Sedation, Analgesia, and Paralysis in the Intensive Care Unit

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The intensive care unit (ICU) is an extremely stressful environment where anxiety is prevalent, pain frequent, rest difficult, and sleep often impossible. Relief of pain and anxiety is often neglected while efforts focus on immediate life-threatening concerns. A growing awareness of ICU-imposed stress and the increasing popularity of some modes of mechanical ventilation such as extended ratio ventilation have highlighted the need for effective sedation, analgesia, and occasionally, paralysis.

The goal of therapy is to provide adequate analgesia, sedation, and anxiolyis without causing adverse autonomic or cardiopulmonary consequences. Above all, sedation and paralysis must be used for the comfort and well being of the patient—not that of the staff. Akin to the operating room setting, a balanced, multimdrug approach is usually the best way to maximize patient comfort and minimize side effects. On the rare occasions when it is not possible to relieve discomfort, amnesia is desirable. Nonparalyzed patients should be sedate but sufficiently relaxed to communicate their needs to nurses and physicians; sedation to unconsciousness is mandated during paralysis. The art of pain control is difficult at best in this setting, where patient comfort must be balanced against the numerous adverse drug effects. Unfortunately, concerns over safety often cause nurses and physicians to err on the side of insufficient relief of patient discomfort.¹

The understandable reluctance to sedate patients who are not receiving mechanical ventilation for fear of producing respiratory depression often leaves unintubated patients anxious and in pain. In addition to the discomfort itself, unrelieved pain can cause splinting that leads to atelectasis. Pain also discourages activity, promoting deep venous thrombosis and deconditioning. While every effort should be made to maximize patient comfort, excessive sedative or analgesic use can produce numerous complications. Excessive sedation causes hypotension, gastrointestinal hypomotility, and masks the occurrence of intercurrent illnesses. Pharmacologic obtundation also reduces tidal volume, vital capacity, minute ventilation, and inhibits forceful coughing.

Correctable Factors Causing Agitation

Agitation or lack of patient cooperation should not be regarded as a "sedative deficiency." Before sedating or sedating and paralyzing uncomfortable patients, especially those being mechanically ventilated, it is critical that correctable problems be excluded. Endotracheal tube patency and position should be confirmed, and ventilator set-up and connections should be double checked. Hypoxemia, pneumothorax, and distention of the stomach and bladder should be excluded. Shortly after intubation, patients often have difficulty interfacing with the ventilator and comfort may be enhanced by varying ventilatory mode, tidal volume, flow rate, and trigger sensitivity. The administration of 5 to 10 ml of 2 percent lidocaine into the endotracheal tube after intubation can reduce tracheal irritation and patient discomfort early after intubation.

Choosing Pharmacologic Agents

The choice of a sedative or paralytic drug, dosage, and route of administration should be made rationally based upon pharmacologic properties of the drug and individual patient requirements. Three common problems occur with the use of sedative, analgesic, and paralytic drugs in the ICU. Probably the most common error is inadequate use of analgesics, particularly administration of insufficient doses of analgesics on too infrequent a schedule. The second most common problem is the use of ultra-short-acting agents when long-term (days) sedation, analgesia, or paralysis is the goal. Use of short-acting agents theoretically offers the flexibility of rapid interruption of drug effect, but rapid reversal is rarely necessary in the ICU, and undersedation is often the result of using short-acting drugs. When drug effects must be reversed, naloxone promptly interrupts narcotic effects, and flumazenil can counteract benzodiazepine effects. The use of short-acting drugs for long-term indications is also costly and even short-acting compounds and their metabolites can accumulate in the critically ill when used for hours or days, negating their "short-acting" advantages. The third and unforgivable error is paralyzing awake patients. This practice is never acceptable and must be avoided at all cost.

Analgesics

Narcotics

Narcotics are the mainstay of ICU analgesia. There is a vast experience with these potent pain relievers, and generally, the actions of these drugs are predictable and rapidly reversible. Operating room experience has taught that the opioids are excellent analgesics but poor amnestic agents, and use of narcotics alone results in an unacceptably high incidence of recall in paralyzed patients. When customary doses are used alone, narcotics cause few hemodynamic or respiratory effects. Although low narcotic doses are sufficient for analgesia, large doses (up to ten times the usual analgesic dose) may be necessary to produce surgical grade anesthesia, and at these "anesthetic" doses, narcotics are more likely to produce adverse effects. The addition of neuromuscular blockers, barbiturates, benzodiazepines, or phenothiazines is more likely to result in hypotension. Opioid-induced hypotension is often a combination of direct vasodilation, vagally mediated bradycardia, and histamine release. These complications can be minimized by using the lowest effective...
narcotic dose, slow rates of administration, and assuring that an adequate circulating intravascular volume is present before dosing. The histamine releasing potential of narcotics is minimal unless large intravenous doses are given rapidly (meperidine and morphine are probably the most potent histamine releasers). Histamine effects can be prevented by pretreatment with H1 and H2 blockers.

Respiratory depression is a feature common to all narcotics. Blunted hypercapnic and hypoxic drives result in a reduced minute ventilation. On occasion, the respiratory depressant effects of narcotics may be beneficial in some dyspneic patients by reducing the senses of shortness of breath.20,22,24

Unfortunately, most narcotics and their metabolites accumulate in patients receiving prolonged treatment, especially those with hepatic or renal failure or both.25 All narcotics eventually depend upon hepatic biotransformation before renal excretion of the transformed products. Commonly used synthetic opiates (fentanyl, sufentanil, alfentanil) are highly lipid-soluble. Therefore, the action of isolated doses of these drugs is not terminated by drug metabolism but by redistribution of the drug out of brain to other body compartments (predominately skeletal muscle). With long-term use, however, patients become "saturated" with the drug requiring, metabolism for termination of drug effect.

Gastrointestinal hypomotility is common during narcotic use and often complicates efforts at enteral feeding. Clinically significant biliary tract spasm is a rare complication of opiate use. The combination of direct central nervous system effects and reduced gut motility can cause nausea, vomiting, and constipation.

The reluctance to use narcotics for long-term pain relief because of concerns of dependence and addiction are largely unfounded. Addiction rarely develops in medically ill patients without a previous history of substance dependence. For pharmacologically paralyzed patients, sedation and analgesia are mandatory, making the question of dependence moot.

Epidural narcotics and patient-controlled analgesic infusions have been significant advances in pain control.30-34 Patient-controlled analgesia usually provides better pain relief while using a lower total narcotic dose and minimizing the risk of excessive sedation.34 Selective use of catheter-delivered intrapleural topical anesthesia (bupivacaine or lidocaine) is also a promising therapy to reduce narcotic requirements in postoperative or trauma patients.33

The narcotic antagonist, naloxone, promptly reverses the effects of excessive narcotic sedation. Intravenous doses of 0.4 to 2 mg are usually sufficient for at least transient narcotic reversal. Naloxone's duration of action is not as long as many commonly used narcotics, necessitating close observation and occasionally repeated naloxone administration to prevent recurrence of sedation.

Morphine is an inexpensive drug with a relatively rapid onset of action and 1 to 3 h half-life. Morphine's lower lipid solubility than the synthetic opiates produces a slower onset of action. The most common mistake made in the use of morphine is to administer too little too infrequently. Based upon morphine's half-life, the drug must be given every 2 to 3 h. Intermittent doses of 5 to 10 mg intramuscularly or intravenously, or 1 to 3 mg/h (0.03 to 0.15 ml/kg/h) by constant intravenous infusion are usually adequate for relief of moderate pain in the average sized adult. In the ICU, the intravenous administration rate of morphine should probably not exceed 10 mg/min to minimize the risk of hypotension. Although morphine is an excellent analgesic, high doses or combined use with a benzodiazepeine is required to produce unconsciousness mandated by the use of paralytic agents. Low doses of morphine rarely produce hypotension; however, high morphine doses or combined use with benzodiazepeines is much more likely to result in significant blood pressure reductions.35-38 A small fraction of morphine is directly excreted by the kidney without metabolism, but the majority of a dose of morphine is hepatically metabolized before renal excretion of the metabolites.39 Therefore, the action of morphine is prolonged in renal and hepatic failure.

Meperidine offers no substantial advantage over morphine. Meperidine's atropine-like structure and vagolytic and histamine-releasing tendencies often cause tachycardia and hypotension. Meperidine's major metabolite, normeperidine, is active, accumulates in patients with renal failure, and has been associated with seizure activity when present in high concentrations. Meperidine is also a greater myocardial depressant than other narcotics.

Fentanyl is a very potent (50 to 100 × the potency of morphine), highly lipid soluble, synthetic narcotic with a very rapid onset and brief duration of action. Initial analgesic doses of 0.5 to 10 µg/kg can be titrated upward as necessary to provide pain relief. Anesthetic doses are tenfold higher than analgesic doses.36 Fentanyl's chief advantage is its minimal hemodynamic effect for a given level of analgesia.31,32,38 With initial use, fentanyl's effects are brief because the drug's action is terminated by redistribution down the concentration gradient out of the brain toward less lipophilic compartments.36,37 With repeated doses or continuous infusion, large stores of fentanyl accumulate that must be metabolized to terminate the drug's action. Because of the accumulation of fentanyl in tissue, its effective half-life may exceed that of morphine with prolonged administration.37 Fentanyl and its metabolites accumulate to an even greater degree in the presence of hepatic and renal dysfunction.

Profound chest wall rigidity may develop after any opiate administration, however, fentanyl is the most common offender. Chest wall rigidity may be so severe that spontaneous or assisted ventilation is impossible unless neuromuscular paralysis intubation and mechanical ventilation are undertaken. Fortunately, this side-effect is rare and is seen most commonly when large intravenous doses are given rapidly to elderly patients. High doses of fentanyl may also cause seizures. The biggest disadvantage of fentanyl is its high cost relative to morphine.

The recent availability of a transdermal formulation offers another potentially useful route to delivery up to 50 to 100 µg of fentanyl per hour. Unfortunately, the skin slows diffusion of fentanyl into the circulation producing a long lag time (hours) between patch application and effective analgesia that usually requires interim parenteral analgesic doses. Removal of the patch does not rapidly terminate the drug's effect because the skin also serves as a fentanyl reservoir. The total dose of fentanyl required for analgesia is substantially lower when using transdermal delivery because hepatic first pass extraction is avoided. A very high
incidence of nausea has been reported with transdermal dosing.

Alfentanil is a synthetic opiate more potent than morphine but less so than fentanyl. Because alfentanil is also a nonionized, lipid-soluble drug with a small volume of distribution, its onset of action is rapid and its duration brief. Consciousness returns rapidly after administration of anesthetic range doses of alfentanil, making this drug useful for brief painful procedures. Absence of active metabolites results in minimal drug accumulation, however, alfentanil’s effects are modestly prolonged by hepatic failure.\(^6\)\(^7\) Sufentanil is 400 to 1,000 times as potent as morphine but in the intensive care unit does not offer any significant advantages over fentanyl. Vagally mediated bradycardia and potent reductions in blood pressure are other disadvantages of this drug.

**Nonsteroidal Anti-inflammatory Agents**

Nonsteroidal anti-inflammatory agents (NSAIDs) are often overlooked in the ICU because of their antiplatelet activity and reputation to cause bleeding and renal insufficiency. The NSAIDs are potent antipyretic analogues especially effective for musculoskeletal pain. These simple inexpensive compounds (eg, aspirin, and ibuprofen) often suffice for pain relief alone but are also synergistic with narcotics. A major drawback to the use of NSAIDs is that most of these agents are only available in oral formulations. Only one nonsteroidal compound, ketorolac, is currently available in parenteral form, but ketorolac does not offer unique properties to justify its substantial cost when compared to other analogues. The antiplatelet activity of these drugs is occasionally advantageous in patients with coronary or cerebral ischemia. The cyclooxygenase inhibiting activity of most NSAIDs makes them a poor choice for patients with baseline impairment of renal function, coagulation disorders, or active bleeding.

**Sedative-Anxiolytic Agents**

**Benzodiazepines**

Benzodiazepines are sedative-anxiolytics that promote amnesia. Of the three drugs most commonly used in the ICU, lorazepam\(^44\) is the most potent amnestic agent followed by midazolam\(^4\) and diazepam.\(^44\) It is difficult to separate pain from anxiety as anxiousness heightens the awareness of pain. Therefore, despite absence of direct angesic properties, benzodiazepines can lower analgesic (especially narcotic) requirements. When narcotics are the primary analgesic, the addition of a benzodiazepine significantly reduces recall of unpleasant events and potentiates the narcotics analgesic properties.\(^4\)\(^5\) A wide safety margin exists for most of the benzodiazepines with midazolam having the narrowest therapeutic range. Benzodiazepines possess advantageous nonsedative effects, most notably anticonvulsant\(^4\)\(^5\) and muscle relaxant properties but are also useful in the prophylaxis and treatment of alcohol withdrawal syndrome. Although not as potent as barbiturates, benzodiazepines do reduce cerebral oxygen consumption, intracranial pressure, and cerebral blood flow.

Benzodiazepines have minimal cardiovascular effects unless used in large doses or in combination with narcotics or neuromuscular blocking drugs.\(^6\) Tachycardia and minimal reductions in mean arterial pressure are predominately the result of vasodilation. As with narcotics, benzodiazepine-induced blood pressure changes are most common in patients with underlying cardiac disease, those using beta-blockers, and in the elderly and volume-depleted. All benzodiazepines exhibit mild dose-dependent reductions in minute ventilation but on rare occasion cause apnea. Apnea is most common following rapid administration of large intravenous doses of midazolam or diazepam in chronically ill elderly patients and patients receiving concomitant narcotics.

All benzodiazepines share similar disadvantages. These highly lipid-soluble drugs accumulate in fat after repeated or prolonged use, resulting in delayed recovery. Avid protein binding also predisposes hypoproteinemic patients to high concentrations of free (active) drug, and frequent interactions with other protein-bound drugs are common. Benzodiazepines require hepatic metabolism and/or excretion, therefore liver disease prolongs the action of these drugs (oxazepam may be the exception). Psychological and physiological dependence has been reported with each of the benzodiazepines, and withdrawal syndromes have been seen after prolonged use of high doses of benzodiazepines (especially lorazepam).\(^6\)

Diazepam is a long-acting sedative-amnestic-anxiolytic available in oral or parenteral forms. In the ICU, diazepam’s use should probably be confined to the intravenous route because of its unpredictable absorption from muscle. Unfortunately, phlebitis is prone to develop after repeated intravenous injections (midazolam shares this side effect to a lesser degree). Diazepam’s high lipid solubility results in a rapid onset of action, and its large volume of distribution and slow hepatic removal produce a long half-life. Prolonged actions are advantageous when attempting to sedate patients for hours to days but for short-term sedation (minutes to an hour), midazolam may be preferable. Intravenous doses of 2 to 5 mg (0.04 to 0.2 mg/kg) given every 5 to 10 min are reasonable to initiate therapy. Diazepam is inexpensive and when combined with a narcotic provides a good balance of analgesia, sedation, and amnesia.\(^\)\(^6\)\(^9\)

Midazolam is a potent benzodiazepine with a short duration of action. The lipid solubility of midazolam and its ability to cross the blood brain barrier produce a rapid onset of action (2 to 3 min) in most patients.\(^6\)\(^8\) A steeper dose response curve than other benzodiazepines suggests that initially, lower doses of midazolam and closer observation are indicated to avoid inadvertent excessive sedation. Starting doses of 0.5 to 1.0 mg (0.01 to 0.1 mg/kg) given intravenously at 5- to 15-min intervals are reasonable. Isolated doses of midazolam are eliminated by hepatic extraction and metabolism. The effective half-life of midazolam is much longer following prolonged intravenous infusion as the drug accumulates in fat.

When combined with topical or local anesthetics, midazolam is nearly an ideal agent to provide sedation and analgesia during brief ICU procedures such as bronchoscopy, central line placement, or bone marrow aspiration. Compared to diazepam, midazolam is expensive, usually making the cost of long-term intravenous sedation prohibitive. Midazolam has gained the reputation of producing an extraordinary degree of respiratory depression compared to
other benzodiazepines, although there is little evidence to support this claim. Whenever parenteral sedatives are used, trained personnel and appropriate equipment should be available to deal with potential respiratory depression.

Lorazepam has a slower onset and longer duration of action than midazolam or diazepam. The high affinity of lorazepam for cellular receptors produces its long duration of action. Because of its minimal cardiovascular effects and potent amnestic properties, lorazepam represents a good sedative choice for performing “awake” endotracheal intubation and other brief procedures. Initial intravenous doses of 1.0 mg (0.03 to 0.04 mg/kg) may be repeated every few minutes until the desired degree of sedation is achieved. Other advantages are lorazepam's predictable intramuscular absorption and oral availability. Chlordiazepoxide is limited to oral use and is most popular for the prophylaxis of delirium tremens.

The competitive benzodiazepine receptor antagonist, flumazenil, can rapidly reverse the respiratory and central depressant effects of benzodiazepines in up to 80 percent of patients. Flumazenil has no effect on ethanol-, barbiturate-, narcotic-, or tricyclic antidepressant-induced central nervous system depression. Flumazenil is rapidly cleared by the liver, making its effective half-life substantially shorter than that of most benzodiazepines. Akin to the naxone-opioid story, up to 10 percent of patients given flumazenil for benzodiazepine overdose relapse into a sedated state making careful observation essential. High doses of benzodiazepines, long duration of therapy, and concomitant narcotic use lowers the success rate of flumazenil. Intermittent doses of 0.2 mg at 1-min intervals (up to 1 mg total) are usually effective. Total doses should be limited to 3 mg/h. Flumazenil often causes nausea and vomiting and should be used cautiously since it may precipitate withdrawal symptoms (agitation and seizures) in chronic benzodiazepine users. Flumazenil is rarely needed in the ICU and should be regarded as an adjunct to airway protection and ventilation in the management of benzodiazepine overdose. Flumazenil is also expensive.

Barbiturates

Barbiturates sedate by depressing reticular activating system function. The more lipid-soluble barbiturates (eg, thiopental, thiamyl, and methohexital) have rapid onset of action because the luxuriously perfused lipophilic brain becomes rapidly saturated with drug. Almost as rapidly after isolated doses, redistribution out of the brain is responsible for termination of the drug’s effects. The less lipid-soluble barbiturates, (eg, phenobarbital) have a slower onset of action and longer recovery time. Once widely used, barbiturates now have limited application in the ICU because of numerous adverse reactions. Barbiturates are potent cardiovascular depressants, reducing vascular tone and cardiac output and increasing heart rate. Cardiovascular depression frequently results in life-threatening hypotension when large bolus doses or barbiturates are used. Hypotensive effects are most prominent in the elderly, the volume depleted, and in patients with underlying cardiovascular disease. The nearly immediate onset of action of some ultrashort-acting barbiturates makes them useful for “rapid sequence intubation” of carefully selected patients.

Barbiturates decrease the ventilatory response to hypoxia and hypercapnia and reduce tidal volume and respiratory rate. Barbiturates do not produce muscle relaxation nor relieve pain and may paradoxically increase pain intensity. Barbiturates also rapidly induce tolerance and dependence and because most members of this class of drug are highly protein-bound and hepatically metabolized, they are subject to numerous drug interactions. Concurrent administration of other protein-bound drugs (eg, phenytoin) displaces bound barbiturates thereby potentiating their effects. Malnutrition, nephrosis, and cirrhosis potentiate barbiturate actions by reducing serum proteins, hence increasing the free fraction of drug in plasma. After hepatic oxidation or glucuronidation to water soluble compounds, barbiturate metabolites are renally excreted.

Barbiturates are cerebral vasococontractors that reduce intracranial pressure to a greater extent than mean arterial pressure. Reductions in cerebral oxygen consumption of up to 50 percent add to the brain-preserving effects of these agents. Aggressive fluid replacement and vasopressor drug use is almost always required to preserve blood pressure among patients subjected to barbiturate coma.

In the ICU, barbiturate use should probably be limited to the following: (1) anticonvulsant therapy; (2) induction of coma for cerebral preservation; (3) rapid sequence induction.

Phenothiazines

Phenothiazines are sedative antiemetics which may be used to potentiate the analgesic and sedative effects of narcotics. With the exception of antiemetic effects, the combination of phenothiazines and narcotics offers no substantial advantage over the more commonly used benzodiazepine-narcotic combination. Phenothiazines have the disadvantage of inducing dystonic (extrapyramidal) reactions in a small minority of patients.

Neuromuscular Paralytic Agents

A detailed account of neuromuscular physiology is beyond the scope of this paper; however, recent excellent reviews are available on this topic.

Mechanism of Action of Neuromuscular Blockers

Normally, neural impulses reach the neuromuscular junction causing calcium-mediated release of acetylcholine into the junctional space. Acetylcholine then binds to specific receptors on the muscle causing a sodium-potassium flux or depolarization. Through a combination of acetylcholine reuptake and local degradation by “true or specific” acetylcholinesterase, muscle repolarization, and hence, the opportunity for repeated contraction is rapidly restored. A second nonspecific plasma enzyme, pseudocholinesterase, metabolizes acetylcholine and acetylcholine-like molecules. Neuromuscular blocking drugs act by either blocking acetylcholine receptors without activating them, or by actively competing with acetylcholine for receptors at the neuromuscular junction known as nondepolarizing or depolarizing agents respectively.

Depolarizing blockers stereoechemically resemble acetylcholine and act by mimicking the normal depolarizing action of acetylcholine at the neuromuscular junction. Accumulation of depolarizing blockers in large concentrations at the
neuromuscular junction by administration of relative overdoses of drugs causes a depolarizing Na⁺-K⁺ flux across the muscle. Because depolarizing blockers are not metabolized in the neuromuscular junction by acetylcholinesterase, persistent depolarization occurs preventing additional muscle contractions until the motor endplate is repolarized. Repolarization cannot occur until the depolarizing neuromuscular blocker diffuses out of the synaptic cleft. As depolarizing drugs leave the neuromuscular junction, they are metabolized by plasma or pseudocholinesterase. Because depolarizing neuromuscular blockers mimic acetylcholine, they cause muscle fasciculations.

Nondepolarizing blockers act by passively occupying acetylcholine binding sites or sodium-potassium ion channels thereby competitively blocking acetylcholine’s depolarizing action.

Indications

Neuromuscular paralyzing drugs are now almost routinely used to produce surgical grade muscle relaxation in the operating room and have recently become commonly used in the ICU. 36-38 There is currently great controversy surrounding the use of paralytic agents with many clinicians contending that there is no role for these drugs in appropriately sedated patients. Experience with these inherently dangerous agents must come from carefully supervised use and cannot be safely learned by reading about them alone. In the ICU, paralytic agents are rarely needed when adequate sedation is employed. Paralysis must never be used without sedation adequate to produce unconsciousness and should be used for the shortest possible period of time.

Four major indications exist for the use of neuromuscular blockers in the ICU. 36-38 Muscle relaxation to facilitate endotracheal intubation is probably the most common indication, but extreme caution must be used. As a general rule, the more likely one believes paralysis is needed to accomplish intubation, the less likely it is that paralytic drugs should be used. For example, use of paralytics in obese patients, or those with spinal instability or head or neck trauma who are inherently difficult to intubate without paralysis can result in complete upper airway obstruction. When using paralytic drugs for intubation, provisions to surgically secure the airway must always be made.

Rarely, neuromuscular blockers can aid patients with medical conditions like tetanus in which muscular contraction is itself harmful. 39 Likewise, patients suffering cardiovascular or metabolic instability because of intractable convulsive activity may transiently benefit from neuromuscular blockade. Paralytic agents do nothing, however, to terminate chaotic cerebral electrical activity or to protect the brain of seizing patients and obscure accurate clinical assessment of seizure activity. Therefore, it is imperative that patients having seizures who are paralyzed have continuous electroencephalographic monitoring to exclude the possibility of “nonconvulsive” status epilepticus. It is rare that a combination of benzodiazepines, barbiturates, and phenytoin is unable to terminate seizure activity without the use of paralytic agents. Paralysis can also be used to prevent activity-induced increases in intracranial pressure in head-injured patients.

Neuromuscular blockers are occasionally useful to facilitate mechanical ventilation. 36, 44-45 Modes of ventilation with prolonged inspiratory times (inverse or extended ratio, airway pressure release, and volume control ventilation) are sometimes actively opposed by patients. 46, 47 The practice of permissive hypercapnia is also uncomfortable for many patients. Again, in most cases, sedation alone is usually sufficient to provide comfort, facilitate ventilation, and lower peak airway pressures. High levels of positive end-expiratory pressure (PEEP) are uncomfortable, and in response, patients may actively contract expiratory muscles to oppose the volume-recruiting effects of PEEP. In most such patients, sedation alone is sufficient to permit PEEP-induced volume recruitment. Theoretically, neuromuscular paralysis can also be used to reduce oxygen consumption in patients with very marginal oxygenation, but there is little evidence that paralysis is superior to deep sedation and mechanical ventilation in such patients. 48, 49

Cautions

Paralysis has many dangers. Most problematic is the potential for paralysis of inadequately sedated patients. The terror of awake paralysis is unthinkable. 17, 18 However, even trained observers may have difficulty recognizing inadequate sedation. 50, 51 Hypertension, tachycardia, diaphoresis, and lacrimation are the only possible physiologic responses of an unsedated paralyzed patient. Deeply sedated and paralyzed patients are helpless: unrecognized extubation, ventilator malfunction, or arterial line disconnection can be fatal. Paralyzed patients are also prone to develop decubitus ulcers and nerve compression syndromes unless properly padded and frequently repositioned. Corneal erosions may also develop unless meticulous eye care is maintained. By preventing normal activity, neuromuscular blockers predispose patients to the formation of deep venous thrombi and muscle atrophy.

Paralytic agents also obscure the diagnosis of intercurrent conditions by preventing patient communication and by concealing physical symptoms. For example, paralytic drugs blunt the development of fever, and intra-abdominal disasters such as cholecystitis or appendicitis may go undetected because abdominal rigidity does not develop. Paralysis also obscures the diagnosis of angina, hypoglycemia, seizures, and central nervous system dysfunction.

Essentially all data on the duration of paralysis are derived from use of these drugs in the surgical setting. Such information very likely does not apply to prolonged paralysis in the ICU where the number of drug doses, renal and hepatic function, and the generation of active metabolites differs from the operating room setting. Rarely, prolonged paralysis or malignant hyperthermia may be encountered, and these will be addressed separately. Recently, numerous reports of prolonged muscle weakness after long-term administration of the corticosteroid-derived neuromuscular blockers has raised concerns, but a cause and effect relationship between paralytic agents and prolonged weakness has not yet been firmly established. 71, 74 The potency and duration of paralytic agents are affected by concomitant medications and medical conditions: burns, 75-79 edema, and use of methylxanthines, 80-84 phenytoin, 80-84 lithium, 80 corticosteroids, 80 and carbamazepine 77 all reduce or antagonize the effectiveness of paralytics. Edema-
atous states produce complex problems. By increasing the volume of distribution of neuromuscular blockers, edema makes initial paralysis more difficult to achieve. However, the large reservoir of drug that accumulates in edema fluid may lead to a prolonged recovery phase. Recent reports indicate that higher doses of paralytic agents may be required after prolonged use in the ICU.96

Respiratory acidosis and metabolic alkalosis,66-91 hypokalemia, hyperkalemia, hypocalcemia, and hypermagnesemia all potentiate the neuromuscular blockade.92-96 Patients with "deinnervation hypersensitivity," caused by neuromuscular diseases such as myasthenia gravis and Guillain-Barre syndrome, are particularly sensitive to depolarizing paralytic agents.92-96 Use of beta blockers, calcium channel blockers, cyclosporine, aminoglycosides, tetracycline, clindamycin, and the antiarrhythmics, procainamide and quinidine, also potentiate neuromuscular blockers.97-100 The activity of paralytic agents will also be prolonged in hypothermic patients.

Histamine release is a feature of four commonly used nondepolarizing paralytics being most common with tubocurarine, followed by metocurine, atracurium, and mivacurium.100-104 Although histamine release can cause hypotension and bronchospasm, histamine's effects can be minimized by slow drug administration and by pretreatment with H1 and H2 blockers.

**Depolarizing Neuromuscular Blockers**

Currently, succinylcholine is the only depolarizing agent in use. Succinylcholine has a very rapid onset of action (seconds) because of its low lipid solubility and a brief duration (<10 min) because of rapid degradation by plasma cholinesterase. Most of an administered bolus dose of succinylcholine never reaches the neuromuscular junction as it is rapidly degraded in the blood by pseudocholinesterase. The depolarization induced by succinylcholine causes fasciculations in skeletal muscle but does not effect smooth muscle action.107 Rapid intravenous injection of succinylcholine (1 mg/kg) is preferred by many for intubation because of its rapid onset, brief duration, and absence of smooth muscle action. Hypothermia decreases the metabolism of succinylcholine resulting in prolonged paralysis.

Succinylcholine is not without side effects. Most adult patients develop a sympathomimetic response, however, histamine release and resultant hypotension may occur especially when succinylcholine is combined with barbiturates. Succinylcholine is not ideally suited for repeated injection nor for prolonged constant infusion because when given in this manner, it causes vagal stimulation and bradycardia, an effect more prominent in children. If more than one dose of succinylcholine is ever necessary, atropine should be given intravenously prior to the second dose.

Depolarization causes muscle contraction, and hence, the release of potassium from muscles. Plasma potassium increases of 0.5 to 1 mEq/L are common and in patients with peritonitis, burns, multiple trauma, or rhabdomyolysis, hyperkalemia may be life threatening.106-111 Patients with increased numbers of acetylcholine receptors secondary to the deinnervation hypersensitivity of neuromuscular disease are especially prone to this complication.

Vomiting secondary to abdominal muscle contraction and postparalysis muscle pain commonly result from succinylcholine use but may be attenuated by pretreating with a subparalyzing (10 to 15 percent of the usual) dose of a nondepolarizing blocker.112 Succinylcholine-induced stimulation of extraocular muscles may raise intraocular pressure. Prolonged paralysis in patients with pseudocholinesterase deficiency and malignant hyperthermia113-114 rarely occurs with the use of succinylcholine and will be discussed separately. No agent is capable of pharmacologic reversal of neuromuscular blockade produced by depolarizing drugs, and the administration of cholinesterase inhibitors may paradoxically prolong succinylcholine-induced paralysis.

**Nondepolarizing Neuromuscular Blockers**

Nondepolarizing neuromuscular blockers act by preventing acetylcholine's depolarizing action at its receptor. Nondepolarizing neuromuscular blockers may be conveniently grouped by several basic properties: duration of action, route of metabolism and excretion, propensity to release histamine, and the tendency to cause vagal blockade (Table 1). Many of the nondepolarizing neuromuscular blockers (pancuronium, vecuronium, pipercuronium) chemically resemble or are derived from corticosteroids. As with most classes of drugs, it is best to become familiar with the characteristics of a small number of drugs to avoid unknown effects. All nondepolarizing neuromuscular blockers are capable of producing paralysis of a longer duration (20 to 90 min) than that of succinylcholine. Each nondepolarizing neuromuscular blocker has a slower onset of action than succinylcholine but only by a matter of seconds.

**Table 1**—**Nondepolarizing Neuromuscular Blockers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset, Min</th>
<th>Duration</th>
<th>Histamine Release</th>
<th>Vagal Blockade</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mivacurium</td>
<td>1-2</td>
<td>Short</td>
<td>+</td>
<td>0</td>
<td>Extensive</td>
<td>Minimal</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>1-2</td>
<td>Intermediate</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Hepatic&gt;renal</td>
</tr>
<tr>
<td>Atracurium</td>
<td>1-2</td>
<td>Intermediate</td>
<td>+</td>
<td>0</td>
<td>Mostly nonenzymatic</td>
<td>Minimal</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>2-3</td>
<td>Long</td>
<td>0</td>
<td>0</td>
<td>Minimal</td>
<td>Renal</td>
</tr>
<tr>
<td>Metocurine*</td>
<td>1-2</td>
<td>Long</td>
<td>+ +</td>
<td>0</td>
<td>Minimal</td>
<td>Renal</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>1-2</td>
<td>Long</td>
<td>0 to +</td>
<td>+</td>
<td>Moderate</td>
<td>Renal&gt;hepatic</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>1-2</td>
<td>Long</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Renal</td>
</tr>
<tr>
<td>Tubocurarine*</td>
<td>1-2</td>
<td>Long</td>
<td>+ + +</td>
<td>0</td>
<td>Minimal</td>
<td>Renal&gt;hepatic</td>
</tr>
<tr>
<td>Gallamine†</td>
<td>Long</td>
<td>0 to +</td>
<td>+</td>
<td>Minimal</td>
<td>Renal</td>
<td></td>
</tr>
</tbody>
</table>

* Uncommonly used because of histamine-releasing potential and autonomic blockade.
† Rarely used because of potent vagolytic actions.
The duration of action ranges from 20 to 30 min for mivacurium to often more than an hour for pipecuronium, pancuronium, doxacurium,\(^1\) metocurine, and tubocurarine. Pancuronium is the least expensive of the long-acting nondepolarizing agents. Unfortunately, pancuronium, tubocurarine, metocurine, doxacurium, and pipecuronium are renally excreted after greater or lesser metabolism making them poor choices in patients with renal insufficiency. Pancuronium also undergoes substantial (~20 percent) hepatic metabolism yielding active metabolites, therefore hepatic failure precludes its safe use. pancuronium has modest histamine-releasing properties and has vagolytic effects that may cause tachycardia and hypotension.

Vecuronium is widely used because of its intermediate duration of action and paucity of cardiovascular effects when administered in usual doses.\(^2\) Vecuronium is in large part (~80 percent) removed by hepatic metabolism and biliary excretion and therefore is a poor choice in patients with liver disease. Although not directly cleared by the kidney, vecuronium has two metabolites that are cleared by the kidney. Reports of prolonged paralysis after vecuronium administration in patients with renal insufficiency make the wisdom of vecuronium use in renal failure suspect.

Atracurium and mivacurium have potential advantages in patients with hepatic or renal failure because both drugs undergo extensive plasma degradation. Mivacurium is broken down by plasma pseudocholinesterase, and atracurium undergoes esterase degradation and spontaneous breakdown called "Hoffman elimination." Atracurium is probably the single best paralytic agent for patients with renal failure. Although the clinical importance is uncertain, atracurium's metabolism yields laudanosine, an excitatory tertiary amine, that causes seizures when high doses are given to animals. The breakdown of atracurium is delayed by severe hypothermia and by acidosis, but unlike most other neuromuscular blockers, its termination is not impaired by advanced age. Metocurine and gallamine are the least favorable choice for patients with kidney failure because of their extensive renal metabolism. With isolated hepatic failure, the total renal clearance associated with gallamine may make it seem like an ideal drug, but gallamine's potent vagolytic effects are usually limiting. (Tubocurarine, doxacurium, pancuronium, vecuronium, and pipecuronium are all also, at least in part, renally excreted.)

General recommendations can be made for nondepolarizing neuromuscular blocker use in certain patient groups. Patients with unstable hemodynamic status are least likely to have adverse cardiovascular effects from atracurium or vecuronium.\(^3\) Patients with normal hepatic and renal function who require paralysis for more than 1 h can have this accomplished most economically with pancuronium, provided vagal blockade and resultant tachycardia is not detrimental. In patients with hepatic and/or renal failure, atracurium and mivacurium offer the advantage of plasma metabolism. Atracurium's longer duration of action makes it preferable for patients requiring several hours of paralysis. Since they require intact renal function and are potent histamine releasers, tubocurarine and metocurine do not appear to have any niche in ICU patients. Likewise, in the ICU setting, doxacurium, pipecuronium, and vecuronium do not appear to offer any substantial advantage over pancuronium with respect to duration, side effects, elimination profile, or cost.

Because of its rapid onset of action, succinylcholine has traditionally been used to minimize the risk of aspiration during "rapid sequence induction," but nondepolarizing neuromuscular blockers may be used as well. The onset of action of nondepolarizing neuromuscular blockers is hastened by administration of large doses or subparalytic "priming doses" given several minutes before a large paralytic dose. Large doses speed the onset of paralysis but also exaggerate side effects and the duration of paralysis. Vecuronium and mivacurium represent good choices of nondepolarizing neuromuscular blockers for rapid sequence intubation because even large doses have minimal side effects, both drugs exhibit a priming effect, and both have an intermediate duration of paralysis.

Complications of Paralytic Agents

Prolonged Paralysis: Pseudocholinesterase, also known as plasma cholinesterase, is a plasma enzyme that metabolizes acetylcholine and succinylcholine. Pseudocholinesterase normally metabolizes the vast majority of a succinylcholine dose long before it has an opportunity to reach the neuromuscular junction. Genetic and acquired reductions in levels of this enzyme increase the duration of succinylcholine-induced paralysis. Between 1 and 5 percent of patients are heterozygous for plasma cholinesterase resulting in an extension of the duration of succinylcholine-induced paralysis by only several minutes in most cases. These will be tense minutes indeed if intubation cannot be accomplished. Approximately 1 out of 2,500 to 3,000 persons has a homozygous deficiency for pseudocholinesterase, extending the duration of the paralysis of succinylcholine from minutes to 6 to 8 h.

Since the goal of therapy in the ICU is usually to produce paralysis lasting hours (unlike the goal in the surgical suite), prolongation of succinylcholine-induced paralysis is usually of little consequence unless intubation cannot be accomplished. Unfortunately, there are no certain clinical clues to pseudocholinesterase deficiency short of a clear history of a prior adverse occurrence. In general though, plasma cholinesterase levels are decreased in liver disease, renal failure, advanced age, pregnancy, marked anemia, and organophosphate toxicity. In such patients, neuromuscular paralysis must be used with caution if at all.

Virtually none of the nondepolarizing blockers is destroyed by acetyl- or plasma cholinesterase. Instead, their effects are terminated by hepatic metabolism and/or renal excretion. The exception to this rule is mivacurium which does undergo some destruction by pseudocholinesterase. If paralysis is mandatory in a critically ill patient with suspected pseudocholinesterase deficiency, atracurium is a good choice because it does not require plasma cholinesterase, nor hepatic or renal metabolism for termination of drug effect.

Malignant Hyperthermia: Malignant hyperthermia is a rare genetic disorder that can be precipitated by use of neuromuscular blocking agents usually in combination with an inhalation anesthetic. The mechanism of malignant hyperthermia is unknown but involves abnormal cellular calcium metabolism. Clinical characteristics include the
rapid development of muscular rigidity and high fever. Huge increases in metabolic rate result in profound metabolic acidosis and massive CO₂ production and O₂ consumption. Because of metabolic derangements and cardiac ischemia, ventricular arrhythmias are common. Untreated, malignant hyperthermia is often deadly. Treatment consists of removing the offending agent(s) and administering intravenous dantrolene. \(^{17,176}\)

**Assessment of Neuromuscular Blockade**

It may be fortuitous that the diaphragm is one of the muscles most resistant to paralytic drugs requiring 90 percent or more receptor blockade to produce paralysis. It is difficult to assess the degree of neuromuscular blockade in the ICU. Use of a peripheral nerve stimulator provides the best index of the intensity of neuromuscular blockade, but in practice, this is rarely done.\(^{17}\) More commonly, the effects of neuromuscular blockers are allowed to lapse before subsequent doses are given. This policy allows emergence from paralysis and permits serial clinical assessment. When patients are intermittently allowed to recover movement, administration of an overdose of neuromuscular blocker becomes unlikely. As a practical bedside test, if a patient is able to sustain a head lift off the bed for 5 s or more, paralysis is effectively reversed. The head lift maneuver provides a more reliable clinical sign of reversal than negative inspiratory force, vital capacity, tongue protrusion, or grip strength. Approximately 75 to 80 percent receptor occupancy is required to cause any muscle weakness, with 90 to 95 percent blockade needed for complete muscular relaxation.

**Reversal of Neuromuscular Blockade**

Even when used in the operating suite, controversy surrounds the need for reversal of neuromuscular paralysis, and in the ICU, it is rarely necessary. Reversing agents act by raising acetylcholine levels in the neuromuscular junction. Therefore, reversing agents are not effective for blockade resulting from depolarizing agents (succinylcholine) or from profound (ion channel) blockade due to nondepolarizing blockers. Neostigmine, pyridostigmine, and edrophonium are the three agents available to reverse mild depolarizing blockade. Neostigmine is the most commonly used reversing agent in the ICU, but only one in four ICU physicians commonly uses paralytic reversers. The major toxic effect of these drugs is muscarinic stimulation resulting in severe bradycardia and salivation. The muscarinic effects may be blocked by pretreatment with anticholinergic drugs like atropine or glycopyrrolate.\(^{17,178}\) Without extensive training and experience, reversal of neuromuscular blockade should be avoided.

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