Ephedramine therapeutic effectiveness for allergic rhinitis treatment: a double blind placebo controlled trial

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Abstract

Background : Allergic rhinitis is a common allergic disease worldwide. To date there was no curable treatment. **Study design:** Double blind placebo controlled clinical trial. **Patients and Methods:** Ephedramine was evaluated as treatment for allergic rhinitis. One hundred and twenty subjects were included in the study. The patients was divided into two groups (A) and (B), given either placebo or ephedramine (acombination of pseudoephedrine HCl 60mg plus chlorpheneramine maleate 2.5 mg). The drug was given twice daily for subsequent four weeks. Patients with allergic rhinitis and associated conditions were involved in the study. **Results:** Our patients demonstrate a very well response to ephedramine; 44.8% had complete remission from congestion at the end of trial while 78.8% had remission from Rhinorrhoea, 71.1% remitted from sneezing and 80.4% had complete remission from pruritus. The corresponding values in placebo group were 31.5%, 31.5%, 17.8% and 31.4% respectively. Side effects of ephedramine include headache (32.7%), dizziness (27.7%), and dry mouth (21.8%). The same above side effects were reported in placebo group, but with lower frequency. **Conclusion:** Ephedramine was effective as treatment for allergic rhinitis and associated conditions with non significant side effects and minimized antihistamine effect of chlorpheneramine maleate by α-adrenergic effect of pseudoephedrine.

فعالية مادة الإفدرامين في علاج حساسية بطانة الأنف

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حساسية بطانة الأنف موجودة وعلى نطاق واسع حول العالم ولحد الآن لا يوجد علاج شافي للمشكلة وإنما التخفيف منها أجريت هذه الدراسة على عينة من المرضى بعد إعطائهم مادة الأفدرامين (60 ملغ من السيدوفدرين مع 2.5 ملغ من الكلوروفينرامين) أعطيت على شكل جرعتين في اليوم ولمدة أربعة أسابيع حيث كانت هنالك استجابة واضحة لهذه المادة (48.8%) ذهبت علامات الإحتقان بصورة كاملة أما رشح الأنف فقد توقف بنسبة (78.8%) كذلك فإن (71.1 %) اختفى العطاس منهم في حين إن حكة الأنف اختفت بنسبة (80.4 %) . أما بالنسبة للتأثيرات الجانبية للدواء وكانت (32.7 %) الم الرأس وكذلك (27.7 %) كان هنالك حالة عدم الإتزان أما جفاف الفم فقد وجد بنسبة (21.8 %). لذلك فإننا نستنتج ومن خلال هذه الدراسة ان مادة الافدرامين هي مادة فعالة في علاج حساسية بطانة الأنف.

Introduction

Allergic rhinitis is extremely common and affects approximately 10 – 2-% of general population[1]. The disease has been estimated to account for up to four billion US dollars in health care each year[2]. There are three components related to the cost of the illness. There are direct medical costs which include physician visit, procedures, hospitalization and medication. Indirect costs sustained by the patients business such as lost days of work, decreased productivity or days of school missed. Intangible costs are 'quality of life' issues and reflect the psychological aspect of the disease on the patient, the patient's family, and the community. These later two the indirect and intangible are most difficult to quantitative. However, if one spends less on direct cost, such as pharmacotherapeutic control of allergy, then both indirect and intangible costs may rise[3]. When a patient in experiencing the constellation of symptoms of rhinitis, combination product of antihistamine and long acting adrenergic agonist is often preferable. Examples of such agents include combination of pseudoephedrine with loratadine or terfinadine[4]. Since terfinadine and astemizole were linked to ECG QT prolongation and serious ventricular arrhythmia and high possibility of significant drug interaction[4]. Thus this study conducted to evaluate the combination of adrenergic agonist and H1 histamine antagonist as treatment for allergic rhinitis.

Materials and Methods

Study population

Individual with allergic rhinitis and related disorders are involved in the study. Any patient included in the trial may be identified as representative of some feature class of patients to whom the trial's finding may be applied. In addition, one wish to focus on the type of patient considered most likely to benefit from new treatment under investigation. However, one does not wish to be so restrictive about patient entry that the trial remains small and it's finding lack generality. The principle aspects to consider are: The disease state under investigation. Hence mean strict criteria of patient eligibility are needed. A comprehensive medical, environmental and life style history is essential. Clinical examination to determine the primary features of rhinitis. Secondary features may also occur in the oropharynx, middle ear, paranasal sinus, and conjunctivitis is often present[1]. Criteria for exclusion from the study are[5]: Any patient who receive treatment in previous 5 days; presence of lymphoid malignancies ; presence of thyroid disease; steroids therapy; diabetic patient or with immunossuppresion; presence of infection, common cold; patients with rhinitis symptoms due to, Neoplastic, foreign body, CSF Rhinorrhoea, neurogenic, medicamentosa.

Methods of patients evaluation

The evaluation of each patient at the start of the study needs to be done in an objective, accurate and consistent manner so that the research as a whole provides a meaningful assessment. Baseline assessment before treatment starts[5]. Base line assessment performed to measure the patients clinical condition, though in addition background information on personal characteristics (e.g age and sex), epidemiological informations, clinical history and family history also collected. Skin tests are performed to asses atopic status and to confirm sensitivity to allergens suspected of causing symptoms. Multiple positive tests are clear indication of atopy.

Spirometry done to all patients, by computerized spirometer available in Asthma and Allergy Center in Baghdad the result compared with predicted value.

Principal criteria of patient response

These include: Congestion/ Rhinorrhea /Sneezing /Pruritis /Nasal mucus appearance/ Nasal polyps/ Skin test/Eosinophilia and Serum IgE.

Study design

A randomized controlled clinical trial, A double blind placebo controlled trial.

Treatment schedule

Each patient included in the trial received treatment according to randomization list. One tablet twice daily for one week.

Results

Patients receiving ephedramine show a good response in comparison to patients receiving placebo. That is to say that 44.8% of patients who receive ephedramine have complete improvement from congestion ($P< 0.05$), 78.7% have complete improvement from Rhinorrhoea ($P<0.005$), 71.7% have complete improvement from sneezing ($P<0.005$) and 80.4% have complete remission from pruritus ($P<0.005$), (Table. 1). In patients receiving placebo only 28% had recovery from congestion and 64.9% have same congestion till fourth visit. Only 31.5% of patients received placebo and were presented with rhinorrhea, show improvement after fourth visit while 59.6% have no any improvement till the fourth visit. Complete remission from sneezing and pruritus shown in 17.8% and 31.5% respectively (Table. 1). While 32 from 56 patients that receiving placebo and have sneezing show no remission at the end of fourth visit. Pruritus still present in 33 from 54 patients (61.1%) in all four visits for placebo group. Considering the improvement at the second visit in the group of patient receiving ephidramine. The best results obtained for pruritus (43.9%) which show good response with less severity of symptoms at second visit. At third visit of patients receiving ephedramine, the best results obtained in patients with sneezing and a good response at third visit were demonstrated in 37.7%. Eosinophil count was measured in each visit weekly. In the second visit of ephedramine group, eosinophilia was detected in 50.9% as same as first visit but then decline to 20.8% in third visit (Table. 2). While in placebo group, 64.6% show eosinophil count as that of first visit, and 27.6% same as that of the second visit, and in fourth visit only 13.8% show the same eosinophil count as that of third visit (Table. 2). Side effects frequency in patients receiving ephedramine indicate that 32.7% have headache, so headache is prominent side effects of ephedramine, followed by dizziness (27.2%), dry mouth (21.8%), tiredness (14.5%), insomnia and nausea (12.7%). (Fig.4). In placebo group still headache is the prominent side effect (18.4%), followed by dry mouth (12.3%) and insomnia (10.7%). (Table. 3).

Table (1):- Patients response to ephedramine treatmnet

Sign/ Symptom	Patients response [percent]					
	2nd visit		3rd visit		4th visit	
	Ephed.	Control	Ephed.	Control	Ephed.	Control
Congestion	0	14	22.4	10.5	44.8	31.5
Sneezing	35.5	14.2	37.7	10.7	71.1	17.8
Rhinorrhoea	42	7.4	36.1	14.8	78.7	31.4
Pruritus	43.9	7.4	24.3	14.8	80.4	31.4

Ephed. : ephedramine.

Table (2):- Frequency of Eosinophilia

Percent in comparison to previous visit	Percent of eosinophilia					
	2nd visit		3rd visit		4th visit	
	Ephed.	Control	Ephed.	Control	Ephed.	Control
Same	50.9	64.6	50	27.6	20.8	13.8
Less	18.3	15.3	20.8	61.6	25	67.6
More	4.1	20	1.6	10.7	0	18.4

Table (3):- Frequency of side effects [percent]

Side effect	Epedramine Group	Control group
Headache	32.7	18.4
Tiredness	14.5	4.6
Insomnia	12.7	10.7
Dizziness	27.2	4.6
Constipation	7.2	3
Diarrhea	3.6	3
Nausea	12.7	3
Vomiting	3.6	1.5
Dry mouth	21.8	12.3

Discussion

All rhinitis symptoms including congestion, sneezing, rhinorrhea, and pruritus respond well to treatment since first week, except congestion which is not improved. In another study performed to measure the efficacy and safety of loratadine plus pesudoephedrine in patients with seasonal allergic rhinitis and mild asthma[6]. All four rhinitis symptoms responded within the first week and remained significantly improved in patients treated with loratadine plus pseudoephedrine compared with those given placebo. In the present study

patient receiving placebo have very little response as compared with those given ephedramine. To our knowledge, there was no study for the efficacy and safety of chlorpheneramine maleate plus pseudoephedrine but there were studies about the combination of anti-histamine (H_1- antagonist) plus pesudoephedrine done in Germany about the effect of semprex-D (acrivastine 8 mg plus pseudoephedrine 60 mg) and diphenhydramine on learning in young adults with seasonal rhinitis[7]. In the combination of antihistamine chlorpheneramine maleate 2.5 mg plus pseudoephedrine 60 mg (as in this study), the better symptom response demonstrated in patient receiving ephedramine was pruritus (80.4%), while in patient receiving placebo was congestion (31.5%). The least symptom response in patient receiving ephedramine was congestion (22.4%) while in patients given placebo it was sneezing (17.8%). Many studies have demonstrated that the efficacy of combination of antihistaime and oral decongestant drugs in the manegment of allergic rhinitis is superior to the efficacy of either component alone[8-10] Combination of drugs are also useful in the management of eosinophilic non allergic rhinitis and in the supportive treatment of viral and bacterial and may be helpful in some patients with nasal hyper -reactivity, particularly when associated with prominent rhinorrhea or post nasal discharge[5]. Ephedramine is helpful in relieving the symptoms of allergic rhinitis, and suppress allergic response to various antigens. This agreed with the study done by Nelson and co-workers[5]. Results from other studies[11,12]. suggest physiologic antagonism between the sedating effect of antihistamine and stimulating activities of pseudoephedrine. Earlier, Gaillard and Versuin had demonstrated the same antagonism between the separate and combined effects of an older more sedating antihistamine azatadine and psendoephedrine. The former impaired, the latter improved and the combination failed to affect performance in a a choice reaction time test[13]. A study done by Groselaude M. et al to evaluate the combination of antihistamine cetirizine 5 mg and pseudoephedrine retard 120 mg as treatment for asthma. They found that the combination was more effective. Sneezing, rhinorrhea, nasal and ocular pruritis were better controlled by combination than by pseudoephedrine alone and also better than cetirizine alone[14]. They found that the combination is well tolerated and superior to each given alone for moderate to severe allergic rhinitis. Regarding the side effects in patients receiving ephedramine, haedache is the most prominent side effect followed by tiredness. The problem of sedation with antihistamine is minimized by combination of α-sympathomimetic drug with it. The efficacy of sympathomimetic (as opposed to antihistamine) in relieving nasal congestion provides the rationale for the use of antihistamines and oral decongestant in single fixed-dose, cholenergic effects of antihistamine were minimized, and dry mouth was found only in 12 patients (21.8%) receiving ephedramine compared with (12.3%) in patients receiving placebo. Other side effects like dizzeness, constipation, diarrhoea, nausea and vomiting are found, putting in mind symptoms due to rhinitis itself like mouth breathing with dry mouth and headache, so no expected adverse reactions were observed, this agreed with another study for efficacy of combination (anti histamine plus pseudoephedrine)[14]. In Conclusions, many operational problems faced in this study like discontinuation of the

treatment by the patients, non compliance with the protocol or treatment failure. Another problem is difficulty to follow-up the patient because of personal or environmental factors or because of fearing of possible adverse reaction. Despite these problems, the study did have some positive being on the few if any study efficacy and safety of the drug. Ephedramine is effective in treatment of rhinitis symptoms especially pruritus, rhirorrhea, and sneezing it is more comfortable for the patients because of simple taken twice daily and good response. Majority of patients with allergic rhinitis or associated conditions have good response to ephedramine. The drug is desirable by most of the patients because of minimal sedating effect of antihistamine, less dry mouth, less dizziness and less effect on performance of the patient. Minor sedation effect on driving, learning or operating machinery was recorded.

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