Lesson 276: PreAnesthetic Assessment of the Patient With Acute Intoxication by “Ecstasy”

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Needs Statement

The use of the street drug “ecstasy” has become increasingly prevalent among teenagers and young adults in the United States. Anesthesiologists are charged with the task of delivering safe anesthesia in cases requiring emergency surgery, regardless of the substances patients may have eaten, drunk, or self-injected before the event necessitating surgical intervention. Although most anesthesiologists are well versed in the intricacies of managing patients intoxicated with alcohol, cocaine, or narcotics, newer “club drugs” present a challenge. “Ecstasy,” in particular, is the most commonly abused club drug and potentially the most dangerous for patients in the perioperative period. Familiarity with the effects of “ecstasy” and the potential pitfalls of administering an anesthetic to an acutely intoxicated user of this drug is crucial, given that anesthesiologists may expect to encounter emergency cases involving substance abuse—as either an inciting or a coincidental event.
Learning Objectives

At the end of this activity, the participant should be able to:

1. Identify the signs and symptoms of acute intoxication with “ecstasy.”
2. List the known adverse effects associated with the abuse of “ecstasy.”
3. Describe the pharmacodynamic effects of “ecstasy.”
4. Outline the steps in the metabolic breakdown of “ecstasy.”
5. Indicate any likely drug interactions with anesthetic agents.
6. Formulate a rational approach to the preoperative assessment of the patient who abuses “ecstasy.”
7. Describe common perioperative pitfalls and their appropriate management in the patient who abuses “ecstasy.”
8. Discuss the role, if any, of dantrolene in the treatment of “ecstasy”-induced hyperthermia.
9. Present an appropriate anesthetic plan.
10. Anticipate postoperative complications.

Case History

A 22-year-old man with an unknown medical and surgical history was admitted for emergency repair of a compound fracture of the left humerus. He was unable to give a coherent history, but a friend stated that the patient had been at a “rave” and had fallen down a flight of stairs on his left side. The friend said he did not know if the patient had taken any illicit substances, although “X” was available at the party, along with alcohol. He believed the patient to be healthy because he played college baseball.

On physical examination, the patient was oriented only to person and place, and he appeared to be in pain. He could follow commands, but when asked specific questions, he mumbled to himself. His height was 5 ft 9 in, and he weighed 165 lb. Vital signs were as follows: heart rate, 115 beats/min; blood pressure, 157/88 mm Hg; respiratory rate, 13 breaths/min; and O2 saturation, 99% on room air. His skin felt warm to the touch. Examination revealed a Mallampati class II airway, a thyromental distance of more than 6.5 cm, and a full range of motion in the neck and temporomandibular joints. His lungs were clear; a cardiovascular examination was remarkable only for tachycardia. Results of computed tomography of the head without contrast were negative for intracranial mass or hemorrhage. An analysis of electrolytes found a sodium level of 127 mEq/L.

Patients who abuse illicit substances present an immense challenge to the anesthesiologist, who may encounter them when they are admitted for emergency, nonemergency, elective, or obstetric surgery. Such patients may display the effects of acute or chronic drug use. The use of alcohol, cocaine, amphetamines, or opiates commonly causes perioperative complications, but the advent of designer and club drugs demands a new paradigm in anesthetic management. Most anesthesiologists are familiar with the challenges of managing a patient acutely intoxicated with cocaine, opiates, alcohol, or amphetamines. This lesson focuses on the club drug “ecstasy” (3,4-methylenedioxymethamphetamine [MDMA]). Along with γ-hydroxybutyrate, ketamine, and flunitrazepam, MDMA is classified as a club drug because of its use predominantly at dance parties (“raves”) and in dance clubs.
In the United States, an estimated 19.7 million people (or about 8.1%) older than 12 years of age used illicit drugs in 2005; about 500,000 of them had taken MDMA at least once during the year before the survey. 1 According to the Texas Commission on Alcohol and Drug Abuse, the age range of those who attend raves—where “ecstasy” is prevalent—is 13 to 40 years. MDMA is available at 70% of raves, according to one study. A 2001-2002 survey in Chicago found that approximately 40% of 18- to 40-year-olds had gone to a rave, and roughly half of them had taken a club drug.

Given that motor vehicle accidents are the leading cause of morbidity and mortality in this age group, and that 38% of all traffic fatalities involve a substance-impaired individual, an anesthesiologist on call may see a “raver” admitted for emergency trauma surgery. In 2005, 10.5 million people reported driving under the influence of an illicit drug. High rates of alcohol and illicit drug use have been documented among persons who died of trauma of all causes. The fact that most recreational drug users travel to and from venues late at night and may combine MDMA with any number of other illicit substances strengthens this inference. It is hard to quantify MDMA abuse as a direct cause of trauma or other emergencies requiring surgical intervention; however, it is reasonable to assume, especially in large urban centers serving coastal communities where use of the drug is relatively common, that the on-call anesthesiologist will be required to administer anesthesia to an acutely intoxicated MDMA abuser at least once in his or her career.

Characteristics of “Ecstasy”

The street drug “ecstasy” is a hallucinogenic amphetamines analog known by various names among recreational drug users, including “XTC,” “X,” “E,” and “Adam.” 2 MDMA was patented in 1914 by Merck Pharmaceuticals as an appetite suppressant. 3 Given its reported entactogenic effects of enhancing communication and perceived closeness to others, it became popular in the 1970s when it was promoted as an adjunct to psychotherapy. Despite this potentially beneficial clinical use, the widespread abuse of MDMA prompted the Drug Enforcement Administration to issue a schedule I classification for the drug in 1985. Since that time, MDMA abuse in the United States has steadily risen. Illicit MDMA is most often taken orally as a small pill or capsule. Because it is produced illegally, the purity of street MDMA is highly variable, with numerous compounds commonly mixed into the final product (Table 1). 4 Indeed, the concentration of MDMA itself may vary, making the accidental ingestion of larger-than-intended doses likely. Therefore, cases of acute MDMA intoxication should be approached as cases of polysubstance intoxication.

The molecular structure of MDMA closely resembles that of the hallucinogen mescaline and the stimulant amphetamine. These structural relationships are predictive of the effects of MDMA on the user. MDMA has a potent effect on the (increased) release and (decreased) reuptake of serotonin and dopamine. 5,6 MDMA may also have direct agonist properties at serotonergic and dopaminergic receptors, as well as monoamine oxidase inhibitor effects. In addition, results of in vitro studies suggest an indirect agonist effect on norepinephrine release. 7

<table>
<thead>
<tr>
<th>Table 1. Common Components of Street “Ecstasy” Tablets</th>
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<tbody>
<tr>
<td>Amphetamine</td>
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<tr>
<td>Atropine</td>
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<td>Caffeine</td>
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<tr>
<td>Cocaine</td>
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<td>Dextromethorphan</td>
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<td>Diazepam</td>
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<td>Diphenhydramine</td>
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<tr>
<td>Ephedrine</td>
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<td>Ketamine</td>
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<td>Methamphetamine</td>
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The effects of MDMA may develop within 20 minutes after ingestion and last up to 8 hours. In the clinical setting, MDMA has been found to produce feelings of well-being and euphoria. Subjective effects are numerous and include heightened alertness, a feeling of “closeness” to others, increased emotional lability, decreased aggression, and sexual arousal. Cardiovascular activation—in the form of hypertension and tachycardia—is common. Lethargy, fatigue, anorexia, and depression often develop a few hours after ingestion.

The drug is metabolized principally through the cytochrome P-450 2D6 (CYP2D6) enzyme. Phase II metabolism of MDMA is poorly understood. One metabolite has been shown to be an inhibitor of CYP2D6 in vitro; however, no in vivo studies are available. Inhibitors of the CYP2D6 enzyme (eg, cocaine, methadone, haloperidol, fluoxetine, paroxetine) block the main metabolic pathway of MDMA and may result in a substantial increase in the concentration of the drug. Benzodiazepines are metabolized mainly by the CYP3A4 enzyme, and their metabolic interaction with MDMA is likely limited. Prescription drugs that are pro-serotonergic (eg, fluoxetine, amphetamines, St. John’s wort, tramadol, lithium) may increase the serotonergic effects of MDMA.8

### Adverse Effects

The adverse effects of MDMA intoxication are of great concern to the anesthesiologist who encounters acutely intoxicated patients (Table 2). A constellation of signs and symptoms may be observed with acute intoxication, such as tachycardia, hypertension, mydriasis, bruxism, sweating, and agitation with or without hyperthermia.9,12

Hyperthermia is the most common adverse effect and the leading cause of MDMA-related mortality; temperatures as high as 42°C have been reported. The mechanism of hyperthermia is most likely related to serotonergic effects in the hypothalamic thermoregulatory center, compounded by sustained muscular hyperactivity (associated with long periods of dancing in a warm environment such as a dance club), an increased metabolic rate and rigidity, and a disregard for normal body signals.13 Pre-existing susceptibility to malignant hyperthermia (MH) may be exacerbated by the ingestion of MDMA, as supported by studies in which MDMA was used to induce MH in genetically susceptible pigs. The

<table>
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<th>Table 2. Adverse Effects Associated With MDMA Intoxication</th>
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<tr>
<td><strong>Cardiovascular</strong></td>
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<tr>
<td>Hypertension/tachycardia</td>
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<tr>
<td>Increased myocardial oxygen demand/myocardial infarction/cardiomyopathy</td>
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<tr>
<td>Hypotension/cardiovascular collapse</td>
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<tr>
<td>Disseminated intravascular coagulation</td>
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<tr>
<td><strong>Hepatic</strong></td>
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<tr>
<td>Necrosis/steatohepatitis</td>
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<td>Fulminant hepatic failure</td>
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<tr>
<td><strong>Metabolic</strong></td>
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<tr>
<td>Hyponatremia</td>
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<td>Hyperkalemia</td>
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<tr>
<td>Hypermetabolic state</td>
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<tr>
<td><strong>Musculoskeletal</strong></td>
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<tr>
<td>Rigidity</td>
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<tr>
<td>Rhabdomyolysis/extreme elevation of creatine phosphokinase levels</td>
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<tr>
<td><strong>Neurologic/cerebrovascular</strong></td>
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<td>Central thermogenesis</td>
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<td>Hallucinations</td>
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<td>Anxiety</td>
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<td>Seizures</td>
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<td>Subarachnoid hemorrhage</td>
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<td>Cerebral infarction</td>
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<td>Venous sinus thrombosis</td>
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<td><strong>Pulmonary</strong></td>
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<tr>
<td>Pneumothorax/pneumomediastinum</td>
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<tr>
<td><strong>Renal</strong></td>
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<td>Acute renal failure</td>
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<td>MDMA, methylenedioxyamphetamine</td>
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most dreaded consequence is hyperpyrexia leading to rhabdomyolysis, disseminated intravascular coagulation, and multiple-organ failure.

Sympathetic stimulation by MDMA increases myocardial oxygen demand and causes tachycardia, vasoconstriction, hypertension, and possibly acute myocardial infarction and dilated cardiomyopathy, if the stimulation is profound and prolonged. Severe hypotension and a low cardiac output also may be encountered after initial tachycardia and hypertension as a consequence of catecholamine depletion or autonomic dysregulation. Indeed, a hemodynamic catastrophe and sudden death may result in an otherwise healthy individual intoxicated with MDMA. Cerebrovascular events such as subarachnoid hemorrhage, cerebral infarct, and venous sinus thrombosis have been reported.

Electrolyte disturbances in MDMA abusers are particularly dangerous. Hyponatremia—from the direct effects of MDMA or from excessive water intake during extreme physical activity and hyperthermia—has been associated with MDMA-related seizures, stupor, and incontinence. Studies have shown that MDMA use can induce a marked increase in plasma levels of antidiuretic hormone, which may compound the need for increased water intake.

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Many other systems may be affected by acute MDMA intoxication. Hepatotoxicity with hepatonecrosis and fulminant liver failure is well described. Pneumothorax and pneumomediastinum—the mechanisms for which are unclear—also have been reported. Acute renal failure may occur as a consequence of rhabdomyolysis and elevated creatine phosphokinase levels lasting for up to 4 days after hospitalization.

**Patient Management**

Management of the MDMA-intoxicated patient undergoing anesthesia requires the identification and a firm understanding of the symptoms that are most common and likely to affect the prognosis. Stabilization of the patient according to advanced cardiac life support protocols when appropriate is the first priority, and this may be initiated in the emergency room. As in every case, a complete history and physical examination are crucial but not always feasible when a patient arrives for emergency care. A history may have to be obtained from the patient’s friends or family, or from bystanders arriving with the patient at the hospital. A directed physical examination is critical, with particular attention paid to the vital signs (suspicion is heightened if the patient is hyperthermic) and cardiopulmonary findings. Initial studies that may help the anesthesiologist’s approach are nonspecific (eg, electrocardiography and electrolyte analysis).

If a patient in the emergency room is suspected of having abused MDMA and requires immediate intubation, succinylcholine should be used cautiously; risks include compounding the MH-promoting effects of MDMA with succinylcholine and worsening myonecrosis-induced hyperkalemia if present. In addition, the bruxism associated with “ecstasy” may make securing the airway more challenging; one should be prepared for a difficult intubation regardless of the patient’s age and body habitus. If the patient is conscious and capable of protecting his or her airway, anxiolysis with midazolam or diazepam may be useful; it also raises the seizure threshold before the patient is moved to the operating room.

In the operating room, it is imperative to manage the patient for hyperthermia, cardiovascular instability, and hyponatremia, and to prevent renal failure and hepatotoxicity. Standard American Society of Anesthesiologists monitors should be applied, with particular attention to body temperature. Wide swings in hemodynamic parameters are to be avoided, given the increased risk for
cardiomyopathy and coronary or cerebral vasospastic events. Therefore, before the induction of anesthesia, placement of an intra-arterial blood pressure monitor may be warranted to allow closer hemodynamic monitoring.

A rapid-sequence induction is generally necessary in patients admitted for emergency surgery. Propofol and thiopental are appropriate induction agents; ketamine may stimulate the central nervous system and induce the release of catecholamines from potentially exhausted stores. However, a patient with extreme cardiovascular compromise may necessarily receive ketamine for induction. The effect of etomidate on hemodynamic values tends to be minimal; etomidate, however, may increase seizure activity (attenuated by the preinduction administration of benzodiazepines).

Paralysis with a nondepolarizing agent immediately slows the generation of heat, lowering body temperature. Nondepolarizers—as distinct from succinylcholine—are not associated with MH. For this reason, rocuronium may be ideal for initiating a rapid-sequence induction and maintaining paralysis throughout the case.

Severe hypertension may develop during direct laryngoscopy. Methods commonly used to blunt this response (eg, I.V. lidocaine, opioids) are appropriate. Regional anesthesia, which relies on patient cooperation and assured airway reflexes, should generally be avoided.

The maintenance of anesthesia with gaseous agents should generally be accomplished with nitrous oxide. Volatile gases may be pro-arrhythmogenic and are known triggers of MH, so they are best used conservatively. Patients with hepatic compromise may be especially sensitive to them. An infusion of the opioid remifentanil, which is metabolized by blood and tissue esterases, serves the dual role of blunting sympathetic output and lowering the amount of anesthetic gas needed for surgery. Fluid and electrolyte levels must be evaluated with great care and abnormalities corrected promptly, but safely, in the operating room. As previously mentioned, placement of an intra-arterial catheter facilitates serial blood studies.

The potential pitfalls encountered in treating MDMA-intoxicated patients are many in the intraoperative setting. If intraoperative hypertension and tachycardia are evident, the use of labetalol, with its \( \alpha \)- and \( \beta \)-adrenergic blocking effects, is preferred. Pure \( \beta \)-adrenergic blockade will exacerbate hypertension by tipping the balance of catecholamine action to \( \alpha_1 \)-adrenergic receptors. If intraoperative hypotension is encountered, a rapid infusion of crystalloid or the use of direct \( \alpha_1 \)-adrenergic agonists is prudent. Avoidance of indirect agonists (eg, ephedrine) precludes the theoretical catastrophe generated when an already exhausted sympathetic nervous system is prompted to release catecholamines.

Hyperthermia must be treated promptly to avoid rhabdomyolysis and disseminated intravascular coagulation. Basic measures are obligatory, such as the administration of cold fluids and the avoidance of warming blankets. Given the presumed central mechanism of MDMA-induced hyperthermia, the use of dantrolene is controversial because it inhibits the release of calcium from the sarcoplasmic reticulum. However, studies have found that dantrolene may help to relieve exertional heat stroke, which is possibly a component of MDMA-induced hyperthermia. Furthermore, in 2006, Hall and Henry noted that during hyperthermia, the calcium levels required for the coupling of excitation and contraction are reduced; hyperthermia alone can then cause contraction and, subsequently, heat production and increased metabolic demand.\(^{14}\) The authors concluded that dantrolene, which raises
the calcium requirements for excitation–contraction coupling, may be of some benefit even if it does not directly counteract the root causes of hyperthermia.

The results of in vitro studies suggest that MDMA causes calcium elevations in myoplasm similar to those associated with MH, which would seem to support the use of dantrolene as a treatment modality. However, the use of dantrolene for controlling thermogenic effects has not been widely accepted, although it has been frequently suggested for the management of MDMA-induced hyperthermia.15

An uneventful emergence from anesthesia should be possible, provided that the patient has been stable intraoperatively. If wide swings in blood pressure and heart rate have occurred, it may be preferable to extubate at a deeper plane, when the level of anesthesia is still significant but the patient is breathing spontaneously. The postanesthetic care of such patients should focus on the correction of any residual metabolic abnormalities that were not treated intraoperatively (eg, hyponatremia) and the maintenance of normothermia. If major abnormalities persist, continued intubation is prudent.

Management of the Case Presented

Our patient was admitted for orthopedic surgery after the acute ingestion of “ecstasy.” Given his altered mental status, a general anesthetic was administered. Before induction, an intra-arterial catheter was placed following local infiltration of the skin with lidocaine. The patient’s preinduction heart rate was 105 beats/min, axillary temperature 38.2°C, and blood pressure 148/85 mm Hg. He was preoxygenated and underwent a rapid-sequence induction with 100 mg of lidocaine, 140 mg of propofol, and 90 mg of rocuronium. His blood pressure remained stable during the induction period. An intranasal temperature probe recorded the patient’s temperature of 38°C. A forced-air blanket set to the temperature of the ambient air (22°C) was applied, and during the case 3 L of cold normal saline was administered for hydration. The patient received a total of 350 mcg of fentanyl throughout the case and was maintained on a nitrous oxide–propofol anesthetic without complications. He did not require any labetalol for blood pressure control. The sodium level was slowly adjusted during the case with an infusion of normal saline; an arterial sample taken before emergence indicated a sodium level of 135 mEq/L. The patient’s temperature before emergence was 36.6°C, heart rate 67 beats/min, and blood pressure 128/79 mm Hg. He recovered well from surgery and was discharged home 2 days later.

Summary

The anesthesiologist may encounter a patient who has been abusing “ecstasy” during an admission for emergency surgery. The clinician should be knowledgeable of the mechanisms and effects of “ecstasy” in order to deliver a safe anesthetic. Patients acutely intoxicated by “ecstasy” may be hyperthermic and hyperdynamic, and they may have other dangerous complications. In such cases, a conservative approach that includes a thorough preoperative assessment, rapid-sequence induction, and appropriate monitoring is crucial for a sound anesthetic course. Although the use of dantrolene is still controversial, profoundly hyperthermic patients who do not respond to other cooling measures may receive the drug safely and with good effect.
References*


*A complete list of references for this article is available directly from the author by e-mail: demarisa@gmail.com.
Post-test

1. Which of the following compounds is not commonly found in “ecstasy” (3,4-methylenedioxymethamphetamine [MDMA]) pills?
   a. Caffeine  
   b. Heroin  
   c. Ketamine  
   d. Amphetamine

2. Which adverse effect is responsible for most MDMA-related mortality?
   a. Hypertension  
   b. Acute renal failure  
   c. Hyperthermia  
   d. Hyponatremia

3. The molecular structure of MDMA most closely resembles that of:
   a. mescaline and amphetamine  
   b. serotonin and dopamine  
   c. dopamine and mescaline  
   d. atropine and cocaine

4. The role of dantrolene in the treatment of MDMA-induced hyperthermia remains controversial. The mechanism of action of dantrolene is:
   a. interference with the coupling of excitation and contraction at the level of the muscle fiber  
   b. central effects on the thermoregulatory center  
   c. slowing of neuronal transmission to muscle  
   d. lowering of calcium levels inside the sarcoplasmic reticulum
5. A trauma patient who has sustained bilateral femoral fractures tells the anesthesiologist he took “ecstasy” at a “rave” before being involved in a motor vehicle accident. The patient became progressively hypotensive and was rushed for emergency admission to the operating room. All of the following statements are true, except:

a. A rapid-sequence induction is warranted.
b. Induction with ketamine is contraindicated because it can potentiate the hyperdynamic effects of MDMA.
c. The use of volatile agents is reasonable if hepatic failure is not suspected.
d. Cooling blankets and cold I.V. fluids may be needed in this case.

6. The pharmacodynamics of “ecstasy” most closely resemble those of which illicit substance:

a. ketamine
b. cocaine
c. heroin
d. marijuana

7. The hyponatremia in acutely intoxicated users of “ecstasy” can be attributed to:

a. excessive intake of water resulting from increased physical activity
b. natriuresis
c. decreased secretion of antidiuretic hormone
d. all of the above

8. An infusion of remifentanil potentiates the minimum alveolar concentration of volatile agents and blunts sympathetic output. What accounts for the termination of action of remifentanil?

a. Metabolism by blood and tissue esterases
b. Hepatic metabolism
c. Redistribution
d. Hofmann elimination

9. Which of the following is not a direct consequence of uncontrolled hyperthermia?

a. Disseminated intravascular coagulation
b. Rhabdomyolysis
c. Renal failure
d. Myocardial infarction

10. The adverse effect associated with MDMA that may lead to a difficult airway situation is:

a. increased secretions
b. bruxism
c. relaxation of pharyngeal tissues
d. mucosal hemorrhage