

ANTIALLERGIC ASPECTS OF TREATMENT OF OTITIS MEDIA WITH EFFUSION IN ADULT PATIENTS

SARGSYAN G.V.^{1*}, ASATRYAN O.M.¹, MELIKSETYAN V.F.², SHUKURYAN A.K.^{1,3}

¹ Department of ENT diseases, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

² ENT and Plastic Surgery Department, "Armenia" Republican Medical Center, Yerevan, Armenia

³ ENT Department, Erebouni Medical Center, Yerevan, Armenia

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ABSTRACT

The study demonstrates that treatment with montelukast in combination with bilastine is potentially beneficial in terms of a clinical improvement in adult patients suffering from otitis media with effusion. The antihistamine, i.e. bilastine, used in the given study, is a non-sedative antihistamine and is classified as second-generation H1 antagonist. Montelukast is an orally active compound, which bonds with high affinity and selectivity to the CysLT1 receptor. Hence the use of bilastine in tandem with montelukast significantly decreases the secretion of mucin. Moreover, they mitigate the risk of edema, as for the capillary penetration it is on the whole repaired. The inflammation caused by vasodilatation usually increases capillary permeability. Vasodilatation is caused by inflammatory mediators such as histamine, leukotrienes (C4, D4, E4), prostaglandins (PgE2, PgI2). The inflammatory mediators increase the penetration of capillary and can cause edema of tissue. The inflammation leads to hypersecretion of mucus (effusion). The hypersecretion of mucus is caused by mediators such as leukotrienes (C4, D4, E4) and prostaglandins (PgE2, PgI2). The montelukast can decrease the secretion of mucus. The montelukast blocks the leukotriene receptors type of CysLT1 in mucous glands. As for bilastine it blocks the histamine receptors type of H1.

Present study aimed to evaluate the effect of the combination of montelukast and bilastine on shortening the duration of effusion in successfully treated otitis media with effusion in adults.

The study group consisted of 36 peoples (age range of 14-60 years), who were diagnosed with otitis media with effusion of at least 2 months duration. The people were randomized into one of three groups. The treatment packs containing montelukast 10 mg (tablet) and/or bilastine 20 mg as the active drug were prepared, numbered and distributed. Improvement in bilateral tympanometric findings in the combination therapy group was greater than in the other groups.

KEYWORDS: middle ear effusion, montelukast, bilastine, mucociliary clearance, unified airway model.

INTRODUCTION

The American Academy of Otolaryngology – Head and Neck Surgery Foundation, the American Academy of Pediatrics, and the American Academy of Family Physicians provide evidence-based recommendations to manage otitis media with effusion, defined as the presence of fluid in the middle ear without signs or symptoms of acute ear infection [Rosenfeld R et al., 2016]. Otitis media with effusion is histologically a chronic inflammatory condition. An underlying stimulus leads to an inflamma-

tory reaction with production of more mucin and altered, more viscous mucin types, which then overwhelms normal mucociliary clearance of the middle ear with functional blockage of the Eustachian tube, resulting in the accumulation of a thick mucin-rich middle ear effusion [Straetemans M et al., 2001]. The overexpression of mucin genes is also exacerbated by cigarette smoke. The effusion may occur as a consequence of acute otitis media taking an extended period of time to resolve; e.g. weeks or months [Tachibana F et al., 1996].

Other theories for the development of otitis media with effusion have been postulated. Eustachian tube dysfunction was often thought to cause middle ear effusion through negative pressure in the middle ear cleft; recently, however, a more complex

ADDRESS FOR CORRESPONDENCE:

Gayane V. Sargsyan
2 Koryun Street, Yerevan 0025, Armenia
Tel.: (+374 99) 69-01-00
E-mail: gvsm@mail.ru

role for the Eustachian tube has been described [Takahashi H et al., 1990]. It is thought to have a role in pressure regulation, secretion clearance, and protection from nasopharyngeal pathogens. Reflux of gastroesophageal acid can also contribute to Eustachian tube dysfunction and subsequent otitis media with effusion. The percentage of patients with high pepsinogen I concentrations in their middle ear effusions was higher in those with gastroesophageal reflux-related symptoms than in those without symptoms. Moreover, otitis media with effusion was present bilaterally in a higher percentage of patients with gastroesophageal reflux-related symptoms. There were patients in whom pepsinogen I levels decreased after receiving treatment for gastroesophageal reflux [Sone M et al., 2007]. Genetic factors, including that influencing host immune response also play a role. Immunological and genetic factors, in addition to Eustachian tube characteristics, play a role in the etiology of chronic suppurative otitis media; however, many aspects require further investigation.

Although a large number of epidemiologic studies have identified allergy as a risk factor for the effusion, the role of allergy in the pathogenesis of otitis media with effusion is still controversial [Takahashi H et al., 1990; Kariya S et al., 2003]. A recently proposed model, termed the unified airway model, hypothesizes that the upper and lower airways are an integrated system linked by physiologic and pathophysiologic mechanisms. Allergic rhinitis, asthma, and rhinosinusitis are characterized by a Th2-mediated response with infiltration of eosinophils and lymphocytes [Hurst D, Venge P, 2000; Krouse J et al., 2007]. The middle ear mucosa is just an extension of the unified airway model, as histologically it is lined with the same pseudostratified, ciliated columnar epithelium as found in the upper and lower airways. Also, similar to the rest of the airway, the middle ear cleft is capable of eliciting an allergic response [Scarano E et al., 1997; Hurst D, Venge P, 2000]. Based on these facts, numerous studies have been performed to evaluate the effects of anti-allergic treatment on otitis media with effusion. Histamine is a well-known primary early-phase inflammatory mediator. Bilastine is a second generation non-sedative antihistamine. Cysteinyl leukotrienes, late-phase mediators and a major cause of edema, mucous production, and Eustachian

tube dysfunction, have been shown to be elevated in the middle ears of adults with effusion [Finkelstein Y et al., 1994]. Montelukast is a leukotriene receptor antagonist with proven efficacy in allergic rhinitis and asthma [Van Adelsberg J et al., 2003].

Present study was designed to test the hypothesis that the combination of montelukast and bilastine may have a beneficial effect on shortening the duration of the effusion in successfully treated otitis media with effusion in adults.

MATERIAL AND METHODS

Present study was a randomized, prospective, double-blind, placebo-controlled trial conducted between February 2015 and December 2016 in ENT and Plastic Surgery Department of "Armenia" Republican Medical Center.

The study consisted of 51 people (28 females and 23 males) with age range of 14-60 years who were divided into 7 groups, diagnosed with otitis media of at least 2 months duration. People were observed without treatment during these 2 months and were excluded if they had an anatomic or physiologic defect of the ear or nasopharynx, untreated underlying disease, previous adverse reaction to treatment medication, and if they could not be followed up in the otolaryngology clinic. The presence of middle ear fluid in at least one ear was confirmed by otoscopy by the otolaryngologist and validated via tympanometry. The physician scored ear findings based on an otoscopy scale (Table 1).

TABLE 1
Characteristics of groups of examined patients according to the otoscopic findings

Groups	Otoscopy pictures
I (n=8)	Ear effusion without erythema
II (n=8)	Erythema, air-fluid level, clear fluid
III (n=5)	Erythema, complete effusion, no opacification
IV (n=10)	Erythema, opacification with air-fluid level or air bubble (s), mild bulging
V (n=5)	Erythema, complete effusion, opacification and mild bulging
VI (n=7)	Erythema, bulging rounded doughnut appearance of the tympanic membrane
VII (n=8)	Erythema, bulging, complete effusion and opacification with bulla formation

Patients with otoscopic findings of group VI or VII (15 patients) were excluded from the study as they correlated with acute otitis media. Ears with definitive evidence of effusion were documented by flat (type B) tympanogram, whereas ears with a normal tympanogram or a sharp tracing with negative pressure of -200 were evaluated as being free of effusion. Surgical treatment is recommended when otitis media with effusion lasts 4 months or longer and causes persistent hearing loss. Finally, audiometric tests were performed in all cases before and after treatment, but for the purposes of this study these data were not considered. The results of tympanometry were monitored before, and in one and three months after the end of treatment. All patients have received local nasal corticosteroid drops with intranasal douche of saline solution during this therapy.

The patients were randomized into three groups: 36 peoples with otitis media with effusion randomly received one of the treatment packs described in table 2. The treatment packs contained montelukast 10 mg (tablet) and/or bilastine 20 mg as the active drug or placebo. After each treatment otoscopy and tympanometry were repeated for all participants.

After treatment (one and three months later), the prevalence of type A tympanogram was significantly higher in combinative therapy group compared with other two groups of therapy (Table 3).

Distribution of patients: A total of 36 subjects were enrolled and randomly assigned to 1 of the 3 treatment groups (each group had 12 subjects). The subjects ranged in age from 14 to 60 years. The treatment groups were comparably relative to demographic characteristics (age and gender). We found a significant difference between the montelukast, bilastine and placebo groups, and we suggested that montelukast may be used in the treatment of otitis media effusion. In the present study, the bilateral otoscopic sign and tympanometric findings scores for the montelukast – bilastine combinative therapy group were significantly better than for the other two groups after treatment. It was important that montelukast might show good efficacy in decreasing the duration of middle ear fluid in otitis media effusion. This means that bilastine, montelukast, and also the combination therapy were all effective. In addition, this finding was supported by the improvement in tympanometric findings.

TABLE 2
Division of examined patients into groups
incompliance with the type of medicamentous
treatment

Treatment groups (n=36)	Treatment
I (n=12)	Montelukast 10 mg tablet with bilastine 20 mg
II (n=12)	Bilastine 20 mg with placebo
III (n=12)	Montelukast 10 mg tablet with placebo

TABLE 3
Tympanometric findings of examined patients
before and after different types of medicamentous
treatments

Treatment with the given medication	Tympanograms	Tympanograms	
		Before treatment	After treatment
		in one month	in three months
Bilastine with placebo (n=12)	Type B	type C-8	type C-5
		type A-2	type A-6
		type B-2	type B-1
Montelukast with placebo (n=12)	Type B	type C-6	type C-4
		type A-5	type A-8
		type B-1	type B-0
Montelukast with bilastine (n=12)	Type B	type C-3	type C-1
		type A-8	type A-11
		type B-1	type B-0

DISCUSSION

Numerous epidemiologic studies have identified allergy as a risk factor for otitis media effusion [Kariya S et al., 2003]. According to a recently proposed model, the upper and lower airways are an integrated system linked by physiologic and pathophysiologic mechanisms. Moreover, some authors noted that the middle ear mucosa is just an extension of the upper airway mucosa of the nose and nasopharynx; it is lined with the same pseudostratified, ciliated columnar epithelium [Doyle W et al., 1984; Tos M, 1984]. Many studies have supported the presence of a Th2-mediated hypersensitivity in the etiology and maintenance of the effusion. In addition, the localization of histamine and cytokines in the middle ear suggests the role of allergy in the development of otitis media effusion [Martin Misener R, 2007].

Cysteinyl leukotrienes, products of arachidonic acid metabolism, are important in the pathogenesis

of middle ear effusion [Tachibana F et al., 1996]. Montelukast blocks cysteinyl leukotriene receptors and inhibits endogenous mediators of inflammation in allergic airway diseases. Montelukast is very safe and rapidly absorbed. Experiments have shown that histamine causes vasodilatation and increases the permeability of the middle ear mucosa, the two cardinal signs of middle ear inflammation [Fradly R et al., 1977]. The antihistamine used in this study, bilastine, is a non-sedative antihistamine and is classified as second-generation H1 antagonist. It is a non-drowsy antihistamine as it does not penetrate the brain in significant amounts. In the present study, we evaluated the effects of montelukast, bilastine, and the combination of montelukast with bilastine on the improvement of the effusion. Some authors demonstrated that montelukast was effective in the resolution of the effusion, but not in decreasing the submucosal accumulation of neutrophil leukocytes in otitis media effusion. They emphasized that montelukast is only a selective CysLT1 blocker and is ineffective for BLT1 and BLT2 receptors, which have a potent neutrophil chemoattractant action, and this fact might be the reason for these data [Combs J, 2004]. These reports and our results explain that montelukast may have a beneficial effect

in the improvement of otitis media effusion. We hypothesize that the effects of some synergy between montelukast and bilastine on the inflammatory process might lead to an additional effect in improvement of the effusion [Martin Misener R, 2007]. Furthermore, when we evaluated the improvement in otoscopic sign scores between groups, we found that the results for the combination therapy group were significantly better than for all other groups. In the present study, we have shown significant benefit of montelukast in combination with bilastine treatment. The doses of montelukast and bilastine used in this study were the standard doses recommended for the treatment of upper respiratory tract allergy. Although the pharmacologic dose for counteracting the effects of otitis media effusion is unknown, we anticipated the same mechanism of action. It is possible that higher doses might produce better response.

Thus, combinative usage of montelukast and histamine blockers – bilastine with otitis media may improve middle ear mucociliary clearance, Eustachian tube ventilation, avoiding in some cases the need for surgery and exposure to surgical complications, and may prevent recurrences of otitis media or development of chronic suppurative otitis media.

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