A ^{99m}Tc-DTPA ventilation study in monitoring the effect of budesonide in asthmatic children

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Abstract

This study was performed *to identify* the role of technetium-99m diethylene triamine penta-acetic acid (^{99m}Tc DTPA) aerosol ventilation scintigraphy in the initial assessment and follow-up of children with bronchial asthma. *In this prospective study* conducted over a period of 2 years, 45 children (35M, 10F) aged 6-12 yrs (8.4 ± 2.2 years) with newly diagnosed moderate persistent bronchial asthma were included. Peak expiratory flow (PEF) was measured and asthma symptom scores were calculated. Ventilation scintigraphy was performed after inhalation of ^{99m}Tc DTPA aerosol. The studies were repeated after 4 weeks of treatment with 400mcg budesonide daily. Pre and post treatment ventilation patterns were described, semi-quantified and compared. *Three patterns of ventilation were observed*: a) homogenous (19/45), b) central airway deposition (21/45) and c) inhomogenous (5/45) with corresponding central: peripheral counts per pixel ratio of 1.265, 1.865 and 1.324 respectively. Ventilation pattern showed improvement (more counts in the periphery) in 22/45 children. Sixteen of 45 patients showed homogenous ventilation in both baseline and follow-up studies; abnormal central deposition was seen in both studies in 2/45. Five out of 45 children (3 with initial homogenous and 2 with initial inhomogenous patterns showed worsening on the follow-up scan after 4 weeks. *In conclusion,* semi-quantitave ventilation scintigraphy with ^{99m}Tc DTPA aerosol in asthmatic children repeated after 4 weeks treatment with budesonide showed better correlation with clinical symptom scores than PEF rates in monitoring response to treatment.

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Introduction

Bronchial asthma is the most common chronic respiratory disorder of childhood, with an ever increasing prevalence worldwide ranging variably from 1% to 18% [1-3]. The International Study of Asthma and Allergies in Children (ISAAC) has shown 3%-17% prevalence of atopic disorders like asthma, allergic rhinoconjunctivitis, and atopic eczema in different areas of India [4].

The status of asthma can be judged and monitored by symptoms, or objectively by means of measurements like forced expiratory volume in 1sec (FEV1), or by the ratio of FEV1 to forced vital capacity (FEV1/FVC) or by peak expiratory flow (PEF) [1]. However these investigations are effort dependant**,** and require high degree of motivation and cooperation from the patient**,** and therefore may not be sufficiently reliable [5, 6]. Radionuclide lung ventilation scintigraphy is semi-quantitative**,** effort independent and better reproducable. The radiation burden to the children from this study is not more than 0.5mSv [7]. Additional information from the scans of this technique is available as compared to spirometry. Our study was carried out to assess the utility of this lung investigation study in asthmatic children before and after treatment with budesonide.

Patients and methods

In a prospective study conducted over a period of 2 years, 45 children, 35 male and 10 female 6-12 years of age with moderate persistent bronchial asthma [8,10] were included. None of these children experienced any difficulty in performing the procedure for ventilation scintigraphy. The study was approved by the thesis committee of our Institute. Patients presenting with transient wheeze mimicking asthma such as following respiratory tract infections, children with acute severe asthma, and children less than 6 years of age were not included in the study. Subjects with a history of treatment with a bronchodilator or hospital admission during the preceding week with co-morbid respiratory conditions, active tuberculosis and congenital heart disease were also excluded.

Baseline measurements

Peak expiratory flow measured by mini Wright's peak flow meter (mini Wright Cat No 3103001, U.K.) and percentage calculated against the expected/predicted as per Indian norms of Parmar et al (1977) [9] were recorded.

Asthma symptom score was calculated from a symptom diary maintained by the child and/or the parents over the preceding seven days, retrieved from the case files. In the diary records, 6 items were scored by history of cough, wheezing, difficulty in breathing, missing school, exercise intolerance and use of rescue medication. A score of zero was given for absence and 1 for presence of each of the items. Thus the total weekly score could vary from 0 to 42. The symptoms' diary was reviewed at each visit and total score was calculated and recorded (Table 1).

Ventilation scintigraphy

Ventilation scintigraphy was performed in all patients using technetium-99m diethylene triamine penta-acetic acid (^{99m}Tc DTPA) in the dosage of 0.37-0.74MBq/kg through the inhaled route using a nebuliser [7]. Patients stood in front of the nebuliser. Two mL of ^{99m}Tc DTPA containing the required dose were added to the nebuliser chamber. The mouthpiece was placed in the subject's mouth and after ensuring that there were no leaks, the nose was clipped. The patient was asked to breathe normally, through the mouthpiece for a period of 4min. Thereafter the mouthpiece was removed and the throat rinsed to reduce contamination persisting in the mouth. Static images were acquired on a dual head large field of view gamma camera (Ecam, Siemens; Erlangen, Germany) coupled with a low energy general purpose collimator in the anterior, posterior, both lateral and oblique views; 200,000 counts were acquired per view.

Table 1. *Clinical parameters of the study group at baseline and follow-up after 4 weeks*

	Baseline	Follow-up
Symptom score*	11.87 (10.29-13.36)	1.26 (0.54-1.97)
PEFR percentage*	81.09 (76.1-86.06)	88.17 (83.9-92.4)
Homogenous ventilation*	19	30
Inhomogenous ventilation	5	1
Central deposition*	21	14

*PEFR, Peak expiratory flow rate, * statistically significant P<0.05*

Image interpretation

The ventilation images were compared with reference images that depicted the bronchopulmonary segments by two nuclear medicine physicians (RK and AB). The pattern of tracer deposition in the airways was assessed on the ventilation scan and defects, if any, were then correlated.

Ventilation scans were visually categorized into the following patterns: a) a pattern of homogenous ventilation was defined as one where uniform aerosol deposition was noted throughout the lung fields on both sides. b) Relatively greater aerosol deposition in the trachea and the proximal lung area was defined as a pattern of predominantly central deposition. c) Patchy aerosol deposition throughout the lung or presence of irregular clumps of aerosol deposition was defined as an inhomogenous pattern of ventilation (Table 2).

In the ventilation images, regions of interest (ROI) were drawn manually over the central one third and peripheral two thirds of the respective lung fields in both anterior and posterior images of the baseline study. Care was taken to maintain the ratio of the number of pixels in the central region to that in the peripheral region, to approximately 1:3. The stomach was excluded from these regions. The ROI were directly copied onto the corresponding anterior and posterior follow-up images using standard available software. The geometric means of the counts within the central and the peripheral regions from the anterior and posterior images were obtained. The ratio of the mean counts in the central region to those in the periphery (C/P ratio) was obtained in both lungs separately. Considering asthma as a global pulmonary pathology, mean counts from both lungs were also obtained for both baseline and follow-up studies. Comparing the baseline and the follow-up studies, patients' response to treatment was categorized as follows: a) Improvement, defined as a pattern

Table 2. *Comparison of baseline study parameters*

	Pattern of radio-aerosol distribution		
	Homogenous (n=19)	Inhomogenous (n=5)	Central (n=21)
Mean C/P ratio (95% CI)	1.265 (1.21-1.31)	1.324 (1.14-1.50)	1.894 (1.68-2.10)
PEFR% (95% CI)	85.07 (76.3-93.8)	81.8 (60.1-103.4)	77.33 (70.6-83.9)
Symptom score (95% CI)	11.1 (8.8-13.6)	11.8 (3.8-19.7)	12.5 (10-15.1)

CI, Confidence interval; C/P, Central to peripheral ratio; PEFR, Peak expiratory flow rate

of predominantly central deposition or inhomogenous ventilation changing to a homogenous pattern in the follow up study. b) No change, when both baseline and follow-up studies showed similar patterns of ventilation either homogenous, central deposition, or inhomogenous. c) Worsening, when homogenous ventilation in the baseline study turned into either an inhomogenous pattern or a pattern of central deposition.

Treatment protocol

Based on the severity of persistent asthma, children were prescribed treatment according to the practice followed in the Pediatric Asthma Clinic of our institute. The subjects with moderate persistent asthma received 400mcg budesonide delivered by inhalation in two divided doses daily for 4 weeks. Budesonide is an inhaled corticosteroid that is used in the therapy of persistent asthma in children. It lowers the airway inflammation that is responsible for the manifestations of asthma. It is approved by the National Asthma Education and Prevention Program for treatment of asthma. All children were advised to take 200mcg salbutamol by inhalation route in case of any acute respiratory symptoms. While a detailed history of individual salbutamol use in the interim period between the two scans is not available, none of the patients used salbutamol on the day of the study.

Follow-up protocol

All children were followed-up after four weeks in the Asthma Clinic according to the established clinical protocol. They were evaluated based on the history of clinical symptoms during the preceding four weeks and examined clinically. Their symptom cards were reviewed and the asthma symptom score calculated for the four weeks of budesonide treatment preceding the follow-up examination. Each child underwent peak expiratory flow rate (PEFR) measurement and ventilation scintigraphy as described above, at the end of four weeks.

Statistical analysis

The data analyzed for distribution showed skewed distribution. Therefore a non parametric test (Kruskal Wallis test) was used to compare the groups and Wilcoxon signed rank test was used to determine if the changes in the variables from baseline to follow-up studies were significant.

Baseline study

A total of 19/45 subjects showed homogenous ventilation pattern (a) on the initial study despite being symptomatic. Inhomogenous distribution (b) was noted in 5/45 children while characteristic central airway deposition (c) was noted in 21/45 children. The C/P ratio in the group showing central deposition was significantly higher than that in the other two groups ($P<0.05$), while the symptom scores and PEFR were no different among the groups (Table 2).

Follow-up study

Clinical parameters of the study group at baseline and follow-up after 4 weeks are shown in Table 1. The symptom score and PEFR improved significantly in all children.

Scintigraphic findings

On follow-up, a total of 22/45 children showed improvement in the ventilation patterns with 14/45 improving to homogeneous pattern and 8/45 showing only minimal central aerosol deposition (Fig. 1). Despite improvement in the symptom score, 5/45 (3 with initial homogenous and 2 with initial inhomogenous patterns) showed worsening in the scan findings and 2/45 continued to show predominant central airway deposition of aerosols. Sixteen of 45 patients showed homogenous ventilation in both baseline and follow-up studies.

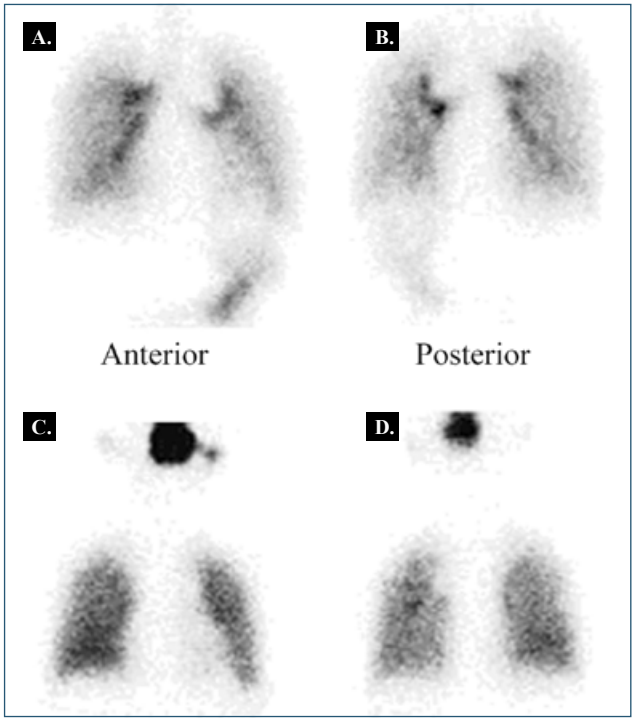
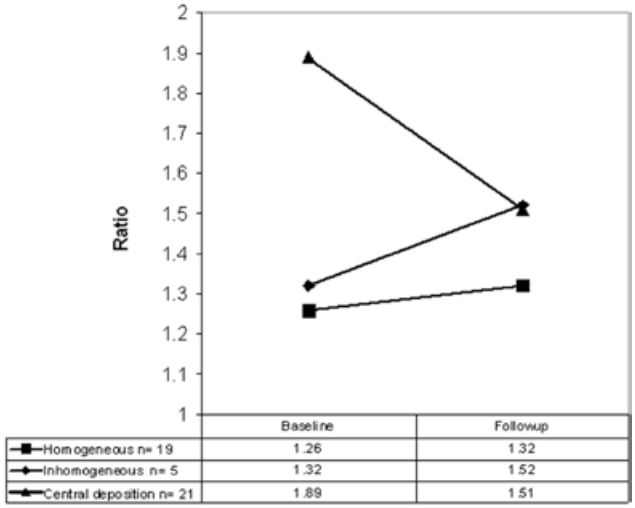


Figure 1. Aerosol ^{99m}TcDTPA ventilation scan showing central airway deposition in the baseline study (**A, B**) with homogenous ventilation at follow-up (**C, D**)

The mean C/P ratios of both lungs at baseline and after treatment in each of the three groups were compared. In the group showing baseline central airway deposition, there was a statistically significant change ($P<0.01$) from 1.89 to 1.51 after budesonide treatment. However, no significant change was detected in the groups showing homogenous and inhomogenous ventilation in the baseline study (Fig. 2).



upper line: central deposition n=21, medium line: inhomogeneous n=5, lower line: homogeneous n=19

Figure 2. Trend in the mean C/P ratio of both lungs in the three respective groups based on the findings on baseline study

In all children, there was better correlation of the scintigraphic findings (P=0.08) than the PEFR (P=0.35) to the symptom score. In the group of children who showed improvement the clinical scores, PEFR and C/P ratios showed significant improvement. In the children who continued to show central aerosol deposition, the clinical scores as well as the PEFR also did not change significantly from baseline to follow-up (P<0.05).

Discussion

Scintigraphy has been reported to demonstrate the airway obstruction effectively in the form of deposition of aerosol particles predominantly in the central airways [11-14]. More homogenous distribution of the aerosols into the peripheral lung has been demonstrated following broncho-dilator and steroid treatment. Scintigraphy has the advantage that it is performed on tidal respiration, which does not strain the patient. The ventilation scan also demonstrates the regional status of the airways in each lung individually. Aerosol particles have been shown to demonstrate airway changes in a similar way to that of gases [15]. We have used ^{99m}Tc DTPA aerosol particles for the ventilation study due to its availability, ease of preparation and low cost of the radiopharmaceutical (approximately 15 Euros per vial).

Others [16] evaluated 15 children on fluticasone treatment with pre and post treatment ventilation scans. In their study, the follow up scan after one week demonstrated improvement in peripheral ventilation in all. In comparison, our study included 45 patients followed-up after at least 4 weeks, as the maximum effect of treatment is noted after a period of 1-2 weeks. We also correlated the scintigraphic findings with clinical variables as described. The results of our study are consistent with other authors who observed ventilation abnormalities even in asymptomatic children [15, 17-20]. When quantification was taken into account, the scans showing central airway deposition demonstrated a C/P ratio greater than 1.5 in most cases. Improvement was not uniform in all subjects, with some showing residual obstruction after 4 weeks of treatment. It is possible that longer follow-up may better show long term effect of treatment in these children. To the best of our knowledge, follow up ventilation scintigraphy after budesonide has not been reported previously in bronchial asthma. Both budesonide and fluticasone are considered second generation inhaled corticosteroids with enhanced anti-inflammatory activity as compared to beclomethasone due to less first pass metabolism. However, systematic reviews of comparisons show similar efficacy of both drugs [10]. Budesonide is in itself the generic name of the drug. Its chemical form is (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde.

Our method was different from that used in some other studies where the counts in an automatically defined central region of interest were expressed as percentage of the whole lung counts estimated only from the right lung in the posterior view and expressed as diffusion percentage [16]. The automated software to define regions appears more objective and this forms a limitation of our study. However, as an identical region was used in both the initial and the follow up study, the data may be considered comparable with less subjectivity.

We found that, in patients showing clinical improvement, scintigraphic findings showed a trend similar to the clinical scores and PEFR. When no change in ventilation findings was detected after treatment, clinical scores and PEFR also did not show any significant change. Our findings indicate that scintigraphic findings are complimentary to other investigative findings. In the 5 subjects in whom scintigraphy showed worsening on follow up, the PEFR did not show any significant change while only the clinical scores indicated some improvement. This may possibly be due to persistent subclinical airway obstruction, attributable either to residual broncho-constriction or to prolonged expiration/ inspiration (reduced I/E) ratio. Lung perfusion scintigraphy was not studied in this work to avoid unnecessary radiation exposure. We also did not evaluate mucociliary clearance rates in our study. Lack of correlation of our findings with FEV1 levels, which better represents the status of the airways, is also a limitation of our study. Since small airways constriction is represented on scintigraphy, a better clinical correlate would have been the forced expiratory flow between 25% to 75 % of forced vital capacity [20].

Single photon emission tomography of the ventilation scans may demonstrate pathologically significant changes in asthmatic children more effectively than spirometry [21]. Since our study was performed with ^{99m}Tc-DTPA, the count rates obtained were better than those that may have been obtained from radiolabelled gases and permitted tomographic imaging. Semi-quantification on the transaxial and coronal images of the tomographic slices may yield more objective values than on planar anterior and posterior images. Further studies may better define the role of ventilation scintigraphy in the follow up of children who do not demonstrate the expected clinical response to treatment.

In conclusion, the results of this study suggest that, in children with moderate persistent asthma, ventilation scintigraphy was well tolerated and demonstrated semi-quantitatively the favourable effect of budesonide on treatment.

The authors declare that they have no conflicts of interest.

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