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The Effectiveness of Epinastine Hydrochloride for Pediatric Sleep-Disordered Breathing Related Symptoms Caused By Hyperesthetic Non-Infectious Rhinitis

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Abstract

Objectives: The aims of this study were to prospectively evaluate the effectiveness of oral epinastine hydrochloride in pediatric outpatients with Sleep-Disordered Breathing- (SDB) related symptoms caused by hyperesthetic non-infectious rhinitis, and to assess their Quality of Life (QOL) prior to and following treatment.

Study design: Prospective

Methods: Pediatric outpatients (9 boys and 10 girls; average age, 5.6 years [SD=1.4]), with SDB related symptoms influenced by hyperesthetic non-infectious rhinitis were recruited. The children were all treated with oral epinastine hydrochloride dry syrup for 4 weeks. Before and after the 4-week treatment period, the following data were collected from each participant: otolaryngological findings, obstructive sleep apnea-18 (OSA-18) scores, and evaluation of QOL.

Results: Epinastine hydrochloride significantly improved the swelling of the inferior nasal turbinate mucosa and decreased the quantity of nasal discharge. The initial total mean OSA-18 score was 58.5, whereas the total score reduced to 22.8 after oral epinastine hydrochloride treatment. Significant ($p < 0.01$) differences were found between pre- and post-treatment total OSA-18 scores as well as pre- and post-treatment measurements of domains of sleep disturbance, physical symptoms, and caregiver concerns.

Conclusions: Epinastine hydrochloride therapy may improve nasal findings and QOL in pediatric outpatients with SDB related symptoms caused by hyperesthetic non-infectious rhinitis.

Keywords: Epinastine hydrochloride; Pediatrics; Hyperesthetic non-infectious rhinitis; Allergic rhinitis; Sleep-disordered breathing; OSA-18

Introduction

Sleep-Disordered Breathing (SDB), which includes Obstructive Sleep Apnea (OSA) syndrome and upper airway resistance syndrome, refers to a spectrum of sleep disorders sufficiently intense to cause clinical symptoms.

The exact prevalence of SDB in children is unknown, but the prevalence of OSA is approximately 2% [1]. Studies have shown that the Quality of Life (QOL) of children with OSA syndrome can be affected, and there is now evidence that children with this syndrome may have emotional problems, impaired school performance, hyperactivity, aggressive behavior, or withdrawal behavior [2,3].

The children with nasal and paranasal sinus diseases represented by allergic rhinitis and sinusitis results in nasal breathing disorder and causes sleep disorder breathing easily. Especially in Japan, the prevalence of pediatric allergic rhinitis has been increasing [4]. Polysomnography of children with allergic rhinitis showed that more microarousals compared to control group [5]. Also, the frequency of OSA in children was increased in subjects with positive multi antigen Radio Allegro Sorbent Test (RAST) results compared to those with negative RAST results [6]. Those reports suggested that the relationship between allergic rhinitis and OSA. On the other hand, Arens et al. [7] reported that children with OSA had significantly more opacification of maxillary sinuses, sphenoid sinuses, prominence of inferior nasal turbinate(s), and deviation of the nasal septum and those results suggested the relationship between OSA and paranasal diseases.

A frequent cause of OSA in children is pharyngeal and palatine tonsillar hyperplasia, which causes nasal obstruction and chronic mouth breathing. For this reason, the initial recommended treatment for pediatric OSA is surgical removal of the adenoids and tonsils. However, the frequency of residual mild OSA after adenotonsillectomy is estimated at 45-50% [8-10]. When residual OSA after adenotonsillectomy exists, other approaches are advocated. Rizzi et al. [11] reported that there was a significant correlation ($P<0.005$) between total nasal resistance and snoring, oral breathing and daytime sleepiness in SDB children. Sullivan et al. [12] reported that the effectiveness of radiofrequency treatment of inferior nasal turbinates against the residual OSA after adenotonsillectomy. Therefore, we hypothesized that the oral anti-allergic drugs for allergic rhinitis would be effective for pediatric SDB caused by hyperesthetic non-infectious rhinitis which includes allergic rhinitis.

The aim of our study was (1) to evaluate the effectiveness of epinastine hydrochloride, a second-generation antihistamine used to treat allergic rhinitis in Japan, for children with symptoms of Sleep-Disordered Breathing (SDB) caused by hyperesthetic non-infectious rhinitis (allergic rhinitis) and (2) to assess, using the questionnaire, the children's QOL prior to and following treatment.

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Methods

The study protocol was approved by the local Ethics Committee (Yamaguchi Society for allergic disease in otolaryngology, Ube, Japan). The prospective cross-sectional study was conducted between April, 2007 and October, 2007. We studied patients who came to the twenty-four Otolaryngology Outpatient Clinic in Yamaguchi Prefecture, Japan and written informed consents were obtained from all patients. Inclusion criteria were pediatric patients ranged between 3 to 7 years old who presented with both SDB related symptoms during sleep like snore, witnessed apnoeas, frequent arousals, nocturnal sweating, failure to thrive, hyper extended neck, and allergic rhinitis defined as hyperesthetic non-infectious rhinitis by Japanese Guideline for Allergic Rhinitis.

The hyperesthetic non-infectious rhinitis is characterized by hypersensitivity [4]. However, this type of rhinitis is not inflammatory, except for the allergic rhinitis. Therefore, this should reasonably be eliminated from the classification of rhinitis and regarded as a disease similar to allergy or hypersensitivity diseases. However, this was placed into this classification in view of potential clinical convenience.

Exclusion criteria were patients with hypersensitivity against the epinastine hydrochloride, palatine tonsillar hypertrophy, bronchial asthma and/or atopic dermatitis for which treatment was being administered.

All of the children were administered oral epinastine hydrochloride dry syrup (0.05 g/kg, once a day before sleep) for 4 weeks. Before the treatment, complete ear, nose, and throat physical examinations were performed. Sleep studies for diagnose of OSA were not examined.

The QOL of the patients was assessed by asking the patients' caregivers to complete the OSA-18 survey [13] before and 4 weeks after treatment. The OSA-18 survey (Figure 1) consists of 18 items grouped into 5 domains: sleep disturbances (4 items), physical suffering (4 items), emotional distress (3 items), daytime problems (3 items), and caregiver concerns (4 items). The score for each item is 1-7, ranging from "none" to "all of the time." The classification of health-related impact on QOL from the total OSA-18 scores was recommended by Franco et al. [13]. A total score of less than 60 suggests a small impact, whereas scores between 60 and 80 suggest a moderate impact, and scores above 80 suggest a large impact. Wilcoxon rank-sum test were used to evaluate the relationship between patients' QOL, as defined by the OSA-18 scores, and intake of epinastine hydrochloride.

We also conducted a rhinoscopic examination to evaluate the effects of epinastine hydrochloride on inferior nasal turbinate mucosal swelling and nasal discharge before and 4 weeks after treatment. Mucosal swelling and nasal discharge were rated according to the "The Practical Guideline of Management of Allergic Rhinitis criteria" [14]. The extent of inferior nasal turbinate mucosal swelling and nasal discharge was scored (Table 1) before and after epinastine hydrochloride treatment and evaluated with Wilcoxon rank-sum test.

Results

Twenty-one children with hyperesthetic non-infectious rhinitis and sleep-disordered breathing were included in the study. Two subjects did

None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
1	2	3	4	5	6	7

Sleep Disturbance
During the past 4 weeks, how often has your child had...
...loud snoring?
...breath holding spells or pauses at night?
...choking or made gasping sounds while asleep?
...restless sleep or frequent awakenings from sleep?

Physical Symptoms
During the past 4 weeks, how often has your child had...
...mouth breathing because of nasal obstruction?
...frequent colds or upper respiratory infections?
...nasal discharge or a runny nose?
...difficulty in swallowing food?

Emotional Distress
During the past 4 weeks, how often has your child had...
...mood swings or temper tantrums?
...aggressive or hyperactive behavior?
...discipline problems?

Daytime Function
During the past 4 weeks, how often has your child had...
...excessive daytime sleepiness?
...a poor attention span or concentration?
...difficulty getting up in the morning?

Caregiver Concerns
During the past 4 weeks, how often have the problems described above...
...caused you to worry about your child's general health?
...created concern that your child is not getting enough air?
...interfered with your ability to perform daily activities?
...made you frustrated?

MAXIMUM SCORE: 126

Figure 1: OSAS quality of life survey (OSA-18). [8]

		Score		
Nasal Findings	**3**	**2**	**1**	**0**
Inferior nasal turbinate mucosal swelling	Middle turbinate not seen	Intermediate between (3) and (1)	To centre of middle turbinate	None
Nasal discharge	Filled	Intermediate between (3) and (1)	Small amount adhered to the skin	None

Table 1: Nasal finding score.

Subjects (n = 19)	Mean of pre-treatment scores	Mean of post-treatment scores	Wilcoxon rank-sum test P value
Inferior nasal Turbinate mucosal swelling	2.1 ± 0.40	1.1 ± 0.87	<0.001
Nasal discharge	1.52 ± 0.77	0.74 ± 0.99	0.01

Table 2: Pre and post treatment nasal finding scores.

Domain	Mean of pre-treatment scores	Mean of post-treatment scores	Wilcoxon rank-sum test Pvalue
Sleep disturbances	13.7 ± 9.8	5.0 ± 6.2	0.003
Physical symptoms	14.3 ± 9.9	6.0 ± 7.4	0.006
Emotional distress	10.4 ± 8.6	4.4 ± 5.1	0.015
Daytime problems	8.1 ± 8.4	4.2 ± 6.3	0.12
Caregiver concern	12.1 ± 12.2	3.3 ± 3.9	0.007
Total OSA	58.5 ± 42.1	22.8 ± 24.6	0.003

Table 3: Pre- and post-treatment total and domain OSA-18 scores.

not return the questionnaires after the 4-week treatment; therefore, 19 subjects (9 boys and 10 girls; average age, 5.6 years (SD=1.4)), were evaluated. Epinastine hydrochloride significantly reduced the swelling of the inferior nasal turbinate mucosa and decreased the quantity of nasal discharge. The score for both swelling and nasal discharge significantly decreased after the 4-week treatment (p<0.001 and 0.01) (Table 2). Furthermore, the initial total mean OSA-18 score was 58.5; whereas this score reduced to 22.8 after four weeks of oral epinastine hydrochloride treatment. The differences in the total OSA-18 scores, the domains of sleep disturbance, physical symptoms, and caregiver concerns between the start of the study and after 4 weeks of treatment with epinastine hydrochloride were significant (p values=0.003, 0.006, 0.007, and 0.003; Table 3).

Discussion

OSA syndrome is characterized by interactions between nocturnal episodic hypoxemia, hypercapnia, and sleep fragmentation. It is important to emphasize here that delayed treatment of or untreated OSA may result in irreversible morbidity [15]. Gozal et al. reported that in rodent models of OSA oxidative stress and inflammatory processes increase neuronal cell loss in the brain regions responsible for learning, behavior, executive function, and memory [15-18]. Therefore, in addition to OSA symptom severity, the extent of end-organ morbidity may be accounted for by genetic variances in defense mechanisms and injury-related pathways.

The initial recommended treatment for pediatric OSA is surgical removal of the adenoids and tonsils. However, the frequency of residual mild OSA after adenotonsillectomy is estimated at 45-50%, with an additional 20-25% displaying moderate-to-severe OSA after surgery and only 25-35% has no symptoms. When residual OSA after adenotonsillectomy is moderate-to-severe, administration of nasal continuous positive airway pressure (CPAP) is usually recommended [19]. However, the cost–benefit ratio of CPAP in milder cases of residual OSA does not justify its use, and other approaches are advocated.

The effectiveness of nasal steroids against allergic rhinitis has been reported [20-22], but there are few reports concerning the effectiveness of oral anti-allergic drugs for children with allergic rhinitis-induced SDB. In this study, we evaluated the effect of epinastine hydrochloride on both the improvement in nasal findings, as determined by The Practical Guideline of Management of Allergic Rhinitis criteria [14] and the QOL, which was assessed by the OSA-18 survey. Polysomnography was not performed because it is expensive and difficult to perform due to the small number of sleep technicians in our prefecture.

Epinastine hydrochloride is a second-generation antihistamine used in Japan for allergic rhinitis. Okuda and Okubo reported that in a multicenter, randomized, double-blind, placebo-controlled study in children with perennial allergic rhinitis randomly allocated to receive either epinastine or ketotifen for 2 weeks, the total nasal symptom severity scores were -1.42 for those children treated with epinastine [23]. Okubo and Gotoh also reported that, when used during a nasal provocation test with Japanese cedar pollen allergen, epinastine hydrochloride significantly decreased the number of sneezing attacks and the quantity of nasal discharge for 3 h after drug administration as compared to the placebo [24]. In our study, as in previous reports, epinastine hydrochloride significantly decreased both the swelling of the inferior nasal turbinate mucosa and the quantity of nasal discharge. Both the nasal finding scores for swelling and nasal discharge significantly decreased after the 4-week treatment.

It is well known that the association between SDB and allergic rhinitis appears strongest in children. Epinastine hydrochloride improved swelling of the nasal mucosa and reduced nasal discharge. As a result, nasal obstruction improved and the total mean score of the OSA-18 reduced significantly. The effect of second generation anti-histamine drugs for nasal obstruction is limited, but the nasal cavities of children are narrow and easy to obstruct by a small amount of nasal discharge. Therefore, the epinastine hydrochloride significantly improved the nasal obstruction.

In this study, we used the Japanese translation of the OSA-18. To ensure that the questionnaire had been correctly translated into Japanese, we created an English translation of the Japanese version and verified the accuracy of the translation with the author of the OSA-18. Prior to this study, we also used the Japanese version of the OSA-18 to evaluate the QOL of 5 pediatric SDB patients (age range, 3-7 years; median age, 4.6 years) after adenoidectomy or adenotonsillectomy

[25]. According to the results of the OSA-18, 4 of the children who underwent tonsillectomy or adenotonsillectomy showed improvement in physiological parameters of sleep and in QOL; however, 1 child displayed worsened physiological parameters of sleep after surgery due to re-enlargement of the adenoid, and a decrease in QOL was identified through the OSA-18. Our results demonstrated that the Japanese translation of the OSA-18 must be useful for the evaluation of QOL in SDB children.

Several options have been reported for the medical management of allergic rhinitis-induced OSA in children. Nasal steroids may be beneficial, but they are not recommended for long-term therapy [21]. Nasal steroids may be prescribed temporarily until a referral can be made for treatment. Systemic steroids are occasionally used to decrease upper airway obstruction, such as in patients with infectious mononucleosis (because of anti-inflammatory and lymphocytic effects). One study suggested that systemic steroids failed to affect the size of the tonsils or adenoids, the severity of inflammation as shown on polysomnography, or the symptomatology in patients with OSA [26].

Anti-inflammatory therapy is increasingly being recognized as an alternative to surgery and as an effective intervention in residual mild OSA after adenotonsillectomy. Daily montelukast treatment for 16 weeks was shown to significantly improves adenoid size and polysomnography-recorded, respiratory-related sleep disturbances [27]. While double-blind, placebo-controlled studies have yet to be reported, the use of montelukast for mild SDB before or after adenotonsillectomy is a useful contribution to the currently available therapies for treating SDB in children. A combination of nasal steroids and oral montelukast for 12 weeks has been shown to normalize sleep respiratory parameters in an open-label study conducted in children with residual mild SDB after adenotonsillectomy (Apnea hypopnea index between 1 and 5) [28].

Only a few reports have suggested that effective treatment against nasal congestion of perennial allergic rhinitis improves the quality of sleep. In a study conducted by Santos et al. [29] in a small cohort of subjects (N=31), compared to placebo, the leukotriene receptor antagonist montelukast improved the symptoms of perennial allergic rhinitis and reduced daytime fatigue and daytime somnolence in patients with perennial allergic rhinitis. According to the results of our study, epinastine hydrochloride improved the symptoms of hyperesthetic non-infectious rhinitis and reduced the domains of sleep disturbance of OSA-18. Therefore epinastine hydrochloride is another candidate for alternative therapy for mild OSA.

Our study had several limitations that should be considered. First, we did not administer an allergy test to the children; therefore, object is defined as hyperesthetic non-infectious rhinitis patients. However, judging from frequency, almost all patients were thought to have allergic rhinitis. Further, our study consisted of patients recruited from 24 outpatient clinics in our prefecture; therefore, patient selection was well randomized. Second, any kind of sleep study was not performed. In Japan, due to small numbers of sleep technicians and other social reasons, polysomnography has not been commonly used in children. We are now planning a study in this area with video recording in the near future.

Conclusions

Epinastine hydrochloride therapy demonstrated positive clinical effects on both nasal findings and the QOL of pediatric outpatients with symptoms of SDB caused by allergic rhinitis. Epinastine hydrochloride therapy may be a candidate for anti-inflammatory therapy for allergic rhinitis-induced SDB.

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