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WILEY
Hemodynamic and Pharmacokinetic Analysis of Oxymetazoline Use During Nasal Surgery in Children

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**Objectives/Hypothesis:** Oxymetazoline is an α-adrenergic agonist that is commonly used as a topical hemostatic agent in the operating room during ear, nose, and throat surgery. We assessed the hemodynamic effects and systemic absorption of topically applied oxymetazoline in children undergoing various nasal procedures.

**Study Design:** Prospective trial.

**Methods:** Children ages 2 to 17 years undergoing functional endoscopic sinus surgery, turbinate resection, or adenoidectomy were enrolled. The surgeon placed oxymetazoline-soaked pledgets (1.5 mL of 0.05% solution) according to our usual clinical practice. Blood samples for oxymetazoline assay were drawn at 5, 10, 20, 45, 90, and 150 minutes, and hemodynamic data were recorded at 5-minute intervals. Data analysis included mixed-effects regression and population pharmacokinetic/pharmacodynamic modeling.

**Results:** The analysis included 27 patients, age 7 ± 4 years, who received between 2 and 12 pledgets (3–18 mL of oxymetazoline). Relative bioavailability compared to the spray formulation was 2.3 (95% confidence interval [CI]: 1.6-3.2), with slow absorption from the mucosal surface (absorption half-life 64 minutes; 95% CI: 44-90). Mean arterial pressure did not increase with oxymetazoline instillation at the observed oxymetazoline serum concentrations (0.04-7.6 μg/L).

**Conclusions:** Despite concerns regarding oxymetazoline administration to mucosal membranes, we found that hemodynamic changes were clinically negligible with our usual clinical use of pledgets soaked in oxymetazoline. Compared to data on oxymetazoline in spray formulation, bioavailability was increased twofold with pledgets, but systemic absorption was very slow, contributing to low serum concentrations and limited hemodynamic effects.

**Key Words:** Oxymetazoline, pediatric, nasal surgery, hemodynamics.

**Level of Evidence:** 1b

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**INTRODUCTION**

Oxymetazoline is an α-adrenergic agonist that is commonly used as a topical sympathomimetic agent in over-the-counter decongestant sprays as well as a topical hemostatic agent in the operating room during ear, nose, and throat surgery. Its topical vasoconstrictive actions on blood vessels define its clinical utility as both a decongestant and a topical hemostatic agent. Given these effects, it is commonly used by otolaryngologists to produce vasoconstriction, thereby limiting blood loss and improving surgical field visualization during functional endoscopic sinus surgery (FESS), turbinate surgery, and adenoidectomy. Although there is generally limited vascular absorption when oxymetazoline is administered in larger doses, or when there is increased uptake due to vascular injury, this drug can lead to systemic hemodynamic effects including systemic and pulmonary hypertension. These events can cause hemodynamic instability, profound bradycardia, pulmonary edema, and cardiac arrest.

It remains unclear if these cardiovascular effects are related to excessive dosing or an idiosyncratic response, as dose- or concentration-response relationships and pharmacokinetic data are lacking, particularly in the pediatric population. Giannakopoulos studied the cardiovascular effects and pharmacokinetics of oxymetazoline following the intranasal administration of a tetracaine/oxymetazoline spray at two different doses in 12 adult dental patients. The authors administered the maximum recommended dose (18 mg tetracaine and 0.3 mg oxymetazoline) as three sprays (0.1 mL/spray) to each nostril. One to 3 weeks later, twice this dose was administered as six sprays to each nostril. Hemodynamic variables remained clinically stable with a decrease in heart rate (HR) at 40 and 50 minutes observed after the recommended dose (7.5 bpm) and after twice the...
maximum recommended dose (6.1 bpm). There was also an increase in diastolic blood pressure (BP) (5.9 mm Hg) at 90 minutes, after twice the maximum recommended dose was administered. Tetracaine plasma concentrations were undetectable in most participants, whereas concentrations of its major metabolite, para-butyramino-benzoic acid, were dose dependent (i.e., patients in the twice-maximum recommended dose administration group had approximately twice the levels compared to the single maximum recommended dose administration group). Oxymetazoline concentrations from the twice-maximum recommended dose administration were approximately 50% greater than those from the maximum recommended dose administration, with an elimination half-life of 1.72 to 2.32 hours.

There are limited data available that describe oxymetazoline pharmacokinetics in children, and little to no information regarding the hemodynamic effects of oxymetazoline when used intraoperatively during general anesthesia. The current study sought to assess the hemodynamic effects and measure the systemic absorption of topically applied oxymetazoline in patients undergoing otolaryngologic procedures including FESS, turbinate surgery, and adenoidectomy. Our primary hypothesis was that BP would increase following oxymetazoline administration. Our secondary aims were to characterize the pharmacokinetic properties of oxymetazoline and establish the association between serum oxymetazoline concentrations and hemodynamic parameters during these clinical procedures.

MATERIALS AND METHODS

This prospective study was approved by the institutional review board (IRB) of Nationwide Children’s Hospital, and parental consent was obtained (IRB14-00723). The study was registered at clinicaltrials.gov (NCT02453841). Patients, ranging from 2 to 17 years of age, were enrolled if they were scheduled for FESS, turbinate resection, or adenoidectomy with the planned use of intraoperative topical oxymetazoline. Patients were excluded if they have been treated with oral decongestants or antihistamines within 24 hours of surgery, were currently taking medications known to affect coagulation function including nonsteroidal anti-inflammatory agents, had a history of nasal trauma within the past 3 months, had a history of epistaxis within the past 3 months, had a history of hypertension or cardiac disease, or were allergic to oxymetazoline.

For the purpose of the study, there was no change in the conduct of the general anesthetic care. Standard anesthetic care included premedication with midazolam (0.5 mg/kg to a maximum of 15 mg), administered 15 to 45 minutes prior to the procedure at the discretion of the attending anesthesiologist. Anesthesia was induced by the inhalation of incremental concentrations of sevoflurane in oxygen or the intravenous administration of propofol. Endotracheal intubation was performed and maintenance anesthesia provided by sevoflurane in air/oxygen to maintain an adequate depth of anesthesia with vital signs (HR and BP within 20% of baseline) and a bispectral index at 40 to 60. Fluid administration included a total of 15 mL/kg for procedures lasting <1 hour or maintenance plus replacement of deficit for procedures >1 hour. BP and HR and were recorded at 5-minute intervals until discharge from the postanesthesia care unit or the final blood draw, whichever came first. Ten pledges were placed in 15 mL of oxymetazoline (0.05% solution) so that each pledge contained 1.5 mL of oxymetazoline. The surgeon placed oxymetazoline-soaked pledges to achieve hemostasis and improve operative conditions. Additional pledges were placed by the surgeon as needed, according to our usual practice. The surgeon made two different observations at the termination of the procedure to assess the amount of bleeding and ease of hemostasis, including a four-point scale to record subjective bleeding following removal of pledges (0 = none, 1 = minimal/restricted, 2 = moderate/diffuse ooze, and 3 = severe/bloody) and a six-point scale to assess ease of hemostasis (1 = very easy, 2 = easy, 3 = usual, 4 = some effort required, 5 = difficult, and 6 = extremely difficult).

Blood samples for oxymetazoline assay were drawn at 5, 10, 20, 45, 90, and 150 minutes via a second intravenous cannula, placed after the induction of anesthesia. Each blood sample was collected in a 3-mL heparinized tube. Immediately following collection, the tube was gently inverting 8 to 10 times to mix the anticoagulant in the tube with the blood and then placed on ice. The plasma was separated using standard centrifugation procedures (centrifuge tube approximately 10–15 minutes at 2000 g). The plasma was transferred to a separate tube and stored at −80°C. Samples were thawed at room temperature for 30 minutes, and 150 µL from each sample was transferred to a 1.7-mL centrifuge tube. Next, 10 µL of deuterated oxymetazoline were added into each tube as an internal standard. Samples were then treated with 320-µL methanol, which was prechilled at −20°C, vortexed briefly, and incubated in ice for 5 minutes before centrifugation at 4,000 g at 4°C for 5 minutes. The supernatants of each sample was collected, filtered through 0.2-µm polytetrafluoroethylene membrane filters and then injected into liquid chromatography tandem mass spectrometry for analysis.

Statistical Analysis

We retrospectively analyzed hemodynamic data in a cohort of 12 patients undergoing similar procedures under a separate, IRB-approved study (IRB14-00481) before beginning data collection in this current study. Hemodynamic data were retrospectively compared between measurements taken just before oxymetazoline instillation and measurements taken approximately 15 minutes after instillation. The largest difference in BP was noted to be 5 mm Hg (pooled standard deviation [SD] = 12), and within-subject correlation was 0.7, suggesting that a sample size of 30 patients would be sufficient to detect an effect of similar size on a test of paired means with 80% power at a 95% confidence level. We initially planned to enroll 10 patients undergoing each of the three procedures (FESS, turbinate reduction, adenoidectomy) but ultimately enrolled a total of 30 patients undergoing any of these procedures because procedures were frequently combined.

For initial data analysis, study data were summarized using mean ± SD, median with interquartile range (IQR), or count with percentage, as appropriate. The incidence of bradycardia and tachycardia after oxymetazoline instillation was determined using thresholds of HR <1st or >99th percentile for age, respectively. Similarly, the incidence of hypertension after oxymetazoline instillation was determined using age-specific normative tables with hypertension defined as systolic BP >99th percentile for age, gender, and height. The primary analysis aimed to compare hemodynamic variables before and after pledge insertion. As patients frequently received multiple pledges, a mixed-effects linear regression model was fitted for each hemodynamic outcome, accounting for a patient-level random intercept. To account for the varying number and timing of pledges inserted during the procedure, the primary independent variable in this analysis was the cumulative number of pledges inserted as of each time point. In a subset of hemodynamic data collected after blood was drawn for oxymetazoline assay, we also used mixed-effects linear regression models to estimate hemodynamic outcomes as a function of the highest oxymetazoline serum concentration within the past 5 minutes.
Mixed-effects models controlled for patient age, gender, body mass index-for-age percentile (underweight, <5%; normal weight, 5%–84%; overweight ≥85%), American Society of Anesthesiologists physical status (I or II), and time since procedure start. Analysis of hemodynamic outcomes was performed using Stata/IC 14.2 (StataCorp, College Station, TX). Two-tailed P < .05 was considered statistically significant.

**Population Modeling**

Data were analyzed using nonlinear mixed effects models (NONMEM 7.1; Globomax LLC, Hanover, MD). A two-compartment linear disposition model with first-order absorption and first-order elimination was used to analyze oxymetazoline time-concentration profiles. The model was parameterized in terms of clearance (CL), intercompartmental clearance (Q), two volumes of distribution (V1, V2) and an absorption half-life (Tabs1/2). Data were limited, so to estimate the relative bioavailability of the nasal pledgets (FPLEG/SPRAY) compared to spray, we used prior information from a study of oxymetazoline nasal spray in adults.13 Adding the prior information to the compartment models enabled us to estimate this relative bioavailability and absorption half-times. The parameter estimates were standardized for a body weight of 70 kg using an allometric modelP.14,15

\[ P_i = P_{std} \left( \frac{W_i}{W_{std}} \right)^{PWR} \]

where \( P_i \) is the parameter in the ith individual, \( W_i \) is the weight in the ith individual, and \( P_{std} \) (e.g., CLstd, Qstd, V1std, V2std) is the parameter in an individual with a weight \( W_{std} \) of 70 kg. The PWR exponent was 0.75 for clearance, 0.25 for half-times, and 1 for distribution volumes.16

Review of mean arterial pressure (MAP) changes during the procedure suggested an increase in MAP over time. These MAP changes were characterized using a sigmoid Emax model:

\[ Effect_{TIME} = MAP_{BASE} + E_{MAX,TIME} \left( \frac{TIME^{HILL}}{50,TIME + TIME^{HILL}} \right) \]

where \( E_{MAX,TIME} \) is the maximal increase in MAP score over the study period, \( T_{50,TIME} \) is the halftime describing this change, \( HILL \) describes the slope for this change, and \( MAP_{BASE} \) is the MAP before administration of phenylephrine. Once these background changes were identified, we attempted to discern MAP changes attributable to oxymetazoline. Oxymetazoline concentration was linked directly to MAP using an additional Emax model to describe drug effect:

<table>
<thead>
<tr>
<th>Covariate</th>
<th>SBP, mm Hg, N = 496 Observations</th>
<th>DBP, mm Hg, N = 496 Observations</th>
<th>MAP, mm Hg, N = 496 Observations</th>
<th>HR, bpm, N = 508 Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient (95% CI)</td>
<td>P Value</td>
<td>Coefficient (95% CI)</td>
<td>P Value</td>
<td>Coefficient (95% CI)</td>
</tr>
<tr>
<td>No. of pledgets inserted since procedure start</td>
<td>-0.1 (-0.9 to 0.7)</td>
<td>.761</td>
<td>-0.9 (-1.4 to -0.3)</td>
<td>.002</td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.9 (-0.4 to 21)</td>
<td>.167</td>
<td>0.4 (-0.4 to 1.3)</td>
<td>.280</td>
</tr>
<tr>
<td>Gender</td>
<td>Male Ref.</td>
<td>6.8 (-2.4 to 16.1)</td>
<td>.148</td>
<td>10.5 (3.2 to 17.7)</td>
</tr>
<tr>
<td>Female</td>
<td>Ref.</td>
<td>10.5 (3.2 to 17.7)</td>
<td>.005</td>
<td>11.3 (5.2 to 17.5)</td>
</tr>
<tr>
<td>BMI for age</td>
<td>Underweight</td>
<td>-8.2 (-16.4 to -0.04)</td>
<td>.049</td>
<td>5.3 (0.3 to 10.3)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>Ref.</td>
<td>5.3 (0.3 to 10.3)</td>
<td>.036</td>
<td>2.8 (-1.9 to 7.5)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.4 (-6.8 to 9.4)</td>
<td>.728</td>
<td>5.6 (-0.7 to 11.8)</td>
<td>.080</td>
</tr>
</tbody>
</table>

ASA status

| I | Ref. | -9.5 (-18.7 to -0.4) | .041 | -8.4 (-15.4 to -1.3) | .020 | -6.8 (-12.4 to -1.2) | .018 | -4.8 (-17.2 to 7.6) | .444 |
| II | Ref. | -9.5 (-18.7 to -0.4) | .041 | -8.4 (-15.4 to -1.3) | .020 | -6.8 (-12.4 to -1.2) | .018 | -4.8 (-17.2 to 7.6) | .444 |

ASA = American Society of Anesthesiologists; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; SBP = systolic blood pressure.
Effect_{DRUG} = \left( \frac{E_{MAX} \cdot DRUG \cdot CP}{Cp + C_{50}} \right),

where \( E_{MAX} \) is the maximum BP effect, \( Cp (\text{mcg.L}^{-1}) \) is the serum oxymetazoline concentration, and \( C_{50} (\mu g.L^{-1}) \) is the concentration producing 50\% \( E_{MAX} \). The observed MAP was the addition of these two effects (\( \text{Effect}_{DRUG} + \text{Effect}_{TIME} \)).

The pharmacokinetic (PK) and pharmacodynamic (PD) data were analyzed using a modeling process whereby the PK parameters were estimated separately and then fixed in the PKPD model (known as the population PK parameters and data method).\(^{17,18} \)

Additive and proportional error models were used to describe unknown PK residual error. An additive error model was used for PD residual error. Population parameters, covariate effects, and variances were estimated using the first-order conditional estimation method with interaction. Model selection required a statistically significant improvement in the NONMEM objective function between nested models, equating to a reduction >3.84 based on a \( \chi^2 \) distribution with 1 degree of freedom (\( \alpha < .05 \)).

**RESULTS**

Of 30 patients enrolled, two were excluded due to the inability to obtain blood samples, and one was excluded due to recent antihistamine use. The remaining 27 patients included 19 boys and eight girls, ranging in age from 2 to 17 years (7 ± 4 years). Ten patients were <5 years of age. Several patients had more than one procedure performed, accounting for the total number of procedures exceeding 27. Procedures performed in these patients included nine FESSs, 13 turbinate reductions, and 18 adenoidectomies. Study sample characteristics are...
A two-compartment linear disposition model with first-order absorption and first-order elimination was used to analyze time-concentration profiles. Population estimates of clearance (CL), intercompartmental clearance (Q), volumes of distribution (V1, V2), standardized to a 70-kg person using structural estimates; FPLED/SPRAY = bioavailability of the pledget relative to oxymetazoline spray; Tabs1/2 = absorption half-life.

Multivariable analyses of repeated-measures hemodynamic data are summarized in Tables II and III. In the initial analysis using all available time points, pledget insertion (cumulative number of pledgets inserted as of each time point) was associated with minor changes in BP and HR. For example, insertion of an additional oxymetazoline pledget was associated with a decrease in MAP of 0.7 mm Hg (95% confidence interval [CI]: −1.2 to −0.2 mm Hg; \( P = .012 \)) and a decrease in HR of −0.7 bpm (95% CI: −1.5 to 0.0; \( P = .500 \)), controlling for time since procedure start and patient characteristics. In the secondary analysis evaluating correlation between oxymetazoline serum levels and hemodynamic parameters, we included measurements taken within 5 minutes of each blood sample (Table III). No statistically significant changes in BP or HR were associated with greater oxymetazoline serum concentration in this analysis.

The authors compared the maximum change in MAP, SBP, and DBP at any single point during the procedure from baseline in patients <5 years of age and patients ≥5 years of age. The maximum change in MAP, SBP, and DBP from baseline for age <5 years was 40 (IQR: 24–46), 32 (IQR: 26–47), and 42 (IQR: 34–46), respectively, compared to age ≥ 5 of 34 (IQR: 19–37; \( P = .431 \)), 36 (IQR: 22–46; \( P = .808 \)), and 34 (IQR: 24–43; \( P = .345 \)). In addition, the authors compared the percentage of patients whose MAP, SBP, and DBP exceeded baseline by 20% in these two groups. In the age <5 years group, MAP, SBP, and DBP exceeded the 20% threshold in 13%, 11%, and 56%, respectively, compared to the ≥5 years age group of 6% (\( P < .001 \)), 0% (\( P = .346 \)), and 29% (\( P = .234 \)).
The two-compartment model adequately described time-concentration profiles. The pharmacokinetic visual predictive checks are shown in Figure 1. Population parameter estimates are shown in Table IV. Modeling revealed a relative bioavailability compared to the spray (F\textsubscript{PLEG/SPRAY}) formulation of 2.3 (95% CI: 1.6-3.2) with slow absorption from the mucosal surface (Tabs\textsubscript{1/2} 64 minutes; 95% CI: 44-90). Progressive increases in MAP over the duration of anesthesia were described by the Emax model. Pharmacodynamic visual predictive checks are shown in Figure 2. We were unable to demonstrate any effect on MAP attributable to oxymetazoline instillation, once these progressive MAP changes were characterized in the model.

DISCUSSION

When administered in large doses or rapidly absorbed, oxymetazoline can be associated with systemic and pulmonary hypertension.\textsuperscript{3-9} Despite this concern, the PKs and PDs of oxymetazoline in children are not well understood, and associated intraoperative hemodynamic effects have not been previously characterized. In this study, we prospectively evaluated oxymetazoline serum concentration and hemodynamics in children undergoing ear, nose, and throat surgery, where use of pledgets soaked in oxymetazoline is part of our routine clinical practice. Compared to previous reports where oxymetazoline was administered using a spray, we found that its bioavailability was increased two-fold, but absorption was very slow, with an absorption half-time of 64 minutes. Hemodynamic changes associated with oxymetazoline instillation and serum concentration of oxymetazoline were minimal. We postulate that the absorption from the nasal mucosa may be slowed by the drug’s local vasoconstrictor effect on the vasculature of the nasal mucosa. This may reduce systemic absorption and contribute to hemodynamic stability and observed serum concentrations similar to those reported in other studies, despite larger and repeated oxymetazoline dosing and a higher bioavailability with the current pledget administration.\textsuperscript{8,13}

Although oxymetazoline is readily available as an over-the-counter medication, its hemodynamic profile may be concerning especially when higher than recommended doses are administered. The impetus for this study was the concern of the safety of the drug, given anecdotal reports of cardiovascular collapse.\textsuperscript{7,9} It has been suggested that these hemodynamic effects may be related to overdosing. Latham and Jardine demonstrated up to a 75-fold increase in the volume of oxymetazoline administered when the over-the-counter spray bottle was held inverted.\textsuperscript{9,15} Given the supine position of patients on the operating-room table, it is common practice to hold the bottle inverted and squeeze it. Although squeezing the bottle in the upright position resulted in a mist with the delivery of 28.9 \pm 6.8 \mu L of fluid, with the bottle inverted, the average volume delivered was 1037 \pm 527 \mu L (range: 473–2196 \mu L). With the bottle upright, the amount delivered is effort independent; however, it becomes effort dependent when the bottle is inverted and squeezed. Given such concerns, our institution replaced nasal spray application with oxymetazoline-soaked pledgets to minimize volume and adjacent tissue exposure. The current study intended to provide data on the use of oxymetazoline with pledgets, by discussing with our surgeons how much they thought they needed to use, measuring the amount administered, and then determining the amount absorbed and the associated hemodynamic changes, to evaluate the safety of the current dosing regimen. Our surgical colleagues noted that the amount used in this study provided adequate topical vasoconstriction, hemostasis, and surgical visualization.

Our conclusions about the safe use of oxymetazoline in this study are limited by some aspects of the study design and data analysis. First, we cannot rule out variability in the amount of oxymetazoline in each pledget, although we attempted to standardize the amount per pledget by ensuring that the entire volume of oxymetazoline (15 mL) was absorbed by 10 pledgets. Furthermore, we noted variation across patients regarding the number of pledgets that were used and whether they were placed all at once or sequentially. In patients where pledgets were placed multiple times, the duration between pledget insertions was not standardized. Additionally, the duration for which each pledget was inserted was not standardized, because this is not held constant in our routine clinical practice. Although we attempted to standardize the anesthetic care and fluid management, including the agents used, and to maintain a constant level of anesthesia using a depth of anesthesia monitor, we noted hemodynamic changes during the procedure, particularly steady increase in MAP. Accounting for this trend in MAP, we found no independent association between oxymetazoline administration and increase in MAP. When comparing hemodynamic changes in patients age <5 years old to patients >5 years old, we noted a greater frequency of patients with MAP, SBP, and DBP exceeding baseline by >20%. This current study was not powered for such a subgroup analysis, and future studies should focus on this at-risk population. The paucity if pediatric oxymetazoline PK/PD data in the literature required the use of adult bioavailability data for the (\textsubscript{F\textsubscript{PLEG/SPRAY}}) calculation. The nasal absorptive surface area increases with age and is smaller than in the adult. The impact of this on absorption is offset by the duration of exposure of oxymetazoline pledgets to the nasopharyngeal mucosa.

CONCLUSION

Our data demonstrate no notable hemodynamic change with clinically relevant doses of oxymetazoline used during pediatric ear, nose, and throat surgery. Our findings are consistent with the minor cardiovascular changes noted by Giannakopoulos et al. at similar concentrations of oxymetazoline used during dental procedures. Although greater standardization of oxymetazoline administration is desirable in further studies estimating PKPD parameters of this drug in pediatrics, our study design reflected current use of oxymetazoline in our practice. Given the slower systemic absorption of oxymetazoline noted with pledgets as compared to previous reports on the spray formulation, another area for future study may be to determine whether the use of pledgets is...
associated with greater hemodynamic stability than use of oxymetazoline spray.

BIBLIOGRAPHY


