Miller-IV Anaesthetic Agents

• IV Anesthetic Agents

• PROPOFOL

History

Propofol (Diprivan) is the most recent intravenous anesthetic to be introduced into clinical practice. Work in the early 1970s on substituted derivatives of phenol with hypnotic properties resulted in the development of 2,6-di-isopropofol. 325 The first clinical trial, by Kay and Rolly 326 and reported in 1977, confirmed the potential of propofol as an anesthetic induction agent. Propofol is insoluble in water and therefore was initially prepared with Cremophor EL (BASF A.G.). Because of anaphylactoid reactions associated with Cremophor EL in this early formulation of propofol, 327 the drug was reformulated in an emulsion. Propofol has been used for induction and maintenance of anesthesia as well as for sedation.

Physicochemical Characteristics

Propofol (Fig. 9–17) is one of a group of alkylphenols that have hypnotic properties in animals. 328 The alkylphenols are oils at room temperature and are insoluble in aqueous solution, but they are highly lipid soluble. The present formulation consists of 1 percent (wt/vol) propofol, 10 percent soybean oil, 2.25 percent glycerol, and 1.2 percent purified egg phosphatide. In the United States, disodium edetate (0.005%) was added as a retardant of bacterial growth. Propofol has a pH of 7 and appears as a slightly viscous, milky white substance. Propofol is available as a 1 percent solution in 20-mL clear glass ampules, 50- and 100-mL vials, and in 50-ml prefilled syringes. It is stable at room temperature and is not light sensitive. If a dilute solution of propofol is required, it is compatible with 5 percent dextrose in water.

Metabolism

Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulfate 329 to produce water-soluble compounds, which are excreted by the kidneys. 329 Less than 1 percent propofol is excreted unchanged in urine, and only 2 percent is excreted in feces. 329 The metabolites of propofol are thought not to be active. Because clearance of propofol exceeds hepatic blood flow, extrahepatic metabolism or extrarenal elimination has been suggested. Extrahepatic metabolism has been confirmed during the anhepatic phase of patients receiving a transplanted liver. 330, 331 The lungs do not seem to be the site of this extrahepatic metabolism; however, in *in vitro* studies with human kidney and small intestine, microsomes in these tissues demonstrated an ability to form propofol glucuronide. 332 Propofol itself results in a concentration-dependent inhibition of cytochrome P-450 and thus may alter the metabolism of drugs dependent on this enzyme system. 333

Pharmacokinetics

The pharmacokinetics of propofol following a wide range of doses as well as following continuous infusions has been evaluated by numerous investigators, 329, 334, 335, 336, 337, 338, 339 and it has been described by both two- and three-compartment models (see Table 9–3). Following a single bolus injection, whole blood propofol levels decrease rapidly as a result of both redistribution and elimination (Fig. 9–18). The initial distribution half-life of propofol is 2 to 8 minutes. 329, 335 In studies using a two-compartment model, the elimination half-life has varied from 1.0 to 3 hours. 329, 334, 338, 339 Studies in which the disposition of propofol was better described by a three-compartment model have given initial and slow distribution half-lives of 1 to 8 minutes and 30 to 70 minutes and an elimination half-life of 4 to 23.5 hours. 335, 336, 337, 339, 340 This longer elimination half-life is indicative of a deep compartment with limited perfusion, which results in a slow return of propofol back to the central compartment. Owing to the rapid clearance of propofol from the central compartment, the slow return of propofol from this deep compartment contributes little to the initial rapid decrease in propofol concentrations. The context-sensitive half-time for propofol (see Fig. 9–5) for infusions of up to 8 hours is less than 40 minutes. 341 Because the required decrease in concentration for awakening following anesthesia or sedation with propofol is generally less than 50 percent, recovery from propofol remains rapid even following prolonged infusions. The volume of distribution of the central compartment has been calculated as 20 to 40 L, and the volume of distribution at

steady state has been calculated as 150 to 700 L. 329, 334, 335, 336, 337, 338, 339 The clearance of propofol is extremely high—1.5 to 2.2 L/min. 329, 334, 335, 336, 337, 338, 339 This exceeds hepatic blood flow, and extrahepatic metabolism has been demonstrated. 330, 331 The equilibrium constant for EEG effect for propofol is 0.291 min–1, and the half-life of equilibrium between plasma concentration and EEG effect is 2.4 minutes based on suppression of the EEG. The time to peak effect is 92 seconds. 342

TABLE 9–3. Pharmacokinetic Variables of Commonly Used Intravenous Anesthetics
FIGURE 9–18 Simulated time course of whole blood levels of propofol following an induction dose of 2.0 mg/kg. Blood levels required for anesthesia during surgery are 2 to 5 ?g/mL, with awakening usually occurring at a blood level lower than 1.5 ?g/mL.
FIGURE 9–5 The context-sensitive half-times for commonly used intravenous anesthetic drugs are displayed. The context-sensitive half-time is the time for the plasma level of the drug to drop 50 percent after cessation of infusion. The duration of infusion is plotted on the horizontal axis. Note that the rapidity with which the drug level drops is directly related to the time of infusion (i.e., the longer the drug is infused, the longer the half-time). Also note that etomidate, propofol, and ketamine have significantly shorter half-times than thiopental and diazepam, which makes them more suitable for prolonged infusion.

The pharmacokinetics of propofol may be altered by a variety of factors (e.g., gender, weight, preexisting disease, age, and concomitant medication). 335, 336, 339, 343, 344 Propofol may impair its own clearance by decreasing hepatic blood flow. 345 Probably of greater clinical significance is that propofol may alter its own intercompartmental clearances because of its effects on cardiac output. Women have a higher volume of distribution and higher clearance rates, but the elimination half-life is similar for males and females. 335, 339 The elderly have decreased clearance rates but a smaller central compartment volume. 336, 339 In addition, patients presenting for coronary artery bypass surgery seem to have different pharmacokinetic parameters compared with other adult populations. When a patient is placed on a cardiopulmonary bypass machine, there is an increase in the central volume and initial clearance, thus necessitating higher initial infusion rates to maintain the same propofol plasma concentration. 346 Children have a larger central compartment volume (50%) and a more rapid clearance (25%). 347 In children older than 3 years, volumes and clearances should be weight adjusted 348 (Ch. 59). Children less than 3 years of age also demonstrate weight-proportional pharmacokinetic parameters but with greater central compartment and systemic clearance values than in adults or older children 348 . This finding explains the higher dosing requirements in this age group. 349 Hepatic disease appears to result in a larger steady-state and central compartment volumes; clearance is unchanged, but the elimination half-life is slightly prolonged. 343 The effect of fentanyl administration on propofol pharmacokinetic parameters is controversial. Some studies suggest that fentanyl may reduce intercompartmental and total body clearance rates as well as volumes of distribution. 350 When propofol was administered with alfentanil at similar infusion rates, the measured propofol concentrations were 22 percent greater than when propofol was administered alone. 351 A separate study found that fentanyl did not alter propofol pharmacokinetics following a single dose of both drugs. 352 Some of these differences in propofol pharmacokinetics when given with an opioid may be explained by studies in cats that showed that pulmonary uptake of propofol is reduced by 30 percent when propofol is administered immediately following fentanyl but not if it is administered 3 minutes later. 353 In addition, *in vitro* studies on human hepatocytes demonstrated that propofol inhibited in a dose-dependent manner the enzymatic degradation of both sufentanil and alfentanil. 354 Propofol kinetics are unaltered by renal disease. 344

Pharmacology

Effects on the Central Nervous System

Propofol is primarily a hypnotic. The exact mechanism of its action has not yet been fully elucidated; however, evidence suggests that it acts by promoting the function of the ?1 subunit of GABA through activation of the chloride channel and thereby enhancing inhibitory synaptic transmission. 355, 356, 357 Propofol also inhibits the NMDA subtype of glutamate receptor through modulation of channel gating. 358, 359 This action may also contribute to the drug‘s CNS effects. The hypnotic action of propofol is pressure reversible, and it adheres to the correlation exhibited by other general anesthetics between anesthetic potency and octanol/water distribution coefficient. 360 Unlike barbiturates, propofol is not antianalgesic. 361 Propofol at subhypnotic doses helps in the diagnosis and treatment of central, but not neuropathic, pain. 357

The onset of hypnosis following doses of 2.5 mg/kg is rapid (one arm-brain circulation), with a peak effect seen at 90 to 100 seconds. 362, 363 The ED50 of propofol is 1 to 1.5 mg/kg following a bolus. 362, 364, 365, 366 The duration of hypnosis is dose-dependent, being 5 to 10 minutes following 2 to 2.5 mg/kg. 362, 367 Age markedly affects the 95 percent effective dose (ED95) induction dose of propofol, being highest at ages less than 2 years (ED95 2.88 mg/kg) and decreasing with increasing age. 368 At subhypnotic doses, propofol provides sedation and amnesia. 369, 370, 371 Propofol infusions of at least 2 mg/kg/h were necessary to provide amnesia in unstimulated volunteers. 372 Awareness during surgery at higher infusion rates has been reported. 373 During surgical procedures, extremely high infusion rates may be necessary to prevent awareness if propofol is used as the sole anesthetic. 374 Propofol alters mood following short surgical procedures to a lesser extent than thiopental. 375 Propofol also tends to produce a general state of well-being. 375 Hallucinations, 376 sexual fantasies, and opisthotonos 377 have been reported following propofol administration.

The effect of propofol on the EEG as assessed after 2.5 mg/kg followed by an infusion demonstrates an initial increase in alpha rhythm followed by a shift to gamma and theta frequency. High infusion rates produce burst suppression. 378 EEG power analysis indicates that amplitude increases after induction but is thereafter unaltered at propofol blood concentrations of 3 to 8 ?g/mL. 379 At propofol concentrations greater than 8 ?g/mL, amplitude markedly decreases, with periods of burst suppression. 379 There is a strong correlation between the logarithm of blood concentration of propofol and the percentage of activity content, and there is an inverse correlation with percentage of activity content. 379 The bispectral (BIS) index is a new derivative of the EEG. Propofol causes a concentration-dependent decrease in the BIS index, with 50 and 95 percent of patients unable to respond to a verbal command at a BIS value of 63 and 51, respectively (Fig. 9–19). The propofol concentration at which 50 percent of volunteers failed to respond to verbal command was 2.35 ?g/mL. Lack of recall was observed in 95 percent of patients at a BIS value of 77. 380 Propofol produces a decrease in amplitude of the early components of somatosensory evoked potentials, 381 as well as a small nonsignificant increase in latency of the P40 and N50 components. 381 Like other intravenous anesthetics, propofol does not alter brain-stem auditory evoked potentials. 382 There are, however, a dose-dependent prolongation of latency and a decrease in amplitude of cortical middle latency auditory potentials, which are concentration-dependent. 382 Auditory evoked potentials show an abrupt change in the auditory evoked potential index between awake and nonresponsive patients. This finding differs from the BIS index, which tends to show a trend of decreasing BIS values and increasing sedation and loss of consciousness with propofol administration. 383

FIGURE 9–19 The relationship between the bispectral (BIS) index and probability of consciousness (i.e., response to verbal command) using the logistic regression analysis for volunteers receiving propofol, isoflurane, or midazolam. The probability of response was no different among the three different anesthetics used. It can also be noted that 95 percent of the volunteers were unconscious with a BIS index of 50 or less.

The effect of propofol on epileptogenic EEG activity is controversial. Initial studies in mice indicated that propofol neither induced convulsions nor provided anticonvulsant activity. 384 Several more recent reports have shown in a variety of models a direct anticonvulsant effect of propofol, which is dose-dependent. 385, 386 In a few reports, propofol has been used to treat epileptic seizures. 387, 388 Propofol also results in a shorter duration of motor and EEG seizure activity following electroconvulsive therapy as compared with methohexital. 389 Interestingly, propofol has been associated with grand mal seizures and has been used for cortical mapping of epileptogenic foci. 390, 391 In 17 patients undergoing cortical resection for intractable epilepsy, 2 mg/kg propofol resulted in markedly reduced or ablated seizure activity. 392 When propofol was administered at sedative doses in 14 patients with complex seizure disorders, no effect on seizure activity was noted. 393 There have been a few reports of convulsions following propofol administration that have occurred several (6) days following anesthesia. Although the majority of these patients had a history of previous convulsions, a few did not. The incidence of this adverse effect is rare (?1 in 50,000 administrations). 394 There have also been reports of tolerance developing to propofol following either repeat anesthesia or prolonged infusions (days). 395, 396 There have not been reports of acute tolerance during a single case of anesthesia. In addition to tolerance, addiction to propofol has been reported. 397

Propofol decreases ICP in patients with either normal or increased ICP 398, 399, 400, 401, 402 (Ch. 52). In patients with normal ICP, the decrease in ICP (30%) is associated with a small decrease in cerebral perfusion pressure (10%). 401 The addition of small doses of fentanyl and of supplemental doses of propofol ablates the rise of ICP secondary to endotracheal intubation. 401 Normal cerebral reactivity to

carbon dioxide and autoregulation are maintained during a propofol infusion. 398, 403, 404 In patients with elevated ICP, the decrease in ICP (30–50%) is associated with significant decreases in cerebral perfusion pressure 399, 405 and therefore may not be beneficial. Propofol reduces CMRO2 36 percent. 398 With a background of 0.5 percent enflurane, propofol still reduces CMRO2 by 18 percent, whereas lactate and glucose metabolism remains unchanged. 402 By measuring arteriovenous oxygen content difference, cerebral metabolic autoregulation is maintained during burst suppression with propofol. 406 Propofol administered to burst suppression results in significantly better neurologic outcome and less brain tissue injury in an incomplete ischemia model in rats, as compared with fentanyl. 407 Propofol also provides cerebral protective effects following an acute ischemic insult to the same degree as either halothane or thiopental. 408, 409 The neuronal protective effect of propofol may be due to the attenuation of changes in adenosine triphosphate, calcium, sodium, and potassium caused by hypoxic injury. 410 Propofol acutely reduces intraocular pressure by 30 to 40 percent. 411, 412 As compared with thiopental, propofol produces a greater decrease in intraocular pressure, and following a small second dose, it is more effective in preventing a rise in intraocular pressure secondary to succinylcholine and endotracheal intubation. 412

The propofol Cp50 for loss of response to verbal command in the absence of any other drug is 2.3 to 3.5 ?g/mL. 413, 414, 415 The propofol Cp50 (arterial whole blood concentration) to prevent movement on skin incision is 16 ?g/mL. This is markedly reduced by increasing concentrations of fentanyl or alfentanil. 413, 414, 416 The propofol Cp50 for skin incision when combined with benzodiazepine premedication (lorazepam 1–2 mg) and 66 percent nitrous oxide is 2.5 ?g/mL (venous). 417 This concentration is reduced to 1.7 ?g/mL when morphine (0.15 mg/kg) rather than lor-azepam is used for premedication. 418 The concentration of propofol (when combined with 66% nitrous oxide) required during minor surgery varies from 1.5 to 4.5 ?g/mL, 338, 339 and that for major surgery varies from 2.5 to 6 ?g/mL. 419 Awakening usually occurs at concentrations lower than 1.6 ?g/mL, 338, 339, 367 and orientation occurs at concentrations lower than 1.2 ?g/mL. 338, 339 Age also affects the propofol concentration required to provide adequate anesthesia. 339

Effects on the Respiratory System

Propofol affects the respiratory system in a manner qualitatively similar to the action of barbiturates. 420, 421, 422 Apnea occurs after an induction dose of propofol; the incidence and duration of apnea appear dependent on dose, speed of injection, and concomitant premedication. An induction dose of propofol results in a 25 to 30 percent incidence of apnea. 419, 420 The apnea occurring with propofol, however, may be prolonged to more than 30 seconds. The incidence of prolonged apnea (>30 seconds) is further increased by addition of an opiate, either as premedication or just prior to induction, 419, 420, 423 and it is greater with propofol than with other commonly used intravenous induction agents. 420, 423 The onset of apnea is usually preceded by marked tidal volume reduction and tachypnea. 422 Following a 2.5-mg/kg induction dose of propofol, the respiratory rate is significantly decreased for 2 minutes, 420 and minute volume is significantly reduced for up to 4 minutes, a finding that indicates a more prolonged effect of propofol on tidal volume than on respiratory rate.

A maintenance infusion of propofol (100 ?g/kg/min) results in a 40 percent decrease in tidal volume and a 20 percent increase in respiratory frequency, with an unpredictable change in minute ventilation. 422 Doubling the infusion rate from 100 to 200 ?g/kg/min causes a further moderate decrease in tidal volume (455–380 mL) but no change in respiratory frequency. 422 The ventilatory response to carbon dioxide is also decreased during a maintenance infusion of propofol. 422 At 100 ?g/kg/min, there is a 58 percent reduction in the slope of the carbon dioxide–response curve. 422 This is similar to the 50 percent depression of carbon dioxide responsiveness measured with 1 MAC of halothane 424 or after a brief infusion of 3 mg/kg/min of thiopental. 425 Doubling the infusion rate (and presumably the blood level) of propofol results in only a minimal further decrease in carbon dioxide responsiveness. 422 This is in contrast to halothane, with which use of twice the MAC results in halving the carbon dioxide response. 424 Propofol, 1.5 to 2.5 mg/kg, results in an acute (13–22%) rise in PaCO2 and a decrease in pH. 426, 427, 428 PaO2 does not change significantly. 426, 427, 428 These changes are similar to those seen following an induction dose of thiopental. 427, 428 During a maintenance infusion of propofol (54 ?g/kg/min), PaCO2 is moderately increased from 39 to 52 mm Hg. 429 Doubling this infusion rate does not result in a further increase in PaCO2. 429 Propofol (50–120 ?g/kg/min) also depresses the ventilatory response to hypoxia. 430

Propofol induces bronchodilation in patients with chronic obstructive pulmonary disease. 431 Propofol, however, does not appear to provide as effective bronchodilating properties as halothane. 432

Effects on the Cardiovascular System

The cardiovascular effects of propofol have been evaluated following its use both for induction and for maintenance of anesthesia 298, 426, 427, 428, 429, 433, 434, 435, 436, 437, 438 (see Table 9–4). The most prominent effect of propofol is a decrease in arterial blood pressure during induction of anesthesia. Independently of the presence of cardiovascular disease, an induction dose of 2 to 2.5 mg/kg produces a 25 to 40 percent reduction of systolic blood pressure. 298, 426, 427, 428, 429, 433, 434, 435, 436, 437, 438 Similar changes are seen in mean and diastolic blood pressure. The decrease in arterial pressure is associated with a decrease in cardiac output/cardiac index (?15%), 427, 429, 436, 437, 438 stroke volume index (?20%), 429, 437, 438 and systemic vascular resistance (15–25%). 427, 429, 436, 437 Left ventricular stroke work index is also decreased (by ?30%). 437 When looking specifically at right ventricular function, propofol produces a marked reduction in the slope of the right ventricular end-systolic pressure–volume relationship. 439 In patients with valvular heart disease, pulmonary artery and pulmonary capillary wedge pressure are also reduced, a finding that implies that the resultant decrease in pressure is due to a decrease in both preload and afterload. 426 The decrease in systemic pressure following an induction dose of propofol appears to be due to both vasodilation and myocardial depression. Both the myocardial depressant effect and the vasodilation appear to be dose-dependent and plasma concentration–dependent. 440 The vasodilatory effect of propofol appears to be due both to a reduction in sympathetic activity 441 and to a direct effect on intracellular smooth muscle calcium mobilization. 442, 443

TABLE 9–4. Hemodynamic Changes After Induction of Anesthesia With Nonbarbiturate Hypnotics

Heart rate does not change significantly after an induction dose of propofol. It has been suggested that propofol either resets or inhibits the baroreflex, thus reducing the tachycardic response to hypotension. 300, 444 Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction. 445

During maintenance of anesthesia with a propofol infusion, systolic pressure remains between 20 and 30 percent below preinduction levels. 429, 437 In patients allowed to breathe room air during a maintenance infusion of 100 ?g/kg/min of propofol, there is a significant decrease in systemic vascular resistance (30%), but cardiac index and stroke index are unaltered. 437 In contrast, in patients receiving a narcotic premedication and nitrous oxide with an infusion of propofol (54 and 108 ?g/kg/min) for maintenance during surgery, systemic vascular resistance is not significantly decreased from baseline, but cardiac output and stroke volume are decreased. 429 This is probably explained by the observation that propofol infusions produce a dose-dependent lowering of sympathetic nerve activity, thereby attenuating the reflex responses to hypotension. In the presence of hypercarbia, the reflex sympathetic responses are better maintained. 416 Increasing the infusion rate of propofol from 54 to 108 ?g/kg/min (blood concentration 2.1–4.2 ?g/mL) produces only a slightly greater decrease in arterial blood pressure (?10%). 429 The peak plasma concentrations obtained following a bolus dose are substantially higher than those seen with a continuous infusion. Because the vasodilatory and myocardial depressant effects are concentration-dependent, the decrease in blood pressure from propofol during the infusion phase is much less than that seen following an induction bolus. When propofol was compared with midazolam for sedation after coronary revascularization, propofol resulted in a 17 percent lower incidence of tachycardia, a 28 percent lower incidence of hypertension, and a 17 percent greater incidence in hypotension. These differences in hemodynamic parameters resulted in no difference in the number or severity of ischemic events between the two groups. 439

Heart rate may increase, 428, 435 decrease, 426, 434 or remain unchanged 433 when anesthesia is maintained with propofol. An infusion of propofol results in a significant reduction in both myocardial blood flow and myocardial oxygen consumption, 298, 435 a finding that suggests that the global myocardial oxygen supply/demand ratio is preserved.

Other Effects

Propofol, like thiopental, does not potentiate neuromuscular blockade produced by both nondepolarizing and depolarizing neuromuscular blocking agents. 446, 447 Propofol produces no effect on the evoked electromyogram or twitch tension 446 ; however, good intubating conditions after propofol alone have been

reported. 448 Propofol does not trigger malignant hyperpyrexia and is probably the anesthetic of choice in patients with this condition. 449, 450

Propofol following a single dose or a prolonged infusion does not affect corticosteroid synthesis or alter the normal response to ACTH stimulation. 451 Propofol in the emulsion formulation does not alter hepatic, hematologic, or fibrinolytic function. 452, 453, 454 However, lipid emulsion per se reduces *in vitro* platelet aggregation. 455 Anaphylactoid reactions to the present formulation of propofol have been reported. In at least some of the patients, the immune response was entirely due to propofol and not to the lipid emulsion. A high percentage of the patients developing the anaphylactoid response to propofol had a previous history of allergic responses. In patients with multiple drug allergies, propofol should be used with caution. 456 In most people, the present preparation does not trigger histamine release. 457

Propofol also possesses significant antiemetic activity at low (subhypnotic) doses. 458 It has been used successfully to treat postoperative nausea in a bolus dose of 10 mg. 459 It has also been used successfully to treat refractory postoperative nausea and vomiting. 460 The median concentration of propofol that was associated with an antiemetic region was 343 ng/mL. 461 This concentration can be achieved by a propofol infusion of 10 to 20 ng followed by 10 ?g/kg/min. Propofol used as a maintenance anesthetic during breast surgery was more effective than 4 mg of ondansetron given prophylactically in preventing postoperative nausea and vomiting. In the same study, the maintenance propofol infusion was also superior to adding propofol only at the end of the procedure (sandwich technique). 462 The difference in efficacy of propofol in preventing postoperative nausea and vomiting between the propofol maintenance method and the sandwich technique is that the propofol concentration drops rapidly after the sandwich technique below the therapeutic concentration, whereas with the maintenance technique, although the propofol concentration decreases rapidly to allow awakening, any further decrease is much slower and is maintained above therapeutic concentrations for several hours. Propofol as an infusion of 1 mg/kg/h (17 ?g/kg/ min) has also provided excellent antiemetic action following anticancer chemotherapy. 463 The antiemetic effect of propofol has been shown not to be due to an action on dopamine-2 receptors. 464 Propofol at subhypnotic doses has also been reported to relieve cholestatic pruritus and was as effective as naloxone in treating pruritus induced by spinal opiates. 465 Propofol causes a dose-dependent decrease in the thermoregulatory threshold for vasoconstriction, but it has little effect on the sweating threshold. 466

Propofol only decreases polymorphonuclear leukocyte chemotaxis but not adherence phagocytosis and killing. This action contrasts with the effect of thiopentone, which inhibits all these chemotactic responses. 467 However, propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli.* 468 These findings are particularly pertinent in view of the observation of increased life-threatening systemic infections associated with the use of propofol. 464, 469 It was also noticed that opened vials and syringes of propofol in hospitals where these infections occurred had positive cultures for the offending organisms. The intralipid that acts as the solvent for propofol is an excellent culture medium. Ethylenediaminetetra-acetic acid has been added to the formulation of propofol in an attempt to retard such bacterial growth. Strict aseptic technique must still be observed.

Uses

Induction and Maintenance of Anesthesia

Propofol is suitable for both the induction and maintenance of anesthesia and has also been approved for use in neurologic and cardiac anesthesia (Table 9–9). The induction dose varies from 1.0 to 2.5 mg/kg, 362, 470, 471 and the ED95 in unpremedicated adult patients is 2.25 to 2.5 mg/kg. 470, 472 Premedication with an opiate and or a benzodiazepine markedly reduces the induction dose. 365, 366, 473 Increasing age also reduces the dose of propofol required to induce anesthesia. 474, 475 A dose of 1 mg/kg (with premedication) to 1.75 mg/kg (without premedication) is recommended for inducing anesthesia in patients older than 60 years of age. 475 To prevent hypotension in sicker patients or in patients presenting for cardiac surgery, a fluid load should be administered as tolerated, and the propofol should be administered in small incremental doses (10–30 mg) until the patients lose consciousness. The ED95 (2.0–3.0 mg/kg) for induction is increased in children, primarily because of pharmacokinetic differences. 472, 479

TABLE 9–9. Uses and Doses of Propofol

Propofol, when used for induction of anesthesia in briefer procedures, results in a significantly quicker recovery and an earlier return of psychomotor function as compared with thiopental or methohexital, irrespective of the agent used for maintenance of anesthesia. 478, 479, 480 The incidence of nausea and vomiting when propofol is used for induction is also markedly lower than following the use of other intravenous induction agents, probably because of the antiemetic properties of propofol. 472, 479

Because of its pharmacokinetics, propofol provides a rapid recovery and is thus superior to barbiturates for maintenance of anesthesia, 480, 481, 482 and it appears equal to enflurane and isoflurane. 364, 478, 483 Recovery from desflurane is slightly more rapid than recovery from propofol. 484 Propofol can be given as intermittent boluses or as a continuous infusion for maintenance. 453 Following a satisfactory induction dose, a bolus of 10 to 40 mg is needed every few minutes to maintain anesthesia. Because these doses need to be given frequently, it is more suitable to administer propofol as a continuous infusion.

Several infusion schemes have been used to achieve adequate plasma concentrations of propofol. 480, 485 Following an induction dose, an infusion of 100 to 200 ?g/kg/min is usually needed. 339, 364, 417, 418, 478, 480, 481, 482 The infusion rate is then titrated to individual requirements and the surgical stimulus. When combined with propofol, morphine, fentanyl, or alfentanil reduces its required infusion rate and concentration. 413, 414, 417, 418, 486 Because opioids alter the concentration of propofol required for adequate anesthesia, the relative dose of either opioid and propofol will markedly affect the time from termination of drug to awakening and recovery. Illustrated in Figure 9–20 is the relationship between the concentration of propofol and alfentanil that will prevent a somatic response in 50 percent of patients combined with the time to awakening (on the Z axis) for that specific combination. 487 The infusion rate required to achieve the combination with the shortest recovery is propofol, 1 to 1.5 mg/kg followed by 140 ?g/kg/min for 10 minutes followed by 100 ?g/kg/min, and alfentanil, 30 ?g/kg followed by an infusion of 0.25 ?g/kg/min, or fentanyl, 3 ?g/kg followed by 0.02 ?g/kg/min. Propofol has also been used as a single mixture with alfentanil, containing 1 mg alfentanil (2 mL) to 400 mg propofol (40 mL). When this mixture was administered at infusion rates commonly used for propofol (i.e., 166 ?g/kg/min for 10 min, 133 ?g/kg/min for 10 min, and 100 ?g/kg/min thereafter), it provided an outcome equal to that obtained by using the two drugs as separate infusions. 488

FIGURE 9–20 The interaction between propofol and alfentanil for movement at skin incision is shown. The solid line intersecting the X and Y axes represents the concentration of propofol and alfentanil at which 50 percent of patients did not move on skin incision. Noted as the concentration of alfentanil increases, the concentration of propofol required to prevent movement on skin incision decreases until a plateau is reached at an alfentanil concentration of approximately 200 ng/mL. At higher alfentanil concentrations, there is no further reduction in the amount of propofol required to ensure absence of movement at skin incision. This concentration of propofol is approximately 2.5 ?g/mL, close to the concentration of propofol required for loss of consciousness in the absence of any opioid. The solid line on the Z axis represents the time to awakening and spontaneous ventilation when the indicated concentration of propofol and alfentanil is administered. Note the shortest recovery period with the optimal combination to prevent movement at 50 percent of patients is a propofol concentration of 3.5 ?g/mL with an alfentanil concentration of 85 ng/mL. Note also that increasing either the propofol concentration or the alfentanil concentration from this ideal com-bination results in a prolongation in recovery time. This prolongation in recovery time is more marked with an increase in alfentanil concentration than with an increase in propofol concentration.

Increasing age is associated with a decrease in propofol infusion requirements, 489, 490 whereas these requirements are higher in children and infants. 347 The blood levels of propofol alone for loss of consciousness are 2.5 to 4.5 ?g/mL, and the blood concentrations (when combined with nitrous oxide) required for surgery are 2.5 to 8 ?g/ mL. 338, 339, 367, 417, 418, 483 Similar concentrations are necessary when propofol is combined with an opioid for a total intravenous technique. The knowledge of these levels and of the pharmacokinetics of propofol has enabled the use of pharmacokinetic model–driven infusion systems to deliver propofol as a continuous infusion for the maintenance of anesthesia. 364, 485, 491, 492

For short (<1 h) body surface procedures, the advantages of a more rapid recovery and decreased nausea and vomiting are still evident. 478 However, if propofol is used for longer or major procedures, both speed of recovery and the incidence of nausea and vomiting are similar to those following thiopental/isoflurane anesthesia. 364, 478 A meta-analysis of recovery data following either propofol for maintenance or the newer volatile anesthetics indicated only minor differences in times to reach recovery goals; however, the

incidence of nausea and vomiting remained significantly lower in the patients administered propofol for maintenance. 493

Several studies have investigated the utility of propofol as a maintenance infusion regimen for cardiac surgery. Using reduced and titrated doses of propofol for induction and titrated infusion rates of 50 to 200 ?g/kg/min combined with an opioid for maintenance, propofol provided intraoperative hemodynamic control and ischemic episodes similar to those with either enflurane/opioid or a primary opioid technique. 494, 495, 496, 497

Sedation

Propofol has been evaluated for sedation during surgical procedures 369, 370, 498, 499 and for patients receiving mechanical ventilation in the ICU. 500, 501, 502 Propofol by continuous infusion provides a readily titratable level of sedation and a rapid recovery once infusion is terminated, irrespective of the duration of the infusion. 370, 498, 501, 503 In a study of patients sedated in the ICU for 4 days with propofol, recovery to consciousness was rapid (?10 min). Both the rate of recovery and the decrease in plasma concentration were similar at 24 and at 96 hours, when the infusion was discontinued. In addition, the plasma concentrations required for sedation and for awakening were similar at 24 and 96 hours, a finding that implies that tolerance to propofol did not occur. 503 As noted earlier, there have been more recent reports of tolerance with propofol. Infusion rates required for sedation to supplement regional anesthesia in healthy patients are half or less than those required for general anesthesia (i.e., 30–60 ?g/kg/min). 369, 498 In elderly patients (older than 65 years) and in sicker patients, the infusion rates that are necessary are markedly reduced. 369, 500, 501 Thus, it is important to titrate the infusion individually to the desired effect. A 1992 report 504 linked propofol with several deaths in children requiring sedation for mechanical ventilation secondary to upper respiratory tract infections. The likelihood that propofol was the primary cause has been challenged. However, propofol is not yet approved for ICU sedation in children, and it should not be used for this purpose until definitive studies assessing the drug‘s safety in this population are completed. No such adverse experiences have been reported in adults. A potential advantage of propofol for sedation of ICU patients is that it appears to possess antioxidant properties. 505

Generally, at propofol infusion rates greater than 30 ?g/kg/min, patients are amnesic. 498, 501 In comparison with midazolam when used to maintain sedation, propofol provides equal or better control and more rapid recovery. 370, 498, 501 In mechanically ventilated patients, more rapid recovery translates to more rapid extubation when sedation is terminated. 501 The use of propofol for sedation following cardiac surgery to provide fast tracking has shown that patients can be extubated rapidly using this technique. 506 The incidence of unwanted cardiovascular changes and of ischemic events was similar when propofol or midazolam was used for sedation in patients after coronary artery bypass surgery. 439 Propofol has also been used successfully in patient-controlled sedation. Propofol was rated better than midazolam when used by this technique, probably owing to its much more rapid onset and offset. 507

Side Effects and Contraindications

Induction of anesthesia with propofol is associated with several side effects. These include pain on injection, myoclonus, apnea, decrease in arterial blood pressure, and, rarely, thrombophlebitis of the vein into which propofol is injected. Pain on injection is less than or equal to that with etomidate, equal to that with methohexital, and greater than after thiopental. 314, 452, 477 Pain on injection is reduced by using a large vein, avoiding veins in the dorsum of the hand, and adding lidocaine to the propofol solution. 452 Myoclonus occurs more frequently following propofol than following thiopental but less frequently than following etomidate or methohexital. 477 Apnea following induction with propofol is common. The incidence of apnea may be similar to that following thiopental or methohexital; however, propofol produces a greater incidence of apnea lasting longer than 30 seconds. 417, 423 The addition of an opiate increases the incidence of apnea, especially prolonged apnea. 417, 419

The most significant side effect on induction is the decrease in systemic blood pressure. Addition of an opiate just prior to induction of anesthesia appears to augment the decrease in arterial blood pressure. 438 Perhaps slow administration and lower doses in adequately prehydrated patients may attenuate the decrease in arterial blood pressure. Conversely, the effects of laryngoscopy and endotracheal intubation and

the increases in mean arterial pressure, heart rate, and systemic vascular resistance are less significant following propofol than thiopental.

• ETOMIDATE

History

Etomidate (Amidate, Hypnomidate) was synthesized 236 in 1964 and was introduced into clinical practice 237 in 1972. Its properties include hemodynamic stability, minimal respiratory depression, cerebral protection, and pharmacokinetics enabling rapid recovery following either a single dose or a continuous infusion. In animals, etomidate also provides a wider margin of safety (median effective dose/median lethal dose [ED50 /LD50]) than thiopental (26.4 versus 4.6). 238 These beneficial properties led to widespread use of etomidate for induction, for maintenance of anesthesia, and for prolonged sedation in critically ill patients. Anesthesiologists‘ enthusiasm for etomidate, however, was tempered by reports that the drug can cause temporary inhibition of steroid synthesis after both single doses and infusions. 239, 240, 241 This effect, combined with other minor disadvantages (e.g., pain on injection, superficial thrombophlebitis, myoclonus, and a relatively high incidence of nausea and vomiting) led to several editorials 242, 243, 244 questioning the role of etomidate in modern anesthetic practice. Use of the drug waned significantly following those editorials, but it has been expanding over the past several years owing to a rediscovery of etomidate‘s beneficial physiologic profile combined with a lack of any new reports describing clinically significant adrenocortical suppression.

Physicochemical Characteristics

Etomidate is an imidazole derivative (R-(+)-pentylethyl-1H-imidazole-5 carboxylate sulfate). 238 Its chemical structure is illustrated in Figure 9–14 . Etomidate exists as two isomers, but only the (+) isomer is active as a hypnotic. 245 Its molecular weight is 342.36 kd. 245 Etomidate is water insoluble and is unstable in a neutral solution. It therefore has been formulated with several solvents. 246 Currently, it is supplied as a 2-mg/mL propylene glycol (35% by volume) solution with a pH of 6.9 and an osmolality of 4,640 mOsm/L. Unlike sodium thiopental, when etomidate is mixed with other commonly used anesthetic agents such as neuromuscular blockers, vasoactive drugs, or lidocaine, it does not cause precipitation. 2

Metabolism, Induction, and Maintenance of Anesthesia

Etomidate is metabolized in the liver primarily by ester hydrolysis to the corresponding carboxylic acid of etomidate (major metabolite) or by *N* -dealkylation. 245 The main metabolite is inactive. 247 Only 2 percent of the drug is excreted unchanged, the rest being excreted as metabolites by the kidney (85%) and bile (13%). 247

Etomidate has been used for both induction and maintenance of anesthesia (Table 9–8). The induction dose of etomidate varies from 0.2 to 0.6 mg/kg, 237, 246, 248, 249 and it is reduced by premedication with an opiate, a benzodiazepine, or a barbiturate. 237 Onset of anesthesia following a routine induction dose of 0.3 mg/kg etomidate is rapid (one arm-brain circulation) and is equivalent to that obtained with an induction dose of thiopental or methohexital. 237, 246, 250 The duration of anesthesia following a single induction dose is linearly related to the dose—each 0.1 mg/kg administered provides about 100 seconds of sleep. 251 Repeat doses of etomidate, either by bolus or infusion, prolong the duration of hypnosis. Recovery following etomidate is still usually rapid. 237, 248, 252, 253, 254, 255, 256 The addition of small doses of fentanyl with etomidate for short surgical procedures reduces the required dose of etomidate and allows earlier awakening. In children, induction by rectal administration of etomidate has been obtained with 6.5 mg/kg. Hypnosis occurs in 4 minutes. At this dose, hemodynamics are unaltered, and recovery is still rapid. 257

TABLE 9–8. Uses and Doses of Etomidate

Various infusion schemes have been devised to utilize etomidate as a maintenance agent for the hypnotic component of anesthesia. Most regimens aim to achieve a plasma level of 300 to 500 ng/mL, which is the concentration necessary for hypnosis. 258, 259, 260, 261 Both two- and three-stage infusions have been successfully used. These consist of an initial rapid infusion of 100 ?g/kg/min for 10 minutes followed by 10 ?g/kg/min thereafter, 261 or of 100 ?g/kg/min for 3 minutes, 20 ?g/kg/min for 27 minutes, and 10 ?g/kg/min

thereafter. 258 Loss of consciousness with these techniques occurs after 100 to 120 seconds. 258 The infusion is usually terminated 10 minutes prior to desired awakening. 258

Pharmacokinetics

The pharmacokinetics of etomidate has been calculated following single bolus doses and following continuous infusion 258, 259, 262, 263, 264 (see Table 9–3). The time course of plasma disappearance after a 0.3-mg/kg bolus is shown in Figure 9–15 . The kinetics of etomidate are best described by an open three-compartment model. 262, 263, 264 The drug has an initial distribution half-life of 2.7 minutes, a redistribution half-life of 29 minutes, 262, 264 and an elimination half-life that varies from 2.9 to 5.3 hours. 258, 259, 262, 263, 264 Clearance of etomidate by the liver is high (18–25 mL/kg/min), with a hepatic extraction ratio of 0.5:0.9. 246, 258, 262, 263, 264 Thus, drugs affecting hepatic blood flow alter its elimination half-life. Because redistribution is the mechanism whereby the effect of a bolus of etomidate is dissipated, hepatic dysfunction should not appreciably alter recovery from its hypnotic effect. The volume of distribution at steady state is 2.5 to 4.5 L/kg. 258, 259, 262, 263, 264 Etomidate is 75 percent protein bound. 265 Pathologic conditions altering serum proteins (e.g., hepatic or renal disease) vary the amount of the free (unbound) fraction and may cause a given dose to have an exaggerated pharmacodynamic effect. 265

In patients with cirrhosis, the volume of distribution is doubled, whereas clearance is normal; the result is an elimination half-life that is twice normal. 266 It is likely that the initial distribution half-life and clinical effect are unchanged. Increasing age is associated with a smaller initial volume of distribution and a decreased clearance of etomidate. 267 The relatively short elimination half-life and the rapid clearance of etomidate make it suitable for administration in a single dose, in multiple doses, or in a continuous infusion.

Pharmacology

Effects on the Central Nervous System

The primary action of etomidate on the CNS is hypnosis (Ch. 52), which is achieved in one arm-brain circulation following a normal induction dose (0.3 mg/kg). 246, 268 Etomidate has no analgesic activity. Plasma levels required during the maintenance of anesthesia are approximately 300 to 500 ng/mL, those for sedation are 150 to 300 ng/mL, and those for awakening are 150 to 250 ng/mL 258, 260, 261, 268 (see Fig. 9–15). The mechanism by which etomidate produces hypnosis is not fully elucidated; however, it may be in part related to the GABA-adrenergic system, because its action may be antagonized by GABA antagonists. 269

FIGURE 9–15 Simulated time course of plasma levels of etomidate following an induction dose of 0.3 mg/kg. Plasma levels required for hypnosis during surgery are 300 to 500 ng/mL, with awakening usually occurring at levels lower than 225 ng/mL.

At a dose of 0.2 to 0.3 mg/kg, etomidate reduces CBF (by 34%) and CMRO2 (by 45%) without altering mean arterial pressure. 270 Thus, cerebral perfusion pressure is maintained or increased, and there is a beneficial net increase in the cerebral oxygen supply/demand ratio. 270 Etomidate given in doses sufficient to produce EEG burst suppression acutely lowers ICP by up to 50 percent in patients with already raised ICP, returning raised ICP to almost normal values. 271, 272 The decrease in ICP is maintained in the period immediately following intubation 272 (Ch. 52). To maintain the effects of etomidate on ICP, high infusion rates (60 ?g/kg/min) are necessary. 273 In contrast to the situation with other neuroprotective agents such as thiopental, reduction of ICP and maintenance of burst suppression are not associated with a drop in mean arterial blood pressure. 272 Because cerebral vascular reactivity is still maintained following etomidate administration, 273 hyperventilation theoretically may further reduce ICP when used in conjunction with etomidate. In animals, etomidate has reduced brain disease following acute cortical ischemic insult. 274 In 1993, Takanobu et al 275 reported the neuroprotective qualities of etomidate to be equal to those of thiopental and superior to those of isoflurane in a rat model. Other investigators disagree on etomidate‘s neuroprotective qualities. 276 Deeper structures such as the brain stem may not be afforded ischemic protection by etomidate. 277

A dose of 0.3 mg/kg rapidly reduces intraocular pressure by 30 to 60 percent. 278 The decrease in intraocular pressure following a single dose lasts 5 minutes, but the reduction may be maintained by an infusion of 20 ?g/kg/min. 278 (Ch. 63).

Etomidate produces changes in the EEG similar to those produced by the barbiturates. 279 There is an initial increase in alpha amplitude with sharp beta bursts followed by mixed delta-theta waves, with delta-wave activity predominating prior to the onset of periodic burst suppression. 279 The absence of beta waves in the initial phase of induction with etomidate is the major difference in EEG changes as compared with thiopental. 279 Etomidate has been associated with grand mal seizures 280, 281 and has been shown to produce increased EEG activity in epileptogenic foci. This feature has proved useful for intraoperative mapping of seizure foci prior to surgical ablation. 281, 282 Etomidate is also associated with a high incidence of myoclonic movement. 248, 253 Myoclonus is not thought to be associated with seizure-like EEG activity. 279 Giving etomidate to unpremedicated patients caused an increase in EEG activity in 22 percent of patients versus 17 percent of those receiving thiopental. 283 The myoclonic movement is believed to result from activity either in the brain stem or in deep cerebral structures. 237

The effect of etomidate on auditory evoked potentials is similar to that produced by the inhaled anesthetics, with a dose-dependent increase in latency and a decreasing amplitude of the early cortical components (Pa and Nb). 284 Amplitude and latency of upper limb cortical somatosensory evoked potentials are positively affected following 0.4 mg/kg etomidate, which could theoretically obscure neurologic injury during positioning immediately following induction of anesthesia. 285 Brain-stem evoked responses are unaltered following etomidate administration. 284 Because amplitude depression is less, etomidate may be superior to propofol as an induction agent when monitoring of motor evoked responses to transcranial stimulation monitoring is indicated. 286

Effects on the Respiratory System

Etomidate has minimal effect on ventilation. It does not induce histamine release either in healthy patients or in patients with reactive airway disease. 287 Ventilatory response to carbon dioxide is depressed by etomidate, but the ventilatory drive at any given carbon dioxide tension is greater than that following an equipotent dose of methohexital. 288 Similarly, the response to occlusion pressure is less depressed following etomidate than following an equivalent dose of methohexital. 289 Induction with etomidate produces a brief period of hyperventilation, 290, 291 sometimes followed by a similarly brief period of apnea, 291 which results in a slight (±15%) increase in $PaCO_2$ but no change in the partial pressure of arterial oxygen (PaO_2). 290, 292 The incidence of apnea is altered by premedication. 254, 293 Hiccups or coughing may accompany etomidate induction, with an incidence similar to that following methohexital induction. 246

Effects on the Cardiovascular System

The minimal effect of etomidate on cardiovascular function sets it apart from other fast-acting induction agents 290, 292, 293, 294, 295, 296 (see Table 9–4). An induction dose of 0.3 mg/kg of etomidate given to cardiac patients for noncardiac surgery results in almost no change in heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, stroke volume, cardiac index, and pulmonary and systemic vascular resistance. 292 A relatively large dose of etomidate, 0.45 mg/kg (which is 50% larger than a normal induction dose), 293 also produces minimal changes in cardiovascular parameters. In patients with ischemic heart disease or valvular disease, 292, 295 etomidate (0.3 mg/kg) produces similar minimal alterations in cardiovascular parameters. In patients with mitral or aortic valve disease, etomidate may produce greater changes in mean arterial pressure (an approximate 20% decrease) 290, 297 than in patients without cardiac valvular disease. Following induction (18 mg) and infusion (2.4 mg/min), etomidate produces a 50 percent decrease in myocardial blood flow and oxygen consumption and a 20 to 30 percent increase in coronary sinus blood oxygen saturation. 298 The myocardial oxygen supply/demand ratio is thus well maintained. 296, 298 There is minimal effect on the QT interval. 299

TABLE 9–4. Hemodynamic Changes After Induction of Anesthesia With Nonbarbiturate Hypnotics

The hemodynamic stability seen with etomidate may be due in part to its unique lack of effect both on the sympathetic nervous system and on baroreceptor function. 300 However, etomidate, lacking analgesic

efficacy, may not totally ablate the sympathetic response to laryngoscopy and intubation. 250, 253 For the smoothest hemodynamic induction/intubation sequence, a low dose (1.5–5.0 ?g/kg) of fentanyl is often combined with etomidate. 297, 301

Endocrine Effects

The concern surrounding the endocrine effects of etomidate stems from a letter by Ledingham et al 302 in 1983 concerning ICU patients receiving long-term sedative infusions of etomidate while being mechanically ventilated for 5 days or longer. These investigators noted that in this subset of mechanically ventilated multiple trauma patients, the mortality rate was higher for 1981 to 1982 than among similar patients treated during 1979 to 1980. The earlier group had received primarily morphine and benzodiazepines for sedation, whereas patients in 1981 to 1982 had received primarily etomidate for sedation. It was postulated that adrenocortical suppression secondary to long-term etomidate infusion was the cause of the increased mortality. 239 Another ICU with similar patients receiving etomidate did not note an increased mortality; these patients received high-dose steroids as part of the trauma protocol. 302 This finding helped to confirm that hypothesis.

The specific endocrine effects manifested by etomidate are a dose-dependent reversible inhibition of the enzyme 11-?-hydroxylase, which converts 11-deoxycortisol to cortisol, and a relatively minor effect on 17-?-hydroxylase 303, 304 (Fig. 9–16). This results in an increase in the cortisol precursors 11-deoxycortisol and 17-hydroxyprogesterone as well as an increase in adrenocorticotropic hormone (ACTH). The blockade of 11-?-hydroxylase and, to a lesser extent, 17-?-hydroxylase 303 appears to be related to the free imidazole radical of etomidate-binding cytochrome P-450. 304, 305, 306 This results in inhibition of ascorbic acid resynthesis, which is required for steroid production in humans. 305, 306 The blockade of the cytochrome P-450–dependent enzyme 11-?-hydroxylase also results in decreased mineralocorticoid production and an increase in intermediaries (11- deoxycorticosterone). 240, 241, 243 Vitamin C supplementation restores cortisol levels to normal following the use of etomidate. 306 Because minor adrenocortical suppressive effects were shown to follow even single bolus doses, 240, 303, 307 concerns about the use of etomidate for anesthetic induction arose. 242 No large prospective studies have been done, but several smaller studies have provided some insight into the exact nature of adrenocortical suppression following an induction dose.
FIGURE 9–16 Pathway for the biosynthesis of cortisol and aldosterone. The sites at which etomidate affects cortisol-aldosterone synthesis by its action on 11-?-hydroxylase (major site) and 17-?-hydroxylase (minor site) are illustrated.

Duthie et al 308 demonstrated that in otherwise healthy patients undergoing minor peripheral surgery, plasma cortisol levels were slightly depressed from the preinduction levels for up to 1 hour postoperatively. The nadir of mean cortisol levels did not fall out of the normal range. 11- Deoxycorticosterone, substrate for the etomidate-inhibited 11-?-hydroxylase, peaked at very high levels when compared with the thiopental control group. 308 In another study, patients undergoing orthopedic surgery were given an etomidate induction followed by an infusion of etomidate (average total dose 68 mg). Temporary adrenocortical suppression, as measured by a reduced response to ACTH stimulation, was documented for 6 hours postoperatively and returned to normal by 20 hours postoperatively. Postoperative cortisol levels in the etomidate study patients were not significantly different from those in a group who received a midazolam induction. As in the study of Duthie et al 308 mean cortisol levels in the etomidate group remained in the normal range at all times postoperatively. 309 Other studies have shown similar results when evaluating etomidate induction doses; none reported adverse outcomes secondary to short-term adrenocortical suppression. 240, 241, 303, 307, 308, 309, 310

However, in each of the prospective etomidate studies documenting adrenocortical suppression without associated clinical sequelae, a conclusion of safety was not forthcoming. The reason was that these studies did not address high-stress procedures, in which the benefit of a high cortisol level in response to a major stress could be desirable and etomidate‘s blockade of the response to ACTH could be detrimental. As part of a quality assurance program, we addressed this issue with a small, retrospective analysis of etomidate induction for high-stress procedures (vascular, thoracic, major intra-abdominal, and major retroperitoneal surgery) in 1993. 249 Indices of adrenocortical function and perioperative outcome in patients who received induction doses of etomidate were compared with those in a control group who received thiopental. The incidence of perioperative wound infection, sepsis, miscellaneous infection, myocardial infarction, and hypotension and the need for perioperative vasopressor/inotropic support were evaluated, along with

postoperative serum sodium levels. No difference was found between patients receiving etomidate and those receiving other induction agents for these high-stress procedures. In 1994, the cortisol levels during and after coronary artery bypass surgery were compared in patients receiving total intravenous anesthesia with etomidate/fentanyl (mean etomidate dose of 87 ± 3 mg) versus midazolam/fentanyl. Except for the first hour after induction, cortisol levels were the same or higher in the etomidate group compared with the midazolam group, a finding implying that the body's ability to respond to a high surgical stress was still intact despite relatively high doses of etomidate. This study is further proof that etomidate is probably safe for use in major surgery. 311

In summary, three facts suggest that the issue of temporary adrenocortical suppression following induction doses of etomidate is not clinically significant: (1) there are no known reports of any negative clinical outcome associated with an etomidate induction despite millions of uses; (2) following etomidate induction, the nadir of cortisol levels usually remains in the low normal range and the adrenocortical suppression is a relatively short-lived phenomenon; and (3) high-stress surgery can overcome the temporary adrenocortical suppression caused by etomidate.

Other Effects

Although etomidate provides stable hemodynamics and minimal respiratory depression, it is associated with several adverse effects when it is used for induction. These are nausea and vomiting, pain on injection, myoclonic movement, and hiccups. 237, 246, 248, 252, 253, 254, 255 Etomidate has been associated with a high (30 to 40 percent) incidence of nausea and vomiting. 248, 253, 254, 255, 256 This compares with a reported incidence of 10 to 20 percent with methohexital 246, 254 or thiopental, 253, 312 but some studies have shown no difference. 249, 253 Addition of fentanyl to etomidate further increases the incidence of nausea and vomiting. 248, 253 Nausea and vomiting constitute the most common reasons for patients to rate anesthesia with etomidate unsatisfactory. 255 It seems prudent to avoid etomidate in patients predisposed to nausea and vomiting.

Superficial thrombophlebitis of the vein used may occur 48 to 72 hours after etomidate injection. 313 The incidence may be as high as 20 percent when etomidate is given alone through a small (21-gauge) intravenous needle. Intra-arterial injection of etomidate is not associated with local or vascular disease. 237 Pain on injection, similar in incidence to that with propofol, 314 can be essentially eliminated by injecting lidocaine immediately before injection of etomidate; as little as 20 to 40 mg may be enough. 315 Pain on injection is further reduced by using a large vein. 237, 252 Less successful but somewhat efficacious is premedication with benzodiazepine plus a narcotic. 253, 256 The incidence of pain on injection varies from 0 to 50 percent. The incidence of muscle movement (myoclonus) and of hiccups is also highly variable (0–70%), but myoclonus is reduced by premedication with either a narcotic or benzodiazepine. 256 Both fast and slow injection techniques have also been advocated for reducing myoclonus. 252, 256

Etomidate enhances the neuromuscular blockade of nondepolarizing neuromuscular blockers. 316, 317 Hepatic function is unaltered by etomidate. 246, 262 *In vitro,* etomidate inhibits aminolivulinic acid synthetase, but it has been administered to patients with porphyria without inducing an acute attack of porphyria. 312

The carrier for etomidate, propylene glycol, has also been reported to have some negative effects. Some reports suggest that propylene glycol can be associated with a small degree of hemolysis. 318 Additionally, high-dose prolonged infusion has been reported to result in propylene glycol toxicity (a hyperosmolar state). 319

Uses

The use of etomidate is most appropriate in patients with cardiovascular disease, reactive airway disease, intracranial hypertension, or any combination of disorders indicating the need for an induction agent with limited or beneficial physiologic side effects. The hemodynamic stability of etomidate is unique among the rapid-acting induction agents.

Etomidate has been primarily used in sick patients. In multiple studies, etomidate has been used for induction in patients with a compromised cardiovascular system who are undergoing coronary artery bypass surgery or valve surgery, in patients requiring induction of general anesthesia for percutaneous transluminal

coronary angioplasty, and in other similar situations. 297, 301, 320 In cardiovascular surgery, particularly surgery for aortic aneurysms, etomidate is an excellent anesthetic induction agent. When etomidate is used in combination with fentanyl, titrating etomidate up to 0.6 mg/kg maintains blood pressure and heart rate in a narrow range, preserving coronary perfusion pressure in these patients with probable coronary artery disease while blunting the response to intubation and avoiding unnecessary stress on the aneurysm. For cardiothoracic procedures, especially cardiac and lung transplantation, the required rapid-sequence induction and hemodynamic stability make etomidate the induction agent of choice. For patients with concomitant coronary artery disease and reactive airway disease, etomidate induction does not release histamine, and a relatively large dose (0.6 mg/kg) may be titrated to provide a deep level of anesthesia for intubation without compromising hemodynamics and coronary perfusion pressure. For cardioversion, the rapid onset, quick recovery, and maintenance of blood pressure in these sometimes hemodynamically tenuous patients, combined with continued spontaneous respiration, make etomidate an acceptable choice, 314 although there is one report of myoclonus interfering with electrocardiographic evaluation. 321 Although definitive proof of etomidate's neuroprotective effect in humans is lacking, the combination of animal data and anecdotal reports of successful use of etomidate in neurosurgical procedures such as giant aneurysm clippings makes etomidate a reasonable choice during neurosurgical induction. 261, 272, 274, 322 In addition, etomidate should be considered as an agent to reduce raised ICP when maintenance of cerebral or coronary perfusion pressure is also important. Trauma patients with questionable volume status may be well served by an etomidate induction. Although the indirect sympathomimetic effect seen with ketamine induction is absent, there is no direct myocardial depression and no confusion in the differential diagnosis of postoperative delirium. This is especially important in patients whose trauma may be related to drug and/or alcohol use.

During an infusion, hemodynamic status is well maintained, and adequate spontaneous ventilation is present. 88, 323 The incidence of pain on injection and of myoclonus and thrombophlebitis tends to be less with an infusion technique. 258, 260, 323 A concentrated form of etomidate used for continuous infusion in Europe is not available in the United States.

Short-term sedation with etomidate is useful in hemodynamically unstable patients, such as those requiring cardioversion 314 or those requiring sedation following an acute myocardial infarction or with unstable angina for a minor operative procedure 301 or for intubation both in the emergency room and in the ICU. In addition, etomidate has been used to produce short-term sedation for placement of retrobulbar block and for electroconvulsive therapy instrumentation, during which maintenance of spontaneous respirations and quick recovery are important features. When used during electroconvulsive therapy, etomidate can produce longer seizures compared with other hypnotics. 324

Prolonged sedation for patients in the ICU, although initially popular following the release of etomidate, is now contraindicated owing to inhibition of corticosteroid and mineralocorticoid production, with subsequent increase in morbidity. 239, 242, 302

• PHENCYCLIDINES (KETAMINE)

History

Phencyclidine was the first drug of its class to be used for anesthesia. It was synthesized by Maddox and introduced into clinical use in 1958 by Greifenstein et al 114 and in 1959 by Johnstone et al. 115 Although phencyclidine proved useful as an anesthetic, it produced unacceptably high adverse psychologic effects (hallucinations and delirium) in the postanesthetic recovery period. Cyclohexamine, a congener of phencyclidine, was tried clinically in 1959 by Lear and coworkers, 116 but it was found to be less efficacious than phencyclidine in terms of analgesia and yet to have as many adverse psychotomimetic effects. Neither of these drugs is used clinically today, although phencyclidine is available for illicit recreational use. Ketamine (Ketalar) was synthesized in 1962 by Stevens and was first used in humans in 1965 by Corssen and Domino. 117 It was chosen from among 200 phencyclidine derivatives and proved to be the most promising in laboratory animal testing. Ketamine was released for clinical use in 1970 and is still used in a variety of clinical settings. Ketamine is different from most other anesthetic induction agents because it has significant analgesic effect. It usually does not depress the cardiovascular and respiratory systems, 118, 119 but it does possess some of the worrisome adverse psychologic effects found with the other phencyclidines.

Physicochemical Characteristics

Ketamine (Fig. 9–12) has a molecular weight of 238 kd, is partially water soluble, and forms a white crystalline salt with a negative log of the acid ionization constant (pKa) of 7.5. 118, 119 It has a lipid solubility five to ten times that of thiopental. 120 Ketamine is prepared in a slightly acidic (pH 3.5–5.5) solution and comes in concentrations of 10-, 50-, and 100-mg ketamine base per milliliter of sodium chloride solution containing the preservative benzethonium chloride. The ketamine molecule contains a chiral center and therefore occurs as two resolvable optical isomers or enantiomers (11–12), the commercial preparation being a racemic mixture of both isomers [S-(+) and R-(–)] in equal amounts. 118

Metabolism

Ketamine is metabolized by the hepatic microsomal enzymes responsible for most drug detoxification. The major pathway involves *N* -demethylation to form norketamine (metabolite I), which is then hydroxylated to hydroxynorketamine. These products are conjugated to water-soluble glucuronide derivatives and are excreted in the urine. 118, 119, 121 The activity of the principal metabolites of ketamine has not been well studied, but norketamine (metabolite I) has been shown to have significantly less (between 20 and 30%) activity than the parent compound. 122, 123, 124 Little is known about the activity of the other metabolites, but it is probable that ketamine is the major active drug.

Pharmacokinetics

The pharmacokinetics of ketamine have not been as well studied as those of many other intravenous anesthetics. Ketamine pharmacokinetics have been examined after bolus administration of anesthetizing doses (2 to 2.5 mg/kg), 125 following a subanesthetic dose (0.25 mg/kg) 125, 126 and after continuous infusion (steady-state plasma level ?2,000 ng/ mL). 127 Regardless of the dose, ketamine plasma disappearance can be described by a two-compartment model. Table 9–3 contains the pharmacokinetic values from bolus administration studies. 125 Of note is the rapid distribution reflected in the relatively brief slow distribution half-life of 11 to 16 minutes (Fig. 9–13). The high lipid solubility of ketamine is reflected in its relatively large volume of distribution, nearly 3 L/kg. Clearance is also relatively high, ranging from 890 to 1,227 mL/min, which accounts for the relatively short elimination half-life of 2 to 3 hours. The mean total body clearance (1.4 L/min) is approximately equal to liver blood flow, which means that changes in liver blood flow affect clearance. Thus, the administration of a drug such as halothane, which reduces hepatic blood flow, reduces ketamine clearance. 128, 129

Pharmacology

Effects on the Central Nervous System

Ketamine produces dose-related unconsciousness and analgesia (Chs. 35 and 52). The anesthetized state has been termed *dissociative anesthesia* because patients who receive ketamine alone appear to be in a cataleptic state, unlike other states of anesthesia that resemble normal sleep. The ketamine-anesthetized patients have profound analgesia but keep their eyes open and maintain many reflexes. Corneal, cough, and swallow reflexes may all be present but should not be assumed to be protective. 130 There is no recall of surgery or anesthesia, but amnesia is not as prominent with ketamine as with the benzodiazepines. Because ketamine has a low molecular weight, a pKa near the physiologic pH, and relatively high lipid solubility, it crosses the blood-brain barrier rapidly and therefore has an onset of action within 30 seconds of administration. The maximal effect occurs in about 1 minute. After ketamine administration, pupils dilate moderately and nystagmus occurs. Lacrimation and salivation are common, as is increased skeletal muscle tone, often with coordinated but seemingly purposeless movements of the arms, legs, trunk, and head. Although there is great interindividual variability, plasma levels of 0.6 to 2.0 ?g/mL are considered the minimum concentrations for general anesthesia, 127, 128 but children may require slightly higher plasma levels (0.8–4.0 ?g/mL). 131 The duration of ketamine anesthesia after a single administration of a general anesthetic dose (2 mg/kg IV) is 10 to 15 minutes 119 (see Fig. 9–13), and full orientation to person, place, and time occurs within 15 to 30 minutes. 132

FIGURE 9–13 Simulated time course of plasma levels of ketamine following an induction dose of 2.0 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are 0.7 to 2.2 ?g/mL, with awakening usually occurring at levels lower than 0.5 ?g/mL.

The S enantiomer enables quicker recovery (by a couple of minutes) than the racemic mixture. 133 This is thought to be due to the lower dose necessary to produce an equianesthetic effect and to the 10 percent faster hepatic biotransformation. 134

The duration of ketamine anesthesia is determined by the dose; higher doses produce more prolonged anesthesia, 135 and the concurrent use of other anesthetics also prolongs the time of emergence. Because there is a reasonably good correlation between blood level of ketamine and CNS effect, it appears that ketamine's relatively short duration of action is due to its redistribution from the brain and blood to the other tissues in the body. Thus, the termination of effect after a single bolus administration of ketamine is caused by drug redistribution from the well-perfused to the less well-perfused tissues. Concomitant administration of benzodiazepines, a common practice, may prolong ketamine's effect. 136 When used in combination with a benzodiazepine, the S enantiomer was no different in terms of awareness at 30 minutes, but it was significantly better at 120 minutes than the racemic mixture. 137 Analgesia occurs at considerably lower blood levels than loss of consciousness. The plasma level at which pain thresholds are elevated is 0.1 g/mL or higher. 128 This means that there is a considerable period of postoperative analgesia after ketamine general anesthesia and that subanesthetic doses can be used to produce analgesia.

The primary site of CNS action of ketamine appears to be the thalamoneocortical projection system. 138 The drug selectively depresses neuronal function in parts of the cortex (especially association areas) and thalamus while simultaneously stimulating parts of the limbic system, including the hippocampus. This process creates what is termed a *functional disorganization* 119 of nonspecific pathways in midbrain and thalamic areas. 139, 140 There is also evidence that ketamine depresses transmission of impulses in the medial medullary reticular formation, which is important to transmission of the affective-emotional components of nociception from the spinal cord to higher brain centers. 141 Blockade of CNS sodium channels has been shown not to be the mechanism of action by which ketamine produces anesthesia. 142 There is some evidence that ketamine occupies opiate receptors in the brain and spinal cord, and this property could account for some of the analgesic effects. 118, 119, 143, 144 The S-(+) enantiomer has been shown to have some opioid ?-receptor activity, accounting for part of its analgesic effect. 145 *N*-Methyl-D-aspartate (NMDA) receptor interaction may mediate the general anesthetic effects as well as some analgesic actions of ketamine. 146, 147, 148 The spinal cord analgesic effect of ketamine is postulated to be due to inhibition of dorsal horn wide dynamic range neuronal activity. 149 Although some drugs have been used to antagonize ketamine, no specific receptor antagonist is yet known that reverses all the CNS effects of ketamine.

Ketamine increases cerebral metabolism, CBF, and intracranial pressure (ICP). Because of its excitatory CNS effects, which can be detected by generalized EEG development of theta-wave activity 135 as well as by petit mal seizure-like activity in the hippocampus, 150 ketamine increases $CMRO_2$. Whereas theta-wave activity signals the analgesic activity of ketamine, alpha waves indicate its absence. There is an increase in CBF, which appears higher than the increase in $CMRO_2$ would mandate. With the increase in CBF as well as the generalized increase in sympathetic nervous system response, there is an increase in ICP after ketamine. 151, 152 The increase in $CMRO_2$ and CBF can be blocked by the use of thiopental 153 or diazepam. 152, 154 Cerebrovascular responsiveness to carbon dioxide appears to be preserved with ketamine; therefore, reducing $PaCO_2$ attenuates the rise in ICP after ketamine 152 (Ch. 56).

Ketamine, like other phencyclidines, produces undesirable psychologic reactions, which occur during awakening from ketamine anesthesia and are termed *emergence reactions.* The common manifestations of these reactions, which vary in severity and classification, are vivid dreaming, extracorporeal experiences (sense of floating out of body), and illusions (misinterpretation of a real, external sensory experience). 155 These incidents of dreaming and illusion are often associated with excitement, confusion, euphoria, and fear. 119 They occur in the first hour of emergence and usually abate within 1 to several hours. It has been postulated that the psychic emergence reactions occur secondary to ketamine-induced depression of auditory and visual relay nuclei, leading to misperception and/or misinterpretation of auditory and visual stimuli. 118 Their incidence ranges from as low as 3 to 5 percent 118, 119 to as high as 100 percent. 155 A clinically relevant range is probably 10 to 30 percent of adult patients who receive ketamine as a sole or major part of the anesthetic technique.

Factors that affect the incidence of emergence reactions are age, 156 dose, 119 gender, 157 psychologic susceptibility, 158 and concurrent drugs. Playing music during anesthesia does not attenuate the incidence of psychotomimetic reactions. 159 Pediatric patients do not report as high an incidence of unpleasant

emergence reactions as do adult patients, nor do men as compared with women. Larger doses and rapid administration of large doses seem to predispose patients to a higher incidence of adverse effects. 160, 161 Finally, certain personality types seem prone to the development of emergence reactions. Patients who score high in psychotism on the Eysenck Personality Inventory are prone to develop emergence reactions, 158 and people who commonly dream at home are more likely to have postoperative dreams in the hospital after ketamine. 160 Numerous drugs have been used to reduce the incidence and severity of postoperative reactions to ketamine 118, 119, 162 ; the benzodiazepines seem to be the most effective group of drugs to attenuate or to treat ketamine emergence reactions. Mid-azolam, 118 lorazepam, 163 and diazepam 164 are useful in reducing reactions to ketamine. The mechanism is not known, but it is probable that both the sedative and amnesic actions of the benzodiazepines make them superior to other sedative-hypnotics. Midazolam has also been shown to reduce the psychotomimetic effect of the S enantiomer. 165

Effects on the Respiratory System

Ketamine has minimal effects on the central respiratory drive as reflected by an unaltered response to carbon dioxide. 166 There can be a transient (1–3-min) decrease in minute ventilation after the bolus administration of an anesthetizing dose of ketamine (2 mg/kg IV). 135, 167, 168 Unusually high doses can produce apnea, 169 but this is seldom seen. Arterial blood gases are generally preserved when ketamine is used alone for anesthesia or analgesia. However, with the use of adjuvant sedatives or anesthetic drugs, respiratory depression can occur. Ketamine has been shown to affect ventilatory control in children and should be considered a possible respiratory depressant when the drug is given to them in bolus doses. 170, 171

Ketamine is a bronchial smooth muscle relaxant. When it is given to patients with reactive airway disease and bronchospasm, pulmonary compliance is improved. 172, 173 Ketamine is as effective as halothane or enflurane in preventing experimentally induced bronchospasm. 174 The mechanism for this effect is probably a result of the sympathomimetic response to ketamine, but there are isolated bronchial smooth muscle studies showing that ketamine can directly antagonize the spasmogenic effects of carbachol and histamine. 175 Owing to its bronchodilating effect, ketamine has been used to treat status asthmaticus unresponsive to conventional therapy. 176

A potential respiratory problem, especially in children, is the increased salivation that follows ketamine administration. This can produce upper airway obstruction, which can be further complicated by laryngospasm. The increased secretions may also contribute to or may further complicate laryngospasm. In addition, although swallow, cough, sneeze, and gag reflexes are relatively intact after ketamine, there is evidence that silent aspiration can occur during ketamine anesthesia. 130

Effects on the Cardiovascular System

Ketamine also has unique cardiovascular effects; it stimulates the cardiovascular system and is usually associated with increases in blood pressure, heart rate, and cardiac output (see Table 9–4). Other anesthetic induction drugs either cause no change in hemodynamic variables or produce vasodilation with cardiac depression. The S enantiomer, despite hope that reducing the dose by half (equi-anesthetic potency) would attenuate side effects, is equivalent to the racemic mixture regarding hemodynamic response. 165 The increase in hemodynamic variables is associated with increased work and myocardial oxygen consumption. The healthy heart is able to increase oxygen supply by increased cardiac output and decreased coronary vascular resistance, so that coronary blood flow is appropriate for the increased oxygen consumption. 177 The hemodynamic changes are not related to the dose of ketamine (e.g., there is no hemodynamic difference between administration of 0.5 and 1.5 mg/kg IV). 178 It is also interesting that a second dose of ketamine produces hemodynamic effects less than or even opposite to those of the first dose. 179 The hemodynamic changes after anesthesia induction with ketamine tend to be the same in healthy patients and in those with a variety of acquired or congenital heart diseases. 168, 178, 180, 181, 182 In patients with congenital heart disease, there are no significant changes in shunt directions or fraction 183 or systemic oxygenation after ketamine induction of anesthesia. 184 In patients who have elevated pulmonary artery pressure (as with mitral valvular and some congenital lesions), ketamine seems to cause a more pronounced increase in pulmonary than systemic vascular resistance. 182, 183, 185, 186

TABLE 9–4. Hemodynamic Changes After Induction of Anesthesia With Nonbarbiturate Hypnotics

The mechanism by which ketamine stimulates the circulatory system remains enigmatic. It appears not to be a peripheral mechanism such as baroreflex inhibition, 187, 188 but rather to be central. 189, 190, 191 There is some evidence that ketamine attenuates baroreceptor function via an effect on NMDA receptors in the nucleus tractus solitarius. 192 Ketamine injected directly into the CNS produces an immediate sympathetic nervous system hemodynamic response. 193 Ketamine also causes the sympathoneuronal release of norepinephrine, which can be detected in venous blood. 194 Blockade of this effect is possible with barbiturates, benzo-diazepines, and droperidol. 191, 193, 194, 195 Ketamine *in vitro* probably has negative inotropic effects. Myocardial depression has been demonstrated in isolated rabbit hearts, 196 intact dogs, 197 chronically instrumented dogs, 198 and isolated canine heart preparations. 199 However, in isolated guinea pig hearts, ketamine was the least depressant of all the major induction drugs. 200 The finding that ketamine may exert its myocardial effects by acting on myocardial ionic currents (which may exert different effects from species to species or among tissue types) may explain the tissue and animal model variances in direct myocardial action. 201

The centrally mediated sympathetic responses to ketamine usually override the direct depressant effects of ketamine. There are some peripheral nervous system actions of ketamine that play an undetermined role in the hemodynamic effects of the drug. Ketamine inhibits intraneuronal uptake of catecholamines in a cocaine-like effect 202, 203 and inhibits extraneuronal norepinephrine uptake. 204, 205

Stimulation of the cardiovascular system is not always desirable, and certain pharmacologic methods have been used to block the ketamine-induced tachycardia and systemic hypertension. Successful methods include use of adrenergic antagonists (both ? and ?), as well as a variety of vasodilators 206 and clonidine. 207 However, probably the most fruitful approach has been prior administration of benzodiazepines. Modest doses of diazepam, flunitrazepam, and midazolam all attenuate the hemodynamic effects of ketamine. It is also possible to lessen the tachycardia and hypertension caused by ketamine by using a continuous infusion technique with or without a benzodiazepine. 208 Other general anesthetics, particularly the inhalation anesthetics, 209 blunt the hemodynamic effect of ketamine. Ketamine can produce hemodynamic depression in the setting of deep anesthesia, when sympathetic responses do not accompany its administration.

Uses

The many unique features of ketamine pharmacology, especially its propensity to produce unwanted emergence reactions, have placed ketamine outside the realm of routine clinical use. Nevertheless, ketamine has an important niche in the practice of anesthesiology when its unique sympathomimetic activity and bronchodilating capabilities are indicated during induction of anesthesia. It is used for premedication, sedation, induction and maintenance of general anesthesia.

Induction and Maintenance of Anesthesia

Poor-risk patients (ASA class IV) with respiratory and cardiovascular system disorders (excluding ischemic heart disease), represent the majority of candidates for ketamine induction; this is particularly true for patients with bronchospastic airway disease or patients with hemodynamic compromise based either on hypovolemia or cardiomyopathy (not coronary artery disease). Ketamine bronchodilation and profound analgesia allowing the use of high oxygen concentrations make ketamine an excellent choice for induction in patients with reactive airway disease. Otherwise healthy trauma victims whose blood loss is extensive are also candidates for rapid-sequence anesthesia induction with ketamine. 210 Patients with septic shock may also benefit from ketamine. 211 However, ketamine‘s intrinsic myocardial depressant effect may manifest in this situation if trauma or sepsis has caused depletion of catecholamine stores prior to the patient‘s arrival in the operating room. Use of ketamine in these patients does not obviate the need for appropriate preoperative preparation, including restoration of blood volume. Other cardiac diseases that can be well managed with ketamine anesthesia are cardiac tamponade and restrictive pericarditis. 212 The finding that ketamine preserves heart rate and right atrial pressure through its sympathetic stimulating effects makes ketamine an excellent anesthetic induction and maintenance drug in this setting. Ketamine is also often used in patients with congenital heart disease, especially those in whom the propensity for right-to-left shunting exists. Use of ketamine has also been reported in a patient susceptible to malignant hyperthermia who had a large anterior mediastinal mass, 213 when spontaneous ventilation was required and inhalation anesthetics were contraindicated. 213, 214, 215

Ketamine combined with diazepam or midazolam can be given by continuous infusion to produce satisfactory cardiac anesthesia for patients with valvular and ischemic heart disease (Ch. 49). The combination of a benzodiazepine 208 or of a benzodiazepine plus sufentanil 216 with ketamine attenuates or eliminates the unwanted tachycardia and hypertension as well as postoperative psychologic derangements. With this technique, there are minimal hemodynamic perturbations, profound analgesia, dependable amnesia, and an uneventful convalescence. No comparison of this technique with a continuous benzodiazepine-opioid technique has been made.

Low-dose ketamine as an analgesic has been used following thoracic surgery, 217 in which its lack of respiratory depressant properties and its equivalent pain relief as compared with meperidine make it a third choice when one wishes to avoid narcotics because of their respiratory depressant effects and when there is reason also to avoid non-steroidal agents such as ketorolac. Additional analgesic use can be considered in asthmatic patients. 218

Sedation

Ketamine is particularly suited for sedation of the pediatric patient undergoing procedures away from the operating room. Pediatric patients have fewer adverse emergence reactions 156 than adults, and this feature makes the use of ketamine in pediatrics more versatile. Ketamine is used for sedation and/or general anesthesia for the following pediatric procedures: cardiac catheterization, radiation therapy, radiologic studies, dressing changes, 219 and dental work. 136 Caution is advised in use of ketamine for cardiac catheterization in pediatric patients with elevated pulmonary vascular resistance, because this can be increased by ketamine. 220

Ketamine is often used repeatedly in the same patient. Unfortunately, the literature does not provide information on how many times ketamine anesthesia can safely be administered to one individual, whether frequency of administration is related to tolerance following multiple administrations, and whether or not there are detrimental effects of frequent/long-term use.

Usually, a subanesthetic dose (?1.0 mg/kg IV) is used for dressing changes; this dose gives adequate operating conditions but a rapid return to normal function, including the resumption of eating, which is important in maintaining proper nutrition in burn patients. 118, 119 Often, ketamine is combined with premedication of a barbiturate or benzodiazepine and an antisialagogue (e.g., glycopyrrolate) to facilitate management. The premedications reduce the dose requirement for ketamine, and the antisialagogue reduces the sometimes troublesome salivation.

In adults and children, ketamine can be used as a supplement or an adjunct to regional anesthesia, extending the usefulness of the primary (local anesthetic) form of anesthesia. In this setting, ketamine can be used prior to the application of painful blocks, 221 but more commonly it is used for sedation or supplemental anesthesia during long or uncomfortable procedures. When used for supplementation of regional anesthesia, ketamine (0.5 mg/kg IV) combined with diazepam (0.15 mg/kg IV) is better accepted by patients and is not associated with greater side effects as compared with unsedated patients. 222 Ketamine in low doses can also be combined with nitrous oxide and propofol for the supplementation of conduction or local anesthesia. These techniques of ketamine administration are used in outpatient and inpatient settings, and although patients are comfortable and cooperative, dreams and other unpleasant emergence reactions can occur. 118 In outpatients, premedication with midazolam, concurrent propofol infusion, and intermittent ketamine (for analgesia) in doses less than 3 mg/kg are recommended. 223

Doses and Routes of Administration

Ketamine can be administered intravenously, intramuscularly, orally, nasally, and rectally. 224 Most clinical use involves the intravenous and intramuscular routes, by which the drug rapidly achieves therapeutic levels. The dose depends on the desired therapeutic effect and on the route of administration. Table 9–7 contains general recommended doses for the intravenous and intramuscular administration of ketamine for various therapeutic goals. 118 Because of their side effects, most anesthetic drugs require that dosage be reduced in elderly and seriously ill patients; such a recommendation probably is prudent with ketamine, although data supporting this are not available. Patients who have been critically ill for a prolonged period may have exhausted their catecholamine stores and may exhibit the circulatory depressant effects of ketamine. 225 Ketamine can be given epidurally and intrathecally for operative and postoperative pain

control. The dose used in cancer pain is 1.0 mg (with benzethorium chloride as preservative and 0.05 mg morphine) twice daily, with additional morphine as required. 226 The peak action after intravenous administration occurs in 30 to 60 seconds. Onset occurs in about 5 minutes, with peak effect in about 20 minutes after intramuscular administration. An oral dose of 3 to 10 mg/kg generates a sedative effect in 20 to 45 minutes. The continuous infusion of intravenous ketamine with or without concomitant drugs is a satisfactory method to keep blood levels in the therapeutic range. The use of concomitant drugs such as benzodiazepines permits a lower dose requirement for ketamine while enhancing recovery by reducing emergence reactions. The interaction of ketamine with propofol is strictly additive and not synergistic; thus, the dose of each would be reduced by about half when used together for induction. 227

TABLE 9–7. Uses and Doses of Ketamine

For sedation, ketamine may be given intramuscularly if the patient wishes to avoid awareness of intravenous catheter placement. It has also been administered orally in doses of 3 to 10 mg/kg, with 6 mg/kg providing optimal conditions in 20 to 25 minutes in one study and 10 mg/kg providing sedation in 87 percent of children within 45 minutes in another study. 228, 229 In at least one case, deep sleep was produced by a supposedly sedative oral dose. 230

Side Effects and Contraindications

The common psychologic emergence reactions are discussed earlier. Contraindications to ketamine relate to specific pharmacologic actions and patient diseases. Patients with increased ICP and with intracranial mass lesions should not receive ketamine because it can increase ICP and has been reported to cause apnea on this basis. 231 The S-(+) enantiomer also increases CBF and is probably similarly contraindicated. 232 Ketamine is also contraindicated in patients with an open eye injury or other ophthalmologic disorder, in whom a ketamine-induced increase in intraocular pressure would be detrimental (Ch. 63). Because ketamine has a propensity to cause hypertension and tachycardia, with a commensurate increase in myocardial oxygen consumption, it is contraindicated as the sole anesthetic in patients with ischemic heart disease. 181 Likewise, it is unwise to give ketamine to patients with vascular aneurysms because of the possible sudden change in arterial pressure. Psychiatric disease such as schizophrenia or a history of adverse reaction to ketamine or one of its congeners also constitutes a contraindication. 119 One should also consider carefully using ketamine when there is a possibility of postoperative delirium from other causes (e.g., delirium tremens, possibility of head trauma) and a ketamine-induced psychomimetic effect would cloud the differential diagnosis.

Other side effects include potentiation of nondepolarizing neuromuscular blockade by an undefined mechanism. 233, 234 Finally, because ketamine's preservative, chlorobutanol, has been demonstrated to be neurotoxic, subarachnoid administration is contraindicated. 235 It is probably unwise to administer the drug epidurally for this reason.

• DROPERIDOL

History

General anesthesia with inhaled anesthetics and barbiturates depresses the entire CNS in a nonspecific manner. Laborit and Huguenard 508, 509 in the 1950s sought an anesthetic technique that would produce "artificial hibernation" devoid of circulatory and respiratory depression. Their concept was to use drugs that would produce neurovegetative blockade (multifocal inhibition) of cellular, autonomic, and endocrine mechanisms normally activated in response to stress. 510 The first attempt at developing this concept was the lytic cocktail, containing an analgesic (meperidine), two tranquilizers (chlorpromazine and promethazine), and atropine. Although this combination of drugs did enjoy widespread use for conscious sedation, it produced respiratory depression. It was not used for general anesthesia. Janssen 511 synthesized haloperidol, the first member of the butyrophenones, which became the primary neuroleptic component in neuroleptanesthesia (NLAN). DeCastro and Mundeleer 512 in 1959 combined haloperidol with phenoperidine (a meperidine derivative also synthesized by Janssen) in the forerunner to the current practice of NLAN. Droperidol, a derivative of haloperidol, and fentanyl (a phenoperidine congener), both again synthesized by Janssen, were used by DeCastro and Mundeleer 512 in a combination they reported

to be superior to haloperidol and phenoperidine. This NLAN combination produced more rapid onset of analgesia, less respiratory depression, and fewer extrapyramidal side effects. The fixed combination of droperidol and fentanyl, marketed as Innovar in the United States, is the drug currently used for NLAN.

Droperidol is a butyrophenone, a fluorinated derivative of phenothiazines 510 (Fig. 9–21). Butyrophenones produce CNS depression, characterized by marked apparent tranquility and cataleptic immobility. They are potent antiemetics. Droperidol is a potent butyrophenone, and like the others, it produces its action centrally at sites where dopamine, norepinephrine, and serotonin act. It has been postulated that butyrophenones may occupy GABA receptors on the postsynaptic membrane, thereby reducing synaptic transmission and resulting in a build-up of dopamine in the intersynaptic cleft. 510, 511 An imbalance in dopamine and acetylcholine is thought to occur, which results in alteration in normal transmission of signals in the CNS. The chemoreceptor trigger zone is the emetic center, and “red” astrocytes transport neurolept molecules from the capillary to dopaminergic synapses in the chemoreceptor trigger zone, where they occupy GABA receptors (Fig. 9–22). This is thought to be the mechanism by which droperidol exerts its antiemetic effect. 513

Metabolism and Pharmacokinetics

Droperidol is biotransformed in the liver into two primary metabolites. 514 Its plasma decay can be described by a two-compartment model. The pharmacokinetics 515 is shown in Table 9–3 . The clearance of droperidol is relatively large (14 mL/kg/min), and its elimination half-life is relatively short (103–134 min). 515, 516 Its time course of disappearance from plasma is similar to that of fentanyl (Fig. 9–23), yet the discrepancy in duration of effect of the two has been the subject of criticism, because both are formulated together in Innovar. The seemingly longer CNS action of droperidol has prompted some investigators to postulate that droperidol has a propensity to occupy CNS receptors 515 and that it has greater receptor binding than fentanyl.

Pharmacology

Effects on the Central Nervous System

The effects of neuroleptanesthetics on human CBF and CMRO2 have not been studied. In dogs, droperidol causes potent cerebral vasoconstriction, producing a 40 percent reduction in CBF (Ch. 54). No significant change in CMRO2 occurs during droperidol administration. 517 The EEG in conscious patients shows some reduction in frequency in the range, with occasional slowing to the range. 518 The extrapyramidal and malignant neuroleptic syndrome that sometimes follows droperidol use is discussed later in connection with Innovar.

Effects on the Respiratory System

When used alone, droperidol has little effect on the respiratory system. 519 Droperidol (0.044 mg/kg) given to surgical patients produced a slight reduction in respiratory rate, 520 and droperidol (3 mg IV) had no significant effect on tidal volume in volunteers. 521 More detailed respiratory studies are not available.

Effects on the Cardiovascular System

The predominant cardiovascular effect of droperidol is vasodilation with a decrease in blood pressure (see Table 9–4). This effect is considered to be a result of moderate ?-adrenergic blockade. 514, 522, 523 Importantly, the dopamine-induced increase in renal blood flow (renal artery flowmeter methodology) is not significantly impaired by administration of droperidol. 524 Droperidol has little effect on myocardial contractility. 525 It seems to possess some antiarrhythmic effects that are much like those of quinidine. 525, 526

Uses

Droperidol is used as an NLAN component (see *Innovar*) and as an antiemetic component in general anesthesia. It is an effective antiemetic, 527 the dose for this use varying between 10 and 20 ?g/kg (0.6 and 1.25 mg for a 70-kg person). 528 These doses of droperidol, given at the start of anesthesia for operations lasting 1 hour, reduce the incidence of nausea and vomiting by about 50 percent. These doses given at

induction have little effect on wake-up time, but should they be given at the end of surgery, there could be some residual hypnotic effect. Droperidol is also effective in pediatric patients 529 when the drug is given orally (300 ?g/kg), and the effect can be enhanced when combining it with oral metoclopramide (0.15 mg/kg) Overall antiemetic efficacy of droperidol alone is probably less than that of ondansetron and is associated with more sedation, but costs are less.

A newer use for droperidol is as an antiemetic given as an adjunctive drug intermittently or with continuous infusion for postoperative pain relief as part of a patient-controlled regimen 530, 531 or as epidural supplements to opioids. 532 When used in this fashion, droperidol effectively reduces nausea, but it does increase sedation.