# Issues in Sedation, Paralytic Agents, and Airway Management

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**Objectives**:

- To review the issues concerning the quantity and methods of administration of sedation in the ICU
- To review pharmacokinetics of sedation agents
- To review issues of airway management

**Key words:** assessment; cisatracurium; etomidate; fentanyl; ketamine; morphine; propofol; rocuronium; sedation; vecuronium

## Issues Regarding Sedation in the ICU

Publications from the late 1980s suggested that approximately half of the patients in the ICU described their period of mechanical ventilation as unpleasant and stressful, and that their time requiring mechanical ventilation was associated with fear, agony, and panic. In the late 1990s and more recently, publications have suggested that the administration of large quantities of sedation in the ICU leads to prolonged intervals of mechanical ventilation, longer ICU stays, and increased evaluations of patient's mental status with CT scans.[1,2] The administration of sedation has also been associated with the development of posttraumatic stress disorders and memory problems in the recipients.[3,4] Finally, the administration of sedation has been associated with the development of nosocomial pneumonia.[5] Also, delirium occurs in more than 80% of the patients in the intensive care unit and the administration of sedatives is likely an important contributor.[6] Therefore, it is clear the administration of sedation causes many problems for critically ill patients. The benefits of administering sedation are less clear.

### *Assessment of Sedation*

There is no consensus as to what level of sedation is optimal for patients in the ICU; most likely, the optimal level of sedation will vary depending on the underlying physical and mental problems of each patient and the level of movement that is safe for the patient. A recent investigation documented that the more severely ill a patient is in the ICU, the less the patients remember about their ICU experience.[3] The more severely ill patients tend to receive more sedation, as they require mechanical ventilation for more prolonged periods, and there is some question whether their illness and their medicines may affect short-term memory.[3,4] More is being discovered about the effects of sedatives on cognition, memory, and learning; precise goals may eventually be possible (*ie*, anxiolysis without decreased cognition). Furthermore, we may be able to achieve some anxiolysis with nonpharmacologic interventions; relaxation tapes, warm milk, and herbal tea were shown to be useful in the treatment of hospitalized elderly patients as the administration of these adjunctive "therapies" decreased the need for sedation and decreased the incidence of delirium.[7]

Despite the lack of consensus and our incomplete knowledge, sedation should only be administered after an assessment of the patient is done. Thus, some quantitative assessment of a patient's anxiety should be made before the administration of medication; the patient then should be reassessed after receiving the drug. The most common assessment tool utilized is the Ramsay scale (Table 1). The Ramsay scale is a 6-point scale that describes the patient as anxious and agitated

**Table 1.** *Sedation-Agitation Scale*

| Score | Description |
|---|---|
| 1 | Patient anxious and agitated, or restless, or both |
| 2 | Patient cooperative, oriented, and tranquil |
| 3 | Patient responds to commands only |
| 4 | Brisk response to a light glabellar tap or loud auditory stimulus |
| 5 | Sluggish response to a light glabellar tap or loud auditory stimulus |
| 6 | No response to a light glabellar tap or loud auditory stimulus |

(+3) to unresponsive (–3). The scale includes an assessment of movement; thus, the administration of neuromuscular blockade would preclude the use of this assessment tool

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## Narcotics and Sedative-Hypnotic Agents

All the sedative-hypnotic agents utilized for sedation or to optimize airway management have a depressant effect on blood pressure and cardiac function. The effects vary depending on the patient's age,[8] underlying medical problems, and cardiovascular stability. Furthermore, when drugs are used in combination, their effects are more than additive. This potentiation of effects can be beneficial, as when analgesic effects are intensified; however, combinations of drugs may also potentiate respiratory depression and cardiovascular instability. Therefore, the decision to administer a sedative-hypnotic agent must first address whether the patient is stable enough to tolerate such a medication and if so, what dose the patient will tolerate.

Patients who do not tolerate the cardiac-depressant effects of sedative-hypnotics include patients who are in shock, bleeding, or severely volume-depleted, or who have inadequate cardiac function. Patients who have suffered a cardiac arrest or are very hypotensive either should not be given medications or should be given very small doses of sedative-hypnotic agents, as the drugs will hinder cardiac function. Aging affects the pharmacokinetics and pharmacodynamics of the sedative-hypnotics; furthermore, the sensitivity of the elderly brain to sedative-hypnotic agents appears to be increased.[8] Sedative-hypnotics are also associated with confusion and delirium in the elderly (see the chapter titled "Pain, Delirium, and Ischemia in the Perioperative Period").

Liver disease affects the metabolism of drugs in many ways, and is hard to predict. In severe cirrhosis (associated with altered clotting times and encephalopathy), elimination half-lives of drugs are increased and drug clearance is reduced. These results suggest that smaller doses of drugs should be administered, and should be administered less frequently.[8-10] Metabolisms of drugs that undergo glucuronidation (*ie*, lorazepam, oxazepam) appear to be relatively unaffected by liver disease. Drugs that are metabolized by phase I oxidative pathways (*ie*, diazepam and chlordiazepoxide) are affected by acute and chronic liver disease.[9] Nonetheless, morphine, which undergoes glucuronidation, is associated with an increased half-life and decreased clearance in patients with end-stage, decompensated liver disease.[9]

A retrospective examination of the medical records of 28 patients who required > 7 days of intensive care documented the occurrence of withdrawal symptoms and signs (restlessness, irritability, nausea, cramps, muscle aches, dysphoria, insomnia, myoclonus, delirium, sweating, tachycardia, vomiting, diarrhea, hypertension, fever, seizure, or tachypnea) in nine of these patients.[11] The patients had to have three or more signs, or three or more symptoms, to be considered to have withdrawal. These patients received several-fold higher doses of analgesic and sedative-hypnotic medications than the patients who did not experience withdrawal symptoms.[11] The patients who did *not* experience withdrawal received an average daily dose of fentanyl equivalent to 1.4 mg / d and lorazepam equivalent to 11.1 mg / d. The patients who experienced withdrawal were significantly more likely to have received neuromuscular blocking agents. Increased doses of narcotics and sedatives might have been given to ensure that patients were not paralyzed and awake. The patients who experienced withdrawal symptoms were also significantly younger than those who did not experience the symptoms; the younger patients may be more prone to tolerance of opioids and sedatives, or the younger patients may have been more likely to survive. The authors recommended (1) weaning the doses of the drugs by 5 to 10% per day; (2) that drugs might be weaned even more slowly if both opioids and benzodiazepines are being weaned; and (3) that long-acting oral agents could be given, which can be weaned outside the ICU.[10]

### *Continuous Infusions*

The clearance of a sedative drug is affected by the duration of the infusion of the drug. Both midazolam and lorazepam become longer-acting drugs when they are administered as continuous infusions.[12] Patients also rapidly become tolerant to benzodiazepines when these agents are administered frequently.[12]

As large quantities of sedation and narcotics are frequently administered to critically ill patients, these patients become tolerant and they experience

withdrawal symptoms when these drugs are decreased or stopped (see discussion of withdrawal above). Strategies[1,2] have been formulated to deal with these problems. Daily interruption of continuous infusions decreases the quantity of medications administered.[1] Infusions of dexmedetomidine and ketamine have been utilized to decrease the quantities of sedatives and narcotics given to patients.[13,14] Both dexmedetomidine and ketamine produce analgesia and sedation, and so have been found to decrease the quantity of other drugs given for these purposes. Furthermore, dexmedetomidine has been used to treat sedation-induced withdrawal.[15] The administration of opioids that target kappa or delta receptors may be useful in patients who have received opioids that are mu-receptor agonists (morphine, fentanyl). In the future, endocannabinoids (*ie*, tetrahydrocannabinol, the active ingredient in marijuana) may be used as they appear to cause analgesia through an entirely different set of receptors.[16,17]

### *Assessment of Pain*

Although narcotics are often given with sedating drugs, they are analgesics. Therefore, narcotics or analgesics should be given to the patients who are in pain.

The treatment of pain is not only compassionate, but it is now mandated by the Joint Commission on Accreditation of Healthcare Organizations. Pain associated with procedures should be treated with analgesia. Chronic pain may require therapy other than mu agonists (fentanyl and morphine sulfate), as most patients who have been treated for chronic pain are tolerant to these narcotics.[16,17] Patients with chronic pain may benefit from a multidisciplinary approach to pain treatment.

A patient's pain should be quantified before and after treatment. The typical assessment tool is a visual analog scale, which has been validated and shown to have good interobserver reproducibility.

### *Morphine Sulfate*

Morphine has a rapid initial redistribution phase of 1 to 1.5 min and an initial half-life of 10 to 20 min; the terminal elimination half-life is between 2 and 4.5 h.[18,19] Compared with fentanyl, morphine has low lipid solubility; this is important in that morphine slowly penetrates the blood-brain barrier. Therefore, morphine's peak effect is after 20 to 30 min, whereas the peak effect of the highly lipid-soluble fentanyl is within a few minutes. Fentanyl rapidly redistributes away from the brain and hence is short-acting; in contrast, morphine's low lipid solubility prevents rapid redistribution and causes a longer duration of action (Table 2). The liver primarily metabolizes morphine; however, the kidneys metabolize 40% of the drug. A major metabolite of morphine (morphine-3-glucuronide) has opiate activity and persists in the circulation of patients with renal failure, and can cause prolonged sedation.

The sensitivity to pain decreases with age, opiate receptor density is decreased in the elderly, and there is evidence for reduced activity within the opiate-receptor system with increasing age.[8,9] Elderly patients are found to develop increased concentrations of morphine when compared with younger patients given the same dose, and the morphine concentration persists for longer intervals, suggesting decreased clearance. Therefore, smaller doses of morphine should be used in elderly patients.

Morphine administration is associated with hypotension; doses of 1 to 4 mg/kg IV are commonly associated with hypotension, but hypotension has been reported with doses of 5 mg IV.[18,19] The faster the rate of administration, the more pronounced the hypotension seen; morphine can also be associated with histamine release, and morphine causes arterial and venous dilation that potentiates hypotension. Finally, morphine can slow the heart rate, probably by its stimulation of the vagus nerve and its depressant effects on the sinoatrial node.

**Table 2.** *Pharmacokinetics and Pharmacodynamics of Opioid Agents**

| Drug | Lipid Solubility | Half-Life (h) | Onset of Action (min) | Peak Effect (min) | Duration of Action (h) |
|---|---|---|---|---|---|
| Morphine | Low | 2–3 | 5 | 20–30 | 2–7 |
| Fentanyl | High | 4–10 | 1–2 | 5–15 | 0.5–1 |
| Meperidine | Moderate | 5–8 | 5 | 20–60 | 2–4 |
| Hydromorphone | Low | 2.5–3 | 10–15 | 15–30 | 2–4 |

*Pharmacokinetic and pharmacodynamic parameters are based on single IV dosing in normal patients. Reprinted with permission from Volles and McGory.[9]

Opioid receptors are on many cells of the immune system. Morphine and methadone, mu-receptor agonists, enhance HIV infection of human immune cells *in vitro*.[20,21] There appears to be a modulation of the chemokine or cytokine production by morphine and methadone, which then leads to increased viral infection.[20,21] These data suggest that in the future, the mu agonists morphine and methadone might be proscribed in HIV patients.

*Fentanyl*

Fentanyl is 50 to 100 times more potent than morphine (fentanyl has greater affinity for the mu opiate receptor), so that the usual IV doses are 50 to 100 μg, depending on the condition of the patient. As fentanyl is very lipid-soluble (40 times more lipid-soluble than morphine), it penetrates the central nervous system quickly and leaves it quickly, and therefore has a very rapid onset of action and a short duration of action (Table 2). The onset of action of fentanyl is within 30 s, and its peak effect is within 5 to 15 min.[19,22] The liver metabolizes fentanyl and the kidney eliminates inactive metabolites. Decreased liver perfusion can decrease the clearance of fentanyl. When fentanyl is administered as a continuous infusion, the terminal half-life of the drug is 16 h; prolonged effects seen after infusions or repeated bolus injections of fentanyl occur due to the large amounts of the drug, which accumulate in the fatty tissues and then have to be metabolized by the liver.

Fentanyl is similar to morphine in that fentanyl concentrations are higher in elderly patients, apparently due to decreased clearance of the drug. Fentanyl is more potent in the elderly in that loss of consciousness occurs with smaller doses and chest-wall rigidity occurs more often.[19,22]

Fentanyl administration infrequently causes hypotension; it can cause hypotension by causing bradycardia and decreased sympathetic tone.[19,22] Patients who are maintaining their blood pressure by an increase in sympathetic tone can become hypotensive with the administration of fentanyl.[19,22] The rate of administration appears to affect the development of bradycardia; when fentanyl is administered rapidly, bradycardia more frequently develops.[19,22]

*Remifentanil*

Remifentanil is an ultrashort-acting narcotic with a potency that is similar to fentanyl. Remifentanil penetrates the blood-brain barrier within 1 min, and its blood concentration decreases 50% by 6 min after a 1-min infusion and 80% by 15 min.[23,24] The novel aspect of remifentanil is its rapid hydrolysis by circulating and tissue-nonspecific esterases (the beta-adrenergic blocker esmolol is metabolized by similar enzymatic machinery). Unlike fentanyl, there does *not* appear to be a cumulative effect seen with longer infusions because of this unique metabolism. Organ dysfunction does not appear to alter the metabolism of this drug.[23,24] The clearance of remifentanil is reduced by about 25% in the elderly, according to the product information.

This drug produces respiratory depression, hypotension, bradycardia, and hypertonus of skeletal muscle; the rigidity produced by this drug can make ventilation by mask difficult or impossible. The administration of propofol or a paralytic agent prior to the administration of remifentanil can attenuate the skeletal rigidity seen with the drug. In studies where fentanyl, 1 μg/kg IV, was compared with remifentanil, 0.5 to 1 μg/kg IV, hypotension occurred somewhat more often with fentanyl.[23,24] Peak hemodynamic effects of remifentanil are seen within 3 to 5 min after the administration of a single bolus, and hemodynamic effects are dose-dependent.

It has been shown that when large doses of remifentanil are administered intraoperatively, patients develop acute opioid tolerance. Tolerance occurs more quickly in response to shorter-acting narcotics such as remifentanil and alfentanil. In fact, profound tolerance can be documented after 90 min of remifentanil administration to volunteers. However, it also appears that the administration of large doses of opioids can also produce delayed hyperalgesia, suggesting a central sensitization that reduces the threshold to receptive fields. In support of this, the administration of *N*-methyl-D-aspartate-receptor antagonists before the administration of large doses of opioids can block the hyperalgesia that can be induced by heroin or fentanyl.

*Etomidate*

Etomidate exists as two isomers, but only the + isomer is active; etomidate is R-(+)-ethyl-1-(α-methylbenzyl)-1H-imidazole-5-carboxylate. It is formulated as a 2-mg/mL solution in 35% propylene glycol. The propylene glycol is irritating to veins, and etomidate should not be mixed with other IV solutions. Etomidate had been utilized in critical care units throughout the world because of its characteristics, including its minimal hemodynamic effects, minimal respiratory depression, and cerebral protective effects. However, etomidate causes a dose-dependent, temporary, and reversible inhibition of steroid synthesis after a single dose or after an infusion.[25] Other side effects that discourage its use include nausea and vomiting due to activation of the nausea center (concurrent administration of fentanyl increases the incidence), pain on injection, superficial thrombophlebitis 48 to 72 h after injection, and myoclonus. Etomidate appears to enhance the neuromuscular blockade of nondepolarizing paralytic agents.[26] Nonetheless, etomidate continues to be utilized as it causes minimal hemodynamic perturbations when small doses are administered.

The liver metabolizes etomidate, and its main metabolites are inactive. Doses of etomidate that have been utilized are 0.2 to 0.6 mg/kg; this dose can be decreased if narcotics and/or benzodiazepines are also administered. After 0.3 mg/kg, the effect is seen within the time that it takes the drug to circulate to the brain; redistribution is the mechanism that terminates the effects of a bolus of etomidate. Hepatic dysfunction does not appear to alter the rapid recovery from the hypnotic effects of etomidate.[25,26] The elimination half-life of the drug is 2.9 to 5.3 h.[25,26] In the elderly, the elimination clearance and volume of the central compartment are both decreased, causing a higher blood concentration from a given dose.[25,26]

Etomidate affects transmission at γ-aminobutyric acid-A receptors and may increase the number of γ-aminobutyric acid-A receptors.[25,26] Etomidate causes hypnosis and does not have analgesic activity. Etomidate has minimal effects on ventilation; in fact, etomidate can produce a brief period of hyperventilation, which can be followed by apnea.[25,26] Hiccups and coughing may also be seen after etomidate administration. After the administration of 0.3 mg/kg to patients, there is almost no change in heart rate, mean arterial pressure, mean pulmonary artery pressure, central venous pressure, stroke volume, or cardiac index.[25,26] Etomidate does not affect the sympathetic nervous system or baroreceptor function.

*Propofol*

Propofol, 2,6,-diisopropylphenol, is formulated as a 1% aqueous emulsion, containing 10% soybean oil, 2.25% glycerol, and 1.2% egg phosphatide.[27] EDTA has recently been added to propofol in an attempt to discourage bacterial growth; propofol has been found to be the drug most frequently contaminated by bacteria. An ampule of the drug should be utilized for only one patient; great care should be taken when the drug is used for infusions so that bacterial contamination does not occur.

The effects of propofol 2.5 mg/kg are seen within the time it takes for the drug to circulate to the brain. The duration of the hypnosis is 5 to 10 min after a bolus injection; redistribution and elimination terminate the effects of propofol. Propofol has no analgesic activity but has some antiemetic properties. The clearance of propofol cannot be explained by hepatic clearance alone; there appear to be extrahepatic sites of elimination. The clearance of propofol is extremely rapid, and the recovery from propofol remains rapid even after prolonged infusions.[27] The pharmacokinetics of propofol in patients aged ≥ 65 years reveal that the elimination clearance is slower, but that plasma concentrations appeared similar to those of younger patients.[8,9,27]

Propofol causes a dose-dependent hypotension that is very similar or somewhat greater than the hypotension produced by the administration of thiopental. Propofol causes vasodilation and myocardial depression.[26,27] The hypotensive effects of this drug can be more exaggerated in elderly patients and in patients who have poor cardiac function.[25-27] Propofol causes respiratory depression; initially, an increase in respiratory rate is seen for about 30 s and then apnea occurs. Airway reflexes are depressed, and propofol prophylactically attenuates induced bronchoconstriction by depression of neurally induced bronchoconstriction.[28,29] Propofol does not affect resting airway tone, nor has it been utilized in asthmatics to treat acute bronchoconstriction.[28,29]

Side effects produced by propofol include intense dreams and disinhibition, dystonic or

choreoform movements, pain at the injection site, phlebitis, hyperlipidemia, and pancreatitis.

*Ketamine*

Ketamine, a phencyclidine derivative, is unique among the IV agents in that it causes analgesia as well as amnesia. The drug does not necessarily cause a loss of consciousness, but the patient is not aware; the drug appears to cause a dissociative state by electrophysiologic inhibition of the thalamocortical pathways and stimulation of the limbic system.[30] The drug is a racemic mixture of two optical enantiomers; the S(+) ketamine has approximately fourfold greater affinity at phencyclidine binding sites on the *N*-methyl-D-aspartate receptor than does the R(–) ketamine. The S(+) ketamine appears to allow the use of significantly smaller doses, faster recovery, and possibly fewer side effects; the compound will be in use in Europe.[25,30]

Doses of 0.1 to 0.5 mg/kg of ketamine have analgesic action and can be utilized before the onset of pain for effective preemptive analgesia. Ketamine has an elimination half-life of 3 h. Recovery from an induction dose (0.5 to 1.5 mg/kg) is from redistribution from its receptor. Ketamine causes amnesia, altered short-term memory, decreased ability to concentrate, altered cognitive performance, nightmares, nausea, and vomiting. Thus, it is common practice to administer small doses of benzodiazepine with ketamine; this practice does prolong recovery from ketamine.

Ketamine directly stimulates the autonomic nervous system, releases catecholamines and steroids, causes tachycardia, and increases blood pressure. If a patient cannot release catecholamines (*ie*, is critically ill or has autonomic nervous system blockade), then ketamine administration can cause vasodilation and myocardial depression.[25,26,30] Data regarding ketamine in the elderly are lacking; the emergence phenomena and dysphoria ketamine causes may be difficult for the elderly, particularly if the baseline mental status is not normal.[30]

Ketamine is a useful agent for patients with airway diseases in that it attenuates neurally induced bronchoconstriction.[28-30] It also has a small direct effect on smooth muscle activation; however, it is unclear whether it can be used to ameliorate asthma attacks. Ketamine administration will decrease the neurally induced bronchoconstriction that occurs with airway manipulation during intubation.

*Midazolam*

Midazolam is a water-soluble benzodiazepine that has the notable property of causing antegrade amnesia in conscious patients. Midazolam has an elimination half-life of 2.7 h (compared with 46.6 h for diazepam).[25,26] In the elderly, the elimination half-life is longer and elimination clearance decreases.[8,9] Drug effects are terminated by redistribution, suggesting that pharmacodynamic changes in the elderly cause the prolonged effects seen in this age group.[25,26]

After doses of 0.05 to 0.2 mg/kg of midazolam IV, tidal volumes will decrease by 40%, but minute ventilation remains unchanged.[25,26] However, after slightly larger doses, apnea is seen. When opioids and midazolam are administered together, respiratory depression is assured, as midazolam decreases the tidal volume and the opioids will decrease the respiratory rate. In patients with chronic obstructive airways disease and in patients with altered respiratory drives, more prolonged and more profound respiratory depression has been noted.[25,26]

Midazolam causes more hypotension than etomidate; when given to patients with normal cardiovascular function, small decreases in blood pressure and increases in heart rate are seen. When midazolam was given to patients who had valvular heart disease, some impairment of cardiac function was seen; when it was used for cardiac catheterization in patients with coronary artery disease, these patients experienced approximately a 15% decrease in their mean arterial pressures.[25,26] When patients have significant cardiac dysfunction or are hypovolemic, midazolam will depress cardiovascular function and has been associated with fatalities.

Unlike propofol, ketamine, or etomidate, midazolam will take longer to exert its peak effect on the central nervous system. The drug takes approximately 5 min to achieve its peak effect; recovery of normal central nervous function takes about 20 min after one dose.[25,26] However, in the elderly, prolonged amnesia even during the recovery period may occur.[25,26]

Midazolam and the other benzodiazepines, except for lorazepam or temazepam, have been noted to interact with protease inhibitors including ritonavir, indinavir, nelfinavir, and saquinavir. The interaction involves the inhibition of P-450 –3A enzyme that metabolizes many of the benzodiazepines. Therefore, the levels of the benzodiazepines can be increased

and cause prolonged amnesia and sedation.[31] There is now a warning on the protease inhibitors to avoid administering the above benzodiazepines to patients who are taking protease inhibitors. The warning also exists for meperidine, fentanyl, codeine, and hydromorphone, levels of which are also increased by the protease inhibitors.[31]

*Dexmedetomidine*

$\alpha_2$-Adrenoreceptor agonists have been utilized in veterinary medicine for years. Clonidine, although utilized as an anti-hypertensive therapy, is a powerful therapy for alcohol and drug withdrawal and has been noted to cause sleepiness in patients.[32] Dexmedetomidine was approved by the Food and Drug Administration in 1999 for short-term (< 24 h) sedation and analgesia. The $\alpha_2$-adrenergic receptor mediates its effects by activing guanine-nucleotide regulatory binding proteins (G proteins). Activated G proteins modulate cellular activity by signaling a second messenger system or by modulating ion channel activity. Dexmedetomidine is a specific and selective $\alpha_2$-adrenergic receptor agonist, different from clonidine. Activation by dexmedetomidine results in hypotension, bradycardia, sedation and analgesia, decreased bowel motility, increased secretion of sodium and water in the kidney, decreased insulin release from the pancreas, and decreased salivation.[32]

Comparison of dexmedetomidine and propofol has shown that blood pressure is similarly lowered by both drugs; however, dexmedetomidine lowers heart rate to a greater degree than propofol. Futhermore, dexmedetomidine administration decreased the quantities of narcotic administered to intraoperative or ICU patients (also see above).[14]

## Introduction to Muscle Relaxants

Muscle relaxants are used for several reasons, including facilitating endotracheal intubation, facilitating mechanical ventilation, reducing elevated intracranial pressure, reducing work of breathing, reducing spasms associated with tetanus, and reducing movement associated with status epilepticus.[33] Short-term use is considered < 2 days, because complications have not been reported with administration for < 2 days.[33] Complications associated with muscle relaxants include anaphylaxis, hyperkalemia associated with succinylcholine administration (seen in patients with burns, neurologic injury, muscle trauma, long-term immobilization, or elevated serum potassium), inadequate ventilation of paralyzed patients, inadequate analgesia and sedation of paralyzed patients, and persistent weakness after long-term use.[33,34] Persistent weakness occurs in about 20% of patients who receive muscle relaxants for > 6 days and in up to 70% of patients who are receiving steroids in addition to muscle relaxants.[33] Risk factors for prolonged weakness include use of vecuronium in female patients who have renal failure, high-dose steroids, and > 2-day duration of relaxant administration and administration of high doses of muscle relaxants.

There appear to be several etiologies to the persistent weakness. The persistent weakness may be related to persistent paralysis. Vecuronium has an active metabolite, 3-desacetyl vecuronium, that persists particularly in female patients with renal failure. Pancuronium and pipecuronium also form these metabolites. Therefore, these drugs should not be administered chronically to patients who are in renal failure.

Patients taking corticosteroids who receive long-term muscle relaxants appear to develop a myopathic syndrome characterized by flaccid paralysis, increased creatine kinase, and myonecrosis; these patients recover after many months. Plasma creatine kinase concentrations appear to increase when the myopathy develops; therefore, serum creatine kinase should be monitored in patients taking corticosteroids who are receiving muscle relaxants. All muscle relaxants have been associated with this syndrome.

A motor neuropathy has been reported after the administration of vecuronium, pancuronium, or atracurium. The neuropathy affects all extremities, is associated with absent tendon reflexes, and can be accompanied by muscle wasting. This syndrome also takes months to resolve. Another syndrome consisting of persistent motor weakness with preservation of sensory sensation has been reported in patients receiving pancuronium, vecuronium, or metocurine. These patients do not have normal neuromuscular transmission, and their symptoms also took months to resolve.

Patients do become tolerant to the effects of the muscle relaxants. The tolerance can develop within 24 to 48 h and appears to be due to upregulation of acetylcholine receptors secondary to chronic denervation. One method to decrease the

incidence of tolerance is to minimize the amount of muscle relaxant given; the drug should be given only for a defined clinical outcome. The only reason to monitor the train-of-four method is to document that complete block is not obtained, as the presence of a train-of-four response does not ensure that persistent weakness will not occur.

*Comparison of Muscle Relaxants*

For rapid tracheal intubations, either succinylcholine or rocuronium (Table 3) should be administered. Succinylcholine only lasts for 5 to 10 min, which can be helpful if there is concern that the patient's trachea cannot be intubated. Succinylcholine has several significant side effects, including bradycardia, junctional arrhythmias, ventricular arrhythmias, masseter spasm, and muscle pains. Rocuronium is the first nondepolarizing muscle relaxant that has a fast onset similar to that of succinylcholine; however, paralysis will persist for up to 90 min; thus, mask ventilation and/or tracheal intubation must be successful.

Vecuronium has active metabolites that have been associated with persistent weakness, particularly in female patients with renal failure. Rocuronium does not have active metabolites. Atracurium and cisatracurium are used because their duration of action is not affected by liver or kidney disease. Cisatracurium's duration of action is as long as, if not longer than, that of rocuronium. All muscle relaxants have been associated with allergic reactions. In fact, muscle relaxants are the leading cause of perioperative anaphylaxis (succinylcholine is associated with 48% of the cases).[34] A recent report of cisatracurium-induced anaphylaxis documented that cardiovascular collapse can be the only sign of the allergic reaction.[34]

## Airway Management

When one needs to secure an airway emergently, there are certain principles to remember: oxygenation even without removal of carbon dioxide can save the patient's life, and the complete inability to oxygenate will cause brain damage within 3 min. Therefore, as long as a needle can be placed in the trachea and oxygen can be given, the patient can be kept alive until a surgical airway can be obtained. Percutaneous kits are available to perform emergency cricothyroidotomies; the operator must be able to complete the procedure in < 3 min, and preferably the procedure should be completed within 1 min.

If a patient is not actively vomiting or otherwise soiling the airway, then mask ventilation should be attempted. Successful mask ventilation can require two or more hands, and an oral and/or nasal airway. Mask ventilation is all that is required if aspiration is not a risk and the operator is not expert at tracheal intubation. The complications of mask ventilation include damage to the eyes, insufflation of the stomach, and possible regurgitation.

Intubation of the trachea can be done via conventional laryngoscopy; this procedure requires practice. A laryngeal mask can be placed at the patient's glottic opening by pushing it into the patient's mouth and down the pharynx; proper placement of the laryngeal mask may require less practice and training than conventional laryngos-

**Table 3.** *Properties of Muscle Relaxants Used in the ICU**

| Drug | Initial Dose† (mg/kg) | Duration‡ (min) | Cost Factor§ | Advantages | Complications |
|---|---|---|---|---|---|
| Pancuronium | 0.07–0.1 | 60–120 | 1 | Inexpensive | Tachycardia; active metabolite |
| Pipecuronium | 0.05–0.07 | 60–120 | 5 | CVS stability | Active metabolite |
| Doxacurium | 0.04–0.05 | 60–120 | 5 | CVS stability | None |
| Vecuronium | 0.1 | 30–45 | 20 | CVS stability | Active metabolite |
| Atracurium | 0.05 | 30–45 | 20 | Reliable recovery | Histamine release; active metabolite |
| Rocuronium | 0.6–1.2 | 30–90 | 20 | Rapid onset | None |
| Cisatracurium | 0.1–0.2 | 30–90 | 10 | Reliable recovery | Slow onset; active metabolite |
| Mivacurium | 0.2 | 10–20 | N/A | Short duration | Histamine release; metabolites |
| Succinylcholine | 1–2 | 5–10 | N/A | Fast onset; fast recovery | Hyperkalemia; dysrhythmia |

* CVS = cardiovascular system; N/A = not recommended for long-term use. † For tracheal intubation.
‡ Time from intubation dose until first train-of-four response might return.
§ Numbers are multiples of the cost of pancuronium, which is ~ $10/d.

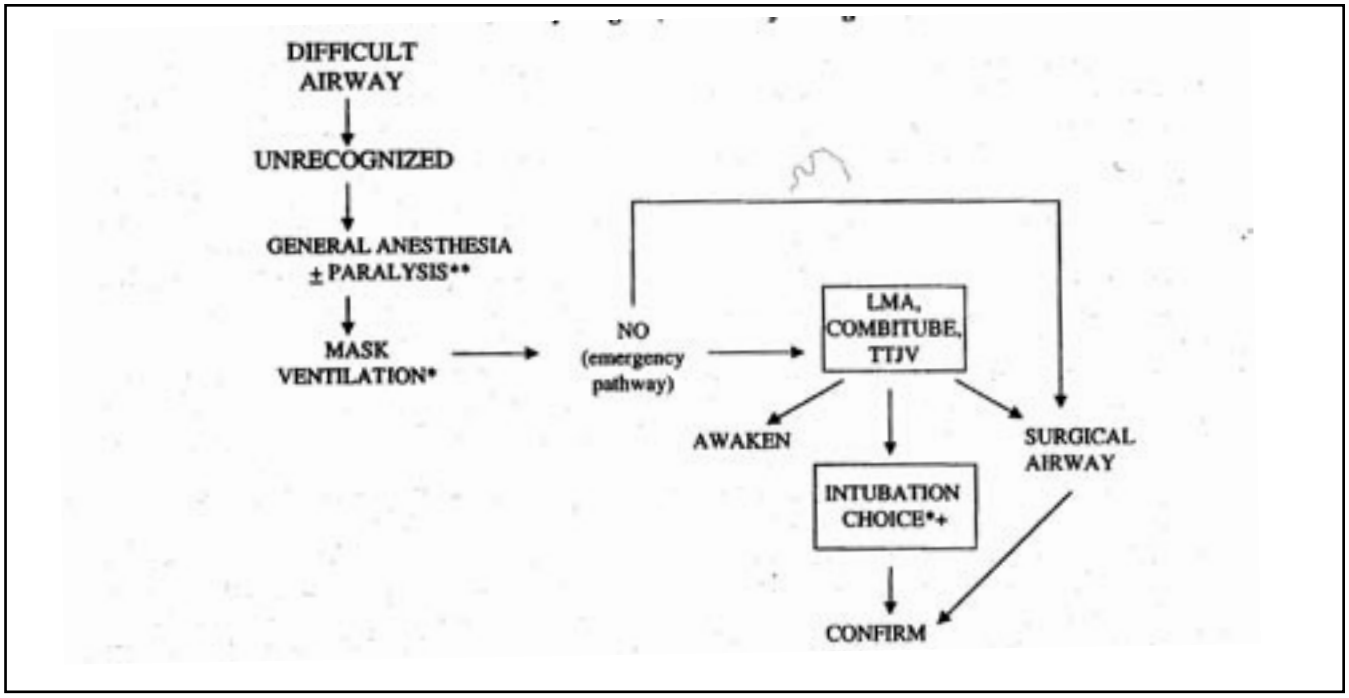


**Figure 1.** Difficult airway algorithm. Reprinted with permission from Benumof.[35]

* Always *consider* calling for help (*eg*, technical, medical, surgical, etc.) when difficulty with mask ventilation and/or tracheal intubation is encountered.

** Consider the need to preserve spontaneous ventilation.

\+ Nonsurgical tracheal intubation choices of laryngoscopy with a rigid laryngoscope blade (many types), blind orotracheal or nasotracheal technique, fiberoptic/stylet technique, retrograde technique, illuminating stylet, rigid bronchoscope, percutaneous dilational tracheal entry. See reference 35 for a complete discussion of these tracheal intubation choices.

copy. The laryngeal mask does not protect against aspiration, but has been utilized in patients whose tracheas cannot be intubated using conventional laryngoscopy. Operators with expertise in tracheal intubation may encounter patients in whom conventional laryngoscopy is unsuccessful. An algorithm is then to be followed; depending on the status of the patient, either the procedure is aborted or a surgical airway is obtained (Fig 1).[35]

Situations in which conventional laryngoscopy may be difficult include restriction of the oral airway, reduced pharyngeal space, noncompliant submandibular tissue, limited atlanto-occipital extension, and partial airway obstruction. Small mouth openings are encountered in patients who have temporomandibular joint disease, scarring near the mouth, congenital and surgical deformities, a large tongue, and diseased teeth. The pharyngeal space can be decreased by edema and by masses. The submandibular tissue can be altered by infection (Ludwig's angina), scarring (as from burns), surgery, radiation, and cancer. Patients who cannot extend their necks include patients in a halo jacket and those with ankylosing spondylitis, cervical disc disease, or cervical spinal injuries. Airway obstruction occurs when epiglottitis, pedunculated tumors and cysts in the airways, large tonsils, mediastinal and subcutaneous emphysema, or edema are present.

## Annotated References/ Suggested Readings

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# Notes