used as an infusion for long-term sedation. Doses of 0.05 to 0.4 mg/kg per hour IV have been shown to be safe and effective in critically ill neonates and children [43,44], including neonates undergoing extracorporeal membrane oxygenation [45]. Dosing in intubated adults should be titrated to an endpoint of adequate sedation, preferably using a sedation scale.

Lorazepam and diazepam are benzodiazepines used frequently for long-term sedation following intubation, but are not recommended for RSI. Both require propylene glycol as a diluent, and there are reports of propylene glycol toxicity associated with long-term infusions [46]. (See "Sedative-analgesia in ventilated adults: Medication properties, dose regimens, and adverse effects", section on 'Benzodiazepines'.)

Ketamine

General use — Ketamine is a dissociative anesthetic agent, structurally similar to phencyclidine. It is unique among sedative agents in that it provides analgesia along with its amnestic and sedative effects. Ketamine is given IV in doses of 1 to 2 mg/kg, with a time to effect of 45 to 60 seconds, and a duration of action of 10 to 20 minutes.

Ketamine acts at many receptors causing a range of effects. The primary mechanism of action is noncompetitive antagonism of glutamate at the N-methyl-D-aspartate receptor-cation channel complex, causing neuro-inhibition and anesthesia. It excites opioid receptors within the insular cortex, putamen, and thalamus, producing analgesia [47,48]. It stimulates catecholamine receptors and release of catecholamines leading to increases in heart rate, contractility, mean arterial pressure (MAP), and cerebral blood flow [47,49-51]. Ketamine decreases the production of vascular nitric oxide, diminishing its vasodilatory effect [52], and inhibits nicotinic acetylcholine receptors [53]. (See "General anesthesia: Intravenous induction agents", section on 'Ketamine'.)

Ketamine preserves respiratory drive and has both a rapid onset of action and analgesic properties. This makes it a good choice for "awake" intubation attempts, when laryngoscopy is performed on a patient who is moderately sedated and topically anesthetized but not paralyzed due to concerns about a difficult airway. (See 'Conditions precluding use of a paralytic' below.)

Ketamine causes sympathetic stimulation and is among the most hemodynamically stable of the available sedative induction agents, making it an attractive choice for hypotensive patients requiring RSI [26,35,49,50]. However, observational evidence and clinical experience suggest that patients who are depleted of catecholamines due to their underlying disease or otherwise have a blunted sympathetic response and may develop hypotension following administration of ketamine for RSI [54-57]. Hypotension may also develop in the general emergency department population receiving ketamine for RSI [26,27,58,59].

In a multicenter, observational study of Emergency Department (ED) patients requiring RSI for both medical and traumatic indications, 18.3 percent of patients sedated with ketamine (n = 738) sustained peri-intubation hypotension compared with 12.4 percent of those sedated with etomidate (n = 6068; effect size difference 5.9 percent; 95% CI 2.9-8.8) [55]. A study using the same airway registry database but limited to ED patients intubated for sepsis reported a higher rate of postintubation hypotension among patients sedated with ketamine (n = 140) compared with etomidate (n = 363), 74 and 50 percent, respectively (odds ratio [OR] 2.9, 95% CI 1.9-4.5) [56]. A review of data from the National Emergency Airway Registry found a postintubation hypotension rate of 29 percent among 1849 patients receiving ketamine at a mean dose of 1.33 mg/kg [27]. Overall, equipoise exists among studies comparing ketamine and etomidate for RSI [26-31,58-60].

Theoretically, ketamine-induced catecholamine release causes bronchodilation. Limited evidence from animal studies suggests the drug may also have direct bronchodilatory effects. Although definitive evidence is lacking, many clinicians use ketamine as an induction agent in severe asthmatics needing RSI. Use of ketamine infusions in subanesthetic doses during asthma exacerbations provides no additional benefit compared with standard therapy [51]. Case reports suggest larger doses may be needed [11].

When considering whether to use ketamine for induction in patients with coronary disease, clinicians must weigh ketamine's potential cardiovascular benefits against its potential to induce cardiac ischemia through sympathetic stimulation. Ketamine appears to have beneficial effects on stunned myocardium in vitro [50]. When used prior to myocardial oxygen deprivation, ketamine resulted in better recovery after reperfusion. Contractility may also improve with ketamine use [49]. Some data suggest the addition of a small dose of fentanyl to ketamine may blunt increases in blood pressure due to a sympathetic response in hypertensive patients requiring RSI [61,62].

The emergence phenomenon, in which patients experience disturbing dreams as they emerge from ketamine-induced anesthesia, is a concern related to ketamine use for procedural sedation or elective anesthesia in adult patients. Re-emergence phenomena are of less concern when

ketamine is used for RSI, after which the patient is generally sedated with benzodiazepines for a substantial period. One study found that while dreams occurred frequently following sedative doses of ketamine, they were generally pleasant, and the frequency of re-emergence phenomena and delirium was markedly reduced by concomitant use of a benzodiazepine [63].

Elevated intracranial pressure — Controversy persists regarding whether ketamine elevates intracranial pressure (ICP) in patients with head injury [64]. Opponents emphasize that ketamine-induced sympathetic stimulation causes ICP elevation, potentially exacerbating the condition of such patients [65,66]. However, when ketamine is used with a GABA agonist, this rise in ICP may not occur [67,68]. Furthermore, by increasing cerebral perfusion, ketamine may benefit patients with a neurologic injury [47,67].

On balance, evidence suggesting ketamine elevates ICP is weak, and evidence that harm might ensue is weaker. A systematic review of 11 studies found no evidence to justify restrictions on ketamine use for RSI in the setting of elevated ICP [69]. We believe ketamine is a reasonable alternative induction agent to etomidate for RSI in patients with suspected ICP elevation and normal or low blood pressure [70-72]. In patients with hypertension and suspected ICP elevation, ketamine should be avoided because of its tendency to further elevate blood pressure.

The best available evidence about this issue comes from two systematic reviews of 10 trials [73] and 11 trials [69], respectively, all involving intubation and mechanical ventilation, which concluded that the use of IV ketamine did not adversely affect patient outcomes, including mortality and neurologic function. Although most trials included in the reviews had methodologic limitations, two randomized controlled trials comparing the effects of prolonged ketamine and sufentanil infusions found no difference in the mean daily intracranial pressure and cerebral perfusion pressure of patients, all of whom had sustained traumatic brain injury.

Other studies suggest ketamine does not interfere with cerebral metabolism, as it does not increase cerebral oxygen consumption and does not reduce regional glucose metabolism [47,74,75]. Ketamine may also offset a decrease in MAP caused by fentanyl, a drug commonly used as part of RSI in patients with a head injury [76].

Propofol — Propofol is a highly lipid-soluble, alkylphenol derivative that acts at the GABA receptor causing sedation and amnesia. Sedation occurs through direct suppression of brain activity, while amnesia appears to result from interference with long-term memory creation [77,78]. Induction doses of 1.5 to 3 mg/kg IV can be used, with a time to effect of approximately 15 to 45 seconds, and a duration of action of 5 to 10 minutes. Propofol does not provide analgesia. In addition to its use for RSI, propofol is used for long-term sedation in critically ill patients, sedation for brief procedures, and induction of anesthesia, all of which are discussed separately. (See "Sedative-analgesia in ventilated adults: Medication properties, dose regimens, and adverse effects", section on 'Propofol' and "General anesthesia: Intravenous induction agents", section on 'Propofol' and "Procedural sedation in adults in the emergency department: Medication selection, dosing, and discharge criteria", section on 'Propofol'.)

The pharmacokinetic properties of propofol do not appear to differ among races or between sexes [79,80], but children appear to have a slightly longer time to peak serum concentration [81].

Propofol reduces airway resistance and can be a useful induction agent for patients with bronchospasm undergoing RSI [25,82,83]. Its neuroinhibitory effects make propofol a good induction agent for patients with intracranial pathology, provided they are hemodynamically stable.

Propofol suppresses sympathetic activity, causing myocardial depression and peripheral vasodilation [84-87]. A decrease in MAP caused by propofol can reduce cerebral perfusion pressure, thereby exacerbating a neurologic injury [88]. The usual decrease in MAP is approximately 10 mmHg, but severe hypotension can develop in patients with underlying hemodynamic instability [89]. In an observational study of intubation practices in the intensive care units of 29 countries (INTUBE study) that involved 2760 critically ill patients, 43 percent experienced significant hemodynamic instability [90]. The use of propofol for induction was the only factor independently associated with hemodynamic instability or collapse (OR 1.28, 95% CI 1.02-1.49).

Propofol does not prolong the QT interval, unlike some other anesthetic agents [91,92]. Serum triglycerides and serum lipase rise during propofol infusions [93]. Although the manufacturer lists egg or soybean allergies as contraindications to the use of propofol, significant allergic reactions to the newer preparation of the drug appear to be rare. (See "Perioperative anaphylaxis: Allergy evaluation and prevention of recurrent reactions".)

Ketamine and propofol combination (ketofol) — The combination of ketamine and propofol ("ketofol") was developed for procedural sedation and is used by some clinicians for induction during RSI. The purported benefit of this combination is to obtain the benefits of each drug (eg, analgesic effects of ketamine), while minimizing the potential harms (eg, hypotensive effects of propofol). In addition, as both medications are potent bronchodilators, the combination may be ideal for patients with bronchospasm. Ketofol is discussed in greater detail separately. (See "Procedural sedation in adults in the emergency department: Medication selection, dosing, and discharge criteria", section on 'Premixed with propofol (ketofol)'.)

Several small studies address the efficacy of ketofol for RSI [94-99]. While sedation is reported to be adequate, ketofol does appear to cause a small decline in MAP (approximately 2 to 6 mmHg in most studies) when used for RSI, although such declines are comparable with or less than those caused by propofol alone. As dosing varies among studies, it is difficult to determine the best approach to dosing.

Barbiturates — Barbiturates are no longer readily available nor widely used as induction agents for intubation. For those with access to these medications, a brief overview of their use is provided here. There is no indication for the use of a barbiturate induction agent instead of etomidate, propofol, or ketamine when these agents are available.

The ultrashort-acting barbiturates interact with the barbiturate component of the GABA receptor complex, causing profound amnesia and sedation. Thiopental sodium was the barbiturate most commonly used for RSI. The induction dose is 3 to 5 mg/kg IV, with a time to effect of less than 30 seconds, and a duration of action of 5 to 10 minutes [100]. Methohexital is another barbiturate used for induction; its induction dose is 1 to 3 mg/kg IV, with a time to effect of less than 30 seconds, and a duration of action of approximately 5 to 10 minutes. Barbiturates do not provide analgesia.

Thiopental suppresses neuronal activity, making it a useful induction agent in hemodynamically stable patients with conditions that can elevate ICP, including seizures, intracranial bleeding, or trauma. However, thiopental is a venodilator with negative cardiac inotropic effects and can induce profound hypotension in the doses used for induction of anesthesia. Clinicians must exercise great care when using it in hemodynamically unstable patients or patients prone to hypotension, such as older adults. For emergency RSI, a dose of 3 mg/kg is used; a reduced dose of 2 or 1 mg/kg is used in the setting of hemodynamic compromise [101]. Reductions in ICP associated with thiopental may be caused in part by a decrease in MAP, which decreases cerebral perfusion.

Thiopental causes histamine release and can induce or exacerbate bronchospasm [102]. Therefore, thiopental should not be used in patients with reactive airway disease. Thiopental and methohexital suppress white blood cell recruitment, activation, and activity, both in vitro [103,104] and in vivo [105-107]. This effect has been attributed to a number of causes, including suppression of nuclear transcription factor [108], an increase in apoptosis [103], and a decrease in phagocytosis [104]. These immunosuppressive effects make barbiturates poor induction agents in the setting of sepsis.

CHOICE OF INDUCTION AGENT

Certain induction agents may offer advantages over others in specific clinical scenarios.

Head injury or stroke — In the patient with potentially elevated intracranial pressure (ICP) from head injury or stroke or other conditions, adequate cerebral perfusion pressure must be maintained to prevent secondary brain injury. This means avoiding significant elevations in ICP and maintaining adequate mean arterial pressure (MAP) [101]. For these reasons, we suggest etomidate for induction of these patients [20]. Ketamine is a reasonable alternative [69,109]. If signs of cerebral herniation are present prior to intubation, we suggest using etomidate and avoiding ketamine [71]. (See 'Etomidate' above and 'Ketamine' above and "Management of acute moderate and severe traumatic brain injury in adults" and "Initial assessment and management of acute stroke".)

If significant hypertension (MAP >120 mmHg) is present at the time of induction, etomidate is strongly preferable to ketamine, as it will not further elevate the blood pressure. In normotensive or hypotensive patients, we favor etomidate, although either agent can be used. In the severely hypotensive patient, a reduced dose (25 to 50 percent less than standard) of either etomidate or ketamine may be used, in addition to appropriate preintubation fluid resuscitation and vasopressor administration.

Midazolam and propofol have been used in head-injured patients, but we do not recommend midazolam as an induction agent in general. In hemodynamically unstable, head-injured patients, both agents should be avoided because of the risk of hypotension-induced brain injury [5,20,88,106,110-112]. If no alternative agents are available, the induction dose of midazolam or propofol should be reduced by 50 percent to minimize risk of exacerbating hypotension and, hence, brain injury.

Status epilepticus — Few studies of rapid sequence intubation (RSI) for status epilepticus have been performed. Based on limited evidence, we suggest propofol or etomidate be used for the induction of RSI in patients with status epilepticus [34]. Midazolam may be used, but its slower onset and propensity for hypotension make it less desirable. (See "Convulsive status epilepticus in adults: Management" and "Nonconvulsive status epilepticus: Classification, clinical features, and diagnosis".)

Propofol has potent antiseizure effects but can cause dose-dependent hypotension, so the dose for RSI must be calculated carefully. The induction dose of propofol is 1 to 2.5 mg/kg and, because of the tendency to produce hypotension, the drug is usually pushed more slowly than other induction agents (over 30 to 45 seconds), making administration and RSI more complex.

We prefer etomidate in the setting of persistent seizures related to acute neurologic trauma in patients at risk for hypotension, which would exacerbate secondary brain injury. Etomidate can cause myoclonus and has a slightly higher rate of electroencephalogram-documented seizure

activity compared with other medications [113-115]. However, it is short-acting and may be used safely for RSI in status epilepticus [116], then followed with a sedative with antiseizure effects, such as propofol or a benzodiazepine, to maintain sedation.

Midazolam may be used for induction, but care must be taken to use doses appropriate for RSI (0.2 to 0.3 mg/kg intravenous [IV] bolus), account for its slower onset, and be wary of dose-dependent hypotension [40,42]. Although evidence is lacking, we suggest ketamine **not** be used in this setting because of its stimulant effects.

Following the administration of a sedative for RSI, appropriate antiseizure treatment should be started as soon as is feasible following successful intubation.

Reactive airway disease — For hemodynamically stable patients with severe bronchospasm requiring intubation, we suggest ketamine or propofol be used for induction because of their bronchodilatory properties [25,51]. Etomidate is an acceptable alternative. In hypotensive patients, we prefer ketamine or etomidate. None of these agents causes histamine release. (See "Acute exacerbations of asthma in adults: Home and office management".)

Cardiovascular disease — We suggest etomidate for induction of the patient with significant cardiovascular disease requiring RSI [17,18,20,117]. The hemodynamic stability it provides and the absence of induced hypertension make it preferable to other sedatives. (See 'Etomidate' above.)

In patients with coronary artery disease or suspected aortic dissection, we suggest giving fentanyl (3 mcg/kg, slow IV push) as a pretreatment agent to mitigate the catecholamine release associated with laryngoscopy and intubation [61,62]. Pretreatment is discussed separately. (See "Pretreatment medications for rapid sequence intubation in adults for emergency medicine and critical care", section on 'Choice of pretreatment agents'.)

Shock — All sedative agents can cause hypotension when administered to patients who are hemodynamically unstable [27,31,59,89,116,118,119]. In addition to preintubation resuscitation to maximize cardiovascular physiology (eg, fluid resuscitation, vasopressor therapy), we suggest decreasing the dose of the sedative agent used for induction of the patient in shock requiring RSI. We use IV etomidate 0.15 mg/kg [118], or alternatively IV ketamine 1 mg/kg. (See 'Etomidate' above and 'Ketamine' above and "Rapid sequence intubation in adults for emergency medicine and critical care" and "Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock".)

Ketamine causes a sympathetic surge that may augment endogenous catecholamines but may also elevate intracranial pressure. Etomidate has been scrutinized because of its transient suppression of endogenous cortisol, but this effect has not been found to be clinically relevant. Both agents cause a small drop in MAP in patients with severe hypotension, but less than other sedative agents. These issues are discussed in detail above. (See 'Elevated intracranial pressure' above and 'Adrenocortical suppression' above.)

CONDITIONS PRECLUDING USE OF A PARALYTIC

Conditions may exist that preclude the use of a paralytic for intubation (ie, precludes rapid sequence intubation [RSI]). The clinician may then decide to use an appropriate sedative or combination of sedatives and topical anesthesia to facilitate laryngoscopy and assess the airway, while allowing the patient to maintain their respiratory drive. This approach, referred to as a "sedated" or "awake" look or "awake intubation," is used when the clinician suspects the airway will be difficult to intubate, and allows the practitioner to verify that laryngeal structures are visible, before committing to paralysis. Awake intubation is reviewed in detail separately. (See "Awake tracheal intubation".)

The sedated-look approach is distinct from the older practice of "intubation with sedation alone" or "nonparalytic RSI," in which the patient receives a full induction dose of a sedative agent, but no neuromuscular blocking agent. The older practice is to be avoided, as it creates a vulnerable, compromised patient in whom intubating conditions are far from ideal [120,121]. In general, if the clinician anticipates a difficult intubation that may preclude successful RSI, an "awake look" or "sedated look" is advised. If the clinician does not anticipate a difficult airway, RSI with a full induction dose of a sedative agent, accompanied by a full dose of a paralytic agent, is advised.

Multiple medications have been studied, primarily in the operating room, to determine which agents are appropriate for "sedated looks" [1,122-129]. In general, the use of topical anesthesia (eg, nebulized 4 percent lidocaine) along with moderate sedation allows for a look into the airway, while enabling the patient to maintain respiratory drive and protective airway reflexes.

Ketamine is gaining popularity in this circumstance because it allows the patient to maintain respiratory drive while providing analgesia, amnesia, and sedation [48,67,123,130]. Ketamine's analgesic properties allow it to be used as the sole agent in the bloody traumatized airway when topical anesthesia is unlikely to work effectively. More research is needed to determine which sedatives are best for "sedated looks" in the emergency setting.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Airway management in adults".)

SUMMARY AND RECOMMENDATIONS

- **Rapid sequence intubation (RSI)** – RSI is the standard of care in emergency airway management for intubations not anticipated to be difficult. RSI involves combining a sedative and a paralytic agent to render a patient rapidly unconscious and flaccid in order to facilitate emergency tracheal intubation and to minimize the risk of aspiration. (See "Rapid sequence intubation in adults for emergency medicine and critical care" and "Rapid sequence intubation (RSI) in children for emergency medicine: Approach".)

- **Preferred induction agents by clinical scenario** – Different clinical scenarios lend themselves to the use of certain sedatives when RSI is needed (table 1). We suggest the following induction agents be used in the specific clinical circumstances described below (**Grade 2C**):

  - **Head injury or elevated intracranial pressure (ICP)** – In the patient with a head injury or potentially elevated ICP, adequate cerebral perfusion pressure must be maintained to prevent secondary brain injury. We suggest etomidate or ketamine for induction of these patients during RSI. For hypotensive patients, etomidate or ketamine may be used. Ketamine should be avoided in patients with hypertension (mean arterial blood pressure >120 mmHg) or if signs of cerebral herniation are present. (See 'Head injury or stroke' above and 'Etomidate' above and 'Ketamine' above.)

  - **Status epilepticus** – We suggest propofol or etomidate be used for induction of RSI. Etomidate may be used when the patient manifests hemodynamic compromise. We suggest ketamine **not** be used because of its stimulant effects. Midazolam is an acceptable alternative, but care must be taken to administer an appropriate induction dose (0.1 to 0.3 mg/kg) and to guard against dose-dependent hypotension. (See 'Status epilepticus' above.)

  - **Severe bronchospasm** – For the **hemodynamically stable** patient with severe bronchospasm requiring intubation, we suggest induction with ketamine or propofol. Etomidate or midazolam is an acceptable alternative. In **hemodynamically unstable** patients with severe bronchospasm, we suggest ketamine or etomidate. (See 'Reactive airway disease' above.)

  - **Cardiovascular compromise** – For induction of the patient with cardiovascular compromise requiring RSI, we suggest etomidate because of the hemodynamic stability it provides. (See 'Cardiovascular disease' above and 'Etomidate' above.)

  - **Shock** – For induction of the patient in shock requiring RSI, we suggest low-dose intravenous (IV) etomidate (0.15 mg/kg) or, alternatively, IV ketamine (1 mg/kg). If etomidate is used in a patient with sepsis and hypotension refractory to treatment with fluid resuscitation and a vasopressor, we suggest that a single dose of glucocorticoid (eg, hydrocortisone 100 mg IV) be given. (See 'Shock' above and 'Etomidate' above and 'Ketamine' above.)

  - **"Awake" intubation** – The use of sedative medications to secure the airway of patients with conditions precluding the use of paralytics is reviewed in detail separately. (See "Awake tracheal intubation".)

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GRAPHICS

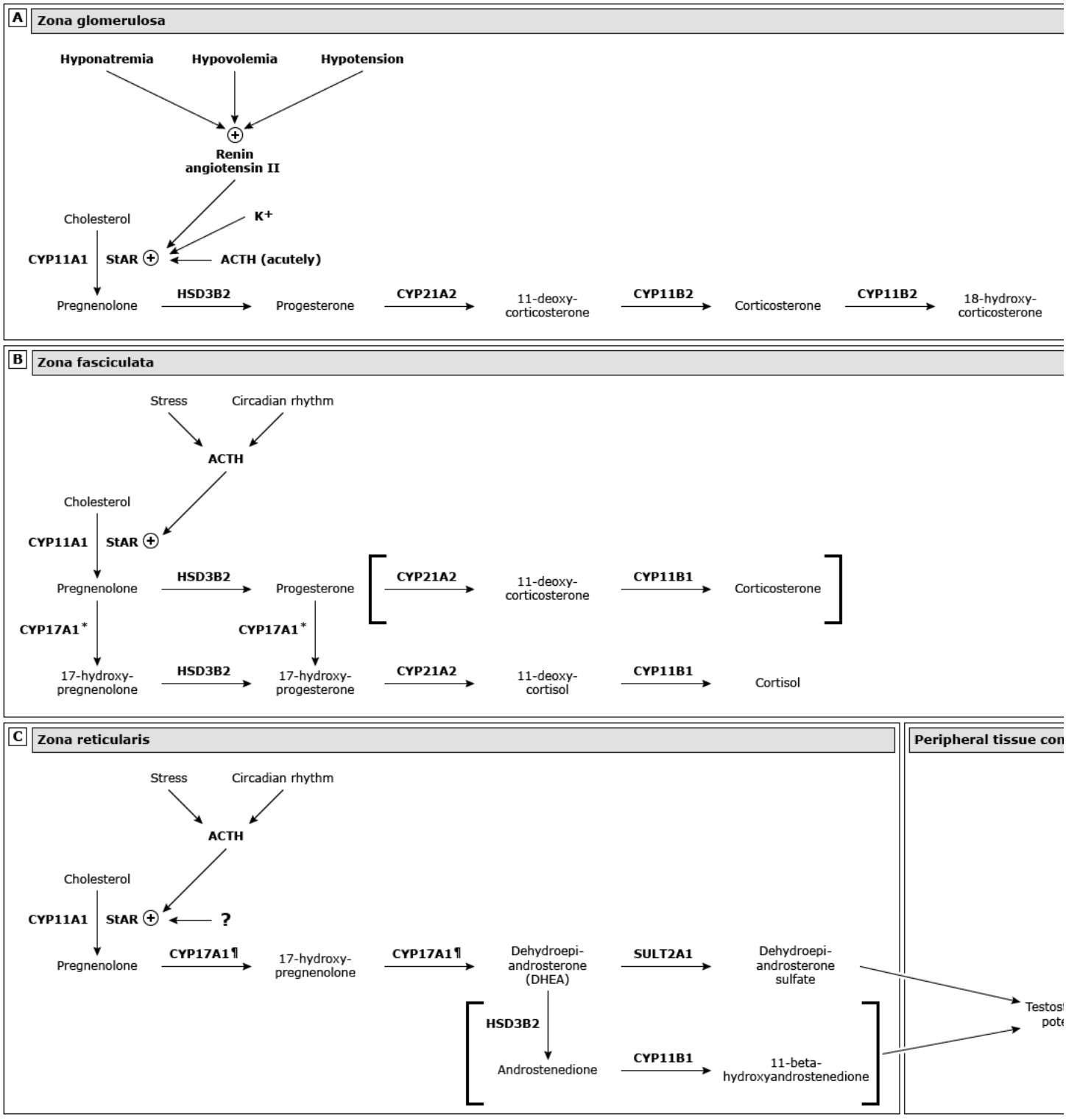
Table 1: **Rapid sequence intubation induction agents for adults**

Drug name	Class	Benefits	Contraindications	Notes	Dose
Etomidate	Imidazole derivative	Excellent sedation with little hypotension	Known to suppress adrenal cortisol production	Use cautiously if patient has sepsis; initial dose of glucocorticoid may be needed	0.3 mg/kg
Ketamine	Phencyclidine derivative, dissociative anesthetic	Stimulates catecholamine release Bronchodilation	Use in patients with elevated ICP or elevated blood pressure is controversial	May be an excellent induction agent for patients with bronchospasm, septic shock, **and** hemodynamic compromise	1 to 2 mg/kg
Midazolam	Benzodiazepines	Potent dose-related amnesic properties	Dose-related myocardial depression can result in hypotension	Frequently underdosed	0.2 to 0.3 mg/kg
Propofol	Alkylphenol derivative	Bronchodilation	No absolute contraindications Dose-related hypotension		1.5 to 3 mg/kg
Thiopental sodium	Ultrashort-acting barbiturate	Cerebroprotective and anti-convulsive properties	Potent venodilator and myocardial depressant; can cause hypotension Relatively contraindicated in reactive airway disease due to histamine release Acute intermittent and variegate porphyrias	May not be commercially available. Rarely used.	3 to 5 mg/kg

ICP: intracranial pressure.

Graphic 64272 Version 11.0

Figure 1: **Normal adrenal steroidogenesis**



(A) Zona glomerulosa (ZG): Controlled primarily by the renin-angiotensin system through angiotensin II as well as potassium ion and ACTH (acutely). Renin secretion is stimulated by hyponatremia, hypovolemia, and hypotension. The ultimate increase in angiotensin II causes vasoconstriction and stimulates aldosterone, thereby increasing renal sodium reabsorption resulting in an expansion of plasma volume.

(B) Zona fasciculata (ZF): Cortisol is the major product because CYP17A1 (17-hydroxylase activity*) predominates. The square brackets ([ ]) indicate that corticosterone synthesized from progesterone by CYP21A2 and then CYP11B1 is usually a minor pathway (except in CYP17A1 [17-hydroxylase*] deficiency).

(C) Zona reticularis (ZR): The question mark (?) indicates that other factors that are not yet defined might be involved in the control of steroidogenesis in the ZR. The square brackets ([ ]) indicate that HSD3B2 production of androstenedione is a minor pathway in the ZR. The relatively weak androgens produced in the ZR can be converted to more potent androgens in peripheral tissue. Refer to other UpToDate graphic content on testosterone formation and metabolism.

ACTH: corticotropin.

* CYP17A1 has high 17-hydroxylase activity in the zona fasciculata but has minimal 17,20-lyase activity because of low expression of a cofactor (cytochrome b5) necessary for full 17,20-lyase activity. Therefore, the ZF is not a source of significant adrenal androgen precursors as in the ZR (C).

¶ In the ZR, CYP17A1 catalyzes 17-hydroxylase and 17,20-lyase activity because of the presence of a cofactor (cytochrome b5).

Courtesy of Hershel Raff, PhD.

Graphic 71558 Version 9.0

Contributor Disclosures

David Caro, MD Other Financial Interest: Airway Management Education Center [Honoraria for national meeting lectures]. All of the relevant financial relationships listed have been mitigated. **Ron M Walls, MD, FRCPC, FAAEM** Other Financial Interest: Airway Management Education Center [Health care provider education and resources]. All of the relevant financial relationships listed have been mitigated. **Jonathan S Grayzel, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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