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A Comparative Study of Clemastine Fumarate, Mebhydrolin Napadisylate and Placebo in the Symptomatic Treatment of Perennial Allergic Rhinitis

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การศึกษาเปรียบเทียบผลของยาคลีมาสตีน, เม็บไฮโดรลีน และยาหลอก ในผู้ป่วยโรคเยื่อบุจมูกอักเสบจากภูมิแพ้ชนิดเรื้อรัง

สมชาติ แสงสอาด, พินิจ ลัญฉนะวนิชย์

ภาควิชาโสต ศอ นาสิก ลารินซ์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

การใช้ยาต้านจุดต้อนรับฮีสตามีน-หนึ่งในการรักษาอาการของผู้ป่วยโรคเยื่อบุจมูกอักเสบจากภูมิแพ้ ยังคงเป็นวิธีการหนึ่งที่ใช้กันแพร่หลายมากในทางปฏิบัติ การศึกษานี้ทำขึ้นเพื่อประเมินประสิทธิภาพและผลข้างเคียงของยาต้านจุดต้อนรับฮีสตามีน-หนึ่ง 2 ชนิด คือ เม็บไฮโดรลีนซึ่งเป็นยาตัวหนึ่งที่ใช้กันแพร่หลายมากกันพอควรและคลีมาสตีน ซึ่งเป็นยาที่ออกฤทธิ์ได้นาน โดยมียาหลอกเป็นกลุ่มอ้างอิง การศึกษานี้ทำในผู้ป่วย 106 ราย โดยวิธี randomizded double-blind parallel พบว่าผู้ป่วยที่ได้รับยาต้านจุดต้อนรับฮีสตามีน-หนึ่ง จะให้ผลดีกว่ากลุ่มที่ได้รับยาหลอกในการระงับอาการจาม คัดจมูก และน้ำมูกไหล เมื่อเปรียบเทียบผลของยาด้วยกันพบว่ายาคลีมาสตีนให้ผลดีกว่ายาเม็บไฮโดรลีน ส่วนผลข้างเคียงของยาทั้งสอง เช่น มึนงง และคอแห้งพบได้น้อย อย่างไรก็ดีการเลือกใช้ยาต้านจุดต้อนรับฮีสตามีน-หนึ่ง ควรพิจารณาถึงการตอบสนองของผู้ป่วยต่อยาเป็นราย ๆ ไป

H_1-receptor antagonists still play an important role in the symptomatic controls of allergic rhinitis. This study was conducted to evaluate the efficacy and side-effects of two H_1-receptor antagonists namely, mebhydrolin which is one of the most widely used antihistamines, and clemastine, a long-acting antihistamine. Placebo was used as a control group. There were one hundred and six patients participating in this study which was a randomized double-blind paralled trial. The results indicated that both mebhydrolin and clemastine are effective in controlling the symptoms of allergic rhinitis, e.g. sneezing, nasal blockade and rhinorrhea. When these two drugs were compared, clemastine was shown to be superior to mebhydrolin in global improvement. However, the response to H_1-receptor antagonist varies from patient to patient, thus we should try first and then select the right one for the right patient.

INTRODUCTION

Allergic rhinitis is a troublesome and common complaint which affects a large section of the population every year. It may begin at almost any age, although the incidence of the first onset is greatest in children and young adults and decreases with age.[1] Many patients suffer from seasonal allergic rhinitis occurring in some seasons. Pollens from plants that depend on the wind for cross-pollination and mold spores are the main agents responsible for this type of allergic rhinitis. In another large group of patients, allergic rhinitis is non-seasonal and is caused by domestic allergens such as house dust. In a third group of patients, vasomotor rhinitis, clinically indistinguishable from the other types, may be due to physical factors, infection, or nervous and emotional factors, possibly aggravated, in some cases at least by undiscovered allergens.

H_1-antihistamines play an important role in the symptomatic controls of allergic rhinitis, since many of the symptoms are due to the local release of the inflammatory vasoactive mediator, histamine. H_1-antihistamines can relieve these disagreeable symptoms and are widely prescribed for this conditions. The beneficial effects of H_1-antihis tamines are, however, often offset by their associated anticholinergic and central nervous system effects, particularly drowsiness. Recently, some long-acting H_1-antihistamines have been available in the country. Clemastine fumarate, one of the long-acting H_1 - anthistamines has been reported as possessing highly effective antihistaminic properties, and causing little drowsiness.[2-4] Among conventional prescribed H_1-antihistamines, chlorpheniramine maleate and mebhydrolin napadisylate are widely used in alleviating the symptoms of allergic rhinitis. There are many previous studies[5-8] compared the efficacy and side effects of chlorpheniramine and clemastine, and the results confirmed the greater benefit of clemastine in relieving the symptoms of allergic rhinitis. Additionally, drowsiness is a common side effect of chlorpheniramine[9] whereas mebhydroline is claimed to be a low sedating H_1-antihistamine. For these reasons, the purpose of this study is to compare the efficacy and side effects of mebhydrolin and clemastine in allergic rhinitis in a randomized double-blind, comparative parallel pattern, by having a placebo-treated group as a control group.

MATERIALS AND METHODS

One hundred and twenty-five patients suffering from perennial allergic rhinitis of both sexes (41 males and 84 females), aged between 17-45 years, attending the Department of Otolaryngology, Srinagarind Hospital were selected for this study. The patients would be seen initially for diagnosis, investigation and examination. Entry to the trial would be determined by the patients fulfilling the following criteria: (a) a past history of perennial allergic rhinitis, for at least one year; (b) symptoms of sneezing, itching, watery rhinorrhea and nasal obstruction; (c) positive skin test to common allergens; (d) negative x-ray sinus; (e) complete blood count: within normal limit; (f) not receiving desensitization, and (i) symptoms severe enough to render medication and occur nearly everday.

Prior to treatment, all other drugs were stopped for one week (as a baseline period), before beginning each test substance. Then the patients were allocated at random one or other of three groups. The first group would receive clemastine which was supplied as 1 mg capsule, the second group mebhydrolin supplied as 50 mg capsule and the third group placebo. Each test substance presented in identical packets and given in accordance with a code administration schedule, was administered twice daily for a period of two weeks. The patients were each given a symptom diary and instructed

to record the main daily symptom, i.e. sneezing, itching, blockade and rhinorrhea. The symptoms ware recorded on a 4-point scale where 0 = no symptoms, 1 = mild (symptoms minimal causing little inconvenience and clearing up in a short time), 2 = moderate (symptoms lasting for several hours, partially incapacitating, recurrent during the day, and 3 = severe (continuous symptoms, severe incapacity, great inference with work). Drowsiness and throat dryness were then assessed on a similar scale serving as four values ranging from 0, denoting the absence of drowsiness or throat dryness to 4 denoting a severe grade. One-way analysis of variance was used for statistical analysis.

RESULTS

One hundred and six out of the 125 patients originally selected completed the trial. Nineteen patients lost their daily cards. The characteristics of the patients in the three groups were similar before study. (Table 1)

The mean symptom scores in each group, comparing the scores of pre-drug baseline to those at the end of the second week of treatment, was shown in Table 2 which shows that all symptoms responded to both antihistamines. (Table 2)

Table 1 Age and sex distribution of this study group

	Group		
	Placebo	**Mebhydrolin**	**Clemastine**
No. of patients	35	29	42
Sex : Male (%)	10 (29%)	8 (28%)	13 (31%)
Female (%)	25 (71%)	21 (72%)	29 (69%)
Age (years) : Mean S.D.	30.97 ± 8.30	30.66 ± 8.93	30.55 ± 7.71

Table 2 The mean symptom scores of placebo, mebhydrolin and clemastine before and after treatment on various symptoms

Symptoms	Mean scores ± S.D.					
	Placebo (N = 35)		Mebhydrolin (N = 29)		Clemastine (N = 42)	
	Before	After	Before	After	Before	After
Itching	0.9306 ± 0.860	0.8633 ± 0.766	1.257 ± 0.948	0.8896** ± 0.701	1.1667 ± 0.826	0.6002** ± 0.614
Sneezing	0.9796 ± 0.791	1.0286 ± 0.725	1.2759 ± 0.900	0.8951** ± 0.674	1.3129 ± 0.791	0.7011** ± 0.503
Blockade	1.5959 ± 0.759	1.3224* ± 0.857	1.8177 ± 0.914	1.2296** ± 0.723	1.8605 ± 0.813	0.9104** ± 0.695
Rhinorrhea	1.3061 ± 0.970	1.2612 ± 0.886	1.3547 ± 0.895	0.8997** ± 0.715	1.4320 ± 0.857	0.7014** ± 0.600
Total scores	1.2031 ± 0.656	1.1189 ± 0.688	1.4335 ± 0.737	0.9960** ± 0.703	1.4430 ± 0.8605	0.7283** ± 0.603

* $p < 0.05$ statistically significant
** $p < 0.001$ statistically significant

Nasal blockade was slightly improved in placebo group. However, the global improvement was observed only in antihistaminic group. (Table 2 & Figure 1)

the mean score of drowsiness showed no statistically significant difference from baseline period in these three groups. Unexpectedly, the score of throat dryness significantly decreased in both antihistaminic groups. (Table 3)

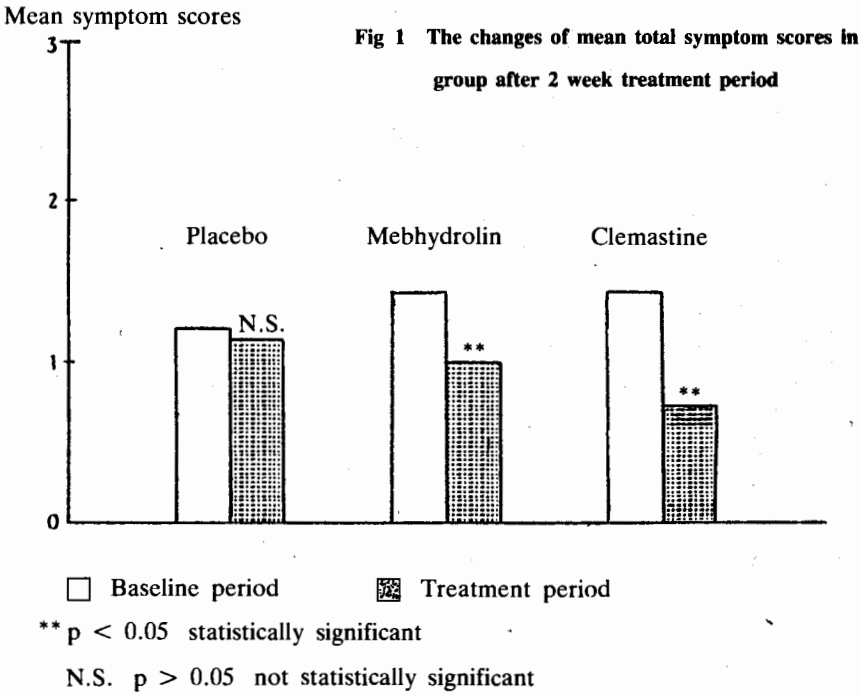


Fig 1 The changes of mean total symptom scores in each group after 2 week treatment period

Table 2 The mean severity scores of placebo, mebhydrolin and clemastine before and after treatment

Symptoms	Mean scores ± S.D.					
	Placebo (N = 35)		Mebhydrolin (N = 29)		Clemastine (N = 42)	
	Before	After	Before	After	Before	After
SIDE EFFECTS						
Drowsiness	0.8245 ± 0.758	0.7531 ± 0.772	0.9360 ± 0.116	0.7889 ± 0.729	0.8367 ± 0.892	0.7279 ± 0.764
Throat dryness	0.7755 ± 0.651	0.6245 ± 0.734	0.9083 ± 0.781	0.6847* ± 0.721	0.9762 ± 0.792	0.6837** ± 0.795

* $p < 0.05$ statistically significant
** $p < 0.001$ statistically significant

Then, we compared the efficacy and side effects among the groups. The results indicated both antihistamines were effective compared to placebo (Table 4). However, Mebhydrolin significantly improves only rhinorrhea whereas clemastine significantly improves sneezing, nasal blockade and rhinorrhea. Comparing the two antihistamine groups, clemastine provides greater benefit than mebhydrolin. It is more effective in relieving the symptoms of itching and nasal blockade. The total scores indicated that clemastine showed significantly greater improvement than mebhydrolin ($P < 0.05$) (Table 4 and Figure 2).

Table 4 Comparison of the mean symptom scores of placebo, mebhydrolin and clemastine

	Mean scores ± S.D.		
	Placebo (N = 35)	**Mebhydrolin (N = 29)**	**Clemastine (N = 42)**
	After treatment	**After treatment**	**After treatment**
Itching	0.8633 ± 0.766	0.8896 ± 0.701	0.6002** ± 0.614
Sneezing	1.0286 ± 0.725	0.8951 ± 0.674	0.7011** ± 0.503
Blockade	1.3224 ± 0.857	1.2996 ± 0.723	0.9104*,** ± 0.695
Rhinorrhea	1.2612 ± 0.886	0.8997*,+ ± 0.715	0.7014* ± 0.600
Total scores	1.1189 ± 0.688	0.9960 ± 0.703	0.7283* ± 0.603

+ { Placebo vs Mebhydrolin / Placebo vs Clemastine } $p < 0.05$ statistically significant

++ Mebhydrolin vs Clemastine $p < 0.05$ statistically significant

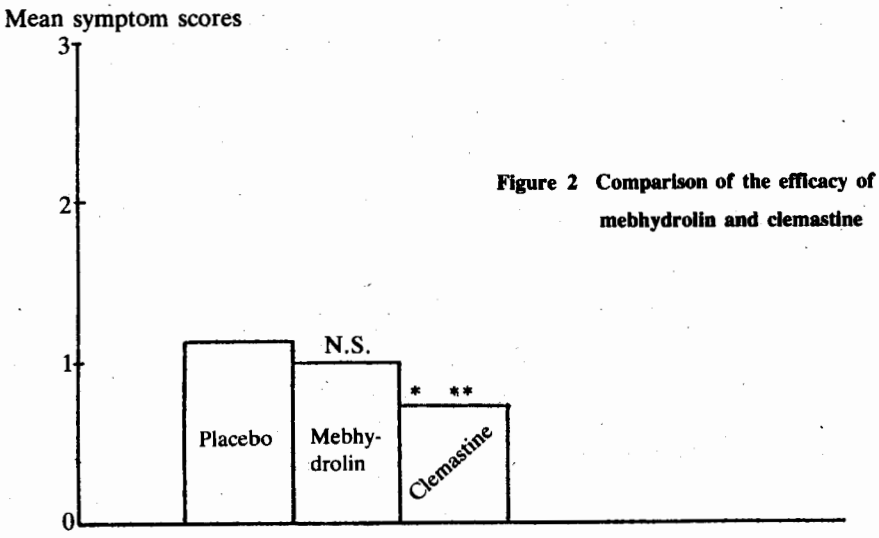


Figure 2 Comparison of the efficacy of placebo, mebhydrolin and clemastine

* { Placebo vs Mebhydrolin / Placebo vs Clemastine } $p < 0.05$ statistically significant

** Mebhydrolin vs Clemastine $p < 0.05$ statistically significant

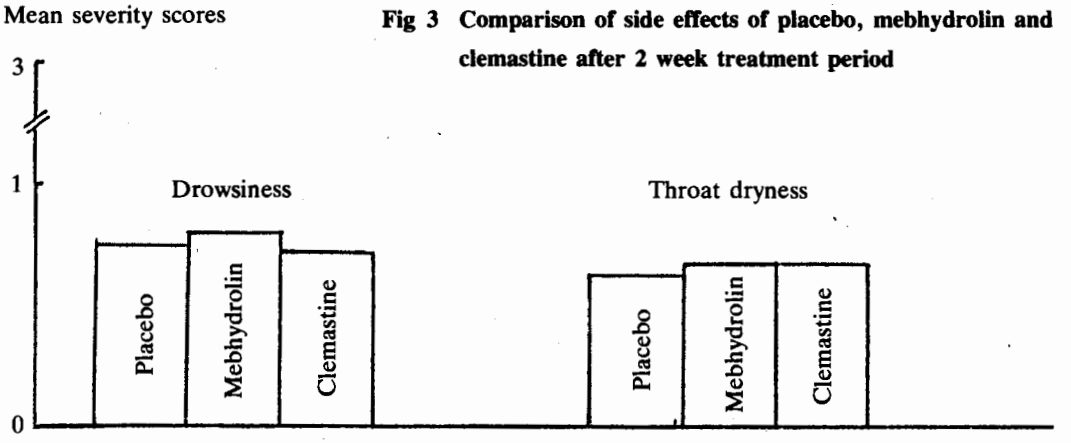
N.S. $p > 0.05$ not statistically significant

Table 5 Comparison of the severity scores of placebo, mebhydrolin and clemastine after treatment

Symptoms	Placebo (N = 35)	Mebhydrolin (N = 29)	Clemastine (N = 42)
	After treatment	After treatment	After treatment
SIDE EFFECTS			
Drowsiness	0.7531 ± 0.772	0.7889 ± 0.729	0.7279 ± 0.764
Throat dryness	0.6245 ± 0.734	0.6847 ± 0.721	0.6837 ± 0.795
Palpitations	0.2020 ± 0.882	0.1847 ± 0.331	0.2687 ± 0.559
Total scores	0.5265 ± 0.498	0.5361 ± 0.435	0.5601 ± 0.563

No statistically significant difference among the group ($p > 0.05$)

Fig 3 Comparison of side effects of placebo, mebhydrolin and clemastine after 2 week treatment period



No statistically significant difference among the group ($p > 0.05$)

Drowsiness and throat dryness seemed to occur in some patients in all groups but there was no statistical significant difference among the groups. (Table 5 and Figure 3)

DISCUSSION

H_1-antihistamines have a well-established place in the management of allergic rhinitis. The prescribing needs to select an antihistamine to combine control with freedom of side effects, without development of tolerance. Mebhydrolin is one of the widely used antihistamines and is claimed to have a low drowsiness effect whereas clemastine, a long-acting H_1-antihistamine, is a benzhydryl ether and differs structurally from

the classical antihistamines. It has been on the market in the United States since 1978. Clemastine has weaker anti-cholinergic properties than most antihistamines, resulting in significantly less drowsiness in patients.[10,11] Clinical studies abroad have shown a high success rate in the treatment of allergic rhinitis and allergic dermatitis, with a low incidence of side effects.[3,5,12,13] It was decided, therefore, to make a simple comparative assessment of the effectiveness and side effects of clemastine, mebhydrolin and placebo, which is given as a control group. The results of this double-blind randomized study have demonstrated that both mebhydrolin and clemastine are significantly effective in controlling the symptoms of allergic rhinitis. However, clemastine relieved or greatly reduced the severity of troublesome symptoms such as itching, sneezing, nasal blockade and rhinorrhea. (Table 4) As judged by the global evaluation made by the patients, clemastine is also regarded as superior to mebhydrolin in controlling symptoms associated with allergic rhinitis. (Table 4, Figure 2). After 2 weeks treatment, clemastine significantly reduced the mean total score compared to mebhydrolin and placebo. It seems that mebhydrolin was more effective than placebo group. However, it was not expected before the study that no statistical difference would be observed between mebhydrolin and placebo group. The reason may be that the evaluation is dependent on the patient's own assessment of symptom amelioration. Obviously patients' views are colored by many variables Whether subtle or not, immediately apparent improvements may be overlooked entirely. No severe sedation and throat dryness were detected in the present study. The mean symptom score of drowsiness was slightly increased in mebhydrolin group and slightly decreased in clemastine group whereas the mean symptom score of throat dyrness was slightly increased in both antihistamine groups. (Table 5, Figure 3) However, there was no statistically difference of these two parameters from placebo groups. Generally, both druts were well tolerated and no serious side effects were reported. Hindmarch I and Parrott A.C.[14] had evaluated the side effects of five antihistamines, namely, chlorpheniramine, mebhydrolin, clemastine, ketotifen and promethazine by measuring on subjective assessments of sleep and the integrity of early morning behaviour and objective assessments of complex psychomotor behaviour and central nervous system arousal. Neither clemastine or mebhydrolin showed any significant impairment in complex reaction time assessments, and the subjective assessments of sleep and early morning hangover showed these two antihistamines to be free from detrimental side effects.

The results presented in this study confirm the observations of other investigators[15-17] that clemastine is a highly effective and well tolerated drug for the symptomatic treatment of allergic rhinitis.

A great number of conventional antihistamines are rapidly absorbed when administered orally reaching therapeutic and peak plasma levels within one hour of dosing. However, their duration of action is relatively short, often requiring a three or four time daily dosage regimen.[18] Clemastine on the other hand exhibits peak plasma levels at three hours[19] and possesses a long duration of action requiring only twice daily dosage. This property may provides a greater benefit to patient with seasonal allergic rhinitis which is most intense in the very early morning.[20] Taking a long-acting antihistamine at nigh on requirement may prove more successful in controlling the rhinitis at the most intense part of its daily cycle, than medication employed in the morning on arising when symptoms already have begun to occur.

Based on our experience from this study, clemastine seems to be a very useful

drug for the treatment of allergic rhinitis. Its long duration of action with twice daily administration and the low sedation profile compared to a well established reference compound, represent important benefits. However, the response to antihistamine, varies from patient to patient, thus we should try first and then select the right antihistamine to the right patient.

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