Opioid Sensitivity in Children with and without Obstructive Sleep Apnea

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ABSTRACT

Background: Opioids are a mainstay of perioperative analgesia. Opioid use in children with obstructive sleep apnea is challenging because of assumptions for increased opioid sensitivity and assumed risk for opioid-induced respiratory depression compared to children without obstructive sleep apnea. These assumptions have not been rigorously tested. This investigation tested the hypothesis that children with obstructive sleep apnea have an increased pharmacodynamic sensitivity to the miotic and respiratory depressant effects of the prototypic μ-opioid agonist remifentanil.

Methods: Children (8 to 14 yr) with or without obstructive sleep apnea were administered a 15-min, fixed-rate remifentanil infusion (0.05, 0.1, or 0.15 μg · kg⁻¹ · min⁻¹). Each dose group had five patients with and five without obstructive sleep apnea. Plasma remifentanil concentrations were measured by tandem liquid chromatography mass spectrometry. Remifentanil effects were measured via miosis, respiratory rate, and end-expired carbon dioxide. Remifentanil pharmacodynamics (miosis vs. plasma concentration) were compared in children with or without obstructive sleep apnea.

Results: Remifentanil administration resulted in miosis in both non-obstructive sleep apnea and obstructive sleep apnea patients. No differences in the relationship between remifentanil concentration and miosis were seen between the two groups at any of the doses administered. The administered dose of remifentanil did not affect respiratory rate or end-expired carbon dioxide in either group.

Conclusions: No differences in the remifentanil concentration–miosis relation were seen in children with or without obstructive sleep apnea. The dose and duration of remifentanil administered did not alter ventilatory parameters in either group.

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EDITOR’S PERSPECTIVE

What We Already Know about This Topic

- Children with obstructive sleep apnea are at greater risk for postoperative hypoxia and other respiratory events as compared with children without this disorder
- There is some reason to believe that children with obstructive sleep apnea may be at greater risk for opioid-induced respiratory depression due to increased sensitivity to the drugs

What This Article Tells Us That Is New

- The authors hypothesized that children with obstructive sleep apnea would be more sensitive to the effects of an opioid (remifentanil) on pupil size—a very good indicator of opioid effects
- While remifentanil did reduce pupil size in the expected dose-related fashion, there were no differences between children with obstructive sleep apnea and those without
- While the authors did not observe any differences in the effect of remifentanil on respiration, the study was not designed to examine this factor in detail

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Childhood obstructive sleep apnea, defined by periodic, partial or complete obstruction of the upper airway during sleep, is a common disorder in pediatric patients, with a prevalence as high as 5.7%.1,2 Children with obstructive sleep apnea often present for surgery and other procedures that require general anesthesia. In fact, the treatment of obstructive sleep apnea is the primary indication for more than 75% of children undergoing tonsillectomy with or without adenoidectomy.3 Tonsillectomy is the most common pediatric operation performed in the United States, with more than 500,000 tonsillectomies performed annually.3 Unfortunately, children at high risk for obstructive sleep apnea are three times more likely to have posttonsillectomy respiratory complications and anesthetic adverse events than children at low risk for obstructive sleep apnea.5,6 and the rate of complications in patients with obstructive sleep apnea posttonsillectomy (16 to 27%) is substantially increased compared to that of the general pediatric postoperative population (0 to 1.3%).7-11 These complications include oxygen desaturation, hypercapnia, obstructive apneas requiring continuous positive airway pressure or airway instrumentation, unexpected intensive care unit admission, and in rare cases, death.

Concerns for a heightened risk of opioid induced respiratory depression make the perioperative use of opioids in children with obstructive sleep apnea particularly challenging, if not controversial. It has been suggested that they may be at risk from overdose if administered what would otherwise be considered a normal dose of opioid.5 Indeed, some pediatric surgical centers automatically reduce by half the administered dose of opioid in any child with a diagnosis of sleep apnea.5 These assumptions have not been rigorously tested. This investigation tested the hypothesis that children with obstructive sleep apnea have an increased pharmacodynamic sensitivity to the miotic and respiratory depressant effects of the prototypic μ-opioid agonist remifentanil.
the opioid dose of patients undergoing tonsillectomy for a diagnosis of obstructive sleep apnea; published guidelines recommend decreasing opioid doses in all patients with sleep apnea, for fear of respiratory depression.\(^{13}\)

Despite the widespread belief that obstructive sleep apnea increases opioid sensitivity, evidence to support this claim comes largely from either animal studies, or from human studies that are limited by their reliance on behavioral scores, rather than using objective markers of opioid sensitivity.\(^{6,9,14-17}\) There is an unmet need to quantify whether there is opioid sensitivity in children with obstructive sleep apnea as compared to children without obstructive sleep apnea. The purpose of this study was to evaluate opioid pharmacodynamics in pediatric patients with and without obstructive sleep apnea, using remifentanil as the prototype opioid. We tested the hypothesis that children with obstructive sleep apnea have increased pharmacodynamic sensitivity to remifentanil, compared to those without obstructive sleep apnea. Pupil constriction (miosis) is the most sensitive measure of opioid effects at subanesthetic drug concentrations, and was used as an objective measure of opioid effect. Sensitivity to remifentanil was assessed using pupillometry, and also respiratory rate and end-expired carbon dioxide in pediatric patients with and without obstructive sleep apnea.

### Materials and Methods

#### Patients and Clinical Protocol

This study was approved by the Washington University in St. Louis Institutional Review Board. Eligible subjects were children, 8 to 14 yr of age, undergoing an elective procedure requiring general anesthesia. Exclusion criteria were an inability to cooperate with study requirements (e.g., IV placement, sitting quietly, or pupillometry). Patients’ parents or legal guardian provided written informed consent and patients provided written assent. Two cohorts of children were studied: those with obstructive sleep apnea and those without obstructive sleep apnea. Children were considered to have obstructive sleep apnea based on their chief complaint, history, and rationale for surgery as documented in the operative surgeon’s preoperative note which stated the indication for surgery as obstructive sleep apnea. Within this group, 9 out of 15 children (60%) presenting for tonsillectomy for obstructive sleep apnea had an overnight sleep laboratory polysomnogram, and all confirmed the diagnosis of obstructive sleep apnea. The remaining six children had at least two of the following: snoring, witnessed breathing pauses or gasping for breath, restless sleep, or daytime somnolence (table 1). In addition, all children with obstructive sleep apnea carried the International Classification of Diseases, Tenth Revision (ICD10) billing codes for Sleep Apnea, Unspecified (G47.30) or Obstructive Sleep Apnea (G47.33) in their medical record.

Children were classified as non–obstructive sleep apnea if they presented for tonsillectomy with or without adenoidectomy with a preoperative diagnosis of Acute Recurrent, or Chronic Tonsillitis (ICD10 codes J03.91 and J35.01), but not obstructive sleep apnea, or if they presented for a procedure requiring general anesthesia and did not have any medical history of obstructive sleep apnea. The medical record of non–obstructive sleep apnea children was assessed for sleep studies and signs and symptoms of obstructive sleep apnea.

### Table 1. Data Supporting the Diagnosis of Obstructive Sleep Apnea.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sleep Study</th>
<th>AHI (Episodes per Hr)</th>
<th>SPO(_2) Nadir (%)</th>
<th>OSA Severity</th>
<th>Snoring</th>
<th>Breathing Pause or Gasping</th>
<th>Restless Sleep</th>
<th>Poorly Rested</th>
<th>Daytime Somnolence</th>
<th>Nocturnal Enuresis</th>
<th>Behavioral Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X</td>
<td>8.1</td>
<td>90</td>
<td>Moderate</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Unk</td>
<td>Unk</td>
<td>Unk</td>
<td>Unk</td>
</tr>
<tr>
<td>2</td>
<td>X</td>
<td>34.9</td>
<td>74</td>
<td>Severe</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Unk</td>
<td>X</td>
<td>Unk</td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>X</td>
<td>46.9</td>
<td>81</td>
<td>Severe</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Unk</td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>X</td>
<td>3.5</td>
<td>90</td>
<td>Mild</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Unk</td>
<td>Unk</td>
<td>Unk</td>
<td>Unk</td>
</tr>
<tr>
<td>5</td>
<td>X</td>
<td>4.8</td>
<td>94</td>
<td>Mild</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Unk</td>
<td>Unk</td>
<td>Unk</td>
<td>Unk</td>
</tr>
<tr>
<td>6</td>
<td>X</td>
<td>8.3</td>
<td>84</td>
<td>Moderate</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Unk</td>
<td>X</td>
</tr>
<tr>
<td>7</td>
<td>X</td>
<td>22.1</td>
<td>92</td>
<td>Severe</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Unk</td>
<td>Unk</td>
<td>X</td>
</tr>
<tr>
<td>8</td>
<td>X</td>
<td>10.5</td>
<td>90</td>
<td>Severe</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Unk</td>
<td>X</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>X</td>
<td>14.0</td>
<td>84</td>
<td>Severe</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>9</td>
<td>100%</td>
<td>60%</td>
<td>33%</td>
<td>40%</td>
<td>47%</td>
<td>13%</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The AHI is reported to 0.1 episodes per hr, and severity is based on the AHI as mild (1 to 5), moderate (6 to 10), and severe (≥11). “No” indicates patient was queried and the request was denied by patient and/or family; “X” indicates yes; “Unk” indicates that the patient was not queried.

AHI, apnea-hypopnea index; OSA, obstructive sleep apnea.
obstructive sleep apnea. One child in the non–obstructive sleep apnea group did exhibit snoring; however, this child also had received a sleep study that indicated the absence of obstructive sleep apnea with an Apnea–Hypopnea Index of 0. None of the other children in the non–obstructive sleep apnea group had snoring, witnessed breathing pauses or gasping for breath, restless sleep, or daytime somnolence described as symptoms in their operative surgeon’s preoperative note.

The study was conducted in the patient’s preoperative holding room prior to surgery. Anesthesia and surgical care were not altered for this study, except that a second 20-gauge preoperative IV catheter was placed in the antecubital fossa for venous blood sampling (one preoperative IV catheter is standard of care for this age group at our institution). Following IV placement, heart rate, pulse oximetry, blood pressure, and nasal cannula end-expired carbon dioxide monitors were placed. Patients breathed room air.

A remifentanil infusion was started and maintained for 15 min at a continuous rate of either 0.05, 0.1, or 0.15 μg·kg⁻¹·min⁻¹. These doses were chosen to target remifentanil plasma concentrations 0.1 to 3 ng/ml, because pupil constriction is maximum at plasma concentrations greater than 3 ng/ml. Remifentanil was administered based on ideal body weight. Ideal body weight was calculated as [(2.3 kg × height (inches) > 60) + 45.5 kg [females] or 50 kg [males]]. Patients’ actual weight was used if they were less than the calculated ideal body weight. A cycled, dose escalation paradigm was used. The first patient in each group received 0.05 μg·kg⁻¹·min⁻¹, the second: 0.1 μg·kg⁻¹·min⁻¹, the third: 0.15 μg·kg⁻¹·min⁻¹, then the dose escalation repeated (i.e., patient four received 0.05 μg·kg⁻¹·min⁻¹). Each dose group consisted of five patients with obstructive sleep apnea and five patients without obstructive sleep apnea for a total of 15 patients each in the obstructive sleep apnea and non–obstructive sleep apnea groups.

Dark adapted infrared pupillometry was performed using binocular infrared pupillometers mounted in light occlusive goggles sampling at 100 Hz. The goggles were paired to a digital eye tracking system that fixates on the pupils (I-Portal, Neuro Kinetics, Inc., USA). Pupil area in pixels was continuously recorded during the study, and later averaged into 10-s bins. Data from both eyes were averaged. Baseline pupil size was defined as the average of the first 30 s of recording. Time-specific pupil size was the average area in the 30 s preceding each blood draw. Fractional pupil size was the time-specific area divided by the baseline pupil area. To measure plasma concentrations of remifentanil, 3 ml blood were drawn at 0, 1, 2, 4, 6, 10, and 15 min following the beginning of the remifentanil infusion.

Respiratory monitoring was performed using nasal cannula and end-expired carbon dioxide monitoring via a Capnostream 20 Bedside Monitor (Medtronic, USA). End-expired carbon dioxide and respiratory rate were recorded before, and 1, 2, 4, 6, 10, and 15 min after starting the remifentanil infusion. Respiratory depression was defined as a respiratory rate less than 8, or oxygen saturation less than 90%. Data regarding altered mental status (e.g., confusion, disorientation, or hallucinations), excessive sedation (failure of the patient to respond to their name called loudly), and any need for external airway support (e.g., jaw thrust, oral or nasal airway insertion, mask ventilation, or intubation) were also collected. Following the 15-min assessment period, the remifentanil infusion was stopped. The patient then proceeded with the planned surgery.

Analytical

To prevent ex vivo remifentanil metabolism, blood was immediately injected into potassium EDTA vacutainers (BD Vacutainer, USA) and plasma separation, acidification, and −80°C storage were performed within an hour of blood draw. Samples were centrifuged at 3,000 rotations per minute at 4°C for 5 min to separate plasma. Plasma (500 μl) was acidified with 3 μl of a nearly saturated 1 g/ml citric acid solution and stored at −80°C until analysis. All samples were analyzed within 3 months of collection.

Venous plasma remifentanil concentrations were determined by liquid chromatography-tandem mass spectrometry, using a modification of a previous method. Protein precipitation was used to prepare samples. An aliquot of 100 μl of thawed patient plasma, calibrator, or quality control plasma was pipetted into discrete wells of a 96-well 2.2-ml polypropylene plate. Fentanyl internal standard (10 μl of 25 ng/ml; Cerilliant, USA), and 300 μl of methanol was added to each sample. The plate was capped and samples were mixed on a plate shaker for 1 min. The plate was then centrifuged at 6,100 rotations per minute for 15 min at 4°C in a Beckman Coulter Ultracefrifuge using a JS-13 rotor. After centrifugation, 200 μl of supernatant was transferred to a new 96-well 0.45-ml polypropylene plate.

Analysis was performed on a triple-quadrupole mass spectrometer (6,500, AB Sciex, Ontario, Canada) equipped with a Turbo Ion Spray ionization source using positive polarity and multiple reaction monitoring. The chromatographic system was a Shimadzu (USA) Prominance HPLC system consisting of two LC-20AD XR pumps with a CTO-20AC oven, a SIL-20AC XR auto-sampler, a DGU-20A5R degasser, and a CBM-20A controller. Chromatographic separation was performed using a Gemini C-18 analytical column (50 × 2.0 mm, 3 μm) with a Gemini C-18 SecurityGuard column (4 × 2.0 mm; Phenomenex, USA). The injection volume was 5 μl and the oven temperature was 25°C. Before each injection the needle was washed with methanol. Mobile phase (0.5 ml/min) was (A) 0.1% formic acid in water and (B) 0.1% formic acid in acetonitrile. The gradient used was 10% B held for 0.5 min and then increased linearly to 80% during the next 2.5 min. B was then immediately re-equilibrated back to 10%. Under these conditions, retention time for remifentanil and fentanyl were 2.2 and 2.5 min respectively. Both Q1 and Q3 quadrupoles were
Remifentanil-miosis Concentration-effect Relationship

Miotic effect as a fractional change from baseline versus remifentanil concentration was analyzed using nonlinear regression with global curve fitting (SigmaPlot; Systat Software, USA). A three-parameter sigmoid inhibitory-EMax logistic function was used:

\[ E(r) = E_{\text{Max}} \times \left(1 - \frac{r}{r + EC_{50}}\right) \]

where \( E(r) \) is the effect at remifentanil concentration \( r \); \( E_{\text{Max}} \) is the maximum pupillary constriction produced by remifentanil; \( r \) is the remifentanil concentration in ng/ml; and \( \gamma \) is the shape parameter that determines the steepness of the concentration effect relationship.

Results

Between September 1, 2015, and October 31, 2017, 507 records of patients aged 8 to 14 yr were assessed for eligibility. Of these, 87 met screening criteria and were approached for participation. Details of screening and enrollment are shown in figure 1. Thirty-three patients agreed to participate. Blood draw failed in three patients; a total of 30 patients underwent a remifentanil infusion and assessment.

Patient demographics are shown in table 2. The obstructive sleep apnea cohort consisted exclusively of children undergoing tonsillectomy (with or without adenoidectomy) for obstructive sleep apnea. The non–obstructive sleep apnea cohort consisted of children undergoing adenotonsillectomy for chronic tonsillitis (four subjects), an interval appendectomy (one subject), circumcision (two subjects), excision of a preauricular cyst (one subject), inguinal hernia repair (two subjects), orchiopexy (two subjects), palatoplasty (one subject), and tympanoplasty (two subjects). No patient had been admitted to the hospital in the past 30 days and no patient was currently taking opioids.

Measured remifentanil venous plasma concentrations through time are shown in figure 2. Pupillometry results are expressed as a fraction of baseline pupil area, and are shown in figure 3 as a function of time following the start of the remifentanil infusion. Remifentanil induced miosis occurred at all doses in both groups of patients. Fractional pupillary constriction as a function of remifentanil concentration from all dosing paradigms were pooled, and miosis was plotted as a function of measured remifentanil plasma concentration (fig. 4). The 95% CI generated from dose-response curves for both non–obstructive sleep apnea and obstructive sleep apnea patients were found to overlap (fig. 4).

Neither respiratory rate (fig. 5A), nor end-expired carbon dioxide (fig. 5B) was appreciably altered in any of the patients during the 15-min remifentanil infusion. There were no serious adverse events. Table 3 summarizes the incidence of respiratory depression, low oxygen saturation, nausea, emesis, altered mental status, excessive sedation, and patients requiring airway support. The incidence of adverse events was not different between patients with and those without obstructive sleep apnea. One patient in the obstructive sleep apnea group that was administered 0.15 \( \mu \)g · kg\(^{-1} \) · min\(^{-1} \) remifentanil did have a respiratory rate of 7 breaths per minute at 10 min, however, their respiratory rate at 15 min was 11 breaths per minute.

Discussion

This study tested the hypothesis that children with obstructive sleep apnea have an increased sensitivity to the miotic and respiratory depressant effects of the \( \mu \)-opioid agonist remifentanil as compared to those without obstructive sleep apnea. When miosis was measured using dark adapted pupillometry, there was no difference in the remifentanil miosis concentration-effect curves between patients diagnosed with obstructive sleep apnea and those without obstructive sleep apnea. No differences in ventilatory parameters (end-expiratory carbon dioxide and respiratory rate) were seen between the groups, although it is likely that the infusion dose, duration, and resultant effect-site remifentanil concentrations, were insufficient to perturb ventilation. We chose to examine pupillary miosis because it is objectively quantifiable, is the most sensitive measure of opioid effect, and occurs at lower plasma concentrations than required for analgesia or respiratory depression.\(^{22} \) In addition, remifentanil miosis dose response curves have been shown to parallel respiratory depression dose response curves and inversely parallel arterial carbon dioxide dose–response curves.\(^{22} \) Studying \( \mu \)-opioid induced miosis also allowed for the evaluation of the opioid dose-response relationship in children with and without obstructive sleep apnea, prior to any confounding by sedative–hypnotics often administered before or coincident with general anesthesia. While remifentanil has unique pharmacokinetic properties, including rapid metabolism by endogenous blood and tissues esterases, it is a prototype \( \mu \)-opioid agonist and results from our study should be generalizable to other opioids. Our results did not demonstrate any difference in the miotic effect of remifentanil in children either with or without sleep apnea. The doses and duration of remifentanil administered did
not perturb ventilatory parameters sufficiently to make clear conclusions regarding any differences between the two groups regarding sensitivity to opioid induced respiratory depression.

Given the previous reports that anesthetized children with obstructive sleep apnea are more likely to develop central apnea following a 0.5 μg/kg IV dose of fentanyl, and that recurrent hypoxemia is associated with an increased sensitivity to morphine, we expected to find an increased pharmacodynamic sensitivity to the miotic effect of remifentanil in children with obstructive sleep apnea. The miotic effect of remifentanil as a function of infusion duration for three different fixed-dose remifentanil infusions (0.05, 0.1, or 0.15 μg · kg⁻¹ · min⁻¹) demonstrated similar μ-opioid induced miosis in both obstructive sleep apnea and non–obstructive sleep apnea patients.

Simply evaluating remifentanil effect versus time curves shows earlier onset of miosis in obstructive sleep apnea patients, and might be interpreted as a greater opioid sensitivity. However, the measurement of remifentanil plasma concentrations enabled a pharmacodynamic analysis. This demonstrated indistinguishable miotic opioid dose-response relationships between obstructive sleep apnea and non–obstructive sleep apnea patients, and adds nuance to any conclusions that would be reached by viewing effect versus time alone. This illustrates the importance of measuring actual drug concentrations when performing drug-response studies.

Measured remifentanil concentrations were higher and more variable in patients with obstructive sleep apnea. It is not immediately apparent why. The obstructive sleep apnea group in our study weighed more than the non–obstructive

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**Fig. 1.** Participant flow diagram. OSA, obstructive sleep apnea.
sleep apnea group (66.1 kg vs. 48.3 kg). This is consistent with a previous study of nearly 500 children with obstructive sleep apnea presenting for adenotonsillectomy, which found that almost half of participants were overweight or obese. Due to obesity, we explicitly chose to dose based on ideal body weight. Remifentanil pharmacokinetics are similar in obese versus lean adults, and we expected pharmacokinetics to be similar in children. Nevertheless, inter-individual variability can lead to several-fold differences in predicted versus measured plasma drug concentrations, especially for short duration, non–steady state infusions. In addition, recent evidence suggests that the Minto model used in our simulation may not be optimal for children. The relevant consideration is that discordance between expected versus measured remifentanil concentrations again illustrates

### Table 2. Demographic Characteristics

<table>
<thead>
<tr>
<th>Remifentanil</th>
<th>Total (n = 30)</th>
<th>Non-OSA (n = 15)</th>
<th>OSA (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11 ± 2</td>
<td>11 ± 2</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Range</td>
<td>8–14</td>
<td>8–14</td>
<td>8–13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.2 ± 24.9</td>
<td>48.3 ± 22.4</td>
<td>66.1 ± 24.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (33.3%)</td>
<td>4 (26.7%)</td>
<td>6 (40.0%)</td>
</tr>
<tr>
<td>Male</td>
<td>20 (66.7%)</td>
<td>11 (73.3%)</td>
<td>9 (60.0%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>23 (76.7%)</td>
<td>12 (80.0%)</td>
<td>11 (73.3%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (20.0%)</td>
<td>3 (20.0%)</td>
<td>3 (20.0%)</td>
</tr>
<tr>
<td>Native American</td>
<td>1 (6.7%)</td>
<td>0 (0%)</td>
<td>1 (6.7%)</td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise noted. OSA, obstructive sleep apnea.
the importance of measuring actual drug concentrations when performing drug-response studies, lest observed clinical differences be misattributed as pharmacodynamic differences.25

There are several possible explanations for why no difference was seen in remifentanil-induced miosis between obstructive sleep apnea and non–obstructive sleep apnea patients. Previous studies that suggest a difference in opioid sensitivity between children with and without obstructive sleep apnea have assumed similar pharmacokinetics without measuring actual opioid plasma concentrations.9,23,24 It is possible that pharmacokinetic rather than pharmacodynamic differences between the groups could account for the apparent difference in opioid sensitivity between children with and without obstructive sleep apnea. Another probable explanation is that different outcomes were used in this versus previous studies. We focused on miosis, the most sensitive measure of opioid effect, while others focused on respiratory depression. While miosis occurred at all three remifentanil doses administered, and venous plasma concentrations less than 1 ng/ml, we did not see an appreciable change in either end-expired carbon dioxide or respiratory rate. The remifentanil dose range and duration, selected to avoid loss of consciousness or apnea, did not alter ventilatory parameters or induce sedation. However, during the concomitant administration of general anesthesia, children with obstructive sleep apnea had a higher incidence of apnea following a 0.5 µg/kg fentanyl bolus compared with non–obstructive sleep apnea children.25 Reduced

### Table 3. Adverse Events during Remifentanil Infusion

<table>
<thead>
<tr>
<th></th>
<th>Non-OSA (n = 15)</th>
<th>OSA (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate &lt; 8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>O₂ &lt; 90%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate &lt; 60/min</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Excessive sedation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Altered mental state</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Re-intubation</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

OSA, obstructive sleep apnea.
posttonsillectomy morphine requirements have also been reported in children with severe obstructive sleep apnea. It is conceivable that altered opioid sensitivity in obstructive sleep apnea patients only occurs at the higher plasma concentrations required for respiratory depression and sedation. Higher doses were not pursued in this study due to safety considerations. A third possibility is that greater sensitivity to opioids in obstructive sleep apnea occurs only in the presence of sedative-hypnotics, which was deliberately avoided in this opioid-specific protocol. Finally, a fourth possibility is a recognized limitation of this study, namely, the reliance on surgeon diagnosis to classify whether patients have obstructive sleep apnea, rather than formal polysomnography. Nonetheless, while our non–obstructive sleep apnea patients did not receive polysomnography, 60% of our obstructive sleep apnea patients did receive formal polysomnography demonstrating obstructive sleep apnea. Furthermore, a majority of children presenting for surgery have only a clinical diagnosis of obstructive sleep apnea, not one based on polysomnography, so these are the data available on which clinical decision are made. In this study, and inherent in the conduct of clinical pharmacology studies in children, is difficulty with recruitment, and for pragmatic reasons, we did not universally use polysomnography for research purposes to diagnose the children in this study. Therefore, we did not categorize the severity of disease for all individuals in either cohort. Indeed, in our study a documented polysomnogram was only available for nine subjects and thus polysomnography incompletely informs our results. Lastly, it is possible that our obstructive sleep apnea patients simply did not have a severe enough disease phenotype to engender altered opioid sensitivity. Both animal and human studies have implicated chronic intermittent hypoxemia as the driver for altered opioid sensitivity. Thus, perhaps only the most severe obstructive sleep apnea patients, i.e., those with nighttime hypoxemia, will experience altered opioid sensitivity.

There are recognized limitations to this investigation. We intentionally did not perform polysomnography on all children and relied on surgeon practices, to simulate real world clinical practice for children with obstructive sleep apnea. Polysomnography is time consuming and expensive. Less than 10% of patients diagnosed with obstructive sleep apnea undergo polysomnography prior to surgery, even for tonsillectomy. Another limitation is that while opioid effects were studied in isolation, to specifically test the opioid–obstructive sleep apnea hypothesis, it is possible that postoperative sensitivities may differ, due either to higher opioid doses or opioid interactions with anesthetics and sedative hypnotics. These possibilities merit further evaluation.

Given the high prevalence of obstructive sleep apnea, many children with obstructive sleep apnea will undergo surgical procedures that require opioid analgesia, including tonsillectomy. Tonsillectomy, while seemingly a minor procedure, is exquisitely painful. Therefore, opioid analgesia is the mainstay of treatment for moderate to severe posttonsillectomy pain. Despite the perioperative use of opioids and other analgesic adjuncts, moderate to severe pain following tonsillectomy is common and can last for days. Treatment for posttonsillectomy pain is often insufficient or ineffective as evidenced by a recent survey where more than 40% of patients experience severe pain as defined as greater than or equal to 7 out of 10 on a numeric rating scale.

The primary focus of this study was neither pain relief nor respiratory depression, but rather the miosis–remifentanil concentration effect relationship in children with and without obstructive sleep apnea. Indeed, it is not possible to extrapolate pupillometry as an explicit and perfect marker for either of these critical clinical endpoints. In addition, our reliance on a nasal cannula for exhaled carbon dioxide concentrations may have limited our ability to quantify significant respiratory depression. Nevertheless, this study questions the notion that all children with a clinical diagnosis of obstructive sleep apnea are more sensitive to opioids. Further studies designed to directly test sensitivity to opioid-induced respiratory depression in this high-volume, vulnerable population, are clearly needed. In conclusion, we did not identify a difference in sensitivity to opioid induced miosis in children with and without a clinical diagnosis of obstructive sleep apnea.

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Competing Interests

The authors declare no competing interests.

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