SELECTED READINGS

IN

ORAL AND

MAXILLOFACIAL SURGERY

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Volume 22, Number 5 October, 2014

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INTRODUCTION

The opioid abusing patient is not uncommonly found in oral and maxillofacial surgery offices.(1) Most oral surgeons feel comfortable with identifying these patients and managing them. However, the drugs abused by our patients go far beyond those one might consider typical (i.e., opioids, marijuana, cocaine, and alcohol). Over the past decade, novel psychoactive substances have emerged, including phenethylamines, piperazines, cathinones, synthetic cannabinoids and other unclassified drugs that pose a significant public health threat and also can be abused by our patients. The abuse of illicit drugs can influence a patient's response to both surgery and anesthesia. It is important for the practitioner to 1) be knowledgeable about the illicit drugs available in the community so as to recognize the signs and symptoms of use, 2) understand the anesthetic complications associated with these drugs and 3) know how to manage drug abuse related emergencies.

As of 2010, 41.7 % of Americans over the age of 12 have taken an illicit drug at some time during their life.(2) A significant number of users are young—22% of those between the ages of 18 and 20 have used illicit drugs. Males are more likely than females to use illicit drugs.(3) There is a growing problem with novel psychoactive substances. In 2012, there were 5,230 exposures to synthetic marijuana reported to poison control centers in the US and there were 2,641 exposures to cathinone ("bath salts"). These numbers decreased to 2,643 and 995, respectively in 2013.(4) It is not clear if these decreases represent declining use, use of alternative substances instead, or users becoming experienced enough to avoid poisoning.

Morbidity and mortality statistics from the American Association for Accreditation of Ambulatory Surgery Facilities (AAAASF) reveal that between 2001 and 2006, there were 23 deaths during 1,141,418 procedures performed in American ambulatory surgery facilities. Three of these deaths were related to postoperative opioid overdose, and two of these patients had a history of drug abuse.(5) Drug abusers may also have a higher likelihood of developing postoperative complications. Serena-Gomez, et al. reviewed complications in mandible fractures and found that 37.5% of all complications were in IV drug-abusing patients.(6) An awareness of drug use is of paramount importance in the care of our patients, for whom we provide surgery, anesthesia, and pain medication. This manuscript will review the most commonly abused illicit drugs as well as provide a brief overview of novel psychoactive substances.

MARIJUANA

Marijuana is the most commonly used illicit substance. At the time of this writing, twenty states and the District of Columbia have legalized the use of medical marijuana and two states have legalized it for medical and recreational use.(7) This section will focus

on the illicit use of cannabis. It can be smoked or eaten, and its use results in intense relaxation and euphoria. It affects memory, pleasure, sensory and time perception and coordination. Chronic use can result in cravings and dependence and withdrawal can occur, during which users may experience irritability, sleep disturbances, anxiety, poor appetite, and craving.(8)

The major psychoactive ingredient of cannabinoids is Δ-9-tetrahydrocannabinol (THC). The primary cannabinoid receptor in the brain is the CB1 receptor. Antagonistic action of the CB1 receptor by THC results in G protein activation that ultimately results in the behavioral effects of cannabinoid use. There is strong evidence demonstrating CB1 receptor down regulation and decreased G protein activation in response to chronic cannabinoid use, resulting in tolerance.(9)

THC is highly lipid soluble and readily crosses the blood brain barrier. The half-life of distribution is approximately 30 minutes and the half-life of the terminal phase is quite variable—it may be up to 56 hours in occasional users, but 28 hours in chronic users.(2,10)

Possible acute effects of marijuana use include confusion, anxiety, inability to problem solve, conjunctival congestion, tachycardia, inaccurate time perception, and dulled reflexes. There may be a green tinge visible on the tongue due to inhaled chlorophyll or green dye. Marijuana may be detected in the urine of a first time user for up to 3 days, but in the urine of a chronic user for 1 to 4 weeks.

Pulmonary Effects of Marijuana Smoking

The pulmonary effects from smoking marijuana are related to inhaled carcinogens and irritants as well as the actual method of smoking. The primary effects of marijuana smoking are inflammatory, causing an increase in coughing, phlegm production, wheezing, bronchitis and reactive airway disease. The level of bronchial inflammation caused by smoking 3 to 4 “joints” per day is equivalent to smoking 20 regular cigarettes per day.(2)

The act of smoking marijuana frequently involves deep inspiration and prolonged breath holding. This act may predispose patients to the development of bullous emphysema, possibly resulting in reduced lung function, and places them at risk of spontaneous pneumothorax.(11) Interestingly, Pletcher, et al. found that low/occasional use of marijuana did not adversely affect the FEV1 or FVC of patients with up to 7 joint-years of exposure.(12)

It has been hypothesized that the act of deep inspiration practiced during marijuana smoking contributes to a higher FVC and total lung capacity and may help preserve lung function. Pletcher, et al.’s study, however, had some limitations; it did not include a high number of heavy marijuana users and it was based on self-reporting of marijuana use, which may have been inaccurate. Due to the mucosal inflammation stimulated by marijuana, users should be expected to be at risk for an increased propensity for bronchospasm, laryngospasm, and upper airway edema compared to the non-smoker.

Cardiac Effects

Marijuana’s cardiac effects are well described as smoking marijuana has been demonstrated to cause a dose dependent heart rate increase from 20% to 100%. This elevation peaks approximately 10 to 30 minutes after starting smoking. Additionally, it is known to cause both elevated blood pressure in the supine position and postural hypotension.(13) Larger doses have been reported to cause bradycardia and hypotension.(14)

There have been reports of an increased risk of myocardial infarction related to marijuana use. The mechanism for this increased risk is not well understood.(13,14,15) This risk may be related to effects of cannabis on microcirculation or to the increase in carboxyhemoglobin that occurs with smoking that decreases the oxygen content of the blood, placing more strain on the heart. Interestingly, there have been reports of increased risk in patients otherwise felt to be at low risk for myocardial infarction with no pre-existing

cardiac issues.(13,14) The use of marijuana may be accompanied by other activities that place the patient at increased cardiac risk, such as the use of cocaine.

Mittleman, et al. performed a case-crossover study of 3882 patients with acute myocardial infarction to evaluate potential triggers for MI.(13) They found that within the first hour after marijuana smoking, the risk of MI was increased 4.8 fold. This risk declined rapidly to 1.7 by the second hour. However, three patients who had an MI within the first hour of marijuana use had engaged in other potential triggering behaviors during that hour as well, including cocaine use and sexual intercourse. Excluding these three patients, the authors found there was still a relative increased risk of 3.2 for MI within the first hour of marijuana use.(13) Although MI related to marijuana use is quite rare, it is important for the care provider to remember that the chronic marijuana user may have elevated cardiac risk, particularly the patient who otherwise seems to have no cardiac risk factors. In general, life-threatening arrhythmias have not been reported in marijuana users, but patients may exhibit occasional EKG changes to include reversible ST segment and T wave abnormalities and some supraventricular and ventricular ectopy.

Neurological and Psychiatric Complications

There is some evidence of a link between cannabis use and ischemic stroke. There are various proposed etiologies of this risk, including orthostatic hypotension, supine hypertension with labile blood pressure, alterations in cerebral vasomotor function, vasospasm, or multifactorial intracranial stenosis.(16) Westover, et al. performed a cross-sectional population-based study of stroke patients and found an adjusted odds ratio of 1.76 for the association between cannabis use and ischemic stroke.(17) After adjusting for all other risk factors they found that 1 % of 998 ischemic strokes were attributable to cannabis use. Wolff, et al. reported finding 59 case reports of cannabis-related stroke, a significant majority of which were ischemic (49) and a small number were TIA's (5).(16) Additionally, Wolff, et al. noted that cannabis users who had a stroke related to cannabis use were most often males who chronically used tobacco and alcohol as well. (16)

Marijuana is well known for its desired psychiatric effects of euphoria, relaxation, and enhanced sensorium, but use also can result in issues with memory, balance, judgment, and time concept. In some cases, disorientation, extreme anxiety, paranoia, and psychosis may ensue. There is evidence linking cannabis use to psychotic symptoms, but evidence of a link between cannabis and development of schizophrenia is controversial.(18)

Anesthetic and Surgical Concerns

The chronic marijuana user should be expected to have a reactive airway and potentially be at higher risk for airway edema and laryngospasm. In the event of airway edema, intravenous dexamethasone may be helpful.(2) Additionally, it should be remembered that due to the practice of deep inspiration and breath holding, these patients may have blebs which could lead to pneumothorax in response to excessive airway pressure.

The cardiovascular effects of marijuana can become an issue during anesthesia, chiefly due to the tachycardia and blood

pressure instability that may occur with acute use. Tachycardia may be potentiated by epinephrine-containing local anesthetics, ketamine or atropine. Acute marijuana intoxication can reduce the anesthetic requirement.

It should also be remembered that the marijuana user could also be using other illicit substances that can have even more concerning effects. As far as drug interactions are concerned, it must be remembered that marijuana is a CNS depressant and the sedative effects of other drugs, such as benzodiazepines, opioids, antihistamines, and barbiturates may be compounded by the use of marijuana.

Cannabis metabolism is not completely understood, but the cytochrome P450 enzyme CYP2C9 is felt to be responsible for its first pass metabolism and the enzyme CYP3A4 is believed to be involved as well. (19) The involvement of this enzyme system is chiefly responsible for the interaction of cannabis with prescription drugs. A literature search by Lindsey, et al., revealed several possible interactions. The most important for oral surgeons include a risk of sedation when cannabis is combined with barbiturates, anticholinergics, sedative-hypnotics, and alcohol.(19)

Potentially, cannabis can interact with tricyclic antidepressants, causing tachycardia or delirium; with selective serotonin reuptake inhibitors causing mania; and with disulfiram causing hypomania. There has been a case report of myocardial infarction after the use of marijuana with sildenafil, perhaps due to interference with metabolism of sildenafil by the cytochrome P450 enzyme system, causing toxic levels of sildenafil to accumulate.(19) Additionally, there has been a case report of a marijuana smoking patient who was on warfarin and experienced episodes of INR's as high as 11.5, (see also *Selected Readings in Oral and Maxillofacial Surgery,* Vol. 21, #3) felt to be related to the influence of marijuana on the metabolism of warfarin. (20)

COCAINE

Cocaine (benzoylmethylecgonine) is the second most commonly abused illicit drug. It is an ester local anesthetic with vasoconstrictive and sympathomimetic properties. Generally, it is used for its stimulant properties, but it also acts as an appetite suppressant. Its anesthetic properties are the result of its ability to reversibly bind to and inactivate sodium channels. Additionally, it binds to dopamine, norepinephrine, and serotonin transport proteins and directly inhibits the re-uptake of these sympathetic amines, resulting in euphoric and sympathomimetic effects such as vasoconstriction and tachycardia. It may be used in various forms. The water-soluble salt cocaine hydrochloride may be snorted ("nasal insufflation"), injected, rolled in paper and ingested, applied to oral mucous membranes, or inserted anally or vaginally. The most common method of use is through nasal insufflation. The insoluble form is a base, which must be smoked.

Crack cocaine is a form of freebase cocaine, but freebase and crack are made differently.(21) To make freebase cocaine, the water-soluble salt cocaine hydrochloride is dissolved in water with the addition of ammonia as a base and ether as a solvent. The ether is presumably evaporated and freebase cocaine is then smoked. However, ether may still remain in the freebase cocaine, potentially resulting in facial or tracheal burns. The production of crack cocaine is simpler, dissolving cocaine hydrochloride in water, mixing it with baking soda and heat-

ing it, resulting in a hard mass ("rock") when dry.(21) Freebase cocaine is less commonly used than crack cocaine. Smoking of crack results in rapid absorption with intense onset of euphoria, but the effect does not last as long as it does when cocaine is snorted. The quick and intense onset of euphoria is responsible for crack's highly addictive quality. Dependence rapidly develops and withdrawal is notable for depression, fatigue, and drug craving. Cocaine is metabolized by plasma and liver esterases and has a plasma half-life of 30 to 90 minutes, with crack having a shorter half-life than the water-soluble form. Metabolites may be detected in the urine for up to 15 days after use.

It is important for the health provider to be able to recognize the clinical manifestations of cocaine use. Up to 10% of chronic users exhibit septal, nasal, or palatal defects that may be related to the intense vasoconstriction and ischemia caused by cocaine use. Significant septal perforations can result in nasal collapse. Those who nasally insufflate cocaine may have a lack of nasal hairs on their dominant side. A common area where cocaine is topically applied is along the maxillary alveolus posterior to the canine, potentially resulting in a well-localized gingivitis in this area. Additionally, some users maintain one long fingernail—usually on the smallest finger (pinky)—which is used as a scoop for the salt form. Those who smoke crack may present with burns or calluses on the tips of their fingers.(2)

Cocaine is well known for its cardiovascular, pulmonary, and neurologic effects; however, it is important to realize that it is not uncommon for adulterants to be combined with cocaine, and these can have effects as well. Levamisole is one such adulterant. The reason Levamisole may be added to cocaine may be to dilute it (and increase volume and profit), enhance sympathetic stimulation; or to monitor supply and distribution by the manufacturers.(22)

Levamisole was originally used as an immunomodulatory drug in the treatment of colorectal cancer as well as some autoimmune and rheumatologic conditions.(23) Rat studies demonstrated that it caused an elevation in endogenous opioids and also modulated the metabolism of norepinephrine, dopamine, and serotonin.(24) It has many side effects including agranulocytosis and leukoencephalopathy and was removed from the U.S. market in 1999. Other side effects of levamisole include neutropenia, vasculitis, arthralgias, possible coagulopathy, purpura, and skin necrosis.(22,23)

In recent years, it has been found in as much as 70% of cocaine and in 3 % of heroin seized in the US as of 2009.(22,25) The presence of levamisole in cocaine came to light in 2008 when cases of unexplainable agranulocytosis in cocaine users were documented and levamisole was detected in seized lots of cocaine.(25)

Another unexpected category of cocaine adulterants is local anesthetics. Manufacturers may be adding these anesthetics in order to dilute the drug or contribute to the nasal mucosal anesthetic effect of cocaine. A recent case report described two cases of seizures and methemoglobinemia in cocaine users.(26) Toxicology results in both patients revealed the presence of lidocaine and benzocaine. Seizure threshold is lowered by cocaine and the addition of local anesthetics may lower that further.

Many other adulterants have been reported including caffeine, aminophenazone (with a risk of agranulocytosis), ephedrine, diphenhydramine, procaine, and phe-

nobarbital, among others.(27) However, levamisole and the local anesthetics seem to be the most common adulterants and it is important for the health provider to be aware of the possible presence of these contaminants because they can cause side effects not normally expected from cocaine alone.

Cardiac Effects

Increased sympathetic tone results from increased levels of norepinephrine, dopamine, and serotonin, resulting in an elevated blood pressure and heart rate. Hypertension, dysrhythmias, myocardial ischemia, cardiomyopathy, and myocardial infarction can also occur. Besides sinus tachycardia, dysrhythmias can include premature ventricular contractions, ventricular tachycardia, ventricular fibrillation, and asystole. It is theorized that one contributor to dysrhythmias may be contraction band necrosis due to myocardial scarring from overstimulation of cardiac muscle fibers in addition to a direct cardiotoxic effect.(28) The cardiovascular effects are not dose dependent—even small doses can be fatal.

There is elevated risk of myocardial infarction in cocaine users regardless of whether or not underlying coronary artery disease is present. There are various theories as to why this increased risk occurs. (29) Increased heart rate, blood pressure, and contractility from sympathetic stimulation causes an increase in myocardial oxygen demand. Cocaine also causes coronary vasoconstriction, reducing myocardial blood flow. Acute increases in arterial blood pressure can disrupt atherosclerotic plaques, and in combination with increased platelet aggregation induced by cocaine, may lead to coronary thrombus formation.(28,29)

Mittleman, et al. evaluated the possibility of cocaine triggering a myocardial infarction in a population of patients with acute myocardial infarction (AMI).(29) Patients were queried as to the use of cocaine and other potential triggers of AMI. In these patients the relative risk of AMI was elevated 23.7 times during the first hour after cocaine use. This risk declined significantly during subsequent hours and was still elevated at hours 2 and 3 after use, but in comparison to non-cocaine use prior to MI, this was not a significant difference. However, the authors did note that the confidence interval for relative risk for MI during hours 2 and 3 after cocaine use were sufficiently wide that one may want to still consider this a timeframe of increased risk.(29) From this data the extrapolated annual excess risk of a coronary event for a daily cocaine user is approximately 1.5% to 3 %.

In an earlier study by Hollander, et al. of 246 patients with chest pain after cocaine use [COCaine Associated CHest PAin (COCHPA study)], the median onset of chest pain after cocaine use was within 60 minutes, corroborating the evidence that the riskiest time for a coronary event in a cocaine user is within the first hour of use.(30) Additionally, they found that an MI occurred in 6% of patients who presented to the emergency department complaining of chest pain after the use of cocaine. Other studies have had similar results with the overall range in incidence of cocaine associated MI being 0.7% to 6%.(31)

There is also an increased risk of aortic dissection in cocaine users. Various chart reviews have reported anywhere from 9.8 % to 37 % of acute aortic dissections being related temporally to cocaine use.(32,33,34) Both Hsue, et al. and Daniel, et al. found that the mean time from use to presentation

was 12.0-12.8 hours, and all three studies cited found that these patients were younger than dissection patients without a history of cocaine use.(32,33,34)

Pulmonary Effects

The pulmonary effects of smoking crack cocaine are related to the high comorbidity with cigarette smoking as well as to the direct effects of crack smoking. Not only is the crack itself toxic, but the crack smoker subjects his lungs to countless other unknown chemicals in the form of adulterants. Like marijuana smokers, crack smokers have an increased risk of developing bullae and subsequent pneumothorax due to the practice of deep inspiration and breath holding.(11) A common complaint of crack smokers is “crack lung”, which presents 1 to 48 hours after smoking with symptoms of fever, pruritis, chest pain, bronchospasm, diffuse alveolar infiltrates without effusion, and eosinophilia.(2) Cocaine users have also been reported to have a higher incidence of pneumonia. Acute crack smoking should be expected to result in coughing, bronchospasm, asthma exacerbation, and production of black sputum.

Central Nervous System Effects

Cocaine lowers the seizure threshold, and when an adulterant such as lidocaine is used the threshold may be reduced even further. Other neurologic effects of cocaine use may include pupillary dilation, hyperreflexia, emotional instability, and cerebrovascular accident.(35) Case reports support a link between stimulant/cocaine use and stroke.(17) In a study of stroke patients aged 18 to 44, Westover, et al. found that cocaine abuse was associated with an increased risk of ischemic and hemorrhagic stroke. The adjusted odds ratio for ischemic stroke in cocaine abusers was 2.03 and for hemorrhagic stroke it was 2.33.(17) For comparison, the adjusted odds ratio for ischemic stroke in hypertension was 5.69 and for hemorrhagic stroke in hypertension it was 7.68. It is believed that this increased risk of stroke from cocaine abuse is due to hypertension, vasculitis, vasospasm, and disruption of cerebrovascular autoregulation.

Hematologic Effects

Cocaine has been associated with increased platelet activation and aggregation.(36) Additionally, it may increase plasminogen activator-inhibitor, increasing the likelihood of thrombus formation.(36) There have been a number of reports in the literature of thrombocytopenia from cocaine abuse;(37,38) the etiology is speculated to be due to bone marrow suppression, excess platelet activation, hypersplenism, autoimmune response, and chronic hepatitis. However, the real risk of thrombocytopenia is questionable. Gershon, et al. studied 671 cocaine-using obstetric patients and found no significant increase in thrombocytopenia compared to non-cocaine-using obstetric patients.(39)

Anesthetic and Surgical Concerns

The anesthetic concerns with the cocaine user are due to cardiovascular effects. Although the first hour after cocaine use clearly seems to be the most dangerous, it is generally recommended that 8 hours pass between last cocaine use and a necessary anesthetic,(2) and more prudent to wait for 24 hours. Due to the risk of arrhythmias, cardiomyopathy, and ischemia,

it is recommended to obtain a preoperative EKG and perform EKG monitoring during procedures. Additionally, care to avoid intravascular injection of epinephrine is required as this could exacerbate cocaine related cardiac ischemia.(2) Additionally, I suggest that ketamine be avoided due to its sympathetic effects on the heart as well as its stimulation of the central nervous system.

It is important to be aware of management of tachycardia, hypertension, and chest pain in the cocaine-using patient. Beta-blockers should be avoided as monotherapy because unopposed alpha-adrenergic stimulation may result in coronary vasoconstriction and hypertension.(2,35) Propranolol is contraindicated because it worsens coronary vasoconstriction.(40) Intravenous hydralazine, a vasodilator, has been used to treat hypertension in these patients, but it has the drawback of causing reflex tachycardia. Labetalol, a combined non-selective beta-blocker and alpha-adrenergic blocker, is considered safe to use to lower blood pressure in cocaine users, but because its beta-blocking effect is greater than its alpha-blocking effect, it still can lead to unopposed alpha activity.

In the cocaine-using patient with chest pain, nitroglycerin and verapamil are considered safe to use.(35) Benzodiazepines are helpful in the management of the patient with chest pain, since they decrease both heart rate and blood pressure. According to the American Heart Association, benzodiazepines and nitroglycerin is first-line therapy for cocaine induced acute coronary syndrome, with the alpha-blocker phentolamine being second-line.(40) When lidocaine is indicated, it apparently does not contribute to further cardiovascular or neurologic toxicity.(19,40)

If hypotension occurs in a cocaine-using patient, low dose phenylephrine is the preferred agent since it has minimal chronotropic and inotropic effects. For the cocaine-intoxicated patient undergoing a general anesthetic, it is useful to provide blood pressure control prior to the stimulation of direct laryngoscopy. Cocaine alters the metabolism of succinylcholine since cocaine is also metabolized by plasma cholinesterases, but it is unclear whether this represents a significant contraindication. (35) Due to the sympathetic stimulation of cocaine, acute use may increase anesthetic requirements.

SYNTHETIC DRUGS

Synthetic drugs (including phenylethylamines, cathinones, tryptamines, and synthetic cannabinoids) encompass a large variety of chemically ever-changing drugs. Drugs made in clandestine laboratories typically are the product of fairly simple processes using readily available components. Potentially toxic components may be used, including shoe polish, drain cleaner, lye, paint thinner, and lithium, to name only a few. Furthermore, the purity of the drug product may be unpredictable because suppliers will often use an array of adulterants. The unpredictability of content, combined with naivety or recklessness on the part of the drug abuser clearly is a dangerous combination that makes it difficult to know what side effects to expect in a patient using synthetic drugs.

The most commonly known synthetic drugs include methamphetamine and 3,4-methylenedioxy-N-methylamphetamine (MDMA), but there are countless other drugs being manufactured. Some have been labeled “bath salts” in an attempt to

legally sell them on the internet. Legislation has occurred to ban these drugs as each becomes available, but when one chemical is made illegal, suppliers simply develop something slightly different.

Mechanisms of action of these drugs are complex, but generally, phenylethamines and tryptamines affect norepinephrine, serotonin, and dopamine. The body's monoamine oxidase system mitigates these effects by inactivating these monoamines. Purposeful or accidental contamination of drugs with monoamine oxidase inhibitors can augment the drug effects, easily leading to overdose.(41)

Methamphetamine

Amphetamines are a class of stimulants sometimes legally prescribed to treat attention deficit disorder, narcolepsy, depression, and to promote weight loss. Amphetamines are a type of phenylethamine. Methamphetamine is the most common illegally synthesized recreational drug. It is the N-methyl analogue of amphetamine.

There are various ways that methamphetamine is synthesized in illegal laboratories. Ephedrine and pseudoephedrine are commonly used ingredients. During the past decade, the United States, in an effort to decrease the availability of methamphetamine, has put restrictions on the sale of ephedrine and pseudoephedrine. As a result, 80% of America's methamphetamine is produced in Mexico and it is extremely potent—reaching levels of 90% purity.(42) Mexican methamphetamine is most commonly found in urban and suburban areas whereas the products of U.S. clandestine labs are usually found in more rural areas.(42)

It is estimated that 35 million people worldwide have used methamphetamine and that 10.0 to 12.5 million Americans have used it at least once and approximately half a million use it weekly. It is highly addictive and is used for its stimulant properties. It may be taken by ingestion, smoking, snorting or injecting intravenously. Smoking is the most common method and results in a rapid high.

The mechanism of action of methamphetamine involves the release of dopamine, norepinephrine, and serotonin in addition to blocking their reuptake. The methamphetamine half-life ranges from 8 to 30 hours, much longer than that of cocaine.(43) Rapid dependence may occur, especially with intravenous use. Additionally, significant tolerance develops and the user may require higher doses in more frequent intervals to achieve the desired result. Chronic use depletes dopamine from the brain and may result in significant dysphoria, exhibiting as suicidality/homocidality, hypersomnia, or severe depression if a patient experiences withdrawal.(43) It is metabolized by microsomal enzymes in the liver, although chronic use does not cause an elevation in these enzymes. The kidney excretes it.

Dental care providers are well aware of the oral manifestations of methamphetamine abuse (i.e., xerostomia, rampant decay, and bruxism). It is believed that salivary flow decreases because of methamphetamine's stimulation of inhibitory alpha 2 adrenergic receptors in salivatory nuclei.(43) Xerostomia, in combination with poor oral hygiene, increased oral acidity from methamphetamine, high carbohydrate diet, and increased vomiting may contribute to the elevated caries rate. The particular pattern

of decay is notable for involvement of buccal smooth surfaces of teeth and interproximal areas of anterior teeth.

Use of methamphetamine results in significantly increased muscle activity that can result in severe bruxism, trismus and can even result in choreiform motor activity of the facial and masticatory muscles.(43) Other clinical cues to the use of methamphetamine include an ammonia odor (a possible ingredient), formication to the point of causing open skin wounds, mood swings, extreme weight loss, and hallucinations. Amphetamine testing, that can detect amphetamine, dextroamphetamine, and methamphetamine, is part of routine urine toxicology.(2)

Cardiac Effects

Similar to cocaine, methamphetamine has strong sympathomimetic effects, resulting in tachycardia and hypertension and potentially contributing to myocardial infarction, arrhythmias, and cardiac failure. Myocardial infarction has not been linked as closely with methamphetamine abuse as it has been with cocaine abuse, but a relationship has been established. Westover, et al. studied 11,011 acute myocardial infarction (AMI) patients aged 18 to 44 in Texas between 2000 and 2003.(44) They found the adjusted odds ratio for methamphetamine abuse leading to AMI to be 1.61. For comparison, the adjusted odds ratio for cocaine use and AMI was 2.14, for tobacco abuse it was 6.32 and for lipid disorder it was 11.61. Their results indicated that in Texas between 2000 and 2003, amphetamine abuse caused 0.2% of AMI's and cocaine abuse caused 1.9%.

Similar to cocaine, methamphetamine is felt to lead to MI because of increased myocardial oxygen demand, increased platelet aggregation, atherosclerotic plaque rupture, and coronary artery spasm. Additionally, autopsy studies have demonstrated that methamphetamine users have coronary artery disease at a rate 3-4 times higher than non-users, and users may develop cardiomyopathy.(44)

As with cocaine, methamphetamine has been demonstrated to be associated with aortic dissection, but the association is stronger with methamphetamine. Westover, et al. reviewed 3116 cases of thoracic and thoracoabdominal aortic dissection in patients aged from 18 to 49 years between 1995 and 2007.(45) They found a significant association between amphetamine abuse and aortic dissection that exceeded the association between cocaine and dissection. The adjusted odds ratio for aortic dissection in methamphetamine abusers was 3.33 and for cocaine abusers it was 1.6. For comparison, the odds ratio for hypertension was 7.68. Patients with aortic dissection related to methamphetamine use were younger than non-users—the average age in methamphetamine users was 41 whereas it was 52 in non-users. The association between methamphetamine use and risk of aortic dissection is felt to be related to the hypertensive effect, the vasculitis or both that may be caused by methamphetamine.(45)

Pulmonary Effects

Methamphetamine is felt to have few significant pulmonary effects. Similar to marijuana and cocaine, smoking methamphetamine may cause barotrauma, resulting in an increased risk of pneumothorax or pneumomediastinum. There have been reports of acute non-cardiogenic pulmonary edema; and methamphetamine use has been associated with an increased risk for idiopathic

pulmonary hypertension. Methamphetamine has bronchodilating effects, so bronchoconstriction is typically not observed.

CNS Effects

Both acute use of and withdrawal from methamphetamine can result in neuropsychiatric symptoms including psychosis, hallucinations, anxiety, or depression. Cloutier, et al. performed a retrospective review of methamphetamine related emergency department visits and found that 18% of methamphetamine related visits were psychiatric in nature.(46) They also found that methamphetamine use was associated with a disproportionate number of psychiatric visits to the emergency department (7.6%). Other neurologic symptoms found in methamphetamine related emergency department visits included altered mental status (6.2%) headache (1%) and seizures (0.83%).

Chronic use depletes the brain's dopamine transporter, believed to be associated with diminished motor performance and impaired verbal learning.(2) In Westover, et al's study of stroke in patients who abuse amphetamines or cocaine, methamphetamine was associated with a higher risk of hemorrhagic stroke than was cocaine.(17) The adjusted odds ratio of the association of methamphetamine use with hemorrhagic stroke was 4.95 and risk of death after hemorrhagic stroke associated with methamphetamine use odds ratio was 2.63. There was no significant association between amphetamine use and ischemic stroke.

Anesthetic Concerns, Management

The methamphetamine-abusing patient should be expected to be subject to risks of possible hypertension, hyperthermia, arrhythmias, and hemorrhagic stroke. The anesthetic concerns with a methamphetamine-abusing patient are similar to those with a cocaine-abusing patient. It is important to remember that methamphetamine has a longer half-life than cocaine. Methamphetamine duration of action is usually 8 to 12 hours, but can be for as long as 24 hours, so a longer waiting time (at least 24 hours) before anesthesia is recommended. If a patient has possibly used methamphetamine over the previous 24 hours, medications that can potentiate sympathetic cardiovascular effects, such as ketamine and epinephrine, should be avoided.(43)

Typically, acute methamphetamine intoxication increases anesthetic requirements.(2) It can decrease the duration of thiopental and can decrease the duration and effectiveness of succinylcholine induced muscle relaxation.(2) Ketamine should be avoided in methamphetamine users, not just because of its sympathetic effects but there is an additive effect in hallucinatory behavior when ketamine is administered in the presence of methamphetamine.(19) Psychosis can develop during anesthetic management of these patients.

It is also important to be aware that chronic use of methamphetamine can reduce catecholamine levels, blunting the sympathetic response to anesthesia-induced hypo-

tension, possibly requiring administration of phenylephrine to support the blood pressure. Anesthetics that cause cardiovascular suppression, such as propofol, should be titrated slowly.(2) As with cocaine, if a methamphetamine-abusing patient experiences hypertension or chest pain, beta-blocker monotherapy should be avoided because the unopposed alpha effects are undesirable. Hypertension or chest pain would be managed in the same way as in cocaine abuse—consider benzodiazepines, nitroglycerin, and phentolamine. Prescribed amphetamines do not seem to alter hemodynamics in adults, so they may be safely continued before an anesthetic.

OPIOIDS

Opioid abuse is on the rise in recent years, especially prescription opioids. In 2005, the lifetime use of heroin was 1.5%, up from 1.2% in 2000. In comparison, lifetime use of non-medicinal prescription opioids was 13.4% in 2005, up from 8.6% in 2000. (47) Opioid analgesic deaths now exceed those from suicide, motor vehicle crashes, and from cocaine and heroin combined.(48) Opioids exert their sedative and euphoric effects through the mu receptor.

A chronic narcotics user may experience withdrawal after 12-14 hours of abstinence, manifested by increased lacrimation, diaphoresis, yawning, rhinorrhea, and restless sleep. As withdrawal progresses, diarrhea, vomiting, and electrolyte imbalances can occur, with acidosis and cardiovascular collapse in the worst cases.(28)

Opioid abuse can take the form of snorting, smoking, or injecting heroin, or oral consumption of opioid analgesics. A clinical cue that a patient may be injecting heroin is the presence of track marks or skin necrosis from subcutaneous injection.

Respiratory Effects

The most notable side effect of opioids is respiratory depression, caused by activation of the mu receptor. Opioids cause decreased chemoreceptor sensitivity to hypercarbia and hypoxia, in addition to causing a reduction in respiratory rate and tidal volume. Large doses of some opioids, such as fentanyl and heroin, can result in chest wall rigidity, further compromising respiratory function. Those who inject heroin have an increased risk of pneumonia and complications from frequent pneumonias.

Cardiovascular Effects

Cardiovascular complications of opioids appear to be associated with certain narcotic drugs. Propoxyphene was removed from the market in 2010 due to its association with fatal arrhythmias. Methadone has been associated with QT interval prolongation, which can lead to Torsades de Pointes. Opioid toxicity can lead to hypotension. Additionally, even at less-than-toxic levels of opioid, hypotension can occur on anesthesia induction, possibly requiring administration of a pressor.

It is noteworthy that heroin addicts may also take clonidine, a centrally acting alpha agonist, to enhance the heroin high. Abrupt withdrawal of clonidine can result in a potentially fatal hypertensive crisis.(2)

Anesthesia, Pain Control and Addiction Management

Acute opioid use decreases anesthesia requirements. Significant tolerance to opioids develops, and chronic use increases anesthesia requirements. Long-term use is believed to lead to opioid hyperalgesia and allodynia. The hyperalgesia and allodynia are believed to be related to activation of n-methyl-d-aspartate (NMDA) receptors, and ketamine has been proposed as a treatment in addition to opioid withdrawal.

Postoperative pain control can be challenging in the chronic opioid user. The opioid requirements may be 2 to 4 times what is necessary for the opioid-naïve patient. Their maintenance dose should be continued in addition to coverage for acute pain. The patient should also take his regular daily opioid dose on the day of surgery. Longer-term pain relief may be improved by opioid rotation because there is incomplete tolerance of different agents. Other adjuncts should be considered as well, such as tramadol, gabapentin, clonidine, intravenous acetaminophen, or non-steroidal anti-inflammatories. Because the pain management of these patients is complex, it is advisable to involve the patient's chronic pain physician in determining appropriate management.

Opioid addiction is treated with methadone or buprenorphine. Methadone can also be used in chronic pain management. It has a very long half-life. The effects last for 24 hours, and can stay in a patient's system for 59 hours. Methadone can cause a prolonged QT interval, leading to Torsades de Pointes. Respiratory depression with overdose is significant, and has resulted in methadone being responsible for 30% of prescription pain medication-related overdose deaths. Because of this significant risk, methadone prescribing should be left to the addiction or pain medicine specialist. Additionally, if possible, one should avoid prescribing other sedating medications such as benzodiazepines to patients taking methadone.

Buprenorphine (Suboxone®, Subutex®) is a semisynthetic opioid analgesic also used for narcotic addiction treatment. Although it also has a long duration of action (elimination half-life is 20 to 73 hours), it has a better safety margin than methadone because it causes less respiratory depression.

CONCLUSION

Unfortunately, drug abuse is quite common. It crosses all socio-economic and educational levels. Drug abusers may not be forthcoming about their use, but it is essential to encourage open communication at all times so the provider can provide care in a safe manner. Because patients may not be forthcoming, providers must recognize clinical signs of drug use and may need to prepare for patient care based on suspicion. Abuse of more than one drug is common. Many drugs, such as the novel psychoactive substances, are not tested for in routine drug screens and would need to be tested for specifically. Recognizing abuse and knowing how to manage these patients safely is essential for reducing surgical and anesthetic risk.

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Selected Readings in Oral and Maxillofacial Surgery is partially supported by Biomet Microfixation (Walter Lorenz Surgical), Jacksonville, Florida

ISSN #1044-7032