ORIGINAL RESEARCH ARTICLE

Tanaffos (2004) 3(12), 57-62

Combination of H1 and H2 Receptor Antagonists in Treatment of Asthmatic Patients

Majid Mirsadraee [1], Parisa Saeedi [1], Habib Emami [2]

[1] Department of Internal Medicine, Islamic Azad University of Mashad, [2] Epidemiology and Biostatistics Division, NRITLD, Shaheed Beheshti University of Medical Sciences and Health Services, MASHAD-IRAN.

ABSTRACT

***Introduction**: It is believed that H1 histamine receptor blocker does not have any beneficial effect on treatment of asthma, but combination of H1 and H2 receptor antagonists has a good effect on chronic resistant urticaria. Since the pathogenesis of asthma and urticaria are similar, we expected that this combination might have some benefits in treatment of asthma.*

***Materials and Methods**: In this study, we selected 66 patients with known diagnosis of asthma in acute exacerbation of their disease. The patients did not have any history of smoking, GERD, postnasal discharge and rhinorrhea, but experienced symptoms such as cough, dyspnea, and wheezing.*

All patients underwent spirometry (Spirosift 3000 Fukuda Denshi), and those who had obstructive pattern and improved FEV1 more than 20% after using bronchodilator were randomly entered either the case or control groups after signing the consent. Spirometry parameters were VC, FVC, FEV1, FEV1/FVC, PEF, FEF 25-75%, MEF25%, and MEF 50%.

Phase 1: Case group treated with 0.5 mg/kg prednisolone and salbutamol orally plus terfenadine (bid) and Ranitidine (tid), for one week.

Phase 2: Case group treated with salbutamol and beclomethasone spray with antihistamines as mentioned, for two weeks.

Phase 3: Same as phase two for one month. Spirometry was done at the end of each phase.

In control group since exclusion of corticosteroid and bronchodilator from treatment was dangerous, management was similar to the case group. The only exception was the omission of antihistamines.

Statistical analysis: Chi-square was used for interpretation of qualitative variables. F statistics and Kruskal Wallis tests as well as paired t- test were used for comparison of changes in spirometry findings.

***Results**: 66 patients finished first and second phases and 24 patients went through the third phase. M/F ratio was 2/3, median age was 33 years in both groups (range10-70 yrs.). Comparison of symptoms between case and control groups showed that in study group during second phase, cough improved more than control group. Otherwise, there were no significant differences in symptoms and signs of the two groups. During all three phases, spirometry measurement showed no significant difference between study and control group, except for MEF25% that improved in study group more than control group in the second phase.*

Conclusion**: Corticosteroids and β-2 agonists are very potent and effective drugs in treatment of asthma. Addition of H1 and H2 histamine receptor antagonists to standard therapy of asthma has minimal effect but in case of troublesome cough that is not relieved with that treatment, addition of antihistamines may be beneficial.* ***(Tanaffos2004; 3(12): 57-62)

***Key words**: Asthma, Antihistamines, H1 antagonist, H2 Antagonist*

Correspondence to: Mirsadraee M

Tel: +98-5118617949

Email address: majidmirsadraee@yahoo.com

INTRODUCTION

Asthma is a common clinical condition and new treatments could help to improve this state and the quality of patients' life. H1 receptor blockers are not known to be effective in the treatment of Asthma (1). However, a combination of H1 and H2 receptor antagonists are thought to be effective in the treatment of chronic resistant urticaria (3). As there are similarities in the immunological pathogenesis of asthma and urticaria, we designed this study to evaluate the effect of H1 and H2 antagonist combination on symptoms and physiologic parameters of asthma.

MATERIALS AND METHODS

We performed a prospective, randomised and controlled clinical trial in outpatient clinic of Aria hospital (Mashad) to evaluate the effect of H1 and H2 antagonist combination on asthma outcome.

1- Patient selection:

Newly diagnosed chronic asthmatic patients or those diagnosed for the first time with acute exacerbation were assigned equally into study and control groups by block randomisation. Criteria for the enrolment of asthmatic patients were based on clinical manifestations (cough, dyspnea, and wheeze) and spirometry examinations (Spirosift 3000 Fukuda Denshi). Criteria for spirometry examination result included an obstructive pattern with an improved FEV1 of more than 20% after bronchodilator usage. Patients with a history of smoking and resistant asthma were excluded from the study.

2- Medical treatment:

Patients were treated in three phases. These phases were 1 week, 2 weeks and 1 month in length, respectively. All patients received a standard treatment of prednisolone (0.5 mg/kg/day) and oral salbutamol (2mg/tid) in phase one followed by salbutamol (2 puff/tid) and beclomethasone spray (4 puffs tid after salbutamol) in the second and third phases. In addition to the above mentioned treatments, the study group received a combination of terfenadine (one tab twice daily) and ranitidine (150mg three times daily). During the study, contact with well known stimulatory agents was prohibited.

3- Outcome measurement:

A questionnaire was used to monitor the clinical improvement of asthma symptoms and signs (cough dyspnea and wheeze). Spirometry examination was performed at the end of each phase. Lung function parameters included VC, FVC, FEV1, PEF, FEF 25-75%, and MEF 25%. A percentile ratio of the examined parameters to the predicted values was calculated and the outcome was measured by the calculation of changes. Chi square, F statistics and Kruskal Wallis tests were used to compare the outcome measurements in both groups.

Ethical considerations: The project was approved by the Medical School Research Committee. We obtained informed consent from all patients to take part in the study. Due to dangers of acute asthma, we did not omit glucosteroid and salbutamol usage in control group.

RESULTS

66 patients (36 cases and 30 controls) finished the first and second phases. Forty- two patients dropped out from the third phase (because of complete resolution or other unknown reasons related to patients themselves) and only 24 patients finished this phase. Male to female ratio was 2 to 3. Median age was 33 years in general (range 10-70 yrs.). The median age for case and control groups was 36 and 24 years, respectively.

In the first phase, the symptoms and signs of asthma improved significantly in both study and control groups (cough, dyspnea and wheeze)($p=0.0002$) (table1). However, there was no significant difference between the two groups

(p=0.26). In the second phase, cough symptom improved more significantly in the case than the control group (p=0.041) (table 2). No other significant difference in symptoms and signs was noted between the two groups. In the third phase, symptoms did not get better and there was no significant difference between the two groups.

Table 1. Summary of clinical findings in patients with asthma treated with H1 and H2 blocker

Clinical findings	Phase of treatment	Asymptomatic	Mild	Moderate	Total	P value of case control
Cough	First	3	13	50	66	0.15
	Second	35	27	4	66	0.025
	Third	13	8	3	24	0.36
Dyspnea	First	1	18	47	66	0.37
	Second	49	17	0	66	0.15
	Third	17	4	3	24	0.4
Wheeze	First	0	10	52	62	0.25
	Second	22	29	13	64	0.2
	Third	11	9	4	24	0.5

Table 2. Improvement of cough in second phase of treatment of asthma with H1 and H2 blocker

	Positive history of cough	Negative history of cough
With H1 and H2 blocker	13	25
Without H1 and H2 blocker	18	10

Table 3. The most important spirometric results of second phase of treatment of asthmatic patients with H1 and H2 blocker

	VC	FVC	FEV1	PEF	PEF 25-75%	MEF 25%
Case	20.44	17.7	17.2	20	21	24.2
Control	15.14	17	20.4	18.1	19.5	18.4
p- value	0.23	0.25	0.38	0.65	0.76	0.35

Spirometry examination showed that at the end of each treatment phase, there were significant improvements in the air flow (p=0.0001) (table 3). However, there was no significant difference in the rate of improvement in the first and third phases between the study and control groups (p=0.090). In the second phase, however, MEF 25%, improved more significant in the study group than the control (p=0.05). In this phase, there was no other significant statistical difference in the lung function parameters.

DISCUSSION

Asthma is one of the most common obstructive lung diseases. Bronchial hypersensitivity leading to bronchial inflammation and spasm which is secondary to exogenous and somehow unknown material is thought to be the aetiology of asthma. Allergens first bind to the IgE on the surface of mastocytes. This leads to release of many mediators (such as histamine) which induces or enhances an asthma attack (type-I hypersensitivity). Histamine receptors in target organs consist of two types: H1 and H2 receptors are present in the bronchi and other organs (1,2,3).

Early studies showed that blocking H1 receptor was effective in the treatment of ordinary (4,5,6) and exercise asthma (7). However, later studies disapprove the role of H1 blockers in the complete resolution of asthma (8,9). Ketotifen as a new H1 blocker later proved to have some efficacy against asthma (10, 11).

H2 receptors are mainly present in heart and stomach (12). Eyre in 1973 (13) and Okpako in 1974 (14) found H2 receptors in the bronchi of cat, sheep and Guinea pig. A further in-vitro study by Dunlop et al. showed H2 receptor in human bronchi (15).

In 1973, Lichtenstein et al. suggested that inhibition of histamine effect was only possible by the blockage of H2 receptors rather than the H1 receptors. This effect was dose dependent (16). A

recent research on CD3 cells from bronchoalveolar lavage and peripheral blood of normal and asthmatic patients showed that histamine can increase IFN- γ, IL5, IL4 and intracellular CAMP. These effects can be blocked by H2 antagonist (17) which is important in asthma pathogenesis. Maconochie et al. (1) used H1 and H2 antagonists in 9 healthy volunteers who experienced asthma symptoms after inhalation of histamine. In this article, it was showed that H1 and H2 antagonists can not block the asthmatic change in volunteers, and these drugs can not substitute for the standard treatment of asthma by using glucocorticoid and leukotriene inhibitors (18, 19, 20, 21).Therefore, we considered a larger sample size and examined the effect of the treatment on true asthamtic patients.

Our results show that antihistamines have some effect on bronchospasm and most importantly can reduce cough symptoms in patients. The treatment should consist of administration of a H2 antagonist or combination of H1 and H2 receptor antagonists. This recommendation is more useful in patients with gastroesophageal reflux and those who experience reflux with β2-agonists and methylxanthines because these two drugs cause GERD.

REFERENCES

1. Maconochie JG, Woodings EP, Richards DA. Effects of H1- and H2-receptor blocking agents on histamine-induced bronchoconstriction in non-asthmatic subjects. ***Br J Clin Pharmacol*** 1979; 7 (3): 231-6.
2. Casterline CL, Evans R. Further studies on the mechanism of human histamine-induced asthma: the effect of an aerosolized H1 receptor antagonist (diphenhydramine). ***J Allergy Clin Immunol*** 1977; 59 (6): 420-4.
3. Meltzer EO. The use of anti-H1 drugs in mild asthma. ***Allergy*** 1995; 50 (24 Suppl): 41-7.
4. Rafferty P, Holgate ST. Terfenadine (Seldane) is a potent and selective histamine H1 receptor antagonist in asthmatic airways. ***Am Rev Respir Dis*** 1987; 135 (1): 181-4.
5. Chan TB, Shelton DM, Eiser NM. Effect of an oral H1-receptor antagonist, terfenadine, on antigen-induced asthma. ***Br J Dis Chest*** 1986; 80 (4): 375- 84.
6. Cookson WO. Bronchodilator action of the anti-histaminic terfenadine. ***Br J Clin Pharmacol*** 1987; 24 (1): 120- 1.
7. Clee MD, Ingram CG, Reid PC, Robertson AS. The effect of astemizole on exercise-induced asthma. ***Br J Dis Chest*** 1984; 78 (2): 180-3.
8. Schuller DE. Adverse effects of brompheniramine on pulmonary function in a subset of asthmatic children. ***J Allergy Clin Immunol*** 1983;72 (2): 175-9.
9. White J, Eiser NM. The role of histamine and its receptors in the pathogenesis of asthma. ***Br J Dis Chest*** 1983; 77 (3): 215-26.
10. Kabra SK, Pandey RM, Singh R, Seth V. Ketotifen for asthma in children aged 5 to 15 years: a randomized placebo-controlled trial. ***Ann Allergy Asthma Immunol*** 2000; 85 (1): 46-52.
11. Hoshino M, Nakamura Y, Sim JJ, Tomioka H. A comparative study of the effects of ketotifen, disodium cromoglycate, and beclomethasone dipropionate on bronchial mucosa and asthma symptoms in patients with atopic asthma. ***Respir Med*** 1998; 92 (7): 942-50.
12. Smythe MA, Zarowitz BJ. Changing perspectives of stress gastritis prophylaxis. ***Ann Pharmacother*** 1994; 28 (9): 1073-85.
13. Eyre P. Histamine H2-receptors in the sheep bronchus and cat trachea: the action of burimamide. ***Br J Pharmacol*** 1973; 48 (2): 321-3.
14. Okpako DT. A vasodepressor action of histamine mediated by H2-receptor activation. ***Eur J Pharmacol*** 1974; 29 (1): 10- 4.
15. Dunlop LS, Smith AP, Piper PJ. The effect of histamine antagonists on antigen-induced contractions of sensitized human bronchus in vitro [proceedings]. ***Br J Pharmacol*** 1977; 59 (3): 475 P.
16. Lichtenstein LM, Gillespie E. Inhibition of histamine release by histamine controlled by H2 receptor. ***Nature*** 1973; 244 (5414): 287- 8.

17. Krouwels FH, Hol BE, Lutter R, Bruinier B, Bast A, Jansen HM, Out TA. Histamine affects interleukin-4, interleukin-5, and interferon-gamma production by human T cell clones from the airways and blood. ***Am J Respir Cell Mol Biol*** 1998; 18 (5): 721- 30.
18. Williams RO 3rd, Patel AM, Barron MK, Rogers TL. Investigation of some commercially available spacer devices for the delivery of glucocorticoid steroids from a pMDI. ***Drug Dev Ind Pharm*** 2001; 27 (5): 401- 12.
19. Ekins-Daukes S, Simpson CR, Helms PJ, Taylor MW, McLay JS. Burden of corticosteroids in children with asthma in primary care: retrospective observational study. ***BMJ*** 2002; 324 (7350): 1374.
20. McMillan RM. Leukotrienes in respiratory disease. ***Paediatr Respir Rev*** 2001; 2 (3): 238- 44.
21. Tohda Y, Kubo H, Iwanaga T, Fukuoka M, Nakajima S. Influence of theophylline on activated lymphocytes and eosinophils in peripheral blood and sputum. ***J Int Med Res*** 2001; 29 (6): 528-36.