JOURNAL OF medical updates
www.jmedupdates.org

Clinical Research / Klinik Araştırma

J Med Updates 2014;4(1):20-24
doi:10.2399/jmu.2014001005

Effect of N-acetylcysteine for the treatment of otitis media with effusion

Efüzyonlu otitis media tedavisinde N-asetilsisteinin etkisi

Osman Fatih Boztepe[1], Taylan Gün[2], Özer Erdem Gür[3], Mehmet Fatih Karakuş[4], Nagihan Bilal[5], Hasan Nedim Arda[6]

[1]ENT Department, Medisu Hospital, Antalya, Turkey
[2]ENT Department, Medical Park Gaziantep Hospital, Gaziantep, Turkey
[3]ENT Department, Antalya Training and Research Hospital, Antalya, Turkey
[4]ENT Department, Ankara Gölbaşı Hasvak Govenrment Hospital, Ankara, Turkey
[5]ENT Department, Kahramanmaraş Necip Fazıl City Hospital, Kahramanmaraş, Turkey
[6]ENT Department, Medicana Hospital, Ankara, Turkey

Abstract

Objective: To show the efficacy of mucopeptid breaking agent N-acetylcysteine on the treatment of otitis media with effusion.

Methods: A total of 64 patients who were admitted to our clinic and diagnosed otitis media with effusion were included in the study. The study group of 33 patients were administered antibiotics, decongestants, and N-acetylcysteine. The control group was treated with only antibiotics and decongestants. Both groups of patients were examined with a low-frequency probe tone (226 Hz) device before, one month, three months and 6 months after the treatment. Tympanometric and pure tone audiometric examination of the patients were performed.

Results: At the end of the first month, recovery rates of the left and right ears in the study and control groups were 66 and 72% vs. 13 and 22%, respectively. At sixth month, recovery rates for the left and right ears in the study group were 91 and 94%, respectively, while the corresponding recovery rates were 48 and 55% in the control group.

Conclusion: N-acetylcysteine can be used in the treatment of otitis media with effusion as a medical agent. However, studies on more patients are needed to evaluate the efficacy and long-term effect of N-acetylcysteine on otitis media with effusion.

Keywords: N-acetylcysteine, otitis media with effusion, medical therapy.

Özet

Amaç: Bu çalışmanın amacı efüzyonlu otitis media tedavisinde mukopeptid kırıcı ajan olan N-asetilsisteinin etkinliğini göstermektir.

Yöntem: Kliniğimize başvuran ve efüzyonlu otitis media tanısı konan 64 hasta çalışmaya alındı. Çalışma grubuna dâhil edilen 33 hastaya antibiyotik, dekonjestan ve N-asetilsistein, kontrol grubuna ise sadece antibiyotik ve dekonjestan uygulandı. Her iki grup, düşük frekanslı prob (226 Hz) cihazı ile tedaviden önce ve tedaviden bir ay, üç ay ve 6 ay sonra incelendi. Hastaların timpanometrik ve saf ton odyometrik muayeneleri yapıldı.

Bulgular: Birinci ayın sonunda, çalışma ve kontrol gruplarında sol ve sağ kulak iyileşme oranları sırasıyla yüzde %66 ve %72'ye karşılık %13 ve %22 idi. Altıncı ayda, sol ve sağ kulak için çalışma grubu iyileşme oranları sırasıyla %91 ve %94 iken, kontrol grubunda bu oranlar %48 ve % %55 olarak bulundu.

Sonuç: N-asetilsistein, efüzyonlu orta kulak iltihabı tedavisinde kullanılabilir. Ancak, N-asetilsisteinin efüzyonlu otitis media üzerindeki etkinliği ve uzun dönem etkilerini değerlendirmek için daha fazla hasta üzerinde çalışmalar yapılması gereklidir.

Anahtar sözcükler: N-asetilsistein, efüzyonlu otitis media, medikal tedavi.

Otitis media with effusion (OME) is characterized by nonspecific inflammation of the middle ear mucosa and secretory transformation of the epithelial layer, resulting in fluid accumulation in the middle ear space.[1,2] Infection and Eustachian tube dysfunction are generally accepted as the most important pathogenetic factors.[3] Despite active

Correspondence: Taylan Gün, MD. Medical Park Gaziantep Hastanesi Mücahitler Mah., Şehitkamil, Gaziantep Turkey.
e-mail: taylangun@gmail.com

Received: December 17, 2013; **Accepted:** January 29, 2014; **Published online:** May 5, 2014

Online available at:
www.jmedupdates.org
doi:10.2399/jmu.2014001005
QR code:

intervention with antibiotics and ventilation tubes the disease has a marked tendency to recur. Thus, a therapeutic strategy capable of reducing the frequency of recurrences is needed.

N-acetylcysteine (NAC) is known to possess antiinflammatory, mucolytic and anti-oxidative properties. In rabbits with OME, we have demonstrated that local application of NAC reduced the extent of inflammation and fibrosis in the middle ear mucosa.[4] In cultured middle ear fibroblasts the cell proliferation and collagen synthesis were reduced significantly by NAC.[5] Based on these results we suggest that instillation of NAC in the middle ear of children with OME might exert a positive influence on the course of the disease after ventilation tube insertion.

In this study, we aimed to show the efficacy of mucopeptide-breaking agent NAC on the treatment of OME.

Materials and Methods

Study Design

This study was approved by the local Institutional Review Board. Written informed consent was obtained from legal surrogates, parents or legal guardians. Sixty-four patients who were admitted to our clinic and diagnosed as OME were included in the study.

Patient selection was made on the basis of tympanometric results and pneumatic otoscope findings. All parents were interviewed and detailed histories of the patients were recorded. Symptoms like ear pain, hearing loss, nasal blockage and discharge, fever, snoring, mouth respiration, cough and sneezing were also recorded. All patients were evaluated by pneumatic otoscope and vascularisation and color of tympanic membrane and its movement with Valsalva manoeuvre were observed. In addition, status of the septum, turbinates, nasal secretions, nasal mucosa, the presence of adenoids and tonsils, and post-nasal discharge were investigated in detail. Detailed physical examinations were performed and patients with active infection, evidence of tympanic membrane adhesion, medical history of allergies and operations such as myringotomy, ventilation tube insertion, adenoidectomy, tonsillectomy and anatomical defects such as cleft palate were excluded from the study.

Patients were randomly divided into two groups: the study group (n=33) and the control group (n=31). The study group received antibiotics, decongestants and NAC, while the control group was treated with only antibiotics and decongestants. In both groups, amoxicillin/clavulanic acid was given at daily doses of 40 mg/kg bid and as a systemic decongestant 45 mg pseudoephedrine was prescribed in children under the age of 6. In children over 6 years of age, a dosage of 90 mg three times a day was given. N-acetylcysteine was administered to children under 7 years of age in the study group at a daily dosage of 400 mg and for children over the age of 7, a dosage up to 600 mg/day divided into three doses.

Outcome Parameters

Both groups of patients were examined with a low-frequency probe tone (226 Hz) using an Interacoustics AZ 26 Impedance Audiometer (Interacoustics, Assens, Denmark) device before, one month, three months and 6 months after the treatment. Tympanometric and pure tone audiometric (Oscilla SM 950 Clinical audiometer with a diagnostic memory; P&A Medical Ltd., London, UK) examinations of the patients were performed. The tympanograms were classified according to the Jerger classification (Table 1).[6] On tympanometric curve, type B curve to C2, type C2 curve to C1 and the changes in each three types of curves to type A have been considered as an improvement. In our study, most patients did not respond to 3 months of treatment and have been followed up with ventilation tube applications. Patients who responded to the treatment were followed up with pneumatic otoscopic and tympanographic monitorization for at least 6 months.

Statistical Analysis

Data were analysed using the Statistical Package for Social Sciences 10.0 for Windows (SPSS Inc., Chicago, IL, USA). Parametric tests were applied to data of normal distribution and nonparametric tests were applied to data of questionably normal distribution. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

Results

The study group included 33 patients (22 females and 11 males), while the control group included 31 patients (19

Table 1. Classification of tympanograms.

Type		Description
Peaked	A	Between +200 and -99 daPa
	C1	Between -100 and -199 daPa
	C2	Between -200 and -399 daPa
Non-peaked	B	No observable peak between +200 and -600 daPa

Table 2. Symptoms and findings according to groups.

		Study group (%)	Control group (%)
Symptoms	Hearing loss	57.6	51.6
	Mouth breathing	51.5	42
	Snoring	63.6	48.4
	Fever	3	0
	Post nasal discharge	18.2	9.7
	Otalgia	3	0
	Ear blockage	12.1	9.7
Findings	TM colour change	67.7	78.8
	Air fluid appearance	32.3	45.5
	Nasal discharge	16.1	27.3
	Adenoid vegetation	22.6	24.2
	Post nasal discharge	19.4	24.2
	Tonsillar hypertrophy	12.9	15.1
	Tonsillar atrophy	9.6	9.1

females and 12 males). The median age of the study group was 6 (range: 4 to 8) years, while the median age of the control group was 5.5 (range: 4 to 8) years. The most frequent symptom was snoring in the study and hearing loss in the control group. There was no statistical difference between the study and the control group based on the symptoms of the patients ($p<0.05$). The most frequent finding in the study and control groups was opacification of tympanic membrane. There is no statistical difference between the groups on the basis of examination findings ($p>0.05$) (Table 2).

The number of patients and controls who underwent tympanometric examinations are shown in Table 3. At the end of the first month, recovery rates of the left and right ears in the study and control groups were 66 and 72% vs 13 and 22%, respectively. At the end of the third month, recovery rates in the study group rose to 84% for the left and to 87% for right ears after termination of the treatment. In the control group, recovery rates for the left ear decreased by 10% and of the right ear increased to 39 percent. At sixth month, recovery rates in the study group for the left and right ears were 91 and 94%, respectively, while the corresponding recovery rates in the control group were 48 and 55%.

In each of the follow-up group, tympanometric values, symptoms and physical findings improved in all patients. Accordingly, tympanogram curves of the study and the control groups at 1, 3 and 6 months after termination of the medical treatment were compared (Table 4). At each of the three controls, improvement in the study group was superior at a statistically significant level when compared with the control group ($p<0.05$).

Table 3. Number of patients according to the tympanometric findings in the patient and control groups.

	Tympanogram type	Pre-treatment		Post-treatment					
				1. months		3. months		6. months	
		Left	Right	Left	Right	Left	Right	Left	Right
Study group	Type B	15	18	1	5	0	0	0	0
	Type C2	13	13	12	10	3	7	0	2
	Type C1	3	2	9	9	6	7	6	1
	Type A	2	0	11	9	24	19	27	30
Control group	Type B	4	10	13	12	17	11	14	9
	Type C2	26	20	14	15	13	15	3	6
	Type C1	1	1	4	4	1	5	10	10
	Type A	0	0	0	0	0	0	4	6

Lack of improvement at each of the three controls was observed in the control group, while only one ear of eight patients (25%) showed improvement in spite of treatment and two patients (6%) needed surgical intervention after medical treatment in the study group. All patients who underwent surgical treatment were followed with a myringotomy. Shepard grommet tube was applied to the patients. The difference found between the two groups in terms of the need for surgical treatment was statistically significant ($p<0.05$).

Table 4. Recovery rates of otitis media with effusion in study and control groups.

	Study group (%)		Control group (%)	
	Right	Left	Right	Left
1st month	66	72	13	22
3rd month	84	87	10	39
6th month	91	94	48	55

Discussion

One of the most common symptoms of OME is hearing deficit. Studies showed that the degree of hearing impairment is independent of the physical properties of effusion but associated with the volume.[7] In the present study, the most common symptom is snoring in the study group and the hearing loss in the control group.

Some authors believe that medical treatments for OME such as antibiotics, steroids, antihistamines, decongestants and mucolytics have no long-term benefits. According to these authors, only the surgical treatment provides long-term benefits.[8] A review on the use of antibiotics showed that the use of antibiotics for OME for a short-term is beneficial contrary to long-term use and delays surgical treatment of symptomatic children with OME.[9] In another study on OME, antibacterial activity of amoxicillin is reported to be significantly superior to that of cephalosporins and macrolides.[10] In our study, amoxicillin and clavulanic acid are preferred in both study and control groups.

A large number of studies have been carried out with mucolytics such as ambroxol, NAC, S-carboxymethylcysteine (CMS) with the intention to show the effects of mucolytics on OME. Brown et al. showed that NAC had a viscosity reducing effect on tracheobronchial mucus¬ and stated that similar pathological processes may also be effective on OME.[11] *In vitro* studies conducted with NAC, mercaptoethanol and CMS showed that CMS was ineffective as a mucolytic agent, while mercaptoethanol and NAC were found to lower the apparent viscosity. This effect is manifested in low doses of NAC. Glycoprotein is responsible for the viscosity of the material in the middle ear effusion. NAC breaks disulfide bonds, reduces the viscosity of the effusion and has an alleviating effect on the pathological process.[11-13] Hori et al. used and compared a low (100 mg/kg/d) and a high dose (200 mg/kg/d) of CMS in the treatment of experimental otitis media. However, prostaglandin 2 and tubotympanic histamine use did not exert an effect on the synthesis of abovementioned chemical mediators and did not support the use of this molecule as a prophylactic agent.[14] Ovesen et al. applied ventilation tubes to their bilateral OME patients, local administration of NAC to the middle ears for 3-7 days reduced the possibility of local recurrence.[15] Majima et al. reported that the use of CMS within a 4-week period after myringotomy reduces the viscosity of the middle ear effusion and significantly accelerates the healing process.[16] Khan et al. postulated that in patients with the OME, compared with placebo, CMS is significantly effective in achieving further resolution of the effusion.[17] Kumazawa and Ushiro in their study of 250 infants with OME, investigated the effectiveness of the treatment with CMS and showed that CMS was 79% successful in the placebo group which was maintained at the rate of 58%. Both the decrease in the amount and viscosity of effusion as well as significant improvement in audiological findings revealed that CMS had a significant beneficial effect compared to placebo.[18] Moore et al. evaluated 283 children in seven different studies and reported CMS as a safe drug for the treatment of OME.[19] In contrast to all of these studies, van der Merwe et al. conducted a study on 60 people and compared bromhexin with placebo in delaying resolution of middle ear effusion.[20] In another study, CMS has been shown to have no effect on the viscosity of the treatment process and, it has been suggested that CMS is ineffective in the treatment of OME.[21] In our study, addition of NAC to the medical treatment in OME patients statistically significantly provided beneficial effects in the treatment of effusion.

Conclusion

As a result, NAC can be used in the medical treatment of otitis media with effusion. However, further studies on a larger-scale patient population are needed to evaluate the efficacy and long-term effect of NAC on the treatment of OME.

Conflict of Interest: No conflicts declared.

References

1. Paparella MM, Schachern PA, Yoon TH, Abdelhammid MM, Sahni R, da Costa SS. Otopathologic correlates of the continuum of otitis media. Ann Otol Rhinol Laryngol Suppl 1990;148:17-22.
2. Yoon TH, Schachern PA, Paparella MM, Lindgren BR. Morphometric studies of the continuum of otitis media. Ann Otol Rhinol Laryngol Suppl 1990;148:23-7.
3. Ovesen T, Børglum JD. New aspects of secretory otitis media, Eustachian tube function and middle ear gas. Ear Nose Throat J 1998;77:770-7.
4. Ovesen T, Paaske PB, Elbrond O. Local application of N-acetylcysteine in secretory otitis media in rabbits. Clin Otolaryngol Allied Sci 1992;17:327-31.
5. Ovesen T, Gaihede M, Ledet T. The effect of N-acetylcysteine on the in 6itro growth of normal rabbit middle ear fibroblasts. Clin Otolaryngol Allied Sci 1993;18:400-5.
6. Zielhuis GA, Heuvelmans-Heinen EW, Rach GH, van den Broek P. Environmental risk factors for otitis media with effusion in preschool children. Scand J Prim Health Care 1989;7:33-8.
7. FitzGerald JE, Green GG, Birchall JP, Pearson JP. Rheologic studies on middle ear effusions and their mucus glycoproteins. Arch Otolaryngol Head Neck Surg 1989;115:462-8.
8. Williamson I. Otitis media with effusion in children. Clin Evid (Online) 2007;2007.pii: 0502.
9. Mandel EM, Casselbrant ML. Antibiotics for otitis media with effusion Minerva Pediatr 2004;56:481-95.
10. Mandel EM, Rockette HE, Paradise JL, Bluestone CD, Nozza RJ. Comparative efficacy of erythromycin-sulfisoxazole, cefaclor, amoxicillin or placebo for otitis media with effusion in children. Pediatr Infect Dis J 1991;10:899-906.
11. Brown DT, Litt M, Potsic WP. A study of mucus glycoproteins in secretory otitis media. Arch Otolaryngol 1985;111:688-95.
12. Cayé-Thomasen P, Tos M. Eustachian tube gland changes in acute otitis media. Otol Neurotol 2004;25:14-8.
13. FitzGerald JE, Green GG, Stafford FW, Birchall JP, Pearson JP. Characterization of human middle ear mucus glycoprotein in chronic secretory otitis media (CSOM). Clin Chim Acta 1987;169:281-97.
14. Hori F, Kawauchi H, Mogi G. Effect of S-carboxymethylcysteine on the clearance of middle ear effusion. An experimental study. Ann Otol Rhinol Laryngol 1994;103:567-75.
15. Ovesen T, Felding JU, Tommerup B, Schousboe LP, Petersen CG. Effect of N-acetylcysteine on the incidence of recurrence of otitis media with effusion and re-insertion of ventilation tubes. Acta Otolaryngol Suppl 2000;543:79-81.
16. Majima Y, Takeuchi K, Sakakura Y. Effects of myringotomy and orally administered drugs on viscosity and elasticity of middle ear effusions from children with otitis media with effusion. Acta Otolaryngol Suppl 1990;471:66-72.
17. Khan JA, Marcus P, Cummings SW. S-carboxymethylcysteine in otitis media with effusion. (A double-blind study). J Laryngol Otol 1981;95:995-1001.
18. Kumazawa T, Ushiro K. Clinical evaluation of S-CMC syrup applied in the treatment of otitis media with effusion. Double blind comparative test with placebo. Acta Otolaryngol Suppl 1988;458:56-62.
19. Moore RA, Commins D, Bates G, Phillips CJ. S-carboxymethylcysteine in the treatment of glue ear: quantitative systematic review. BMC Fam Pract 2001;2:3.
20. van der Merwe J, Wagenfeld DJ. The negative effects of mucolytics in otitis media with effusion. S Afr Med J 1987;72:625-6.
21. Fitzgerald JE, Green GG, Birchall JP, Pearson JP. Mucolytic agents and otitis media with effusion. Biomed Pharmacother 1988;42:505-11.

Please cite this article as: Boztepe OF, Gün T, Gür ÖE, Karakuş MF, Bilal N, Arda HN. Effect of N-acetylcysteine for the treatment of otitis media with effusion. J Med Updates 2014;4(1):20-24.