Comparison of the efficacy of inhaled budesonide and oral choline in patients with allergic rhinitis

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ABSTRACT

Objectives: A single blind parallel group study was conducted to evaluate the effects of oral choline [given as tricholine citrate (TRI)] in patients with allergic rhinitis, and compare its efficacy with intranasal budesonide (BUD).

Method: The study was conducted at the Department of Respiratory Medicine, Vallabhbhai Patel Chest Institute, Delhi, India from February 2001 to April 2002. Sixty patients were randomized into 2 groups after a run-in period of 2 weeks. Group A received intranasal BUD 200 µg twice daily and group B received TRI 500 mg thrice daily. The patients were reviewed every 2 weeks up to 8 weeks. The mean individual symptom score, total symptom score and drug score were significantly reduced in both groups ($p<0.05$) compared to baseline values, with maximum effect occurring within 4 weeks of therapy.

Results: Budesonide showed statistically significant reduction ($p<0.05$) in all the outcome parameters, when compared to TRI. Crossover study between the 2 treatment groups also showed similar results. Seventy-six percent of patients with BUD and 43% of patients with TRI found the drug to be effective.

Conclusion: Both intranasal BUD and oral TRI are effective in relieving symptoms of allergic rhinitis. Budesonide was found to be the statistically superior drug.

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Allergic rhinitis is immunoglobulin E mediated inflammatory disease that is characterized by atopy and clinically with nasal congestion, rhinorrhea, sneezing, itching of nose and post nasal discharge. It may be characterized by an early and late phase response. Intranasal corticosteroids are the most effective class of drugs for controlling the symptoms.[1] Amongst the various steroid sprays, budesonide (BUD) has been found to be very effective.[2] Drawbacks of BUD include lack of immediate clinical effect, and the need for regular administration.

Choline is a lipotropic factor used for mobilization of fat from the liver and essential for the formation of neurotransmitter acetylcholine.[3] Choline is used in phosphatidyl choline (PC) synthesis by the de-novo or the Kennedy pathway.[4] Choline, by increasing the PC level, leads to increase in the membrane PC and thereby decreasing the transmethylation pathway that ultimately leads to decrease in lipophosphatidyl choline (LPC) level and thus decrease in arachidonic acid and leukotrienes. Lipophosphatidyl choline is an important agent for the depolarization of cell membrane, β-adrenergic sub sensitivity, cholinergic over activity and mediators' release thereby, producing inflammatory changes.[5,6]

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Decrease in LPC level restores sensitivity of β-adrenergic receptors and decrease mediators release.[7] Choline was found to have a LPC lowering activity in tracheal tissue of guinea pigs and in the plasma of asthmatics.[8-10] Ganley et al[11] who found suppression of joint anaphylaxis in guinea pigs, first noticed an evidence of anti-inflammatory action of choline. Smith[12] demonstrated inhibition of the release of histamine and slow–reacting substance of anaphylaxis in sensitized guinea pigs. Choline was used as an anti-inflammatory drug in the management of bronchial asthma and was found to be useful in achieving clinical stability, improving pulmonary functions in asthmatics[10] and reducing airway reactivity. Its efficacy has been proven in treating asthma in clinical trials from our laboratory.[10,13,14] Choline magnesium trisalicylate (CMT) was used in one study and was reported beneficial in aspirin induced asthma.[15] The immunological and pathophysiological nature of inflammation in asthma and allergic rhinitis are similar and hence, the present study was aimed to determine the efficacy of oral choline in treating allergic rhinitis and comparing the effect with intranasal BUD.

Methods. Patients presenting with symptoms of allergic rhinitis having at least 2 of the following 5 symptoms (blocked nose, runny nose, nasal itching, sneezing and runny eyes), were included in the study. Sixty patients were included after fully informed consent. The study was conducted in the Department of Respiratory Medicine, Vallabhbhai Patel Chest Institute, Delhi, India. The age group of the patients was 15-45 years to avoid the effect of age on allergic status. All were skin test positive with common aeroallergens. There was no history or spirometric evidence of bronchial asthma in these patients. Current and past smokers with co-existing lung disease or any systemic illness likely to affect the patient management or those on allergen immunotherapy were excluded.

The initial investigations included, hemogram, total leukocyte count (TLC), differential leukocyte count (DLC), chest x-ray post anterior view and water's view of paranasal sinuses, spirometry and skin testing against common aeroallergens. A run in period of 2 weeks was allowed where the patients were allowed to take oral antihistamines and taught proper technique of nasal spray inhalation. Their drug score and symptom score were noted. They were assigned into 2 groups after matching the age, gender and severity of disease. Group A (n=30) consisted of patients taking intranasal BUD 200 μg twice a day while group B (n=30) consisted of patients taking choline 500 mg thrice a day orally as tricholine citrate (TRI) syrup. They continued their respective medicines for 8 weeks. The parameters for evaluation included symptom score, concomitant drug score and personal assessment. The patients were asked to keep a daily record of the symptoms, which were rated on a 3 point scale as 0, 1, 2, 3. The patients were also asked to keep a daily record of rescue medication required, which was noted on a point scale as 0, 1, 2, 3, 4. The patients were asked to report every 2 weeks, and during their visits the symptom score and drug score was noted. Any side effect or drug toxicity was also assessed. A 2 weeks washout period was allowed and then the patients were shifted to another group for cross-over study for 8 weeks. There were a total of 13 patients in the cross-over study as the remaining patients had subjective improvement in their symptoms and did not wish to be part of further study. They were put in 2 cross-over study groups: Group A (n=6) (BUD→TRI), were the patients previously receiving intranasal BUD. They were then given oral TRI 500 mg thrice daily. Similarly, group B (n=7) (TRI→BUD) were patients previously receiving TRI, and they were given intranasal BUD 200 μg twice daily. The results were analyzed using the Statistical Package for Social Sciences software employing Student t-test, paired t-test, unpaired t-test and Analysis of Variance.

Results. The characteristics of 60 patients including age, gender, duration of symptoms, type of symptoms and family history was noted. These characteristics of Group A and B were comparable. The total mean symptom score in the BUD group, which was at start 37.23 ± 13.24, declined to 17.80 ± 10.77 at 2 weeks and 7.43 ± 5.69 at 8 weeks. In the tricholine group (TRI) the total mean symptom score declined from 43.37 ± 10.93 at the baseline to 33.67 ± 15.89 at 2 weeks and 20.63 ± 14.50 at 8 weeks. The decrease was statistically significant ($p<0.05$) in both groups at both points as shown in **Table 1**. The total mean drug score in the BUD group, which was at start 15.40 ± 5.47, declined to 7.90 ± 4.11 at 2 weeks and 1.73 ± 3.72 at 8 weeks. In the tricholine group (TRI) the total mean drug score declined from 14.83 ± 3.12 at the baseline to 14.10 ± 6.81 at 2 weeks and 7.27 ± 7.28 at 8 weeks. The decrease was statistically significant ($p<0.05$) in both groups at both points as shown in **Table 1**. Comparison of the change in mean individual symptom score (namely, for rhinorrhea, sneezing, nose block and nasal itching) from baseline value also showed a statistically significant change ($p<0.05$) in both groups. Comparison of the change in the mean total symptom score and mean drug score between the 2 groups showed statistically better response with BUD ($p<0.05$) when compared to tricholine. (**Table 2**) Changes in the individual symptom score from baseline between the 2 groups were compared. There was statistically significant

improvement in rhinorrhea, sneezing and nose blockage with BUD and TRI. In nasal itching, no statistically significant improvement was found in the BUD group or the TRI group. In the cross-over study, statistically significant improvement in total mean symptom score and drug score was noted during both phases of treatment, namely, initial phase and cross-over phase. These results were obtained both in group A (drug BUD→TRI) and group B (drug TRI→BUD). But when the 2 treatment periods were compared, a significant reduction ($p<0.05$) in drug score and symptom score was found when patients were treated with BUD compared to TRI. (**Table 3**) In personal assessment results, 23 of the 30 patients (76%) in the BUD group noted that BUD was noticeably effective in relieving their symptoms compared to 13 (43%) in the TRI group. Four patients reported adverse effects during BUD treatment. Two experienced dryness of nose and 2 suffered transient nose bleeds. In the TRI group, one patient reported gastric discomfort while 2 complained of loose stools. None of these adverse effects were serious and no patient had to discontinue the treatment.

Table 1 - Total mean of nasal symptom score and drug score in the 2 treatment groups at every 2 weeks up to 8 weeks.

Weeks	Symptom score		Drug score	
	Group A (BUD) N=30	Group B (TRI) N=30	Group A (BUD) N=30	Group B (TRI) N=30
0	37.23 ± 13.24	43.37 ± 10.93	15.40 ± 5.47	14.83 ± 3.12
2	17.80 ± 10.77	33.67 ± 15.89	7.90 ± 4.11	14.10 ± 6.81
4	10.10 ± 7.47	27.67 ± 17.74	2.27 ± 2.52	8.93 ± 8.11
6	9.20 ± 9.41	24.36 ± 15.1	2.07 ± 2.85	8.07 ± 7.69
8	7.43 ± 5.69	20.63 ± 14.5	1.73 ± 3.72	7.27 ± 7.28

BUD - budesonide, TRI - tricholine citrate

Discussion. The current study demonstrated that both intranasal BUD and tricholine are effective in the treatment of allergic rhinitis and produce significant reduction in symptoms. Maximum improvement occurred within the first 4 weeks of therapy. The BUD treated group showed much more clinically and statistically significant reduction in all nasal parameters except nasal itching, total mean symptom scores and drug score when compared with tricholine treated group.

Table 3 - Cross-over study showing mean drug score and mean symptom score for both groups recorded every 2 weeks.

Weeks	Mean drug score		Mean symptom score	
	BUD (week 0-8) → TRI (weeks 10-18)	TRI (week 0-8) → BUD (weeks 10-18)	BUD (week 0-8) → TRI (weeks 10-18)	TRI (week 0-8) → BUD (weeks 10-18)
0	15.4 ± 5.47	14.83 ± 3.12	37.23 ± 13.24	43.37 ± 10.93
2	7.9 ± 4.11	14.1 ± 6.81	17.8 ± 10.77	33.67 ± 15.89
4	2.27 ± 2.52	8.93 ± 8.11	10.1 ± 7.47	27.67 ± 17.74
6	2.07 ± 2.85	8.07 ± 7.69	9.2 ± 9.41	24.36 ± 15.1
8	1.73 ± 3.72	7.27 ± 7.28	7.43 ± 5.69	20.63 ± 14.5
10	4.8 ± 1.30	9.71 ± 2.06	38.01 ± 9	41.1 ± 8.37
12	5.6 ± 2.41	4.43 ± 0.98	33.7 ± 16.61	17.29 ± 5.25
14	6.4 ± 1.52	2.86 ± 1.68	24.71 ± 17.10	10.0 ± 5.39
16	6.0 ± 2.12	1.86 ± 1.35	21.11 ± 11.89	8.14 ± 3.8
18	4 .0 ± 0.71	1.14 ± 0.40	19.1 ± 9.25	7.57 ± 1.43

Weeks 8-10 are wash out period where no drugs are given
BUD - budesonide, TRI - tricholine citrate

Table 2 - Comparison of change in mean total symptom score and mean total drug score between 2 treatment groups at 2 weeks and 8 weeks.

Weeks	Change in symptom score			Change in drug score		
	Group A (BUD) N=30	Group B (TRI) N=30	*p* value	Group A (BUD) N=30	Group B (TRI) N=30	*p* value
2	19.33 ± 19.53	10.43 ± 16.58	0.02	7.50 ± 5.10	0.73 ± 6.73	0
4	27.33 ± 14.71	15.33 ± 13.33	0.03	13.13 ± 5.56	5.90 ± 7.90	0
6	26.56 ± 16.71	19.32 ± 14.01	0.03	13.33 ± 6.01	6.77 ± 7.64	0
8	29.53 ± 13.19	21.50 ± 16.59	0.04	13.67 ± 6.55	7.57 ± 7.33	0

BUD - budesonide, TRI - tricholine citrate

The cross-over study also corroborates the findings of the main study. Budesonide was also rated higher as far as patient preference was concerned. The results using BUD in this study are similar to other studies on allergic rhinitis using intranasal BUD. One such study compared BUD with oral terfenadine, which also showed BUD to be superior.[16] Intranasal BUD has been compared with oral terfenadine, oral disodium chromoglycate and flunisolide and beclomethasone nasal sprays[16-18] in different studies and all of them found BUD to be superior. The results of the present study were found to be consistent with the results of intranasal BUD in treatment of allergic rhinitis as shown in previous studies. Both drugs, namely, BUD and TRI were found to be very safe and well tolerated. Long term studies have confirmed the efficacy and safety of intranasal BUD. Although no long term studies on TRI are available, but in studies using TRI earlier[10,13,14] and in our study, the drug was found to be safe. Choline has been used in aspirin sensitive asthmatic individuals as CMT (introduced in the market in 1978) for the treatment of rheumatoid arthritis.[19,20] Its anti-inflammatory and analgesic effectiveness are similar to that of aspirin and other nonsteroidal anti-inflammatory drugs. Choline magnesium trisalicylate did not provoke any adverse effect on the respiratory tract or any other side effects except for some patients complaining of tinnitus and headache.[15] Choline has anti-inflammatory and anti-anaphylactic properties. Its role in asthma has been studied.[10] Although allergic rhinitis has a similar inflammatory basis of disease and pathogenesis, evaluation of choline as an anti-inflammatory agent in allergic rhinitis has not been tried previously.

The present study suggests that choline may have a similar anti-inflammatory role in allergic rhinitis. Treatment of allergic rhinitis should be fast acting, well tolerated, safe and should retain its efficacy even when taken irregularly. At present, no single treatment encompasses all these criteria. Oral choline fulfills most of these criteria of an effective oral drug for allergic rhinitis but more clinical trials are needed to determine the dose and duration of treatment. Therefore, it may be concluded from the study that the intranasal BUD and oral TRI are effective in relieving most of the symptoms of allergic rhinitis. Budesonide as compared to TRI was found to be statistically superior drug with patients having lesser symptoms, especially nose blockage. Tricholine that has been used for the first time in rhinitis is also a useful drug and it is recommended that more clinical trials, especially using different dosage are needed to firmly establish the role of choline in allergic rhinitis. However at present, it can be used along with intranasal steroids.

References

1. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and Management of Rhinitis. Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. ***Ann Allergy Asthma Immunol*** 1998; 81: 463-468.
2. Mygind N. Glucocorticosteroids and rhinitis. ***Allergy*** 1993; 48: 476-490.
3. Danford DE, Manro HN. Water-soluble vitamins. In: Godman LS, Gilman A, editors. The pharmacological Basis of Therapeutics. 6th ed. New York (NY): Macmillan; 1980. p. 82-86.
4. Pelech SL, Vance DE. Regulation of Phosphatidyl choline synthesis. ***Biochim Biophys Acta*** 1984; 779: 217-251.
5. Kunos G, Young MS, Nickerson M. Transformation of adrenergic receptors in myocardium. ***Nature*** 1973; 241: 119-120.
6. Sun AY, Sun GY. Functional role of Phospholipids of synaptosomal membrane. ***Adv Exp Med Biol*** 1976; 72: 169-197.
7. Morita Y, Chiang PK, Siragonian RP. Effects of inhibitors of transmethylation on histamine release from human basophils. ***Biochem Pharmacol*** 1981; 30: 785-791.
8. Nath P, Joshi AP, Agarwal KP. Biochemical correlates of airway hypersensitivity in guinea pig: Role of lipophosphatidyl choline. ***J Allergy Clin Immunol*** 1983; 72: 351-358.
9. Agarwal KP, Nath P, Agarwal MK, Joshi AP. Increased activity of lecithin cholesterol acyl transferase (LCAT) in asthma (abstract). ***Fed Proc*** 1985; 4: 601.
10. Chhabra SK, Wadhera NR, Gaur SN. Prophylactic treatment of Bronchial Asthma with Theophylline, Disodium Chromoglycate and Choline. ***Indian J Chest Dis Allied Sci*** 1987; 29: 65-76.
11. Ganley OH, Graessle OE, Robinson HJ, Rahway NJ. Anti-inflammatory activity of components obtained from egg-yolk, peanut oil and soya-bean lecithin. ***J Lab Clin Med*** 1958; 51: 709-714.
12. Smith WG. The anti-anaphylactic activity of ethanolamine and choline. ***J Pharm Pharmacol*** 1961; 13: 1-11.
13. Gaur SN, Aggarwal G, Gupta SK. Use of LPC antagonist, choline, in the management of bronchial asthma. ***Indian J Chest Dis Allied Sci*** 1997; 39: 107-113.
14. Gupta SK, Gaur SN. A Placebo controlled trial of two dosage of LPC antagonist—choline in the management of bronchial asthma. ***Indian J Chest Dis Allied Sci*** 1997; 39: 149-156.
15. Szczeklik A, Nizankowska E, Dworski R. Choline magnesium trisalicylate in patients with aspirin-induced asthma. ***Eur Respir J*** 1990; 3: 535-539.
16. Weeke B, Davies RJ, Okuda M. Allergy diagnosis in vivo. In: Myging N, Weeke B, editors. Allergy and vasomotor rhinitis: clinical aspects. Copenhagen **(**Denmark**)**: Munksgaard; 1985. p. 97-107.
17. McArthur JG, Higgins AJ. A comparison of budesonide and BDP aqueous sprays on treatment of hay fever. ***Allergy*** 1998; 43 (suppl): 14.
18. Bjerrum P, Ulum P. Treatment of seasonal allergic rhinitis with budesonide and disodium cromoglycate. ***Allergy*** 1985; 40: 65-69.
19. Blechman WJ, Lechner BL. Clinical comparative evaluation of choline magnesium trisalicylate and acetylsalicylic acid in rheumatoid arthritis. ***Rheumatol Rehabil*** 1979; 18: 119-124.
20. Ehrlich GE, Miller SB, Zeiders RS. Choline magnesium trisalicylate versus ibuprofen in rheumatoid arthritis. ***Rheumatol Rehabil*** 1980; 19: 30-41.