

Obstructive sleep apnoea and polymorphisms: implications for anaesthesia care

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Summary

With a worldwide obesity pandemic, the incidence of obstructive sleep apnoea (OSA) is increasing; obesity is the most significant risk factor in children. Increasing evidence suggests that OSA is in part mediated through markers of inflammation. Systemic and pulmonary hypertension, right ventricular hypertrophy, prediabetes, and other conditions are common. Adenotonsillectomy improves only ~70% of children; 30% require other interventions, e.g. weight loss programs. The gold standard for diagnosis is a sleep-polysomnogram which are expensive and not readily available. The McGill oximetry score (saw-tooth desaturations during obstruction and arousal) is more cost-effective.

Repeated episodes of desaturation alter the opioid receptors such that analgesia is achieved at much lower levels of opioid than in patients undergoing the same procedure but without OSA. This response is of great concern because a standard dose of opioids may be a relative overdose.

Polymorphism variations in cytochrome CYP2D6 have major effects upon drug efficacy and side effects. Codeine, hydrocodone, oxycodone, and tramadol are all prodrugs that require CYP2D6 for conversion to the active compound. CYP2D6 is quite variable and patients can be divided into 4 classes: For codeine for example, poor metaboliser (PM) have virtually no conversion to morphine, intermediate metabolisers (IM) have some conversion to morphine, extensive metabolisers (EM) have a normal rate of conversion to morphine, and ultra-rapid metabolisers (RM) convert excessive amounts of codeine to morphine. Such variations result in some patients achieving no analgesia because there is reduced conversion to the active moiety whereas others convert an excessive amount of drug to the active compound thus resulting in relative or actual overdose despite appropriate dosing.

Thus, OSA patients may have both opioid sensitivity due to recurrent desaturations and altered drug metabolism resulting in higher than intended blood levels of opioid. OSA patients should only receive one-third to half the usual dose of opioid. In those under the age of six, an effort should be made to avoid opioids altogether and use opioid sparing techniques such as alternating acetaminophen and ibuprofen.

Keywords: obstructive sleep apnoea, polymorphisms, obesity, opioid sensitivity, altered drug metabolism

Introduction

Tonsillectomy and adenotonsillectomy (T&A) is one of the most common paediatric surgical procedures in the United States (~500 000/year). A distressing number of children have died within 24 hours of their surgical procedure and these deaths have occurred in the post anaesthesia care unit (PACU), in the ward, and at home. These events have been published in both the anaesthesia and surgical literature.^{1,2} This mini-review will focus on obstructive sleep apnoea (OSA), the now well-known opioid sensitivity associated with chronic repeated desaturation events,³⁻⁶ and the not so well known opioid resistance or sensitivity associated with drug metabolism due to polymorphisms which occur in both adults and children.^{7,8}

Treatment overview

Children suffering adverse outcomes following a tonsillectomy can be somewhat divided into:

1) those due to associated medical conditions (e.g. congenital heart disease, obesity, reactive airway disease, pulmonary and

systemic hypertension,⁹ diabetes, non-alcoholic fatty liver,¹⁰ syndromic children such as Down syndrome, dwarfism);

2) those due to surgical complications (haemorrhage, premature discharge following surgery, excessive opioid prescription), and

3) those due to anesthesia mismanagement (inadequate securing of the airway, anaesthetic overdose, opioid overdose, premature discharge from medical supervision, inadequate postoperative monitoring).

This presentation summarises patient-related factors, opioid induced sensitivity, genomic information regarding duplicated cytochromes resulting in minimal or ultra-rapid conversion of opioids placing children with OSA at particular risk, and recommendations regarding perioperative assessment of children potentially at risk for OSA.

Since the most important contributor to OSA is obesity, it is this population that is at greatest risk. Childhood obesity (greater than the 95th percentile),¹¹ is now pandemic in the USA.¹² Obesity and OSA appear linked to a metabolic syndrome, i.e. hypertension, dyslipidaemia, proinflammatory states, insulin

resistance and other features.^{9,10,13-15} However, the role of anti-inflammatory medications is unclear and unproven.¹⁶

The most common treatment in paediatrics is tonsillectomy or adenotonsillectomy. T&A reduces OSA by ~70%.¹⁷ However, that means 30% are not cured; there is no evidence that tonsillectomy alters outcome except to reduce surgical complications.^{18,19} The estimated mortality in the USA is ~1/2360-1/18000 procedures.¹⁷ Other measures such as weight loss, uvulopalatopharyngoplasty, mandibular advancement, tongue base reduction, CPAP, BiPAP, and variable positive airway pressure (VPAP) may be needed.²⁰

Clinical signs and symptoms

Loud snoring, gasps, pauses in respirations, sleeping in odd positions, cyanosis, morning headaches, enuresis (after six months of continence), night terrors, poor school performance and daytime somnolence are all associated with OSA.²¹ Tonsillar hypertrophy, adenoidal facies, micrognathia, high arched palate, reactive airway disease and systemic hypertension are additional associations. Pulmonary hypertension may be present in ~1.8%.²² The preoperative history must elucidate these factors to clarify who is at risk. A polysomnogram is the gold standard: assessment of the apnoea/hypopnoea index (Table I).^{23,24} The American Society of Anesthesiologists published an updated guideline for perioperative assessment and management;²⁵ and it would be useful to examine that document for assessment of risk although the scoring system is still not validated with a prospective study. Overnight pulse oximetry with periodic desaturation events has been shown to correlate with severity of OSA (the McGill oximetry score) (Table II); repeated episodes of desaturation below 80% indicate severe OSA.^{26,27} The pattern of desaturation events is usually "saw tooth" in nature corresponding to obstruction/apnoea/desaturation followed by arousal, relief of obstruction and re-saturation.²⁸ The assessment of severe OSA has been added to guidelines from the American Academy of Pediatrics (AAP) and paediatric otolaryngologists. Unfortunately, only a minority of children have such an evaluation making it exceedingly important for the anaesthesiologist to ask specific historical questions (described above) so that appropriate perioperative pain management and monitoring can be prospectively organised. A number of questionnaires have been developed in an attempt to provide guidance at a much lower cost but none have proven more than marginally reliable; it appears that four key questions are most likely to be of value: apnoea or pauses in respirations, growth problems, mouth breathing, and obesity.²⁹

Ethnicity

In the USA there is a greater risk for OSA in African-American and Hispanic children compared with Caucasians.^{30,31} Hispanic children with excessive daytime somnolence are three times more likely to have frequent snoring and six times more likely to have witnessed apnoea events.³² African-American children may have independent genetic factors predisposing to both obesity and OSA; reactive airway disease and low socioeconomic status are other associated factors.³³

Analgesia and opioid sensitivity

Repeated episodes of desaturation (in adults and children) alters mu-receptors resulting in analgesia occurring at lower opioid doses than in children (or animal models) who have not experienced repeated desaturation events.^{3-6,34} There is some evidence indicating that adult patients with OSA have increased sensitivity to opioids that may be related to pro-inflammatory mediators such as interleukin-1 β and tumour necrosis factor- α .³ In children, there is a relationship between obesity, inflammatory markers and severity of OSA with some decrease in these markers after tonsillectomy and improvement of OSA.³⁵ Thus children with severe OSA may be analgesic at much lower opioid blood doses compared with children undergoing tonsillectomy for recurrent tonsillitis. Therefore, a standard opioid dose may be a relative overdose in children with OSA; reduce the initial dose of opioid $\frac{1}{3}$ to $\frac{1}{2}$ that of a standard dose. A possible means for assessing risk (not scientifically validated) may be the administration of low-dose opioid during anaesthesia with observation for resulting effects on the respiratory rate; a low opioid dose resulting in a reduction in respiratory rate is suggestive of opioid sensitivity.^{13,36}

Polymorphisms and risk for respiratory depression

The CYP 2D6 cytochrome system is susceptible to polymorphism abnormalities that have marked effects on converting the prodrug codeine to its active metabolite morphine and morphine-6-glucuronide. Patients can be divided into four classes: Poor metaboliser (PM) meaning virtually no conversion to morphine, intermediate metabolisers (IM) meaning some conversion to morphine, extensive metabolisers (EM) meaning normal rate of conversion of codeine to morphine, and ultra-rapid metabolisers (RM) which are able to convert excessive amount of codeine to morphine.⁷ There is increasing evidence of marked ethnic variations in the cytochromes responsible for drug metabolism with over 100 both active and nonfunctional identified.⁷ In particular, a defect in CYP 2D6 results in ~8-10% of children being unable to convert codeine to morphine such that these children receive virtually no analgesia from codeine (slow metabolisers).^{8,37} Of far greater concern is that 0.5-2.0% may have a duplicated CYP 2D6 (duplicate snippets) thus resulting in a more rapid conversion of codeine to morphine (metabolisers), thus producing a much higher blood level than in children with normal cytochromes. Thus in children with duplicated snippets, a relative overdose is possible and when combined with the child who has OSA induced opioid sensitivity, could and has resulted in fatalities.^{38,39} The incidence of such duplicated cytochromes is quite variable and definitely ethnically related, e.g. as high as 29% African/Ethiopian, 3.4-6.5% African American, and 1-2% Northern Europeans.³⁷ Similarly hydrocodone is also subject to marked variability in conversion to hydromorphone which binds to opioid receptors with 30 times greater affinity than the parent compound. Thus hydrocodone can be considered a prodrug and also likely results in minimal analgesia for those with poor conversion whereas ultra-rapid metabolism will result in up to an eightfold greater plasma concentration and potential for

overdose.⁴⁰ Oxycodone is another opioid which is metabolised to its active metabolite oxymorphone which has less analgesic and less respiratory depression properties than the parent compound. One study of postsurgical paediatric patients found greater levels of oxymorphone in children who were RM or EM phenotypes compared with PM and IM phenotypes.⁴¹ The clinical implications of this have not been adequately studied but it would seem that the RM and EM phenotypes would have less analgesia.⁴² Tramadol, like codeine, is a prodrug that requires conversion to its active metabolite and thus also subject to variable metabolism; ultra-rapid metabolism has resulted in at least one fatality.⁷ Slow metabolisers of tramadol could theoretically encounter reduced analgesia.⁴³ Because of these concerns and increasing data regarding cytochrome duplications and drug metabolism, the FDA issued a safety announcement that the use of codeine is contraindicated in children less than 18 years of age and tramadol is not recommended in children 12–18 years of age who are obese or have OSA. (<https://www.fda.gov/media/104268/download>). Codeine has been removed from all over-the-counter cough medicines in the USA and removed from the formulary of all children's hospitals in the USA.⁴⁴

Thus the two main risk factors for postoperative respiratory depression are cytochrome polymorphisms and hypoxaemia altered opioid receptors.⁴⁵ The only opioids at present that are not subject to these variable rates of metabolism to active substrates are oral morphine and hydromorphone.⁴⁶

Alternative approaches to analgesia for OSA patients

Alternative approaches include the use of oral opioids less subject to variable metabolism such as morphine or hydromorphone, the use of lower dosing in children with OSA ($\frac{1}{3}$ to $\frac{1}{2}$ the usual dose), or avoidance of opioids altogether. Recommendations now are to use opioid-sparing approaches such as “around-the-clock” alternating oral acetaminophen with oral ibuprofen, particularly in children under six years of age and avoiding opioids entirely in those with proven or possible OSA.^{23,47}

Surgical considerations

Postoperative pain relates to the surgical approach, e.g. radiofrequency versus dissection versus guillotine versus microdebrider with extensive electrocautery resulting in the most pain. A recent suggestion has been to perform partial tonsillectomy to reduce airway obstruction while avoiding complete tonsillectomy and thus significantly reducing postoperative pain and the need for postoperative opioids.^{18,19} Be aware that airway obstruction may become worse during the first postoperative night despite removal of the enlarged tonsils.⁴⁸

Guidelines

Guidelines regarding the evaluation and management of children at risk for OSA have been published. The AAP reviewed > 3 000 papers and issued a practice guideline for the diagnosis and management of OSA.²¹ They recommended that all children should be screened for snoring, that polysomnography should

be performed in children with signs and symptoms of OSA, recommended tonsillectomy as a first-line treatment, stated that “*high-risk patients should be monitored as inpatients postoperatively*” and then reevaluated to determine if additional treatment is needed. They defined high-risk patients as those under three years of age, those having severe polysomnography documented OSA (oxygen saturation's < 80% during polysomnography or post-surgery or apnoea/hypopnoea index > 24 per hour), those having cardiac complications related to OSA (right ventricular hypertrophy, pulmonary hypertension), those having significant hypercapnia during polysomnography (PECO₂ ≥ 60 mmHg), those with failure to thrive or obesity, craniofacial anomalies, neuromuscular disorders and current respiratory infection.²¹ It is unclear how the AAP committee chose an apnoea/hypopnoea index of > 24 as being at high risk when most laboratories define high risk as having an apnoea/hypopnoea index of > 10. This emphasises the importance of knowing the parameters used by the evaluating facility.

The American Academy of Otolaryngology–Head and Neck Surgery Foundation has issued a practice guideline regarding the indications for polysomnography prior to tonsillectomy in children.²⁴ They made the following recommendations for preoperative polysomnography: children with obesity, Down syndrome, craniofacial abnormalities, muscular disorders, sickle-cell disease, and those with mucopolysaccharidoses. They also recommended polysomnography in children without the above-mentioned conditions where there is discordance between tonsil size and the severity of reported sleep disordered breathing. They further stated that *clinicians should report the results of such studies to the anaesthesiologist prior to induction, that clinicians should admit children with polysomnogram documented OSA if they are under three years of age or have severe OSA (an apnoea-hypopnoea index of ≥ 10 or oxygen saturation < 80% or both)*. They further clarified that in children for whom polysomnography is indicated, that these laboratory-based studies should be conducted preoperatively.

The ASA updated their guideline for the assessment and management of patients with OSA.²⁵ There are two key tables in this document. Table I helps the clinician to assess the signs and symptoms that may indicate patients at risk for OSA (both adults and children). Table II assesses the invasiveness of the surgical procedure (e.g. body cavity), the nature of the surgical procedure (peripheral versus central), the type of anaesthesia administered (general versus regional), involvement of the airway (e.g. tonsillectomy), and the need for postoperative opioids on an extended basis; a score of 5–6 indicates likely OSA and the need for appropriate perioperative management.²⁵ Although these risk assessment tables have not been systematically validated, when placed in perspective with the guidelines from the AAP and the otolaryngologists, it would seem that the ASA guideline is quite useful in estimating potential for OSA and perioperative risk.

Morbidity and mortality surveys

Two surveys (Otolaryngology and Anesthesiology) warrant discussion:

1. The Patient Safety and Quality Improvement (PSQI) Committee of the American Academic of Otolaryngology–Head and Neck Surgery (AAO–HNS) in a 32 question survey reported 40 paediatric deaths; six attributed to bleeding, nine to “med-narcotic”, and 16 as “unexplained cause”.² Of these, one was in hospital and the remaining 15 occurred “out of hospital”.² The ENT survey implicated opioid overdose as the cause in eight deaths. Most importantly ten deaths occurred in children labelled as having OSA and these deaths were unrelated to haemorrhage.
2. I conducted a similar internet-based 42 question survey to all members of the Society for Paediatric Anaesthesia.¹ In addition we queried the American Society of Anesthesiologists Closed Claims Project database for otolaryngology cases involving children. Out of the 731 surveys returned and in the 45 possible cases from the Closed Claims Project, 111 reports. We used the ASA-OSA guideline criteria²⁵ (tables 1 and 2 in that document) to assess those children who might have been at risk for OSA. 57% of the children met the criteria for OSA and 43% for not being at risk for OSA. The at-risk children were more likely to be obese ($p < 0.0001$), to have a higher ASA physical status ($p < 0.0001$), and to be highly related to ethnicity (African American, Hispanic versus Caucasian)($p < 0.0001$).⁴⁹ There was a significantly higher incidence of morbidity and mortality related to haemorrhage in the children assessed to not be at risk for OSA ($p = 0.006$) whereas a greater fraction of the children described as at risk for OSA had the event attributed to apnoea ($p = 0.016$). What was most disturbing is that ten deaths occurred at home, three in a hospital ward after discharge from PACU, and two in the PACU after monitors were removed (one child felt to be “asleep” on his father’s lap and the other “asleep” on the stretcher alongside her mother). It was astonishing that two children died while still in the PACU thus illustrating the insidious way that apnoea may occur in children with OSA; these deaths were attributed to apnoea and very likely preventable.^{23,50}

Conclusion

Obesity has become pandemic in the United States and worldwide. With this, there is a rising increase in the incidence of children at risk for OSA. With the rising costs of healthcare there will be great pressure on clinicians to avoid postsurgical hospital admissions. This, in fact, may create the “perfect storm” in the sense that it will be easy to overlook or to not take adequate time to obtain a complete detailed history to determine which children require postsurgical/anaesthesia admission to the safety net of medical supervision. Unfortunately, even when admitted, without continuous monitoring and observation, these events may still occur; simple admission without proper safeguards may result in a false sense of security.^{1,50} It is unacceptable for children to die or become neurologically injured following an

elective surgical procedure particularly when we have the tools to help predict those who are at risk and to protect those who are determined to be at risk. Therefore, despite the pressure to reduce costs both surgeons and anaesthesiologists are obligated to improve screening procedures, perhaps develop alternate surgical approaches, and to provide adequate postoperative analgesia which is least likely to add to risk.

Table I: Polysomnographic assessment of severity of OSA with the apnoea/hypopnoea index

OSA severity	Number of apnoeas/hypopnoeas [#] per hour [*]
None	0
Mild	1–5
Moderate	5–10
Severe	> 10

^{*}Each polysomnography facility may have a similar but different scoring system

[§] Apnoea is defined as a cessation of breathing for 10 seconds or longer

[#] Hypopnoea is defined as a partial airway obstruction

Table II: The McGill oximetry score for assessing obstructive sleep apnoea¹¹

Score	Severity of nocturnal desaturation events [*]
1 = no risk	No desaturations below 90%
2 = mild risk	Desaturations < 90%
3 = moderate risk	Desaturations < 85%
4 = severe risk	Desaturations < 80%

^{*}Note that this most often takes a “saw tooth” pattern correlating with obstruction/apnoea/desaturation followed by arousal and re-saturation

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