Chapter 10

INTRAVENOUS ANESTHESIA

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INTRODUCTION

Delivering safe and effective anesthesia to casualties with combat injuries presents unique challenges to military trauma anesthesiologists. These casualties may have sustained severe injuries involving significant blood loss and varying degrees of shock. They will be in pain and emotional distress, and possibly suffering from sequelae of prolonged transport such as inadequate ventilation, hypothermia, uncorrected hypovolemia, in any combination. They may have full stomachs, which places them at risk for pulmonary aspiration during general anesthesia.

Certain other conditions in the field further complicate the anesthetic management of these difficult patients. For one, casualties may arrive en masse, exceeding the ability of a small medical staff to provide scrupulous individual monitoring. In these situations, relatively untrained personnel may be required to achieve airway patency and hemodynamic stabilization in the perioperative period. Likewise, recovery care after anesthesia may be marginal. As for the course of the anesthetic itself, bulky and elaborate anesthesia equipment may not be available or practical at the site of combat casualty surgery. In particular, apparatus for the delivery of compressed gases such as oxygen may pose logistical problems.

Ideally, then, an anesthetic approach for combat casualty care should have the following characteristics: preservation of airway reflexes with minimal hemodynamic effects; ease of delivery, which would allow for management by relatively unskilled practitioners; and a minimal requirement for unwieldy or complex anesthetic delivery systems. Unfortunately, no anesthetic technique meets all of these requirements, although many approaches have been used with varying degrees of success in the battlefield setting. Among these are general anesthesia using simple gas-delivery systems, regional techniques, and intravenous anesthesia with or without supplementary inhaled agents. A full discussion of the first two methods is presented in Chapter 8, Closed-Circuit Anesthesia; Chapter 9, Inhalational Anesthesia; and Chapter 12, Regional Anesthesia. In general, their use dictates a significant level of skill on the part of the practitioner, particularly in dealing with hypotension, which is a sequela of both regional and general anesthesia, and from the loss of airway reflexes that ensue from general anesthesia with volatile agents.

Intravenous anesthetic agents are advantageous in the field for many reasons. Transportability and technical ease of administration are excellent. Many of these drugs are able to rapidly induce a state of surgical anesthesia. This is particularly important in traumatized soldiers, as experience has shown most to have full stomachs at the time of injury.[1] To prevent the aspiration of regurgitated material into the lungs, a rapidly induced state of unconsciousness is necessary to facilitate endotracheal intubation and airway protection. With careful use, these drugs will also allow early awakening and extubation of the trachea, shortening stays in the recovery area. Residual analgesia is a benefit with some intravenous agents. These drugs can also be used to supplement inhalational anesthetic agents, providing balanced anesthesia. Some intravenous anesthetic agents can be used as the sole or primary agents for the maintenance of surgical anesthesia by means of an initial bolus followed by continuous infusion. This technique adds a degree of controllability to the duration of action of the anesthetic and reduces the total amount of drug administered, allowing the anesthesia provider to have an awake patient at the end of the case. Such a patient will be easier for recovery area personnel to deal with than an overly sedated or unconscious patient. Indeed, recovery room personnel may be in very short supply or extremely busy. As the patient may receive relatively little attention during this period, recovery time is best kept to a minimum.[2]

INTRAVENOUS ANESTHETIC AGENTS FOR BATTLEFIELD ANESTHESIA

Complete surgical anesthesia, when properly administered, provides amnesia, analgesia, unconsciousness, and muscle relaxation. The ideal anesthetic drug would induce such a state of surgical anesthesia rapidly, be quickly reversible, maintain hemodynamic stability, and be nontoxic to the patient. There is no drug available today that, when used alone, satisfies all of these criteria. However, the intravenous drugs we will discuss in this chapter each provide one or more component parts of the ideal (ie, complete) anesthetic regimen.

Much of the initial anesthetic care of combat casualties consists of the vigorous resuscitation of hemorrhagic shock. It is likely that many of these injured soldiers would not survive the physiological effects of the sudden imposition of a complete

anesthetic, which could compound the hemodynamic instability seen with hypovolemic shock states. Careful selection and meticulous titration of anesthetic agents, whether inhalational or intravenous, usually become feasible only as resuscitative efforts progress. Failure to recognize and adequately treat hypovolemic shock before the induction of anesthesia can convert a casualty to a fatality. Indeed, the careless use of thiopental in hypovolemic patients after the Japanese attack at Pearl Harbor on 7 December 1941 caused a large number of intraoperative deaths and led some anesthesiologists to criticize its use in war casualties.[3] It is clear in retrospect that many of the anesthesia providers involved were unfamiliar with the proper use of this agent. It is also clear that volume resuscitation was inadequate in these cases. Thiopental was subsequently used with good success throughout the remainder of World War II,[4–8] the Korean and Vietnam wars,[1] the Falklands War,[9] and remains a valuable anesthetic drug today when properly administered. The intravenous anesthetic and adjuvant drugs currently available have a broad spectrum of effects, indications, and contraindications (Table 10-1). Each of the agents described in this chapter has unique advantages and disadvantages for the anesthetic management of wartime casualties. The anesthesia provider must be able to assess the clinical situation in each case and select the best anesthetic technique and agents for the casualty.

For some short surgical procedures, one or two intravenous bolus injections of anesthetic agent may be all that is required for patient comfort. For very minor procedures, a subanesthetic dose may be sufficient for analgesia, sedation, and anxiolysis. Subanesthetic doses are also useful for supplementing regional anesthetic techniques. Disadvantages of many of the intravenous anesthetic agents include the possibility of overdosage, with resultant respiratory depression or arrest. Mechanical ventilators may not be available at battlefield hospitals.[2] Because the patient's metabolism of the drug is required for these drugs' termination of action, anesthesia-recovery personnel may be forced to commit themselves to one-on-one care for such patients until they are once again breathing on their own. Intravenous

TABLE 10-1

PHARMACOLOGICAL EFFECTS OF VARIOUS INTRAVENOUS ANESTHETIC AGENTS

Agent	Onset	Duration	Loss of Consciousness	Analgesia	Amnesia
Barbiturates					
Thiopental	Rapid	Ultra-short	Yes	Anti*	Yes
Methohexital	Rapid	Ultra-short	Yes	Anti	Yes
Benzodiazepines					
Diazepam	Slow	Long	High-dose	None	Yes
Midazolam	Intermediate	Intermediate	High-dose	None	Yes
Narcotics					
Morphine	Slow	Long	High-dose	Yes	+/–†
Meperidine	Slow	Long	High-dose	Yes	+/–
Fentanyl	Intermediate	Intermediate	High-dose	Yes	+/–
Sufentanil	Intermediate	Intermediate	High-dose	Yes	+/–
Alfentanil	Rapid	Short	Yes	Yes	+/–
Ketamine	Rapid	Short	Yes	Yes	Yes
Etomidate	Rapid	Short	Yes	No	Yes
Propofol	Rapid	Ultra-short	Yes	No	Yes
Scopolamine	Rapid	Long	No	No	Yes

*Pain perception is increased
†The effect may or may not be present

anesthetic techniques, while technically simple, tend to be less forgiving of error than inhalational techniques. Constant vigilance and attention to detail are mandatory when these drugs are used.

Military medical planners have noted that the limiting factor in performing surgery in the field may be the number of personnel who are trained to administer anesthesia.[2] It is recognized that many military physicians and nurses who have had minimal exposure to anesthesiology as a specialty will have to be trained on the job to deliver a safe anesthetic. Simplicity, technical ease of administration, and the relatively high margins of safety of many of the intravenous anesthetic drugs will permit such personnel to deliver safe anesthesia to combat casualties.

USEFUL DRUGS FOR THE INDUCTION OF ANESTHESIA

When induction of general anesthesia is necessary in casualties with traumatic injuries, two properties of an anesthetic drug are of primary importance. The first is whether the selected drug can be expected to cause serious depression of the patient's cardiovascular system. The patient may be severely hypovolemic from blood loss, exposure, or other causes. The choice of an induction agent must therefore take into account the victim's volume status and degree of hemodynamic compromise. The second important factor in the choice of an induction agent is the rapidity of onset of unconsciousness following intravenous injection. Because soldiers injured on the battlefield nearly always present for treatment with a full stomach,[1] the airway must be rapidly protected with an endotracheal tube to prevent aspiration of gastric contents into the bronchopulmonary tree. A drug with a long onset time will therefore expose the patient to greater anesthetic risk.

Agents that are useful for induction of anesthesia are presented below, grouped by drug type.

Barbiturates

Intravenous barbiturates produce central nervous system depression ranging from mild sedation to coma, depending on the dosage given. The two barbiturates most commonly used to induce anesthesia are sodium thiopental (Pentothal, manufactured by Abbott Laboratories, North Chicago, Ill.) and methohexital (Brevital, manufactured by Eli Lilly and Co., Indianapolis, Ind.). These agents rapidly produce a state of unconsciousness and amnesia without significant analgesia.

Pharmacology

Thiopental is usually prepared as a 2.5% mixture (25 mg/mL), while methohexital is made up as a 1% solution (10 mg/mL). Unconsciousness occurs within seconds following intravenous bolus and lasts for approximately 3 to 5 minutes. Clinical recovery from methohexital is slightly faster than from thiopental.

The brief clinical effect seen after intravenous bolus of these drugs is not due to metabolism, but rather to redistribution of agent from the brain and other vessel-rich organs to less metabolically active compartments. However, multiple doses or continuous infusions may result in slow recovery, owing to protein binding and the slow release of drug from muscle and fatty tissues.[10]

Physiological Effects

Central Nervous System. The barbiturate anesthetic agents induce a state of hypnosis and amnesia. However, they tend to reduce the patient's pain threshold (ie, the *antalgesic* effect), with a resultant significant increase in heart rate and blood pressure during painful or stimulating procedures.[11]

Cerebral metabolic rate is markedly reduced following a dose of a barbiturate drug, which, in turn, causes cerebral vasoconstriction. This effect, in turn, results in decreased cerebral blood volume and reduced intracranial pressure. Cerebral perfusion may improve, as intracranial pressure falls to a greater extent than the mean arterial pressure in normovolemic patients.[11] These effects are very beneficial in the patient with a closed head injury. In addition, the barbiturates are potent anticonvulsant agents.

Cardiovascular System. The principal hemodynamic effects of the barbiturates are a decrease in contractility and an associated increase in heart rate. Dose-dependent decreases in arterial blood pressure, stroke volume, and cardiac output are seen. The mechanisms for the decrease in cardiac output include (1) direct negative inotropic effect on the myocardium, (2) decreased ventricular filling owing to increased venous capacitance, and (3) transiently decreased sympathetic outflow from the central nervous system.[11]

Respiratory System. The barbiturates are potent central nervous system depressants. As a conse-

quence of these effects, they produce profound respiratory depression. This is first seen as a decrease in tidal volume, followed by apnea. Positive-pressure ventilation will be necessary following the usual induction doses of both thiopental and methohexital.

Clinical Use and Contraindications

Both sodium thiopental and methohexital are safe induction agents in the normovolemic casualty whose cardiac function is not compromised. Usual induction doses are 4 mg/mL for thiopental or 1 mg/mL for methohexital (Table 10-2). Although these agents are not the drugs of first choice in trauma patients, experience has shown that they may also be used safely in such cases, provided that the dosages are adjusted downward.[4–6] Easy intubating conditions are generally obtained within 60 seconds when given with succinylcholine for rapid-sequence induction (which is discussed later in this chapter). Thiopental (or methohexital) may also be administered as a continuous infusion following an initial bolus (Table 10-3). This allows a state of surgical anesthesia to be maintained for extended periods. However, these agents accumulate in the tissues when used in this manner, and recovery from anesthesia may be prolonged.

Extreme caution should be used in the hypovolemic casualty or one with cardiac compromise such as tamponade. In general, barbiturates should be avoided as induction agents in these casualties until the hypovolemic state or the cardiac tamponade is corrected.

TABLE 10-2

SUGGESTED DOSE RANGES FOR INTRAVENOUS INDUCTION OF ANESTHESIA

	Casualty's Resuscitation Status	
Agent	**Normovolemic (Dose)**	**Hypovolemic (Dose)**
Sodium Thiopental	2–4 mg/kg	1–2 mg/kg
Ketamine	1–2 mg/kg	0.5–1.0 mg/kg
Etomidate	0.2–0.4 mg/kg	0.1–0.2 mg/kg
Methohexital*	0.5–1.0 mg/kg	0.25 mg/kg
Midazolam*	0.15–0.3 mg/kg	0.075–0.15 mg/kg
Alfentanil	100–200 μg/kg	not known

*Will cause prolonged sedation and respiratory depression

TABLE 10-3

DRUG DOSES FOR CONTINUOUS INTRAVENOUS INFUSION TECHNIQUES

Agent	Loading Dose	Infusion Rate
Ketamine	1.0–2.0 mg/kg	20–50 μg/kg/min
Etomidate	0.2–0.4 mg/kg	40–100 μg/kg/min for 10 min, then 10–40 μg/kg/min
Thiopental	2.0–4.0 mg/kg	0.1 mg/kg/min
Propofol	2.0–2.5 mg/kg	0.1–0.2 mg/kg/min
Alfentanil	100–200 μg/kg*	0.5–2.5 μg/kg/min

*30–40 μg/kg when combined with thiopental

Etomidate

Etomidate (Amidate, manufactured by Abbott Laboratories, North Chicago, Ill.) is an imidazole compound that is chemically unrelated to any other intravenous anesthetic agent. It is a potent sedative and hypnotic agent with rapid onset and recovery, and its use is associated with excellent cardiovascular and respiratory stability in the normovolemic patient.[12]

Pharmacology

As with the barbiturates, etomidate is rapidly distributed to the brain and other vessel-rich groups following intravenous injection. Termination of clinical action occurs as the agent is redistributed away from these highly perfused organs.[13] Etomidate's distribution half-life is in the 2- to 4-minute range. The drug is cleared from plasma 5-fold faster than is thiopental. Etomidate is prepared as a 2% solution (20 mg/mL).

Physiological Effects

Central Nervous System. Intravenous injection causes a rapid, dose-dependent depression of the central nervous system. As with the barbiturates, etomidate is a potent anticonvulsant agent. This anticonvulsant effect lasts significantly longer than its hypnotic and anesthetic effects. In common with the barbiturates, etomidate also causes a significant reduction in the cerebral metabolic rate, with associated cerebral vasoconstriction[14] and decreased intracranial pressure. Cerebral perfusion pressure is not altered appreciably.

Cardiovascular System. In normovolemic patients, etomidate causes no significant changes in heart rate or cardiac output.[12] A slight fall in systemic blood pressure may be noted, secondary to a mild decrease in peripheral vascular resistance. However, in the trauma patient suffering from hypovolemic shock, serious hypotension may result from usual induction doses of etomidate due to suppression of sympathetic nervous system outflow.

Respiratory System. Etomidate is a potent central nervous system depressant. As a consequence of these effects, it produces dose-related respiratory depression. Respiratory rate and tidal volume are affected, although the magnitude is less than that produced by the barbiturate anesthetic agents.[11] Positive-pressure ventilation will be necessary either after an induction dose or during continuous infusions for maintenance of general anesthesia.

Clinical Use and Contraindications

The usual dose range for induction is 0.2 to 0.4 mg/kg (see Table 10-2). The clinical duration of a single bolus injection is 3 to 12 minutes.

Psychomotor recovery is intermediate between that of thiopental and methohexital. Short surgical procedures may be done using etomidate, maintaining anesthesia with repeated, small boluses or continuous infusion (see Table 10-3). Following a bolus injection of 0.2 to 0.4 mg/kg, a continuous infusion can be set up to flow at a rate of 40 to 100 μg/kg/min (20–40 μg/kg/min if nitrous oxide is being used, although nitrous oxide is not available in deployable hospitals). After the initial 10 minutes of infusion, the rate should be reduced to 10 to 40 μg/kg/min. (Many anesthesiologists would supplement this infusion technique with a potent opioid such as fentanyl, since etomidate is an incomplete anesthetic, ie, it provides no analgesia).

Prudence would dictate a reduction in drug dose for induction of anesthesia during the resuscitative phase of shock (ie, in the acutely traumatized battlefield casualty). A good starting dose would be 0.1 mg/kg, titrating more agent as the patient's condition allows.

Two characteristics of etomidate make it useful for anesthesia in the traumatized patient[11]:

- Relative hemodynamic stability; this is most important when the casualty is hypovolemic (eg, in hemorrhagic shock).
- Its effect on the central nervous system; by decreasing intracranial pressure and cerebral metabolic rate while preserving stable hemodynamic parameters, etomidate may prove to be the agent of choice for anesthetic induction in the hemodynamically unstable trauma patient with a head injury.

Relatively minor drawbacks to the use of etomidate include the following[11]:

- Venous irritation; etomidate is dissolved in propylene glycol, giving rise to pain or irritation or both on intravenous injection in some patients. This side effect can be reduced somewhat by prior administration of an opioid drug such as fentanyl.
- Myoclonus; this centrally mediated effect is frequently observed. It is not indicative of awareness, and is not harmful to the patient, per se. Once again, these movements may be reduced by pretreating the patient with an opioid drug.
- Postanesthetic nausea and vomiting; this side effect may be seen in up to 40% of patients on emergence from anesthesia with etomidate, is probably centrally mediated, and may be reduced in incidence if an antiemetic drug such as droperidol is given.
- Adrenocortical suppression; this effect lasts from 6 to 8 hours and is probably not clinically significant unless prolonged or large total doses are administered. Suppression of adrenal steroid production may predispose critically ill patients to sepsis.

Propofol

Pharmacology

Propofol (Diprivan, manufactured by Stuart Pharmaceuticals, Wilmington, Del.) is a recently introduced intravenous anesthetic agent. It rapidly produces unconsciousness following bolus injection, with a time course on onset and recovery very similar to that of thiopental and methohexital. Propofol is completely insoluble in aqueous solution and is therefore administered in a lecithin-based emulsion. Because this emulsion is a very favorable medium for bacteria, strict aseptic technique should accompany its use. The drug is extremely lipid soluble, a property that allows it to cross the blood–brain barrier very quickly. Clinical experience has shown that less residual postoperative sedation and psychomotor impairment follow administration of propofol, and side effects such as nausea and vomiting are uncommon.[15]

Physiological Effects

As do the barbiturates, propofol causes dose-dependent cardiac and respiratory depression.[11,12,15] The magnitude of these effects is similar to those seen with thiopental. Propofol has no analgesic properties but, in contrast to thiopental, neither does it appear to have an antalgesic effect.

Clinical Usage and Contraindications

Induction of anesthesia is achieved with a propofol dose of 1.5 to 3.0 mg/kg (see Table 10-2). Unconsciousness occurs less than 1 minute following an intravenous bolus, and lasts from 4 to 8 minutes. The drug is redistributed and eliminated very rapidly. A continuous infusion or repeated, small-bolus injections may be used to maintain a surgical plane of anesthesia. The drug does not accumulate in the tissues to a clinically significant degree and thus is better suited to continuous-infusion techniques than the barbiturates or etomidate. Recovery is characterized by rapid emergence from anesthesia and minimal postoperative confusion.[15] A continuous infusion may be used following an induction dose of 2.0 mg/kg (see Table 10-3). The infusion rate is titrated to the desired effect, with a usual dose range of 0.1 to 0.2 mg/kg/min (6.0–12.0 mg/kg/h); in critically ill or debilitated patients, the dosage regimen may be halved. This technique is enhanced by the addition of an opioid drug or nitrous oxide for analgesia.

Propofol's greatest advantage over other intravenous anesthetic agents is its relatively rapid elimination from the body. This may diminish the degree of hangover seen after continuous infusions or repeated boluses of the barbiturates and etomidate, and could potentially shorten time spent in the recovery area.[16]

Ketamine

Pharmacology

In the field, the aim of the military anesthesia provider is to deliver the minimum level of anesthesia necessary to provide adequate surgical depth, thereby assuring a rapidly resolving anesthetic state. Ketamine was developed through investigation of phencyclidine (PCP) and cyclohexamine, both of which provide profound anesthesia accompanied by intolerable psychotomimetic effects.[17] Ketamine resembles these drugs structurally, but it delivers sedation, analgesia, and surgical anesthesia with much milder psychic side effects.

The administration of ketamine produces an unusual clinical state called *dissociative* anesthesia (ie, the patient does not move specifically in response to noxious stimuli[18]). Some researchers[19] have postulated that ketamine depresses central nervous system centers that are crucial to the transmission of the emotional component of pain signals from the spinal cord to the higher centers. Others[20,21] believe that ketamine may work through direct suppression of spinal cord activity or by an action on opiate receptors throughout the central nervous system.

Ketamine has a rapid onset of action attributable to its high lipid solubility, and a short duration of action owing to redistribution out of the central nervous system. These features make it very similar to the barbiturate induction agents such as sodium thiopental. When ketamine is administered intravenously, peak plasma levels are achieved in 1 minute, while peak plasma levels following an intramuscular dose are reached by 15 minutes after the injection. Anesthetic effects last approximately 10 to 15 minutes, and analgesia may last as long as 4 hours. The elimination half-life of ketamine from the peripheral tissues is 2 to 3 hours. Therefore, despite the swift termination of its hypnotic effects after an initial injection, prolonged sedation may ensue from repeated doses or infusions. The development of tolerance to ketamine may occur following repeated exposures.

Does ketamine meet the requirements for combat casualty anesthesia? Certainly, it is an extremely useful agent in this setting. Among its many valuable attributes, ketamine

- is nonlabile in solution and easily transported in powdered form, and can be delivered intravenously or intramuscularly;
- provides a rapid, smooth induction to surgical depth anesthesia, as well as an acceptably brief interval to termination of its sedative effects;
- is a profound analgesic, unlike other nonnarcotic intravenous anesthetic agents; and
- allows the patient's stable cardiovascular and respiratory physiology to be maintained, with consequent preservation of blood pressure and airway reflexes.

This last point is probably the most significant. However, this is not meant to imply that a patient under ketamine anesthesia can be left unattended, since apnea, airway obstruction, aspiration of gas-

tric contents, and hypotension may still be seen. Rather, the use of ketamine allows the administration of general anesthesia by relatively unskilled personnel with an increased margin of safety when compared to other, more conventional methods. While not an ideal situation, this may be unavoidable in times of war. On the negative side, ketamine anesthesia has two major drawbacks in the battlefield setting:

- Time to full recovery is prolonged when the drug is used as a maintenance agent, compared with the inhaled anesthetics and many other intravenous drugs.
- The psychic phenomena accompanying emergence may be severe in young soldiers.

Nonetheless, it is clear that ketamine's unique characteristics make it an important tool for use in combat surgery.

Physiological Effects

Central Nervous System. Ketamine has potent analgesic actions. However, because of its unique nervous system effects, the administration of ketamine produces an anesthetic state unlike that of more traditional agents such as thiopental or the opioid narcotics. Thus, it can be difficult to assess anesthetic depth. When surgical anesthesia is achieved with ketamine, the patient's eyes may remain open and exhibit nystagmus as well as intact corneal and light reflexes. Myoclonus is observed frequently, as are actual purposeful movements that are not necessarily in response to painful stimuli. Even with very small doses of ketamine, patients may lose a sense of contact with their environment and an ability to think coherently. Nonetheless, with appropriate dosing, a trancelike state accompanied by profound anesthesia can be achieved, which allows surgery to proceed. A good approach to assessing the adequacy of anesthesia under ketamine is to aim for suppression of reaction to surgical stimulation.[22] In other words, the goal should not necessarily be a completely motionless patient but rather the dissociative state.[18]

An unfortunate aspect of ketamine's central nervous system effects is a phenomenon known as the *emergence* reaction. This refers to an altered mental state experienced by many patients on awakening from the drug, and is characterized by vivid dreams, floating or "out-of-body" sensations, disorientation, and hallucinations. Although these feelings usually end on full awakening, some patients may experience flashbacklike sensations as late as several weeks after receiving ketamine.[17] Frequently they are very disturbing to the patient. The incidence of emergence reactions is on the order of 5% to 30%.[17,23] Predisposing factors include age older than 16 years, female gender, a history of emotional problems, and a history of an active dream life. This phenomenon also occurs more commonly when ketamine is given rapidly, in relatively large intravenous doses, and when atropine or droperidol are given as premedicants. Finally, many anesthesiologists believe that psychic disturbances are exacerbated by a noisy or otherwise stimulating environment.

The most effective prophylaxis against emergence reactions appears to be the concomitant use of a benzodiazepine drug.[24,25] These drugs are useful either as premedicants or when administered during the course of an operation. When ketamine is used solely as an induction agent, followed by maintenance of anesthesia with other drugs, emergence reactions are virtually unheard of in cases lasting longer than 45 minutes.[23] Some investigators[17] suggest preoperative and postoperative counseling regarding possible psychic phenomena as a very effective means for reducing their incidence.

Cardiovascular System. Ketamine causes dose-related increases in arterial blood pressure and heart rate. These effects are believed to derive from direct sympathetic stimulation. Heart rate, blood pressure, and cardiac output are increased, with variable effects on stroke volume and systemic vascular resistance. These effects make ketamine a very valuable drug for the induction of anesthesia in patients who are suffering from hypovolemic shock.[17]

In addition to sympathetically mediated cardiac stimulation and vasoconstriction, ketamine has been shown to dilate vascular smooth muscle and to depress myocardial function by direct actions.[26] If the sympathetic nervous system is depressed by anesthetic or other drugs, or if the patient is critically ill, a bolus injection of ketamine may cause profound cardiovascular collapse. Ketamine-induced direct myocardial depression and peripheral vasodilation are usually effectively masked by its sympathomimetic actions. In the absence of a fully functioning autonomic nervous system, the predominant cardiovascular effect of ketamine is to depress cardiac function.[11] At least one authority[26] has observed decreases in cardiac performance following the use of ketamine in the setting of acute trauma, but most investigations of the cardiostimulatory effects of ketamine in the presence of hemorrhagic shock have shown a significant increase in both systolic and diastolic blood pressure.[26–28] Cardiovascular stimulation may be attenuated by in-

haled anesthetic agents, sodium thiopental, or premedication with a benzodiazepine.[17,29]

Respiratory System. In contrast to the narcotics and barbiturates, ketamine preserves the respiratory response to carbon dioxide.[17] Decreases in the partial pressures of oxygen in arterial blood (Pa_{O_2}) are modest and transient at commonly used doses. Significant respiratory depression occurs when ketamine is given rapidly in high doses.

Ketamine is known to produce bronchial smooth-muscle relaxation, which increases pulmonary compliance in patients with bronchoconstriction.[17] Tracheopharyngeal reflexes are maintained to a greater extent than with other commonly used induction agents, but pulmonary aspiration of gastric contents may occur at even relatively low doses. Finally, salivation is markedly increased on administration of the drug.[30,31]

Relative to other intravenous agents, the effects of ketamine on the respiratory system increase its margin of safety in the field setting. It maintains respiratory drive in the spontaneously ventilating patient, minimizes airway reactivity, and preserves airway-protective reflexes, at least in part. However, this in no way obviates the need for skilled airway management, as respiratory depression or tracheal soiling or both are still possible, particularly when the casualty is not only acutely traumatized but also in a chaotic setting.

Contraindications

Based on the physiological effects just presented, several clinical conditions constitute contraindications to the use of ketamine. As mentioned, since postanesthetic emergence reactions are a troublesome side effect, ketamine probably should not be used when there is preexisting psychopathology.

Ketamine raises intracranial pressure by increasing cerebral blood flow and systemic blood pressure.[11] Likewise, intraocular pressure is increased. Ketamine is therefore contraindicated in casualties who have closed head or penetrating eye injuries, and in all other situations where intracranial or intraocular pressure is raised.

Clinical Use

Ketamine is available in a variety of strengths, most commonly 10 mg/mL, 50 mg/mL, and 100 mg/mL. The usual intravenous induction dose is 1 to 2 mg/kg. (The intramuscular dose for induction of anesthesia is 5–10 mg/kg). Following an intravenous induction dose, ketamine is rapidly distributed to the brain and other vessel-rich groups in a manner analogous to that of thiopental. For short surgical cases, repeated boluses of one half the induction dose may be administered at appropriate intervals as needed. As an alternative to this technique, a solution of 0.1% ketamine may be prepared (1 mg/mL) and a continuous infusion maintained at a rate of 25 to 50 μg/kg/min.

Termination of ketamine's action is due to redistribution (the distribution half-life is 7–11 min) and hepatic metabolism. The elimination half-life is 2 to 3 hours. Effective analgesia is possible with subanesthetic bolus doses of ketamine (0.25 to 0.5 mg/kg).

Initial enthusiasm for ketamine as a possible single-agent, total, intravenous anesthetic has waned somewhat as actual field trials have demonstrated its inadequacies. For example, experiences with ketamine in the Falkland Islands and Southeast Asia have yielded mixed results. In Cambodia, British anesthetists have used ketamine as a sole agent for superficial procedures and brief minor surgeries, but they reported prolonged recovery times, particularly when benzodiazepines were used as a prophylaxis against emergence reactions. In addition, they noted rare laryngospasm and other airway compromise.[32] During the Falklands War, total intravenous anesthesia was employed with success in operations of short duration not involving the body cavity. For more major surgeries in patients in hypovolemic shock, ketamine was recommended as an induction agent and adjunct to maintenance with halothane. In the cases described using this technique, recovery time was not appreciably prolonged despite the routine administration of diazepam at the end of the procedures. Emergence phenomena were not an issue.[33] The consensus drawn from these two experiences is that ketamine delivers adequate anesthesia only for peripheral procedures and when used with a benzodiazepine to prevent postoperative delirium.

In the large majority of cases, airway reflexes were preserved. While supplemental inhaled agents were deemed necessary for casualties who required intraabdominal surgery, total intravenous anesthesia was used successfully for over one half of the casualties who presented to this group of anesthesia providers, owing to the superficial nature of the surgeries involved. Therefore, with a few provisos, it would appear that ketamine as a sole agent is a feasible anesthetic for many situations encountered in wartime.

A marked improvement in outcome was achieved through the introduction of an infusion technique,

which reduces the total administered ketamine dose. Two large series[25,34] describing both minor and major abdominal procedures under continuous ketamine infusion report minimal prolongation of recovery time, with favorable respiratory and cardiovascular effects. Nitrous oxide and muscle relaxants were used, as was diazepam. Very encouraging work has been done by anesthetists in South Africa who have used a ketamine infusion with only muscle relaxation and oxygen-enriched room air for major abdominal cases.[35] A critical feature of their work was the use of a benzodiazepine as the induction agent, which served to prevent emergence phenomena but also prolonged the recovery phase. The clear advantage of such a technique to field anesthesia is that the need to transport compressed gas could be reduced or eliminated by maintaining anesthetized casualties on room air.

Minor Procedures and Transport. Ketamine can be used in a wide range of situations encountered in a field hospital. It probably is most effective in providing anesthesia for peripheral or surface procedures. For minor operations such as debridement, incision and drainage, and delayed primary closure, ketamine may be delivered as a bolus of 0.25 to 1.0 mg/kg, administered intravenously, or 1 to 4 mg/kg, administered intramuscularly. These doses are also appropriate for analgesia during transport. Airway reflexes and respiratory drive generally remain intact in this dose range. Repeat doses may be required at 5- to 15-minute intervals. Another approach is to administer a continuous infusion of 5 to 20 μg/kg/min throughout the procedure. A similar dosage schedule is appropriate for analgesia during transport. Benzodiazepines in small doses will attenuate psychic disturbances, although these are seldom significant with low-dose ketamine.[17,33,36]

For minor surgery such as superficial soft-tissue debridement or brief genitourinary or general surgery, general anesthesia can be accomplished using ketamine 2 mg/kg intravenously or up to 10 mg/kg intramuscularly. Repeat doses may be titrated to abolish purposeful movements or nystagmus. Care must be taken to monitor airway adequacy at these doses, and supplemental oxygen is prudent. However, this technique still represents a relatively safe approach to general anesthesia in a setting where skilled personnel and elaborate equipment or compressed gases may not be available. Emergence reactions will pose a problem at these doses, and administration of a benzodiazepine will necessitate more expert and vigilant care of the airway. Recovery time may take up to 45 minutes or longer, especially if other anesthetic agents are used. Recovery from low-dose ketamine should be well under 30 minutes.[25,37]

Major Procedures. In patients suffering from hypovolemia, severe anemia, or cardiovascular compromise, ketamine is an excellent choice for an induction agent.[23,28] While most intravenous induction agents cause hypotension, ketamine generally will preserve blood pressure and cardiac output in casualties in hypovolemic shock. Doses for induction of anesthesia are in the range of 1 to 2 mg/kg intravenously or 4 to 6 mg/kg intramuscularly, with decreased doses as appropriate when the patient is severely ill or in profound shock. Ketamine is suitable for use in patients with full stomachs, with the usual precautionary measures such as application of cricoid pressure and preoxygenation. In the previously healthy, normovolemic patient, ketamine induction may result in undesired blood pressure elevation.

Ketamine can be used to maintain surgical anesthesia for major intraabdominal or intrathoracic cases in combination with inhaled agents, particularly when hypotension limits the dosage of the latter. Following induction, ketamine may be administered intravenously at 15- to 30-minute intervals, as needed, in boluses of 0.5 to 2.0 mg/kg. The patient breathes a low dose of a volatile agent delivered via a field anesthesia machine or similar equipment, or the agent is given via positive-pressure ventilation as necessary. If available, nitrous oxide may be used to supplement ketamine maintenance. A benzodiazepine administered during the operation will reduce the incidence of postoperative delirium.[17]

Alternatively, a continuous ketamine infusion will maintain surgical anesthesia.[38–40] Use in combination with another agent will minimize the total ketamine dose. Usually, 10 to 30 μg/kg/min with 50% to 70% nitrous oxide or a background volatile agent will be sufficient. Again, a benzodiazepine is recommended. An antisialagogue such as atropine or glycopyrrolate will minimize salivation and upper-airway secretions.

Total Intravenous Anesthesia With Ketamine. Finally, when compressed gases are not available, ketamine can act as the primary agent in a total intravenous anesthetic for major operations. The best results have been obtained using a benzodiazepine for induction, followed by intubation using a muscle relaxant, and then initiation of a ketamine infusion (see Table 10-3) in the range of 20 to 40 μg/kg/min, with controlled ventilation on air or oxygen-enriched air, as available. Although this tech-

nique has been used successfully for abdominal surgery with little postoperative psychic disturbance, recovery time is likely to be prolonged.[35] In the injured casualty in hypovolemic shock, induction is probably more safely achieved using ketamine rather than a benzodiazepine.

Ketamine for Pediatric Anesthesia. The treatment of combat casualties includes the care of civilians, among whom may be injured children. Ketamine has long been a mainstay in pediatric anesthesia, and it adapts well for use in the field. In a child, an intramuscular dose of 5 to 10 mg/kg will provide surgical anesthesia that will last from 10 to 30 minutes. Lower doses may provide adequate sedation for brief, minor procedures. A sedating intravenous dose would be 0.25 to 0.5 mg/kg. Production of significant upper-airway secretions accompanies the use of this agent in children and necessitates the use of an anticholinergic drug (eg, atropine or glycopyrrolate). Although airway reflexes and respiratory drive are generally well preserved, close attention must be paid to adequacy of ventilation, as is done in any case of general anesthesia or deep sedation. The incidence of postoperative psychic disturbances in children is thought to be lower than that in adults.[17,23]

ANXIOLYTIC AND AMNESTIC AGENTS

Anxiety and fear are very common in the preoperative patient, and even more so in wounded soldiers. Severe anxiety may cause significant tachycardia, hypertension, and increased respiratory rate. Oxygen consumption and carbon dioxide production are increased. Such patients may also be uncooperative, irrational, or combative. Finally, serious psychic trauma may occur in some patients due to their recall of events in the operating room—during resuscitative efforts or surgery or both. In addition to the humane considerations, physiological benefits can be attained if the casualty's fear and anxiety are reduced. The agents discussed in the following section have proven useful for producing amnesia to both preoperative and intraoperative events, and some are potent anxiolytics as well. In high doses, some of these agents have a hypnotic effect and may be used to induce an anesthetic state.

Benzodiazepines

The drugs of this class that are most likely to see clinical use during wartime are diazepam (Valium, manufactured by Roche Products, Inc., Manati, Puerto Rico) and midazolam (Versed, manufactured by Roche Laboratories, Nutley, N.J.).

Pharmacology

All the benzodiazepine drugs possess similar anxiolytic, sedative, hypnotic, amnestic, anticonvulsant, and muscle-relaxant properties.[11] While the pharmacodynamics (ie, what the drug does to the body) of diazepam and midazolam are very similar, their pharmacokinetics (ie, what the body does to the drug) are quite different.

Diazepam has a distribution half-life of 30 to 60 minutes and an elimination half-life of 20 hours or more. Its primary metabolite is active and has an elimination half-life of 41 to 139 hours. The clinical effects of an intravenous diazepam dose are seen within 1 to 2 minutes and last from 1 to 3 hours, with widely variable individual responses.

Midazolam is water soluble, more potent than diazepam, and has no active metabolites.[41] Distribution half-life is 7 to 15 minutes, and elimination half-life is 2 to 4 hours. Its higher potency and shorter duration of clinical action make midazolam particularly attractive in situations where a benzodiazepine drug is indicated.

Physiological Effects

Central Nervous System. Diazepam and midazolam are potent anxiolytics, acting on the centers in the central nervous system that generate fear, anxiety, and aggression. In addition to reducing anxiety, these drugs provide excellent amnesia. In high doses, either drug can be used as an anesthetic induction agent (see Table 10-2), although their primary usefulness is as sedative or anxiolytic agents or both. Recovery from an induction dose of midazolam or diazepam is likely to take longer than is practical in a field hospital.

The benzodiazepines raise the seizure threshold. Thus they confer central nervous system protective effects to the patient who receives large (and potentially toxic) amounts of local anesthetic agent during regional anesthetic techniques, as well as to the patient with brain injury from head trauma.

Cardiovascular System. In otherwise healthy patients, minimal cardiovascular effects are seen with diazepam or midazolam.[11,41] Mean arterial pressure is typically decreased from 0% to 15%, and moderate increases in heart rate are seen when midazolam is used (0.15 mg/kg administered intra-

venously over 15 s) for induction of anesthesia. This is considerably less hypotension than is routinely seen when sodium thiopental is used as an induction agent. When midazolam is given in a dose of 0.3 mg/kg, hemodynamic changes are similar to those seen with thiopental at a dose of 4.0 mg/kg. Compared with diazepam, midazolam produces a greater decrease in blood pressure, and a slightly greater decrease in systemic vascular resistance.[42]

Combining other anesthetic drugs with diazepam or midazolam in a healthy patient may cause more hemodynamic depression than either agent used alone. In patients with no preexisting heart disease, combining benzodiazepines with narcotics is necessary to prevent hemodynamic changes associated with laryngoscopy and intubation.[41]

Respiratory System. An induction dose of midazolam significantly reduces the ventilatory response to carbon dioxide and produces respiratory depression. This effect has a slower onset and lasts longer than that obtained with thiopental.[43]

Continual vigilance and monitoring will be required in the trauma patient who has received a benzodiazepine drug, particularly when other potent anesthetic drugs have been administered. Postoperative respiratory depression in such a patient is a very real danger. Death secondary to respiratory arrest is a preventable event when the patient is adequately monitored.

Clinical Use

Although diazepam may be used for induction of anesthesia (at a dose range of 0.5–1.0 mg/kg), its relatively prolonged clinical effects limit its clinical usefulness as a primary anesthetic agent. The drug is poorly soluble in aqueous solution and is supplied in an ethylene glycol carrier solution. This causes a troublesome stinging or burning sensation on injection, particularly with the relatively large doses needed for induction of anesthesia. The true usefulness of diazepam in wartime surgery is as an adjunct to other anesthetic agents and techniques, and in allaying anxiety in the perioperative period. Sedation and anxiolysis are achieved with diazepam by titrating to desired effect, with a typical total dose range of 5 to 10 mg.

Because of its rapid onset of action and relatively short duration of action (60–90 min following an induction dose), midazolam can be used as an alternative to the barbiturates for induction of anesthesia for surgery that is expected to last 2 hours or longer. The dose is 0.15 to 0.3 mg/kg when used for this purpose. When surgery lasts less than 60 to 90 minutes, the anesthesia provider can expect to see significant postoperative respiratory depression with this induction regimen. When titrated to effect with 0.5 to 1.0 mg intravenous boluses, midazolam is an excellent anxiolytic and produces profound amnesia, making it a useful agent in the patient receiving a regional anesthetic technique.

As has already been mentioned, ketamine frequently causes vivid dreaming, nightmares, hallucinations and other emergence phenomena. The incidence of these undesirable effects is significantly reduced when a benzodiazepine is administered concomitantly. A useful regimen is diazepam 0.15 mg/kg administered intravenously 5 minutes prior to induction with ketamine. Midazolam 0.075 mg administered intravenously may be used in place of diazepam. Since ketamine has proven to be a very popular field anesthetic agent during recent conflicts, the benzodiazepine drugs will no doubt be useful adjuncts to its use.

Scopolamine

Scopolamine is a naturally occurring drug, obtained from plants of the belladonna family. Other drugs in this class include atropine and glycopyrrolate (Robinul, manufactured by A. H. Robins Co., Richmond, Va.). All of these agents will reduce salivation and upper airway secretions. Scopolamine possesses unique features that make it useful in trauma anesthesia.

Physiological Effects

Central Nervous System. Scopolamine crosses the blood–brain barrier and depresses the central nervous system. In therapeutic doses (0.4 mg administered intravenously), it causes drowsiness, euphoria, amnesia, fatigue, and dreamless sleep. Scopolamine is 9-fold more potent than atropine as an amnestic agent. (Another antimuscarinic agent, glycopyrrolate, does not cross the blood–brain barrier. This makes it useful when parasympathetic inhibition is desirable but the potential central nervous system effects of scopolamine are not).

Cardiovascular System. Drugs with antimuscarinic effects inhibit the actions of acetylcholine on the postganglionic cholinergic nerves of the parasympathetic nervous system, and thus reduce or inhibit parasympathetic tone. This is seen clinically as an increase in heart rate (usually lasting less than 30 min).

Clinical Use and Contraindications

The severely traumatized battlefield casualty is likely to be suffering from hemorrhagic shock. The nature of the wounds may dictate immediate surgery, even as the anesthesia team is resuscitating with airway management and intravenous fluid therapy. Because of adverse hemodynamic effects, it is unlikely that such a casualty would tolerate the administration of most of the intravenous anesthetic agents we have discussed in this chapter. Scopolamine (0.4 mg administered intravenously), with its minimal cardiovascular effects and its desirable amnestic qualities, may be the only safe anesthetic drug in this circumstance. As resuscitative efforts proceed and the patient's hemodynamic status stabilizes, additional anesthetic agents may be judiciously titrated.

The central nervous system effects of scopolamine are not absolutely reliable, and fully conscious patients may find them unpleasant. For this reason, use of this drug should be reserved for the severely traumatized and unstable patient, or in those cases where drying of upper airway secretions is desirable (eg, if the casualty requires nasal and oral surgical procedures). If they are available, atropine or glycopyrrolate are better choices for the latter indication.

Droperidol

Droperidol is a major tranquilizer of the butyrophenone class with antipsychotic activity and potent antiemetic effects.

Physiological Effects

Central Nervous System. Droperidol may be used in combination with an opioid narcotic to induce a state of neuroleptanalgesia or neuroleptanesthesia. Such states are characterized by altered awareness, sedation, and, ultimately, unconsciousness. During the state of neuroleptanalgesia, the patient remains conscious but may tolerate short, painful surgical procedures. Droperidol is also an excellent centrally acting antiemetic drug.

Cardiovascular System. Droperidol produces mild α-adrenergic blockade with peripheral vascular dilation. The resultant decrease in systemic vascular resistance is seen clinically as a fall in blood pressure. This effect may be very significant in the hypovolemic patient.

Clinical Use and Contraindications

The onset of action of droperidol occurs in 3 to 10 minutes following intravenous (75 μg/kg) or intramuscular (150 μg/kg) injection. The full effect may not be apparent for 30 minutes. With therapeutic doses, the duration of sedative effect is 2 to 4 hours, although alteration of consciousness may persist up to 12 hours. Additionally, intravenous doses greater than 100 μg/kg may result in prolonged postoperative somnolence.

When a neuroleptic technique is chosen, the opioid agent most commonly used with droperidol is fentanyl, generally in a ratio of 50 μg fentanyl per 2.5 mg droperidol. This combination is available premixed and is called Innovar (manufactured by Janssen Pharmaceutica Inc., Piscataway, N.J.). Nitrous oxide is frequently added to the neuroleptanalgesia regimen to induce unconsciousness and neuroleptanesthesia. The effects of droperidol last longer than the analgesic properties of fentanyl. The result may be a patient who is outwardly calm, yet is experiencing pain and mental agitation. A therapeutic dose for sedation (when used alone for this purpose) is 5 to 10 mg for a 70-kg individual.

Droperidol's undesirable effects on blood pressure in therapeutic doses, as well as its unpleasant and prolonged psychic effects, limit its usefulness as an anesthetic agent. However, the drug is a potent antiemetic in doses that cause minimal sedation (0.625–1.25 mg administered intravenously, which is 0.25–0.5 mL of the standard preparation). The awake patient with minimal postoperative anesthetic side effects (such as nausea and vomiting) will be the easiest to care for with the limited resources of the field hospital recovery room.

ANESTHETIC AGENTS THAT PRODUCE ANALGESIA

Analgesia is a very desirable attribute of an anesthetic agent. However, many of the commonly used intravenous anesthetic agents (including the barbiturates, etomidate, and propofol) have no analgesic properties. Analgesic drugs may be used in combination with agents that produce unconsciousness. The benefits of such combined regimens include maintenance of surgical anesthesia with reduced dosages of each drug, and residual postoperative pain relief. This chapter deals primarily with the

opioid narcotic agents. However, it should be noted that ketamine, which is an extremely useful anesthetic-induction agent, provides very potent analgesia in small intravenous bolus doses (5–10 mg). Opioid narcotic agents are the most commonly used analgesics. The term *opioid* refers to compounds that bind to one or more subpopulations of opiate receptors in the central nervous system. Most anesthesiologists classify the opioid drugs on the basis of their primary effects at the opiate receptor site. This classification scheme results in three primary drug groups: the opioid agonists, the agonist–antagonists, and the antagonists. See Chapter 13, Perioperative Pain Management, for a discussion of the use of these agents purely for analgesia.

Opioid Agonist Drugs

The opioid agonist drugs commonly used intraoperatively (either to supplement or to provide the primary anesthetic) include morphine, meperidine, and the relatively recently discovered phenylpiperidine derivatives, namely, fentanyl, sufentanil, and alfentanil. While these agents differ in potency and pharmacokinetics, they share the important properties of dose-related analgesia as well as respiratory depression.[44]

Because the combat medical corpsman may be supplied with prefilled morphine syringes for prehospital field use, it is imperative that the preanesthetic evaluation of the patient should include whether the patient was medicated during or prior to transport to the field medical facility. Failure to ascertain the dose given may lead to the need for prolonged postoperative ventilatory support if additional morphine or other opioid agonists are given intraoperatively.

Physiological Effects

Central Nervous System. The opioid agonists produce analgesia, sedation, euphoria, and a feeling of body warmth. In the absence of pain, dysphoria rather than euphoria may be produced. Analgesia is most effective when administered prior to onset of the painful stimulus. Continuous, dull pain is relieved more effectively than sharp, intermittent pain. These effects are a result of drug interaction with opioid receptors in the brain and spinal cord. Another important effect of the opioids is stimulation of the central nervous system chemoreceptor trigger zone, producing nausea or emesis in many patients.[44]

Cardiovascular System. Direct stimulation of the medullary vagal nucleus may cause bradycardia following a dose of an opioid agonist.[44] Compensatory sympathetic nervous system responses are blunted, producing or contributing to orthostatic hypotension. Hypotension may also be seen secondary to morphine-induced histamine release.[45] This effect is widely variable, and can be mitigated somewhat by slow administration, supporting intravascular volume, slight head-down position, and prior administration of antihistaminic drugs. Meperidine also causes histamine release, but fentanyl and sufentanil do not.[45]

Meperidine is the only opioid drug with a direct myocardial depressant effect (when given in large doses). Also in contrast with the other opioid agonists, meperidine rarely causes bradycardia and may, in fact, be associated with tachycardia. This property probably reflects its structural similarity to atropine. Like morphine, meperidine may interfere with compensatory sympathetic nervous system reflexes. In analgesic doses, meperidine is associated with hypotension more commonly than is morphine.

The principal advantages of fentanyl (and its more recent analogs) are its maintenance of stable hemodynamics due to the absence of histamine release, the relative lack of direct myocardial depressant effects, and the suppression of the stress responses to surgery.

Respiratory System. All opioid agonists depress ventilation. This initially manifests clinically as a decreased rate of breathing with maintenance of tidal volume. With higher doses, tidal volume diminishes as well. Thus, a dose-related increase in the partial pressure of carbon dioxide in arterial blood ($Paco_2$) is seen. It is important to note, however, that morphine and other opioid agonists may actually lower $Paco_2$ values postoperatively in some patients who have been breathing with small tidal volumes because of pain. Pain is a natural antagonist to the respiratory depressant action of opioids.[44]

Respiratory depression in a casualty who has a closed head injury is particularly dangerous. Because opioid narcotic agents depress the ventilatory response to carbon dioxide, increased $Paco_2$ in the spontaneously breathing combat trauma victim will cause increased intracranial pressure with potentially lethal consequences when head injuries are present. Extreme caution must attend the use of opioid narcotics in such patients.

Respiratory depression is also a problem when these drugs are given in dosage ranges high enough

to produce unconsciousness or surgical anesthesia. Because prolonged mechanical ventilatory support will generally be impossible in the austere environment of the combat support hospital, pure narcotic anesthetic techniques will not be useful. The utility of the narcotic drugs will be as adjuncts to inhalational or intravenous anesthetic techniques, using shorter-acting drugs that depress the respiratory system less as the primary anesthetic agents.

Morphine

Morphine is the classic opioid agonist. Intravenous administration of morphine produces a peak effect in about 20 minutes. This relatively slow onset reflects prolonged penetration of the blood–brain barrier by morphine, owing to its poor lipid solubility. The elimination half-life is approximately 2 hours and is largely dependent on excretion by the kidney following conjugation in the liver. A typical intraoperative dose, when morphine is used as an adjuvant agent for general anesthesia, is 0.1 to 0.2 mg/kg. The ideal dose will vary with the duration of the operation. Excellent and relatively prolonged postoperative analgesia generally results when this regimen is used. When morphine is used as the primary anesthetic agent, a dose of 1.0 to 2.0 mg/kg is necessary. The inability to provide adequate postoperative ventilatory support in the field medical environment severely limits the usefulness of the latter technique. Side effects include nausea, pruritus, and depressed ventilatory response to carbon dioxide. When morphine is used with other anesthetic agents, its respiratory depressant effects are augmented. This necessitates careful titration and monitoring in the operating room.

Meperidine

Meperidine (Demerol, manufactured by Sanofi Winthrop Pharmaceuticals, New York, N.Y.) is an older synthetic opioid agonist with one tenth the potency of morphine. Although it has been supplanted by newer and better synthetic drugs for intraoperative use in the United States, meperidine may prove to be readily available in third-world nations, and is still commonly used for analgesia outside the operating room. A typical intramuscular dose for postoperative pain is 1 to 2 mg/kg. If given via the intravenous route, this dose should be reduced by half. Precautions for intraoperative and postoperative meperidine use are similar to those for morphine.

Fentanyl

Fentanyl (Sublimaze, manufactured by Janssen Pharmaceutica Inc., Piscataway, N.J.) is a synthetic opioid agonist that is 100-fold more potent than morphine. It is supplied in a preparation of 50 μg/mL. Fentanyl has a faster onset and shorter duration of action than morphine. Potency and onset are related to the drug's high lipid solubility, and the shorter half-life reflects redistribution.[44] Like thiopental, repeated doses or continuous infusions saturate inactive tissue sites, interfering with the ability of redistribution to lower serum concentrations of the drug. The elimination half-life of fentanyl is 200 minutes, which is actually longer than that of morphine. This apparent contradiction is explained by both redistribution of drug from the active site and the greater volume of distribution of fentanyl. Serum concentration is partially maintained by slow re-uptake from inactive tissue sites.

Clinically, fentanyl has been popular in a wide range of doses. One to two micrograms per kilogram is a useful analgesic dose; 3 to 10 μg/kg is a useful dose range as an adjunct to other anesthetic drugs for induction or maintenance of anesthesia. Once again, prolonged postoperative respiratory depression severely limits the utility of this latter technique in most combat-support medical settings. If intraoperative mechanical ventilation is available, fentanyl may be administered with a continuous-infusion technique. Following a loading dose of 5 to 10 μg/kg (depending on the predicted length of the surgery), a continuous infusion is begun and maintained at 1 to 2 μg/kg/h. If the infusion is stopped 20 to 30 minutes prior to the completion of surgery, the patient will generally awaken promptly with excellent residual analgesia. Used in this manner, fentanyl augments the effects of the volatile anesthetic drugs, allowing the use of lower inspired concentrations of these agents. This technique should not be used unless the patient's respirations are controlled in the operating room.

The shorter duration of action of fentanyl (relative to morphine) allows greater ease of titration in the clinical setting. The absence of histamine release in clinically relevant doses results in less dilation of the venous capacitance vessels, producing less hypotension and a decreased need for temporary fluid supplementation.

Potential problems include persistent or recurrent respiratory depression. Fentanyl circulating in the plasma may be secreted into and sequestered by acidic gastric fluid, with subsequent reabsorption.

This reabsorbed fentanyl will once again act on the central nervous system. Fentanyl may also become trapped in poorly perfused areas of the lung during general anesthesia. Washout of these areas as perfusion improves would also tend to increase the plasma fentanyl level. Other potential problems are bradycardia, which may become hemodynamically significant in the traumatized patient, and truncal rigidity. The latter can make controlled ventilation of the patient quite difficult, necessitating the use of a neuromuscular blocking agent to relax the chest wall. The incidence and severity of both bradycardia and truncal rigidity appear to be related to the rate of administration, and each is readily managed with the appropriate pharmacological intervention.

Sufentanil

Sufentanil (Sufenta, manufactured by Janssen Pharmaceutica Inc., Piscataway, N.J.) is an analog of fentanyl, with an elimination half-life of approximately 156 minutes. Its anesthetic potency is estimated to be 5- to 10-fold greater that of fentanyl. This increased potency is a result of sufentanil's greater affinity for the opioid receptor.[46] The greater potency and more rapid onset of sufentanil make it a more titratable drug than fentanyl. This reduces the incidence and likelihood of tachycardia and hypertension in response to painful stimuli. Side effects and potential problems are the same as those seen with fentanyl.

Like fentanyl, sufentanil is supplied in a strength of 50 μg/mL. For analgesia, 5 to 10 μg administered intravenously may be sufficient. Note that this is 0.1 to 0.2 mL of undiluted drug. Obviously, great care is required when sufentanil is used in this way. This dose may be repeated as necessary to achieve adequate analgesia.

As an adjunct to general anesthesia, sufentanil possesses all the advantages of fentanyl with respect to hemodynamic stability and suppression of the stress response to surgery. It appears to be even better than fentanyl in preventing or reducing the hemodynamic response to endotracheal intubation. When used as part of a balanced anesthetic technique, a useful starting dose of sufentanil is 0.5 to 1.0 μg/kg. As with fentanyl, a continuous infusion may be established at a rate of 0.1 to 0.2 μg/kg/h.

Alfentanil

In contrast to sufentanil, alfentanil (Alfenta, manufactured by Janssen Pharmaceutica Inc., Piscataway, N.J.), the fentanyl analog, is much less potent than its parent compound. Alfentanil is supplied in a strength of 500 μg/mL. It has one tenth to one fifth the potency, one fourth the time to onset of action, and about one third the duration of action of fentanyl. The relatively fast onset and short duration of alfentanil allow for excellent titratability and make it very useful for shorter surgical procedures and continuous infusions.

Alfentanil rapidly crosses the blood–brain barrier because it is almost entirely un-ionized at physiological pH.[46] After an intravenous bolus, plasma levels fall rapidly owing to both redistribution and metabolism. Unlike most other drugs, alfentanil in a continuous infusion does not produce a significant cumulative effect in the length of time that most surgery requires. The elimination half-life is about one half that of fentanyl. The clinical duration of action of this agent may be as little as 15 minutes following an intravenous bolus injection.

When used as part of a balanced anesthetic technique, a continuous infusion is recommended because of its short duration of action. Alfentanil, in a dose of 150 to 300 μg/kg, will induce anesthesia in less than 1 minute. An infusion rate of 25 to 150 μg/kg/h, when combined with another amnestic sedative (such as a low-dose potent inhalational agent), is effective for the maintenance of anesthesia and will produce minimal cumulative drug effect. Such a technique may prove to be very useful in the combat medical facility.

Alfentanil shares with all of the fentanyl analogs the potential for problems with respiratory depression and bradycardia.

Opioid Agonist–Antagonist Drugs

As the name implies, opioid drugs in this group have both excitatory and inhibitory effects at opiate receptor sites in the central nervous system. The mixture of agonist and antagonist properties limits somewhat their clinical usefulness when used as the sole narcotic agents during general anesthesia. A theoretical advantage of these drugs is that their partial antagonist action may reduce the incidence or degree of respiratory depression that is seen with equivalent doses of pure opioid agonist agents. However, this same mechanism limits the achievable degree of analgesia when agonist–antagonist drugs are administered.

Clinical experience has shown that significant respiratory depression remains a potentially serious side effect with these agents, despite their partial antagonist properties. They are most useful as analgesic adjuncts to regional anesthetic procedures,

and in the recovery room. Another potential problem is triggering of the withdrawal syndrome in the opioid-narcotic addicted patient.

Nalbuphine

The analgesic potency of nalbuphine (Nubain, manufactured by Du Pont Multi-Source Products, Garden City, N.Y.) is approximately the same (milligram for milligram) as that of morphine. Onset of action is within 2 to 3 minutes following intravenous injection, with a duration of effect in the range of 3 to 6 hours.

Respiratory depression may occur within the usual dose range (generally 10–15 mg) for preoperative sedation or analgesia. The degree of respiratory depression is similar to that of an equianalgesic dose of morphine. There is a ceiling effect to the magnitude of respiratory compromise; that is, depressed respiration does not become more pronounced as the dose of nalbuphine is increased. However, there also appears to be a ceiling effect to the degree of analgesia achieved with increasing doses of nalbuphine. What this means clinically is that doses in excess of 0.15 mg/kg will confer no greater respiratory depression or analgesia than lower doses.[44]

Butorphanol

Butorphanol (Stadol, manufactured by Bristol Laboratories, Evansville, Ind.) resembles nalbuphine in its clinical usage and effects. It is approximately 5-fold more potent than morphine on a weight basis. Butorphanol may be given intramuscularly (1–4 mg) or intravenously (0.5–2.0 mg). Duration of analgesia is 3 to 4 hours. As with nalbuphine, an analgesic and respiratory depressant ceiling effect is seen.

Opioid Antagonist Drugs

Naloxone (Narcan, manufactured by Du Pont Multi-Source Products, Garden City, N.Y.) is the prototypical narcotic antagonist, with strong affinity for opiate receptors and almost no agonist effect. In cases of opiate-induced respiratory depression (such as might be seen following a relative overdose of narcotic agent during general anesthesia), respiratory rate and tidal volume are promptly increased following an intravenous dose of naloxone. However, the analgesic and sedative effects of these drugs will also be antagonized. Thus, the dose of naloxone should be carefully titrated in 0.1- to 0.2-mg doses (for children, 0.01 mg/kg) at 2- to 3-minute intervals until the desired effect is achieved. The onset of action is rapid (within 2 min) following intravenous injection and is only slightly longer via the intramuscular route.

The clinical effects of naloxone last from 1 to 4 hours, depending on the dose given. The plasma half-life is about 1 hour. Since the respiratory depressant effects of some opioid narcotics may persist longer than the naloxone dose administered, personnel in the recovery room must be informed whenever this drug is used in the operating room prior to transport. Such a patient will require more than usual vigilance in the recovery area to prevent hypoventilation or apnea should the narcotic effect outlast that of naloxone.

Naloxone possesses some undesirable side effects. The most serious potential problems include increased intracranial pressure in the patient with a head injury, hypertension, pulmonary edema, dysrhythmias, and cardiac arrest.[47]

Naloxone (as well as the agonist–antagonist drugs) may precipitate a moderate to severe withdrawal syndrome. The symptoms and signs of acute narcotic withdrawal include irritability, nervousness, mental confusion, generalized pain, diaphoresis, abdominal cramping with diarrhea, nausea, and vomiting. This syndrome appears within 2 minutes of the administration of naloxone to a patient with narcotic dependency, and is self-limiting owing to its short plasma half-life of approximately 60 minutes. Soldiers are not entirely exempt from narcotic abuse, and this history must be obtained preoperatively, if possible.

TECHNIQUES FOR USING INTRAVENOUS ANESTHETICS

Rapid-Sequence Intravenous Induction

Experience with battlefield casualties in Vietnam showed that the majority of wounded soldiers have undigested material in their stomachs at the time of emergency surgery.[1] Regurgitation and aspiration of gastric contents into the tracheobronchial tree causes severe pulmonary dysfunction and is potentially fatal. At the very least, such complications require the allocation of scarce recovery and critical care resources to treat what is nearly always a preventable complication of general anesthesia. The risk of regurgitation and aspiration is markedly reduced when the trachea is intubated with a cuffed

endotracheal tube. This must be accomplished quickly, following the administration of (1) an intravenous anesthetic agent that causes a rapid loss of consciousness and (2) a muscle relaxant with a similar rapid onset of clinical action. Rapid-sequence induction of anesthesia is performed in a definite sequence (Exhibit 10-1).

The intravenous agents that are most useful for rapid-sequence induction of anesthesia include sodium thiopental, ketamine, and etomidate (see Table 10-2). The reader is encouraged to review the specific advantages and disadvantages of these agents. The only currently available neuromuscular blocking agent with a fast-enough clinical onset time for use in a rapid-sequence induction technique is succinylcholine. The following are suggested dose regimens for rapid-sequence induction of anesthesia in combat casualties:

- ketamine (1–2 mg/kg) immediately followed by succinylcholine (1–2 mg/kg);
- etomidate (0.2–0.4 mg/kg) immediately followed by succinylcholine, as above; and
- sodium thiopental (1–4 mg/kg) immediately followed by succinylcholine, as above.

Each of these drug regimens will typically provide good intubating conditions within 45 to 60 seconds. Dosages should be adjusted downward in the hemodynamically unstable patient, particularly when thiopental is being used.

Not uncommonly, a combat casualty may already be unconscious and in a hypovolemic shock state. In such cases, any of the above agents may cause further deterioration of the patient's condition. A rapid-sequence technique using succinylcholine alone may be the safest alternative in such situations. In the worst case, even succinylcholine may be dispensed with and the patient intubated through cricoid pressure. Scopolamine 0.4 mg administered intravenously may provide amnesia during the initial period of resuscitation.

Adjuvants to Inhalational Anesthesia

Following induction of anesthesia with an intravenous drug, surgical anesthesia must be maintained. Most commonly this will be accomplished with a volatile anesthetic agent delivered by draw-over vaporizer or a field anesthesia machine. If the patient is to breathe spontaneously during the procedure, adjuvant drugs such as opioid narcotic agents must be used with extreme caution to prevent respiratory arrest.

When inhalational anesthesia is being used as the primary technique, the addition of a narcotic drug is part of a balanced anesthetic, with the advantages of lower total overall doses of individual anesthetic drugs as well as residual postoperative analgesia (Exhibit 10-2). Because of the respiratory depression that accompanies a balanced anesthetic technique, it is most useful in the field environment in those cases during which the casualty's respirations are to be manually controlled. Such instances would include those there the casualties were undergoing thoracotomies, craniotomies, and major intraabdominal procedures. A muscle relaxant drug is an important component of the technique.

EXHIBIT 10-1

RAPID-SEQUENCE INDUCTION OF ANESTHESIA

1. The patient is given four to five large breaths of 100% oxygen by anesthesia mask.
2. Firm pressure is applied by an assistant with thumb and finger over the patient's cricoid cartilage in the anterior neck. (This compresses the esophagus between the vertebral column and cricoid ring to minimize the risk of passive regurgitation of gastric contents into the posterior pharynx.)
3. The chosen anesthetic agent and muscle relaxant are administered.
4. When the patient is unresponsive and has lost his lid reflex, the larynx is visualized and the endotracheal tube is passed into the trachea. The cuff is inflated. (During the interval prior to intubation, the patient must *not* be ventilated by bag and mask, as air may be forced into the stomach, increasing the risk of regurgitation.)
5. The presence of bilateral equal breath sounds is confirmed. Only after this fifth step is completed should the assistant release the cricoid pressure.

EXHIBIT 10-2

OPIOID NARCOTICS AS ADJUVANTS TO INHALATIONAL ANESTHESIA

- ***Morphine*** 0.1 to 0.2 mg/kg.
- ***Meperidine*** 0.5 to 1.0 mg/kg.
- ***Fentanyl*** 3 to 5 μg/kg on induction of anesthesia. Additional bolus doses of 50 μg/h or a continuous infusion at 1 to 2 μg/kg/h are used for maintenance. Continuous infusions should be stopped 15 to 30 minutes before the end of surgery. An alternative technique is to estimate the time of the proposed surgical procedure. The projected time (in minutes) is divided by 10 and 15. The resulting values represent the fentanyl dose in μg/kg to be administered prior to skin incision, after which no more is given.[1] For example, during a 60-minute procedure, 4 to 6 μg/kg of fentanyl may be given prior to skin incision.
- ***Sufentanil*** 0.5 to 1.0 μg/kg on induction. Additional bolus doses of 5 to 10 μg may be given every 20 to 30 minutes as necessary. If a continuous infusion is to be used, the dosage rate should be 0.1 to 0.2 μg/kg/h following the loading dose. Stop the infusion approximately 30 minutes before the end of surgery.
- ***Alfentanil*** 20 to 60 μg/kg following 2 mg/kg thiopental provides good surgical anesthesia. Larger doses of alfentanil (150–300 μg/kg) will induce anesthesia in less than 1 minute when used alone. Alfentanil's duration of action is quite short (as little as 15 min following a bolus injection). For longer cases, a continuous infusion is necessary to maintain anesthesia. The infusion rate should be set at 25 to 150 μg/kg/h, and can be continued until the end of surgery. The patient can be expected to awaken promptly, but residual analgesia will be relatively short-lived.

1. Ross, AL. How to give an anaesthetic using intravenous analgesics: An alternative from California. *Can Anaesth Soc J*. 1983;30:259-260.

When spontaneous ventilation is to be maintained during general anesthesia for surgery outside the major body cavities, narcotic agents may be administered cautiously as the case is nearing completion. A useful regimen is to reduce slightly the percentage of inspired concentration of the inhalational anesthetic agent. Morphine 0.5 to 1.0 mg is then administered. This is repeated at about 10-minute intervals, to a total morphine dose of 0.1 to 0.2 mg/kg. Respiratory rate and other vital signs must be carefully monitored. Ideally, the last morphine dose is given and the inhalational agent completely turned off 10 to 15 minutes before the end of the procedure. The result is a patient who is spontaneously ventilating with excellent analgesia. This technique works best when the patient is breathing 50% to 60% nitrous oxide, which is shut off as the last skin sutures are in place. Fentanyl may be substituted for morphine and used in a similar fashion, to a final dose of 3 to 5 μg/kg.

Total Intravenous Anesthesia

In contrast to regional techniques and general anesthesia using inhaled gases, total intravenous anesthesia using a single agent seems suited to battlefield use, owing to its relative simplicity (see Table 10-3). Since its introduction in 1970, ketamine has been touted as such an agent. Although ketamine has some untoward side effects, its tendency to preserve blood pressure and airway reflexes make it a very useful drug in the field (see the foregoing section on ketamine in this chapter). It remains the only available intravenous medication that can serve as the sole agent in a general anesthetic.[17] Its use in this manner is described below.

It is conceivable that shortages of various anesthetic agents may occur in forward medical units during wartime. If inhalational anesthetic agents become scarce or unavailable, alternative techniques will become necessary for maintenance of surgical anesthesia. Even in the absence of such shortages, total intravenous anesthesia may occasionally be the technique of choice for brief surgical procedures. Total intravenous anesthesia is possible using a variety of techniques (Exhibit 10-3).

Adjuvants for Regional and Local Anesthesia

For brief, minor surgical procedures, profound anesthetic depth and complicated techniques are not always necessary. If the procedure can be per-

EXHIBIT 10-3

TECHNIQUES FOR TOTAL INTRAVENOUS ANESTHETICS

- ***Ketamine***. An induction dose of ketamine 1.0 to 2.0 mg/kg is preceded by midazolam 1 to 2 mg (or diazepam 5–10 mg). Following induction, a continuous infusion is maintained at 20 to 50 μg/kg/min (2–4 mg/min for a 70-kg soldier). At the lower end of the dosage spectrum, spontaneous ventilation is possible. However, regurgitation and aspiration are still risks. Therefore, in acutely injured patients, the airway should be protected with an endotracheal tube. Midazolam or diazepam will reduce or eliminate emergence phenomena such as unpleasant dreams and hallucinations. When a neuromuscular blocking agent is used, the maintenance dose of ketamine may be reduced somewhat.
- ***Etomidate***. An induction dose of etomidate 0.2 to 0.4 mg/kg is given, followed by a maintenance dose of 40 to 100 μg/kg/min. After 10 minutes, this is reduced to 10 to 40 μg/kg/min. Since etomidate has no analgesic properties, a narcotic (such as fentanyl 3 to 5 μg/kg) may be added to the regimen. For a 70-kg patient, these maintenance doses are 170 to 400 mg/h for the first 10 minutes, followed by a rate of 40 to 170 mg/h. The combination of etomidate, a narcotic agent, and a neuromuscular blocking agent can produce acceptable surgical anesthesia. The infusion should be discontinued 15 to 30 minutes before the end of surgery.
- ***Sodium Thiopental***. Incremental doses of sodium thiopental (1–2 mg/kg) may be titrated to onset of unconsciousness. In this way, spontaneous ventilation may be preserved. This technique is useful for very short procedures and to "smooth" the patient's emergence from inhalational anesthesia. Due to its cumulative central nervous system– and cardiopulmonary-depressant effects, however, thiopental must be administered judiciously. For a surgical case that will last longer than 20 to 30 minutes, a continuous infusion may be prepared by putting 1 to 2 g of thiopental in 250 mL of 5% dextrose in water. Following an induction dose of 2 to 4 mg/kg, a continuous infusion is maintained at 0.1 mg/kg/min. This infusion should be supplemented with an intravenous narcotic and is not recommended unless the patient's respirations are controlled.
- ***Propofol***. Following an induction dose of propofol 2.0 to 3.0 mg/kg, a continuous infusion of 0.1 to 0.2 mg/kg/min (6–12 mg/kg/h) is started. This dose may be reduced by one half or more for critically ill or debilitated patients.
- ***Alfentanil***. An induction dose of alfentanil 150 to 300 μg/kg will induce general anesthesia. A continuous infusion should be set to run at 25 to 150 μg/kg/h for maintenance. Because alfentanil may produce chest-wall rigidity and will definitely cause respiratory depression, the patient should be ventilated mechanically when this technique is used.

formed under local anesthesia, intravenous agents such as the benzodiazepines may be useful in allaying anxiety. Small, intravenous bolus doses of thiopental (1–2 mg/kg) or etomidate (0.1 mg/kg) will not provide analgesia, but may alter consciousness sufficiently to allow a short, painful procedure. If the patient has had no oral intake for at least 6 hours, aspiration risk with these techniques should be minimal. If he has eaten recently, any drug-induced blunting of the airway and gag reflexes should be avoided unless the trachea is protected with an endotracheal tube.

Ketamine is very useful for short procedures in which deep general anesthesia is not required. Incremental bolus doses of 5 to 10 mg provide intense analgesia and altered consciousness. The opioid narcotic agents can also be used in these types of cases. They are most effective if given *before* the painful stimulus. Because they cause more blunting of spontaneous respiration, they allow somewhat less flexibility in dosing than ketamine.

Small-bolus injections of an opioid narcotic drug may be useful in this setting for producing sedation and supplying additional analgesia.

SUMMARY

An impressive number of intravenous anesthetic drugs are available to the anesthesiologist in civilian practice. The wartime anesthesia provider, however, may have to make do with a more limited drug repertoire. It is possible that many physicians and nurses who have little or no training in the field of anesthesiology will be called on to assist in providing this service in battlefield hospitals.

While the combat anesthesia provider may not have access to all of the anesthetic agents described in this chapter, at least one or two agents for each anesthetic indication will almost certainly be available. Thus, only thiopental and ketamine may be available for induction of anesthesia. For analgesia, morphine or fentanyl may be the only drugs in the pharmacy. Perhaps one of the benzodiazepines will be available as well. Whatever the contents of the drug locker, the wartime anesthesia provider must have a rational plan of action for each casualty, and should know how to use safely the intravenous anesthetic agents available in the medical treatment facility.

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