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Topical Nasal Decongestant Oxymetazoline: Safety Considerations for Perioperative Pediatric Use

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The over-the-counter nasal decongestant oxymetazoline (eg, Afrin) is used in the pediatric population for a variety of conditions in the operating room setting. Given its vasoconstrictive properties, it can have cardiovascular adverse effects when systemically absorbed. There have been several reports of cardiac and respiratory complications related to use of oxymetazoline in the pediatric population. Current US Food and Drug Administration approval for oxymetazoline is for patients ≥6 years of age, but medical professionals may elect to use it short-term and off label for younger children in particular clinical scenarios in which the potential benefit may outweigh risks (eg, active bleeding, acute respiratory distress from nasal obstruction, acute complicated sinusitis, improved surgical visualization, nasal decongestion for scope examination, other conditions, etc). To date, there have not been adequate pediatric pharmacokinetic studies of oxymetazoline, so caution should be exercised with both the quantity of dosing and the technique of administration. In the urgent care setting, emergency department, or inpatient setting, to avoid excessive administration of the medication, medical professionals should use the spray bottle in an upright position with the child upright. In addition, in the operating room setting, both monitoring the quantity used and effective communication between the surgeon and anesthesia team are important. Further studies are needed to understand the systemic absorption and effects in children in both nonsurgical and surgical nasal use of oxymetazoline.

STATEMENT OF THE PROBLEM

To date, there are limited objective pediatric data on the safety and specific dosing of topical oxymetazoline (eg, Afrin), and an excessive

abstract

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unmonitored volume of nasal use could lead to serious adverse effects in children.

BACKGROUND

Oxymetazoline hydrochloride 0.05% is the active ingredient in over-the-counter (OTC) nasal spray decongestants (eg, Afrin; Merck Schering-Plough Pharmaceuticals, North Wales, PA). It was first sold as a prescription medication in 1966 and then became available as an OTC medication in 1975. It is currently approved by the US Food and Drug Administration (FDA) for use in patients ≥6 years of age. Oxymetazoline is an α-adrenergic agonist with greater activity at the α2 versus α1 adrenergic receptor.[1] Its action at the peripheral α2-adrenergic receptor on the smooth muscle of the vasculature results in vasoconstriction, thereby defining its clinical utility as both a decongestant and a topical hemostatic agent. It is used off label in the operating room to prepare the nasal passages during nasal intubation and during ear, nose, and throat (ENT) surgery to improve visualization of the airway and to minimize intraoperative or postoperative bleeding.[2,3]

A superior efficacy and safety profile of oxymetazoline has been demonstrated when compared with other topical agents with vasoconstrictive properties, such as phenylephrine, epinephrine, or cocaine.[2–5] Riegle et al[3] compared the topical nasal mucosal applications of oxymetazoline (0.05%), phenylephrine (0.25%), and cocaine (4%) during functional endoscopic sinus surgery in children. Phenylephrine was associated with an increase in blood pressure (BP), and subjective evaluation of bleeding and surgical visualization was best with oxymetazoline. The authors concluded that oxymetazoline was the preferred vasoconstrictor in children. Higgins et al[4] reviewed the use of topical vasoconstrictors during ENT surgery. They compared the efficacy against the risks associated with the topical use of phenylephrine, cocaine, and oxymetazoline and proposed recommendations to reduce the incidence of systemic complications caused by these agents in the operating room. These authors recommended the use of 0.05% oxymetazoline as the initial vasoconstrictor in patients <12 years of age. Their protocol did not include a recommendation for the maximum volume of oxymetazoline.

Despite a long history of use and its potential advantages over other agents, data seem to be limited regarding the pharmacokinetics of oxymetazoline, including uptake when applied to mucosal membranes or the end-organ effects when used in average concentration and volume during the perioperative period. Although the package insert, anecdotal case reports, and various Web-based programs clearly outline the potential for hypertension and cardiac effects related to the use of this product, the authors of this report believe that there has not been effective emphasis placed on such information in the medical literature. Adverse effects may occur not only with excessive dosing but also when oxymetazoline is used within recommended guidelines. Furthermore, delivery from the commercially available bottle may be variable depending on the position of the bottle and the force with which it is squeezed.

Recently, there have been 2 case reports published regarding significant cardiovascular effects related to the routine perioperative use of this medication in healthy children.[6,7] Latham and Jardine[6] reported adverse effects of topical nasal oxymetazoline in a 14-kg 4-year-old boy during dental restoration. After anesthetic induction and before nasal intubation, both nares were sprayed with oxymetazoline 0.05%. The exact number of sprays was not clarified (merely, both nares were treated with oxymetazoline nasal spray). Approximately 5 minutes after endotracheal intubation, the child's BP, measured by a noninvasive BP cuff, increased from 110/52 to 170/110 mm Hg, with a decrease in heart rate from 118 to 65 beats per minute. The hypertension was treated by increasing the sevoflurane concentration; however, the BP remained elevated for up to 60 minutes, with the diastolic BP above 100 mm Hg for 30 minutes. Ramesh et al[7] reported a similar case that involved postoperative hypertension. The patient was a 14-kg 3-year-old boy who presented with chronic nasal obstruction secondary to inferior turbinate and adenoidal hypertrophy. After the induction of general anesthesia and endotracheal intubation for bilateral inferior turbinate reduction with out-fracturing of the turbinate, oxymetazoline-soaked pledgets were placed in both nares. Adenoidectomy was performed by using electrocautery, and hemostasis was augmented with topical application of oxymetazoline at the termination of the operation. The volume of oxymetazoline was not measured. At the completion of the procedure, the child was then transferred to the postanesthesia care unit (PACU). At the time of arrival to the PACU, bradycardia was noted with a heart rate of 48 beats per minute. The BP was 106/84 mm Hg. Bilateral breath sounds were confirmed by auscultation. Atropine (0.1 mg) was administered intravenously, after which the heart rate increased to 135 beats per minute and the BP increased to 166/129 mm Hg. The

oxymetazoline-soaked nasal pledgets were removed immediately, and 10 mg of propofol was administered. Hypertension persisted, and propofol was administered in incremental doses of 10 mg each. Because no direct-acting vasodilators (hydralazine) were immediately available in the freestanding outpatient surgery center, labetalol was administered intravenously in 1-mg increments to a total of 2 mg. The BP and heart rate remained elevated, but at a lower range. During the next hour, the heart rate and BP gradually normalized to their baseline values. No further hypertension was noted during this patient's PACU stay or after discharge during follow-up with his pediatrician.

These 2 case reports and others from the literature demonstrate the potential toxicity from OTC oxymetazoline, which may be dosed without attention to the volume administered. These concerns are not limited to its perioperative administration because toxicity has been reported with its use for routine indications, including as a nasal decongestant. Although used for its topical effects, vascular absorption of oxymetazoline can have profound systemic effects (most commonly, hypertension related to its action on the $\alpha 2$-adrenergic receptors of the smooth muscle of the vasculature). When used in even larger doses in young children, oxymetazoline can activate central adrenergic receptors and lead to serious adverse effects, including cardiovascular instability, respiratory depression, and sedation, which may be potentially life-threatening.[8–11] In 2012, similar adverse events, secondary to accidental ingestion by children 5 years and younger, were reviewed by the FDA, and the FDA included a list of products like oxymetazoline that should be stored out of the reach and out of sight of children at all times.[12] In these reported cases, children were found to be chewing or sucking on the medication bottle or were found to have an empty bottle next to them.[12]

Imidazole derivatives, such as oxymetazoline, are rapidly absorbed across mucosal membranes in children. Hence, toxicity generally develops within minutes, but resolution may take up to 24 hours.[9,10] Exposure to different imidazoline derivatives was reviewed in 72 children between 2 months and 13 years of age, and most children who had adverse effects were younger than 3 years of age.[13] Giannakopoulos et al[14] studied the cardiovascular effects and pharmacokinetics of an intranasal 3% tetracaine and 0.05% oxymetazoline spray at 2 different dose levels in adult dental patients. The authors administered what they considered to be the maximum recommended dose (MRD) of 18 mg of tetracaine and 0.3 mg of oxymetazoline to 12 volunteers. The medication was sprayed onto the nasal mucosa. One to 3 weeks later, twice the dose (36 mg of tetracaine and 0.6 mg of oxymetazoline) was administered. Physiologic measures remained fairly stable throughout the 2-hour period, with no clinical concerns in the patients and no clinically significant differences between the 2 groups. However, the medications were administered over 8 minutes and 20 minutes in the group that received the MRD and the group that received twice the MRD, respectively, rather than the short-term instillation period typically used for ENT surgery, which may explain the lack of changes in BP and heart rate. Tetracaine plasma levels were undetectable in the majority of the participants, but concentrations of oxymetazoline in the group that received twice the MRD were approximately 50% greater than those in the group that received the MRD. The plasma half-life of oxymetazoline was reported to vary from 1.72 to 2.32 hours. However, there are limited pharmacokinetic data in the pediatric population. In a recent prospective pharmacokinetic study of 27 pediatric patients, researchers measured serum concentrations after administration using soaked cotton pledgets during sinus surgery, adenoidectomy, and turbinate reduction. The authors noted lower systemic absorption than that reported with administration from the bottle (spray technique). No significant hemodynamic changes were noted, and no correlation of hemodynamic changes with serum concentrations was noted. Although preliminary, the authors suggest that the extreme systemic effects that have been reported may be related to variable systemic absorption rates and serum concentrations when oxymetazoline is applied in a more diffuse spray technique compared with soaked cotton pledgets, or it is possible that these responses are idiosyncratic and unrelated to delivery techniques and serum concentrations.[15] Additional research is needed to further delineate these factors.

Various studies have demonstrated alarming information regarding alteration of the delivery of oxymetazoline depending on the position of the bottle. The first of these reports, by Latham and Jardine,[6] demonstrated a fact that had previously received no attention in the literature. There was up to a 75-fold increase in the volume of medication administered when the bottle was held inverted. 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 ± 6.8 μL of fluid, the average volume delivered with the bottle inverted was 1037 ± 527 μL (range 473–2196 μL). With the bottle upright, the amount delivered is effort independent; however, it becomes effort dependent when the bottle is inverted and squeezed. Latham and Jardine[6] also demonstrated that each surgical pledget could hold a significant vol (1511 ± 184 μL), a fact that may further increase delivery during ENT surgery. Two additional sets of investigators have confirmed these findings and have also demonstrated significant interindividual variability in the amount delivered based on effort.[16,17] Oxymetazoline is only intended for short-term use of <5 days' duration because the medication can cause rebound nasal congestion and lead to rhinitis medicamentosa with long-term use. In addition, systemic side effects and end-organ injury are unknown with long-term use because only animal studies are available at this time.[18] Given the recent reports in the literature, it seems that the time has come to develop guidelines for the dosing of oxymetazoline in children, especially infants and toddlers.[19–22]

EXISTING GUIDELINES AND JOINT COMMISSION RECOMMENDATIONS

To the authors' knowledge, no published sources of formal practice guidelines or recommendations currently exist for nasal use of topical oxymetazoline. From a Joint Commission general medication standpoint, hospitals, including operating rooms, are required to document the safe administration of medications in the medical record, which includes verification of correct patient, strength, dose, route, labeling, date, and time.[23]

REVIEW OF EVIDENCE

Unfortunately, pediatric pharmacokinetic data on which to base guidelines for use of topical nasal oxymetazoline are limited. The package inserts recommend 2 to 3 sprays into each nostril for patients ≥6 years of age. On the basis of data from Latham and Jardine,[6] which demonstrate that each upright spray delivers 30 μL, this would be a total maximum dose of 180 μL, which is far less than the amount held by 1 pledget or the amount delivered by a single spray from an inverted bottle (1 ± 0.5 mL).

Because topical nasal decongestant oxymetazoline is an OTC medication, pediatric complications related to its use may be underappreciated. Given its nasal delivery via a spray mechanism or soaked cotton pledgets, attention to exact dosing or a process to monitor the dose of oxymetazoline given is frequently absent. There are several reports of morbidity, and until additional pediatric data are available, it appears that it is essential to establish a general consensus for responsible use.

CONCLUSIONS

The American Academy of Pediatrics recommends the following for short-term pediatric topical nasal oxymetazoline use:

General Considerations

1. Because limited data exist, remind pediatricians, advanced practice providers, anesthesiologists, and surgeons of the limited available data for use of OTC oxymetazoline in patients <6 years of age. Although the current FDA approval is for patients ≥6 years of age, medical professionals do elect to use it off label in children <6 years of age for specific conditions in which the potential benefit may outweigh risk (eg, active bleeding, acute respiratory distress from nasal obstruction, acute complicated sinusitis, improved surgical visualization, nasal decongestion for scope examination, other conditions, etc). Providers should be aware of potential adverse cardiovascular effects of an unmonitored volume of administration, which may be most relevant in infants or young children and those with comorbid cardiac conditions.
2. Because of the variable dosing risk, be aware that use of oxymetazoline in the supine position with the spray bottle inverted can result in a significantly higher dose (approximately 1 ± 0.5 mL administered per spray), as compared with the spray bottle in an upright position, which results in 30 μL (0.03 mL) per spray. When possible, to avoid excessive nasal dose administration, use the spray bottle in an upright position with child also upright.

Surgeon, Anesthesiologist, and Operating Room Personnel: Surgical Considerations

1. Avoid administration of an unmonitored medication volume. During a surgical procedure, implement a reliable process to keep track of the total volume of medication that is administered.
2. Effective communication between the surgeon and anesthesiologist should occur with intraoperative use of these medications. Routine monitoring of heart rate, BP, and respiration through the intraoperative and postoperative period is essential. If a second medication bottle needs to be opened for use during a case, ensure that the anesthesiologist is aware.
3. Remove excess medication from pharynx. Both during and at the end of the procedure, suction excess medication that has pooled in the nasopharynx and oropharynx to avoid additional potential mucosal absorption.

Future Perspectives

Encourage the initiation of additional pharmacokinetic trials of topical nasal oxymetazoline in the pediatric patient population, including for both surgical and nonsurgical use. In young children, consider evaluation of the hemostatic efficacy of a half-strength concentration of the agent compared with the full-strength concentration.

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ABBREVIATIONS

BP: blood pressure
ENT: ear, nose, and throat
FDA: US Food and Drug Administration
MRD: maximum recommended dose
OTC: over-the-counter
PACU: postanesthesia care unit

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