The pharmacokinetic and pharmacodynamics profiles of remifentanil in children with obstructive sleep apnea

Experimental Designs And Methods

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Amendment 1 February 23, 2016
## SYNOPSIS

<table>
<thead>
<tr>
<th><strong>Study Title</strong></th>
<th>Remifentanil in children with and without obstructive sleep apnea.</th>
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</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>To examine the pharmacodynamics of remifentanil in children with obstructive sleep apnea undergoing tonsillectomy and adenoidectomy by studying opioid sensitivity markers to determine if this patient population has increased opioid sensitivity compared to healthy children undergoing elective surgery.</td>
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<tr>
<td><strong>Study Period</strong></td>
<td>1 year</td>
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<tr>
<td><strong>Number of Patients</strong></td>
<td>20 patients presenting for tonsillectomy or adenoidectomy and tonsillectomy for obstructive sleep apnea and 20 patients who do not have obstructive sleep apnea presenting for any procedure requiring general anesthesia.</td>
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<tr>
<td><strong>Study Treatment</strong></td>
<td>15 minute remifentanil Infusion of either 0.05, 0.1, 0.15 or 0.2 mcg/kg/min</td>
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<tr>
<td><strong>Study Design</strong></td>
<td>Parallel group study comparing patients with obstructive sleep apnea undergoing tonsillectomy or tonsillectomy and adenoidectomy to controls with no history of obstructive sleep apnea undergoing general anesthesia for any procedure. The study will be conducted in the patient’s preoperative holding area room. Two intravenous catheters will be placed, one for a remifentanil infusion and one for blood draws to measure the blood concentration of remifentanil. Patients will have standard ASA monitors placed with vital signs monitored on a portable monitor, and a remifentanil infusion will be started. Blood draws will be taken at seven time points: zero, one, two, four, six, ten and fifteen minutes. Concomitantly, recordings of end tidal CO2, respiratory rate, and pupil diameter will be made at the seven time points. Secondary observational study: Review of medical records for the amount of perioperative analgesics required and post-operative pain scores to compare between the study group (tonsillectomy and/or adenotonsillectomy for OSA) and a control group of patients presenting for the same surgery for chronic tonsillitis.</td>
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<tr>
<td><strong>Inclusion and Exclusion Criteria</strong></td>
<td><strong>Inclusion Criteria:</strong> a) Children 8-14 years old, b) ASA physical status 1 or 2, c) undergoing tonsillectomy or tonsillectomy and adenoidectomy for known obstructive sleep apnea [study group], or children with no known obstructive sleep apnea presenting for any procedure requiring general anesthetic, [control group]. <strong>Exclusion Criteria:</strong> Inability to cooperate with study requirements (IV placement, sitting quietly, wearing goggles, etc).</td>
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<tr>
<td>Measurements</td>
<td>Measurements include blood concentration of remifentanil, end tidal CO2, respiratory rate, pupil diameter. Measurements are taken at time points zero, one, two, four, six, ten, and fifteen minutes.</td>
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<tr>
<td>Outcomes</td>
<td>Pharmacodynamic profiles (concentration-effect relationship) of remifentanil in children with OSA undergoing tonsillectomy and adenoidectomy compared to children with history of OSA undergoing general anesthesia. Perioperative analgesic use in children with OSA undergoing tonsillectomy and adenoidectomy compared to children undergoing the same procedure for chronic tonsillitis.</td>
</tr>
</tbody>
</table>
Amendment 1
February 23, 2016

Purpose
1) To change the inclusion criteria for the control group and provide administrative clarification regarding this change.
2) Remove an investigator who has left the institution.

Changes
A. Additions: None
B. Deletions: Title Page: Cheryl Maenpaa, MD has left Washington University and was removed as an investigator.
C. Changes:

2. Enrollment:

From: In addition, twenty children in the same age group with no history suggestive of obstructive sleep apnea who are presenting for a tonsillectomy or tonsillectomy and adenoidectomy for other reasons will be included as control subjects.

To: In addition, twenty children in the same age group with no history suggestive of obstructive sleep apnea who are presenting for any surgical procedure will be included as control subjects.

Rationale: The previous control group included patients without obstructive sleep apnea who were having tonsillectomy. As the comparison for the primary outcome is with or without OSA there is no need to limit our control group to patients presenting for tonsillectomy.
3.1 Inclusion Criteria:

From:

3.1.1. Age group between 8 – 14 years old

3.1.2. ASA physical status 1 and 2

3.1.2. Presenting to SLCH for tonsillectomy or adenoidectomy and tonsillectomy

To:

3.1. *Inclusion Criteria – study group*

3.1.1. Age 8 – 14 years old

3.1.2. ASA physical status 1 and 2

3.1.2. Undergoing tonsillectomy or adenoidectomy and tonsillectomy for known obstructive sleep apnea

3.2. *Inclusion Criteria – control group*

3.2.1 Age 8 – 14 years old

3.2.2 ASA physical status 1 and 2

3.2.3 Undergoing any surgical procedure

3.2.4 No known history of obstructive sleep apnea.

Rationale: Administrative clarification.
1. **Background**

Childhood obstructive sleep apnea (OSA), defined by periodic, partial or complete obstruction of the upper airway during sleep, is a common disorder in pediatric patients encountered by the anesthesiologist. The prevalence of OSA in children is as high as 5.7%\(^1-^4\). First line treatment for childhood OSA continues to be tonsillectomy and adenoidectomy, providing a curative rate of upwards of 74%, and a significant reduction in the severity in OSA symptoms in the majority of patients\(^5\). Despite the overall safety of tonsillectomy and adenoidectomy, respiratory complications, including oxygen desaturation to less than 95% and obstructive apneas requiring CPAP or airway instrumentation, frequently occur. OSA remains the most common predictive risk factor for these events to occur\(^6,^7\). Furthermore, sedatives and anesthetics exacerbate the symptoms of OSA peri-operatively by causing increased collapsibility of the upper airway tissues, alteration of the control of breathing and decreasing the ventilatory response to hypoxia and hypercapnia\(^8,^9\). A survey of members of the Society of Pediatric Anesthesia, along with a query from the American Society of Anesthesiology Closed Claims Projects to investigate factors associated with adverse events in children undergoing tonsillectomy found that 46% of the patients who experienced apnea post-operatively were at risk for OSA\(^10\). Additionally, 61% of the total patients with post-operative apnea received opioids\(^10\). Although it was
not reported in this study the percentage of these patients who received opioids were at risk for OSA\textsuperscript{10}, previous studies have shown pediatric patients with OSA require decreased amounts of post-operative analgesic morphine\textsuperscript{5,11-12}. The limitation of these studies, however, is the use of subjective behavioral pain scoring, not objective opioid sensitivity markers, to determine the need for analgesics for appropriate pain control\textsuperscript{5,11-12}. No study to date has examined objective opioid sensitivity markers to determine if patients with OSA do in fact have increased sensitivity to opioids. The purpose of this study is to evaluate the pharmacodynamics (concentration-effect relationship) of the prototype opioid remifentanil in pediatric patients with and without OSA undergoing tonsillectomy and adenoidectomy using objective opioid sensitivity markers to determine if patients with OSA have increased sensitivity to opioid. Our study drug, remifentanil, is an ultra-short acting $\mu$-selective opioid agonist, which is the same receptor at which longer acting opioids such as morphine act. Since the site of action of remifentanil is the same as other opioids, the results of this study will be able to be generalized to other opioids, improving our clinical understanding and practice in this patient population. Opioid effects will be determined by the decrease in pupil diameter, which is the most sensitive measure of opioid effects at the drug concentrations and subanesthetic doses to be used. We will conduct an initial pilot study to determine the feasibility of conducting a larger prospective cohort study in this specific population using this study design.
2. Enrollment

Patients and their families will be given information regarding the study in the ENT surgeon’s office prior to day of surgery. On the day of surgery, the research team will approach the patients and their family at time of presentation for their procedure. Written informed consent will be obtained from the patient’s family and assent will be obtained from the patient at that time. The study group will consist of twenty patients who are presenting for a tonsillectomy or tonsillectomy and adenoidectomy for OSA. In addition, twenty children in the same age group with no history suggestive of obstructive sleep apnea who are presenting for general anesthesia for any procedure will be included as control subjects. Inclusion and exclusion criteria are based on independent risk factors for respiratory complications following tonsillectomy and adenoidectomy. Patients presenting for tonsillectomy or tonsillectomy and adenoidectomy will be approached to participate in both primary and secondary outcome studies. Patients receiving anesthesia for procedures other than tonsillectomy or tonsillectomy and adenoidectomy will be approached for primary outcomes only. Enrollment completion will be achieved once consent for up to eighty patients is obtained, assuming a 50% drop out rate from the study, with an end goal of forty study patients.

As a secondary outcome, we compare post-operative pain scores in the post-anesthesia recovery unit (PACU) in children undergoing tonsillectomy and adenoidectomy and tonsillectomy for OSA (study
group) with those children who undergo the same procedure but do not have a history of OSA (control group). In addition the type and amount of analgesics administered intra-operatively and post-operatively in the PACU, and operating room time will be compared with the results from the aforementioned observational studies\textsuperscript{5, 11}. In an effort to record observation data from a larger patient population, we will also approach the patients presenting for tonsillectomy and adenoidectomy and tonsillectomy who do not wish to participate in the main study, but may be willing to participate in the observational portion of the study. In the two previous studies, a total of 46 patients\textsuperscript{5} and 36 patients\textsuperscript{11} were observed; thus our goal of enrolling 80 patients will provide a sufficient number of patients to compare to the previous studies.

3. Eligibility

3.1. Inclusion Criteria – study group

3.1.1. Age 8 – 14 years old

3.1.2. ASA physical status 1 and 2

3.1.3. Undergoing tonsillectomy or adenoidectomy and tonsillectomy for known obstructive sleep apnea

3.2. Inclusion Criteria – control group

3.2.1 Age 8 – 14 years old

3.2.2 ASA physical status 1 and 2

3.2.3 Undergoing general anesthesia

3.2.4 No known history of obstructive sleep apnea.
3.3. *Exclusion Criteria*

3.3.1. Inability to cooperate with study requirements (IV placement, sitting quietly, wearing goggles, etc).

4. **Methods**

4.1. *Preoperative and Intraoperative Period*

After consent is obtained, in the holding area, two peripheral IVs will be placed with the use of EMLA cream by the research study team, pre-operative RN or primary anesthesia team. One peripheral IV is standard of care for a patient receiving a tonsillectomy and adenoidectomy or tonsillectomy. A maximum of two attempts will be made for the second IV. If the second IV is unable to be obtained, the patient will be excluded from the study. No pre-operative medication will be given.

4.2. *Study Medication and Administration*

Remifentanil, a 4-anilidopiperidine synthetic opioid with a methyl ester side chain, is an ultra short-acting, potent, naloxone-reversible μ-selective opioid agonist. The ester side chain makes the compound susceptible to metabolism by blood and tissue esterases, allowing for rapid metabolism to a substantially less active compound\textsuperscript{13}. Remifentanil has a rapid distribution phase of 0.9 minutes and, in pediatrics, a terminal elimination half-life of about 3.4 to 7 minutes\textsuperscript{14}. Remifentanil is widely used as an intraoperative opioid, and is particularly well-suited for operations of short duration. Due to its extremely short duration of effect, remifentanil is best administered as a continuous infusion.
The study will be conducted in the preoperative holding area room. The parents may stay throughout the study if they desire to. Standard ASA monitors, which include pulse oximetry, non-invasive blood pressure monitoring, telemetry, heart rate monitoring, end tidal CO2 and oxygen monitoring via a nasal cannula with 21% oxygen, will be connected to the patient. Subjects will also be asked to wear a device for measuring pupil diameter for the entirety of the study. It is a goggle, similar to swimming goggles, which contains cameras which measure pupil diameter. The goggle is light occlusive, meaning that the subject will see darkness. Room lights will be on. The primary anesthesia team will be monitoring the patient’s status, including recording the patient's vitals, end tidal CO2, respiratory rate, at each time point. The research team will measure pupil diameter and make blood draws from the second peripheral IV at each time point. Baseline measurements will be obtained. A remifentanil infusion will then be started and maintained at a rate of 0.05-0.2 mcg/kg/min. Remifentanil dosing will be based on ideal body weight, as it has previously been described\textsuperscript{17} that remifentanil dosing based on total body weight versus ideal and lean body weight results in dramatically higher blood concentrations. To achieve a relatively large degree of pupil diameter changes (up to 5 mm), in a normal population, we would target plasma concentrations from 0.1-4 ng/ml. Since the hypothesis is that patients with OSA undergoing tonsillectomy and adenoidectomy or tonsillectomy will have increased response to remifentanil, we will target a
lower peak plasma concentration (2-3 ng/ml). Based on pharmacokinetic simulations (see Figure 1), appropriate remifentanil infusion rates to achieve desired pupil diameter changes and plasma concentrations are anticipated to be 0.05-0.2 mcg/kg/min. We will have four groups with varying infusion rates: 0.05, 0.1, 0.15 and 0.2 mcg/kg/min respectively. Each dose group will consist of five study patients and five control patients.

Figure 1 Simulated plasma remifentanil concentrations in a 30 kg patient at different remifentanil infusion rates. Remifentanil infusion rates simulated were 0.02-0.3 mcg/kg/min. Parameters used were Vd=0.25 L/kg, CL=60 ml/kg/min. ¹⁸

4.3. Patient Assessments

At time point zero, one, two, four, six, ten and fifteen minutes, the research team will record the pupil diameter and draw three milliliters of blood to measure blood levels of remifentanil. Pupil diameter will be measured using a pupillometer (Neuro Kinetics, Inc. Pittsburgh, PA; Figure 2) as described above. Dark-adapted pupil diameter will be continuously recorded passively before and during the opioid infusion. Concomitantly,
the primary anesthesia team will be recording the patient’s end tidal CO2 and respiratory rate at each time point. Collectively, the recordings will be used to examine the effect of a continuous dose of remifentanil as the surrogate markers of opiate effect and sensitivity. Following the fifteen minute assessment period, the remifentanil drip will be stopped. The primary anesthesia team will then proceed with their anesthetic plan for the planned surgery. Anesthesia and surgical care will not be altered for the purposes of this investigation.

Figure 2  Goggle-based pupillometer. For this investigation, pupillometer is fitted with a light-occlusive cover so that the subject is in darkness.

4.4. Conclusion of Study

The study ends with the last blood sample and pupil diameter assessment. Goggles are then removed. Anesthesia and surgical care proceed as usual. Discharge is not affected by participation in the investigation. Additionally, the study ends at any time the patient or parent/caregiver requests it to end.

4.5. Side effects
The most common side effects seen with remifentanil, like other opioids, is nausea and vomiting, although this is decreased with low dose infusion, similar to the dose we will use and shorter duration of infusion. Additionally, if the patient develops nausea and/or vomiting, we will utilize rescue anti-emetic agents as needed. In the event of persistent vomiting, the infusion will be stopped. Remifentanil can also cause sedation and a dose-dependent respiratory depression, for which the patients will be closely monitored. If at any point during the study the patient develops apnea not responsive to verbal command, hemodynamically instability, including hypoxia (SpO₂ <90%), hypotension (systolic blood pressure <30% of baseline), bradycardia (heart rate <60/min), agitation, anxious, uncooperative, or if blood is unable to be drawn from the second peripheral IV, the study will be abandoned.

5. Data Collection and Monitoring

5.1. Clinical Assessments

At time point zero, one, two, four, six, ten and fifteen minutes, the primary anesthesia team will record the patient’s end tidal CO₂ and respiratory rate, while the research team will be measure the pupil diameter. Pupil diameter will be measured using a pupillometer as described above.

5.2. Drug Concentrations

Remifentanil blood levels will be measured using mass spectrometry.

5.3. Secondary Assessments
Post-operative pain scores, amount of analgesics given both intra-operatively and post-operatively and operating time will be extracted from the electronic medical record.

6. Data and Safety Monitoring Plan

In general, the Department of Anesthesiology has developed a specific set of Standard Operating Procedures (SOPs) for clinical research. All individuals working on study are required to read and be familiar with and compliant with the SOPs. The SOPs are in part developed from and are compliant with the Institutional guidelines, including those for a) Interactions with the Washington University Human Subjects Review Committee, b) Informed Consent Development and Implementation, c) Subject Recruitment and Screening, d) Subject Management While on Study, e) Adverse Event Reporting. The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to the use of remifentanil. Based on the small size and relatively low risks nature of the protocol, the PI and mentors are involved in the monitoring plan. A full DSMB is not needed. These individuals will review the annual summary of adverse events. In addition, they will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event.

7. Statistical Methods

7.1. Primary Assessments

To be taken at zero, one, two, four, six, ten and fifteen minutes
7.1.1. Change in end tidal CO$_2$ from baseline over time.

7.1.2. Change in respiratory rate from baseline over time.

7.1.3. Change in pupil diameter from baseline over time.

7.1.4. Remifentanil plasma concentration at zero, one, two, four, six, ten and fifteen minutes.

7.2. Secondary Assessments

7.2.1. Difference in median post-operative pain scores obtained in the PACU between study group and control group. Pain intensity is assessed using the Wong-Baker FACES scale employed by the PACU nursing staff and previously validated\textsuperscript{19}.

7.2.2. Difference in amount of opioids given to study group and control group, both intra-operatively and post-operatively in the PACU. Opioid amounts will be converted to morphine equivalents per kg.

7.2.3. Difference in operating time between study group and control group.

7.3. Analysis

The primary outcome measure is the concentration-effect relationship between plasma remifentanil concentration and remifentanil effects (changes in end tidal CO$_2$, respiratory rate, and pupil diameter (miosis)). These pharmacodynamic curves will be compared between normal subjects and those with OSA. If the hypothesis is correct, we anticipate a significant difference between the pharmacodynamic curves for the two patient groups.

8. Risk Assessment
8.1. *Remifentanil*

Our dose for remifentanil was based on previous studies using both remifentanil for general anesthesia and for conscious sedation. A previous study by Davis *et al*\(^2\) examined the use of remifentanil as an adjunct with inhalational gases for maintenance anesthesia in pediatric patients, ages 2 to 12 years old, undergoing a tonsillectomy, with or without an adenoidectomy. Following induction and tracheal intubation, the patients were placed on a remifentanil infusion at 0.25 mcg/kg/min, in addition to the inhalational gases, for anesthetic maintenance during the surgical procedure\(^2\). Conversely, a study by Litman\(^2\) examined using remifentanil bolus and infusion, along with midazolam, for conscious sedation with an unsecured airway during bone marrow aspiration procedures in 17 children ages 4 to 12 years old. Following an IV bolus of midazolam and bolus of remifentanil, a remifentanil infusion was started, with the successful dose being 0.4 ± 0.2 mcg/kg/min. 4 of the 17 children developed hypoxemia with SpO2 83-89%, while 10 of the 17 children developed apnea, both rapidly corrected with verbal command. None of the children experienced hemodynamic instability or post-procedure emesis at these doses\(^2\).

The most common side effects of remifentanil are respiratory depression, hypotension, bradycardia, nausea and vomiting. Given the side effect profile of remifentanil, the findings from the previous studies, and the lack of surgical stimulus during our study, we chose a significantly lower dose
of remifentanil than used during a general or conscious sedation
anesthetic to minimize the probability of these side effects from occurring.
Additionally, the primary anesthesia team will be present to continually
monitor the patient’s status for safety during the entirety of the study.

8.2. Pupillometer

There is minimal risk associated with the use of the pupillometer. There is
a rare risk of corneal abrasion, which will be minimized by using the
pupillometer per manufacturer’s instructions22.

References

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