Otolaryngology Concerns for Illicit and Prescription Drug Use

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KEYWORDS
- Otolaryngology • Codeine • Narcotic • Cocaine • Sinonasal • Black box

KEY POINTS
- Illicit drug use is common in patients presenting with routine otolaryngology complaints in the inpatient and outpatient settings.
- Medically recalcitrant sinonasal complaints may be related to illicit drug use and drug testing should include illegal drugs and commonly abused prescription narcotics.
- Routine drug testing should be considered for patients with septal perforation or necrosis of midline nasal and palatal structures.
- The FDA warning regarding codeine after pediatric adenotonsillectomy is related to variable codeine metabolism and concern for airway compromise.
- In cases of suspected codeine overdose, testing for the ratio of codeine:morphine metabolites and CYP2D6 allelic variations may identify an ultrametabolizer phenotype as the etiology.

INTRODUCTION

Concern for illicit and restricted drug use in otolaryngology is similar to other surgical specialties with a few notable exceptions. First, many illicit drugs are consumed trans-nasally. Repeated nasal exposure to stimulants or narcotics can cause local tissue destruction that can present as chronic rhinosinusitis or nasoseptal perforation. Care must be taken to ensure exposure to offending agents has ceased before attempting repair and consequently, otolaryngologists may insist on drug testing before proceeding to surgery. Second, the US Food and Drug Administration (FDA) has taken a stance against the use of certain prescription narcotics in pediatric patients. The author has nothing to disclose.

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patients undergoing adenotonsillectomy (AT). A black box warning has been issued on all codeine products, prohibiting their use in tonsillectomies under the age of 18. They have identified an increased risk of death postoperatively with these medications owing to pharmacogenomic properties. Because codeine has traditionally been the most commonly prescribed narcotic, this dramatic stance has shifted the standard practice. Pharmacogenomic testing has been advocated by many, but may not be an economical option.

SINONASAL MANIFESTATIONS OF ILLICIT DRUG USE

Sinus disease is often a disabling chronic condition manifested by nasal obstruction, recurrent infections, nasal discharge, and facial pain. Quality of life can be significantly impacted and patients seek frequent medical care. If medical management fails, which generally includes antibiotics, topical nasal steroids, and saline irrigations, surgery is indicated. Most patients have drastic improvement in sinonasal complaints after endoscopic sinus surgery. Several subsets of patients are predisposed to poor outcomes, including those with nasal manifestations of rheumatologic disease, immunocompromise, sinonasal polyposis, and those actively using illicit intranasal drugs. Before considering surgery in patients with possible drug-related pathology, it is helpful to understand the mechanism of injury and whether the insult is historical or ongoing. Thus, many surgeons require negative drug tests before proceeding with surgery.

Most surgeons underestimate the prevalence of illicit drug use in patients presenting for surgery. A study investigating drug use in patients sustaining maxillofacial trauma found that 47% of urine drug screens were positive despite few patients admitting to the activity. The same researchers tested urine samples from the general population and found 2.5% tested positive for cocaine or amphetamines. Although surgery on patients with recent drug use can be performed, it requires careful anesthetic titrations and awareness by the entire surgical team. Cocaine and amphetamines can cause cardiac arrhythmias owing to their sodium channel blockade. Prolonged QT, ventricular tachycardia, and torsade de pointes are common concerns. Benzodiazepine and narcotic use may potentiate the effects of analgesics administered at routine doses. Given the frequency of abuse in the general population, otolaryngologists should be aware of common manifestations of illicit drug use in patients with head and neck complaints.

Sinusitis and septal perforation related to illicit drugs were initially described in cases of cocaine abuse. Cocaine use is relatively common with 5% of 15- to 34-year-olds using cocaine recreationally; it is the fourth most common illegal drug used after marijuana, heroin, and ecstasy. Its anesthetic properties derive from its ability to block sodium channels similar to amine local anesthetics. Cocaine also has vasoconstrictive effects owing to blockage of catecholamine reuptake and metabolism. Intranasally, vasoconstriction can lead to thinning and ulceration of the nasal mucosa. The bony and cartilaginous septae of the sinonasal tract rely on the mucosal blood supply for oxygenation and nourishment. Prolonged exposure to vasoconstrictors leads to necrosis and degradation of these structures (Figs. 1 and 2). Cocaine additives, often including baking soda, ammonia, lidocaine, or other chemicals, cause inflammatory reactions that can lead to granulation and erosion. Cocaine also impairs ciliary function by reducing beat frequency and ciliary harmony. Cilia are needed to clear debris and secretions from the sinus tracts. If debris stagnates, it can become trapped in sinus cavities leading to inflammation that mimics routine bacterial chronic sinusitis.
After chronic topical use of short-acting vasoconstrictors, like cocaine, nasal mucosa becomes resistant to topical adrenergics. Rhinitis medicamentosa describes a clinical scenario in which mucosal blood vessels are desensitized to normal adrenergic levels and dilate and engorge at rest. The vessels return to normal caliber only when exposed again to concentrated adrenergics, and the effects are generally short lived. Patients then become dependent on topical vasoconstrictors for rhinitis recalcitrant to normal medical management. Because patients may not always see the true effects of their drug abuse, many will seek surgery to alleviate symptoms. However,
during endonasal surgery, short-acting vasoconstrictors are necessary to limit blood loss and facilitate a clean endoscopic approach. Chronic cocaine and amphetamine exposure cause resistance to local application of adrenergics, which can lead to increased operative blood loss and surgical misadventure. Patients actively using drugs are also likely have poor healing and persistence of symptoms after surgery.

Recently, prescription narcotics have become more prevalent in illicit drug use. To hasten the effects of these narcotics, many users crush and inhale tablets of commonly prescribed pain medications including oxycodone, hydrocodone, and codeine. Despite the lack of inherent vasoconstrictive properties, this type of drug use causes similar nasal and sinus complications. Many authors have noted midline ulceration, chronic sinusitis, hyposmia, palatal necrosis, and other associated complaints. Intranasal prescription narcotic use seems to cause pathologic changes to the nasal mucosa not dissimilar to cocaine. Tablet binders that solidify the powder before it is crushed for inhalation can cause an inflammation similar to talc. There also seems to be local immunosuppression in exposed mucosa that allows for colonization and infection of opportunistic fungal species. Repeated and persistent abuse and chronic exposure inevitably leads to irreversible damage to the sinonasal tract. Successful management requires abstention from illicit drug use and frequent operative debridement of inflamed tissue. When illicit drug use is suspected as a source of sinonasal pathology, the surgeon should screen for illegal stimulants and narcotics as well as prescription medication that has been used for recreational purposes.

NARCOTICS AFTER TONSILLECTOMY

Tonsillectomy with or without adenoidectomy, or AT is one of the most common surgeries performed in the United States with more than 500,000 cases annually. It has also been performed, in some iteration, since its first description by Cornelio Celsius in the first century. Historically, AT was predominantly performed for recurrent or severe pharyngeal infections. More recently, there has been a dramatic shift toward surgery for sleep disordered breathing or obstructive sleep apnea (OSA). Although the surgical technique is the same, conceptually and practically, these are different etiologies and should be managed differently in the postoperative setting. AT is the first line therapy for sleep disordered breathing and OSA, especially in younger, preschool-aged children.

OSA is a diagnosis that can only be made on polysomnography (PSG) or a sleep study. During PSG, monitors are attached to a sleeping patient to measure arousals from sleep, airflow through the nose and mouth, and oxygen saturation, among other parameters. The most useful metric derived from this study is the apnea-hypopnea index. Apneas refer to cessation of breathing for at least 10 seconds that lead to desaturations and arousals. Hypopneas refer to a 50% reduction in airflow for the same time period. The apnea-hypopnea index represents the number of times per hour that one of these events occur. In children, an apnea-hypopnea index of greater than 10 or oxygen desaturation below 85% are considered severe OSA. Rosen and colleagues, in their landmark paper, document several risk factors predisposing children to complications after tonsillectomy. Of those, age younger than 3, morbid obesity, and severe sleep apnea significantly increase the risk of morbidity after AT. Children with these risk factors are more likely to have respiratory complications after surgery; many of these complications can be attributable to postoperative narcotic administration.

To better understand the risk of respiratory compromise in the postoperative setting and how it relates to narcotic administration, we have to consider factors unique to OSA patients and the analgesic options available for administration. OSA is a chronic condition that significantly alters respiratory physiology on a nightly basis. While
asleep, restricted airflow exposes these children to prolonged and repeated episodes of hypercarbia. This blunts respiratory response curves and desensitizes the respiratory drive in response to chemoreceptor triggers. OSA patients are also more sensitive to the effects of narcotics. Children with oxygen desaturations of less than 85% on PSG require one-half the analgesic dose of patients without OSA. Additionally, severe OSA alters the distribution of central mu-opioid and neurokinin receptors, further increasing the respiratory suppressant activity of narcotics.

Obesity, frequent in this patient population, leads to fat deposition in the chest wall and pharynx that adds to airway resistance and work of breathing. Postoperatively, pharyngeal edema is expected and further narrows the upper airway. Coupled with the respiratory suppression caused by anesthesia and analgesia, these children are truly set up for respiratory compromise and hypoxia postoperatively. Studies looking at PSG the night after surgery routinely show worsening sleep parameters after surgery. Identifying patients at risk for respiratory compromise and selecting an appropriate analgesic regimen are key to minimizing risk after tonsillectomy.

A Case Against Codeine

The FDA targeted codeine in its 2012 black box warning, prohibiting its use in the United States for AT in children under the age of 18. Leading up to this declaration, between 1969 and 2011 only 10 deaths and 3 morbidities related to codeine administration were reported in the FDA Adverse Events Database. However, this likely underestimated the impact of its use. In a survey of more than 2300 pediatric anesthesiologists, Cote and colleagues identified 129 cases of morbidity or mortality in the postoperative setting, most related to the administration of narcotics. A similar survey of otolaryngologists cataloged 51 mortalities in the postoperative period. Thirty-one percent were of unknown etiology and 22% were directly attributable to narcotic administration. At least 1 case was linked to a genetic predisposition to altered codeine metabolism.

Codeine has historically been used as a safe alternative to morphine and other narcotics. It has an equianalgesic dose of 6 to 10:1 compared with oral morphine and a similar length of action with slower onset. Although this led to its expansive use for acute and chronic pain management in all medical applications, its efficacy as an analgesic has often been scrutinized. Several studies comparing codeine with nonsteroidal antiinflammatory pain medication have shown mixed results, some demonstrating better pain control with the nonnarcotic medications. Codeine itself is a weak opiate with little activity on opioid receptors. Its metabolites are far more active. Codeine is metabolized via 3 separate pathways: glucuronidation to codeine-6-glucuronide, O-demethylation to morphine via cytochrome P450 2D6 (CYP2D6), and N-demethylation to norcodeine via cytochrome P450 3A4 (CYP3A4) (Fig. 3). Fifty to 70% of codeine will form codeine-6-glucuronide and 10% will be converted to norcodeine. Both of these metabolites have similar

![Fig. 3. Codeine metabolism pathways.](image)
affinity to mu-opioid receptors as codeine. Morphine and its metabolites, morphine-6-glucuronide and morphine-3-glucuronide have up to a 200-fold greater mu-opioid affinity and significantly more analgesic and respiratory effects. Codeine's variable efficacy and higher risk profile is attributed to variations in CYP2D6 metabolism, shifting the ratio of codeine and morphine metabolites. There are more than 50 known allelic variants of CYP2D6, each with its own metabolic efficiency. Patients with 2 highly functional alleles produce significantly more morphine and morphine-6-glucuronide for a standard dose of codeine. These patients are often called rapid or ultrarapid metabolizers (UM). Conversely, those with 2 poorly functioning alleles are slow or poor metabolizers and produce less morphine. Owing to the allelic heterogeneity, it is hard to predict how particular patients will respond to the administration of codeine. Studies estimate that close to 20% to 50% of the United States population may be poor metabolizers and produce little to no morphine. Less common, but more concerning, UM individuals may produce 50% more morphine than intermediate metabolizers, with no more than 1 highly functioning allele. In several cases of death after tonsillectomy, UM patients have been identified; however, this association is neither constant nor dependable.

Alternatives to Codeine

Some had advocated for genetic testing before surgery to assess metabolism and tailor narcotic doses for the individual. Although this is a logical approach, focusing on genetic or genomic testing alone would discount the effects of age, diet, activity, comorbidities, and polypharmacy on CYP activity. Additionally, a good corollary for the narcotic dosing dilemma has been described in oncology literature. Oncologic medications like tamoxifen are subject to similar CYP metabolism. Genomic testing to determine therapeutic doses for oncologic effects is only cost effective in medications that have no adequate alternatives. Morphine and oxycodone are examples of narcotics that have more reproducible analgesic effects and are generally preferred to codeine. It is thus hard to argue for preemptive genetic testing in this setting. However, in patients with respiratory suppression or narcotic toxicity after normal codeine dosing, laboratory testing to determine the proportion of codeine and morphine byproducts and genetic testing of CYP2D6 alleles may identify an underlying UM/rapid metabolizer genotype.

SUMMARY

The field of otolaryngology, both adult and pediatric, is subject to unique symptomatology and anatomic changes resulting from patients who are ingesting or administering narcotic analgesic as well as illicit drugs. Furthermore, transnasal administration, in particular, of both prescribed and illicit drugs can pose unique challenges to the otolaryngologist. Clinical laboratory toxicology testing via blood or genetic specimen procurement can provide objective insight into select disease etiologies and alert the clinician to inappropriate drug use as well as provide management support for choice of analgesia toward optimal patient care.

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