Oral-steroid sparing effect of inhaled fluticasone propionate in children with steroid-dependent asthma

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OBJECTIVE: To evaluate the oral steroid-sparing effect of inhaled fluticasone propionate (FP) in eight children with steroid-dependent asthma.

DESIGN AND SETTING: Treatment protocol study at a tertiary pulmonary care centre at a children's hospital.

PATIENTS: Eight children with severe persistent steroid dependent asthma (mean age 11.6 years [range 10 to 13 years], mean duration of asthma 8.37 years [range three to 11 years]) were enrolled in the study.

MEASUREMENTS: Inhaled FP 880 µg/day (two puffs of 220 µg/puff, two times a day) was added to the children's asthma treatment, and attempts were made to reduce the dose of oral steroids by 20% every two weeks over a six-month period. After this six-month period, in the patients responding to inhaled FP, the dose of inhaled FP was reduced to 440 µg/day (two puffs of 110 µg/puff, two times a day) for the next six months. The mean percentage predicted values for forced expiratory volume in 1 s (FEV₁) and maximal mid-expiratory flow rate (FEF_{25%-75%}) were compared during the first month, at two to six months, and at seven to 12 month intervals before and after starting FP. The number of asthma exacerbations, emergency room visits, hospital admissions and number of school days lost were also compared.

RESULTS: Within three months of starting inhaled FP, the mean alternate-day oral steroid dose decreased from 38 mg to 2.5 mg. In addition, six patients (66%) were able to discontinue the use of oral steroids. There was significant improvement in the number of mean emergency room visits per patient ($P=0.016$), mean asthma exacerbations per patient ($P=0.016$), mean hospital admissions per patient ($P=0.016$) and mean number of school days lost per patient ($P=0.004$) while patients were receiving high dose inhaled FP compared with oral steroids. There was no deterioration of any of the above mentioned parameters during the six month period when the dose of inhaled FP was reduced. The mean FEV₁ and FEF_{25%-75%} during the two- to six-month and seven- to 12-month periods showed significant improvement, while the patients were receiving FP compared with oral steroids ($P<0.05$ for both parameters for both time periods).

CONCLUSIONS: High dose inhaled FP 880 µg/day has an important oral steroid-sparing effect. After oral steroids are tapered, patients maintain adequate control of asthma with low dose inhaled FP. These findings suggest that FP may control asthma better than oral steroids.

Key Words: Asthma; Fluticasone propionate; Steroid

L'EFFET D'ÉPARGNE DU PROPIONATE DE FLUTICASONE PAR VAPORISATEUR SUR LES STÉROÏDES ORAUX CHEZ LES ENFANTS ATTEINTS D'ASTHME STÉROÏDODÉPENDANT

OBJECTIF : Évaluer l'effet d'épargne du propionate de fluticasone (PF) par vaporisateur sur les stéroïdes oraux chez huit enfants atteints d'asthme stéroïdodépendant.

MÉTHODOLOGIE ET EMPLACEMENT : Étude d'un protocole thérapeutique au centre de soins pulmonaires tertiaires d'un hôpital pour enfants.

PATIENTS : Huit enfants atteints d'asthme stéroïdodépendant persistant et grave (d'un âge moyen de 11,6 ans [fourchette de 10 à 13 ans]), depuis une moyenne de 8,37 ans (fourchette de trois à 11 ans) ont participé à l'étude.

MESURES : 880 µg/jour de PF par vaporisateur (deux bouffées de 220 µg/bouffée, deux fois par jour) ont été ajoutés au traitement de l'enfant contre l'asthme, et on a tenté de réduire la dose de stéroïdes oraux de 20 % toutes les deux semaines pendant six mois. Après cette période, chez les patients qui avaient réagi au PF par vaporisateur, la dose a été réduite à 440 µg/jour (deux bouffées de 110 µg/bouffée, deux fois par jour) pendant les six mois suivants. Les valeurs moyennes prévues à titre de pourcentage du volume expiratoire maximal par seconde (VEMS) et le volume expiratoire maximal mi-expiratoire (VEM_{25 %-75 %}) ont été comparées au premier mois, entre deux et six mois et entre sept et 12 mois avant et après le début du PF. Le nombre d'exacerbations de l'asthme, de visites à l'urgence, d'hospitalisations et de jours d'absence de l'école ont également été comparés.

RÉSULTATS : Dans les trois mois suivant le début de l'utilisation du PF par vaporisateur, la dose moyenne de stéroïdes oraux aux deux jours a

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chuté de 38 mg à 2,5 mg. De plus, six patients (66 %) ont pu arrêter de prendre des stéroïdes. On a remarqué une diminution importante du nombre moyen de visites à l'urgence par patient ($P=0,016$), d'exacerbations de l'asthme par patient ($P=0,016$), d'hospitalisations moyennes par patient ($P=0,016$) et d'absences de l'école par patient ($P=0,004$) tandis que les patients recevaient de fortes doses de PF inhalé par rapport aux stéroïdes oraux. On n'a observé aucune détérioration de ces paramètres pendant les six mois au cours desquels la dose de PF par vaporisateur a été réduite. Le VEMS et le VEM_{25} % -75 % pendant les

périodes de deux à six mois et de sept à 12 mois ont révélé une amélioration remarquable, tandis que les patients recevaient du PF plutôt que des stéroïdes oraux ($P<0,05$ pour les deux paramètres et les deux périodes).

CONCLUSIONS : De fortes doses de 880 µg/jour de PF par vaporisateur procurent un important effet d'épargne des stéroïdes oraux. Après la diminution des stéroïdes oraux, les patients conservent un contrôle convenable de leur asthme à l'aide de faibles doses de PF par vaporisateur. Ces observations laissent supposer que le PF pourrait mieux contrôler l'asthme que les stéroïdes oraux.

Despite a better understanding and recent advances in the treatment of asthma, severe asthma remains a serious challenge for clinicians. Some patients continue to depend on high doses of systemic steroids to maintain adequate control of their symptoms. Oral steroids are often associated with severe side effects (1-4). Complications of chronic oral steroids use include adrenal suppression, Cushing syndrome, posterior subcapsular cataracts, peptic ulcer disease, osteoporosis and hypertension (1,5,6).

The adverse effects associated with chronic oral steroid use have stimulated a search for other medications that can safely and effectively treat severe asthma, maintain pulmonary function and reduce or eliminate the need for the chronic use of oral steroids (7,8). Many therapeutic agents have been tried, but none have been shown to be an effective and safe alternative for oral steroids (9-11).

Recent studies, in both adults and children, have shown that the use of inhaled steroids can minimize the potential for serious steroid-related side effects; inhaled steroids deliver the drug directly to the airways and can control asthma at lower doses than systemic steroids (1,2,12-22). Inhaled steroids are well tolerated and effective in the management of severe asthma, including oral steroid replacement regimens in patients with steroid-dependent asthma (15,16). Studies have also shown that the use of inhaled corticosteroids can further limit the use of oral steroids in the long term management of severe asthma (12-22). We evaluated the steroid-sparing effect of inhaled fluticasone propionate, 880 µg/day (two puffs of 220 µg/puff, two times a day) in children with severe persistent asthma who were receiving alternate-day oral steroids.

PATIENTS AND MATERIAL

Eight children ages 10 to 13 years (mean age 11.6 years, range 10 to 13 years) with the clinical history of severe persistent asthma (1) were included in this two-year treatment protocol study (one part was prospective and one part was retrospective). Informed written consent was obtained for all investigations and procedures. The inclusion criteria were: age 10 years or older; ability to perform reproducible pulmonary function tests; and clinical symptoms and lung function suggestive of severe, persistent asthma for at least two years. Patients with a history of smoking, or with cardiac, hepatic, renal or

other medical conditions were excluded. All patients were followed for difficult-to-control asthma at the Childhood Asthma Care and Education Center at Kosair Children's Hospital, Louisville, Kentucky. Four patients were male and four were female.

All patients had been taking oral alternate-day corticosteroid (prednisone) for at least one year and the mean alternate-day oral steroid dose per patient for the previous six months was 38 mg. Previous attempts to wean the patients off alternate-day steroids while using other inhaled steroids (either flunisolide 1500 µg/day or triamcinolone acetonide 1500 µg/day) resulted in a worsening of asthma symptoms, and because there was no improvement in lung function with the addition of inhaled steroids in these patients, inhaled steroids were discontinued. Six children were also receiving long acting theophylline, and one was taking long acting salmeterol xinafoate 200 µg/day (two puffs of 50 µg/puff, twice a day) (Table 1). No change in any other asthma medication was made during the study. All the patients received inhaled beta₂-agonist therapy (albuterol 90 µg/puff) as needed for rescue. All the patients were seen every month as a part of their regular follow-up and had pulmonary function tests (PFTs) at each office visit. The number of emergency room visits, hospital admissions, asthma exacerbations requiring short courses of additional oral steroids (prednisone 1 to 2 mg/kg once a day, maximum 60 mg/day for five to seven days), missed school days and PFTs during the previous year were obtained from office medical records.

At the start of the study (baseline), inhaled fluticasone 880 µg/day (two puffs of 220 µg/puff twice a day) was added to the patient's management regimen. Patients were followed for six months (one to six month period) and the above-mentioned parameters were compared. After six months, in the patients who responded to high dose inhaled fluticasone (all patients responded), the dose of inhaled fluticasone was reduced by 50% to 440 µg/day (two puffs of 110 µg/puff twice a day). The same parameters were measured for the next six months (seven to 12 month period) and were compared with the same period of the previous year, when patients were receiving alternate-day oral steroids. Throughout this study, PFTs that were performed within three weeks of an asthma exacerbation were excluded. After starting fluticasone, patients were evaluated bi-weekly for the first two months and then every month for the duration of the study (one

year). Pulmonary function studies were performed at every office visit before and after starting fluticasone for the duration of the study. After two weeks on fluticasone, and if forced expiratory volume in 1 s (FEV₁) was stable, the dose of oral steroids was reduced by 20% of the initial dose on each visit during the six-month period on high dose inhaled fluticasone, while keeping the FEV₁ constant and the asthma clinically stable. Mean percentage predicted for age values for FEV₁ and maximal midexpiratory flow rate (FEF_{25%-75%}) were compared between the first month and the two to six month intervals before and after starting high dose inhaled fluticasone (comparing periods when patients were on oral steroids with periods when patients were on high dose fluticasone and were tapering the use of oral steroids). The same parameters were also compared during the seven to 12 month interval before and after starting fluticasone (comparing the same period of the different years while patients were either on oral steroids or were receiving lower dose of inhaled FP). This was performed to avoid detecting seasonal changes in asthma severity and to measure the efficacy of low dose, inhaled fluticasone.

All PFTs were completed using the same spirometer, Multispiro (Multispiro Inc, Irving, California); the pneumotachometer used was Multispiro model number 7433. Calibration was completed daily according to American Thoracic Society standards. During each arm of the study, all patients used a metered dose inhaled with a spacer device, Aerochamber with inspiratory flow signal (Monaghan Medical Corporation, Plattsburgh, New York). A respiratory therapist taught all patients how to use the spacer device before the start of the study. Proper technique was reinforced with each clinic visit. Standard spacer technique included slow inhalation, with 10 s breath-hold before exhalation, and four to six regular tidal breaths per activation. All patients understood and adequately reproduced the technique. None of the patients developed hoarseness or oral candidiasis during the study. Patients were instructed to wash and clean their spacer once a week.

Compliance was discussed with each patient on each visit before and after starting inhaled fluticasone. Patients had to give the names and the daily doses of all asthma

TABLE 1: Demographic information of participants enrolled in a study of the oral steroid-sparing effects of inhaled fluticasone propionate in children with severe, persistent asthma (n=8)

Parameters	Value
Number of patients	8
Sex (male:female)	4:4
Number of patients on other daily asthma medications	
Long acting theophylline	6 (75%)
Salmeterol xinafoate (100 µg/dose, bid)	1 (12%)
Mean age (years) at the time of starting fluticasone propionate	11.6±0.9
Duration of asthma (years)	8.37±2.55

Values are expressed in mean ± standard deviation

medications with each visit as a part of their regular asthma care. The same physicians took care of the patients during each arm of the study. Serum theophylline levels in the patients receiving long acting theophylline were performed twice a year and with each hospital admission. No patients had a subtherapeutic or toxic level of theophylline throughout the study.

Statistics

In the present treatment protocol study, patients acted as their own controls. Preliminary tests on the data indicated that they were not normally distributed, contraindicating the use of the Student's *t*-test. The differences were not symmetric, precluding the use of the paired Wilcoxon test. Accordingly, the matched-pair sign test was used. This is a conservative, nonparametric test and $P < 0.05$ was considered significant.

The Friedman test was used to evaluate the persistence of the improvement in FEV₁ and FEF_{25%-75%} first noted while patients were receiving high dose inhaled fluticasone compared with oral steroids. It showed no deterioration of the improved lung function during the seven to 12 months while patients were receiving lower doses of

TABLE 2: Tapering of mean oral alternate-day prednisone dose in a study of the oral steroid-sparing effects of inhaled fluticasone propionate (FP) children with severe, persistent asthma

Time period	Oral prednisone alternate day dose (mg)	Number of patients on oral steroids (n=8)	Number of patients off oral steroids
Six months before starting FP	38 (range 20 to 50)	8 (100%)	
At baseline, before starting FP	38 (range 20 to 50)	8 (100%)	
One month after starting FP	30 (16 to 34)	8 (100%)	None
Two months after starting FP	16 (4 to 20)	8 (100%)	None
Three months after starting FP	2.5 (0 to 10)	2 (25%)	6 (75%)
One year after starting FP	2.5 (0 to 10)	2 (25%)	6 (75%)

Values are expressed in mean and range

TABLE 3: Comparison of high dose inhaled fluticasone propionate and alternate-day oral steroids (clinical parameters) in children with severe, persistent asthma

	Fluticasone	Oral steroids	P
Exacerbations per patient per six months	2.12±2.58	64.07	0.016*
Emergency room visits per patient per six months	0.37±0.74	2.87±2.35	0.016*
Hospitalizations per patient per six months	0.50±0.75	2.75±2.49	0.016*
Lost school days per patient per six months	1.75±2.76	12.25±6.27	0.004*

Values are expressed in mean ± standard deviation. *P<0.05 was considered significant

TABLE 4: Comparison of lung function parameters, high dose inhaled fluticasone propionate versus alternate day oral steroids in children with severe, persistent asthma

Parameters	Fluticasone	Oral steroids	P
FEV ₁			
One month	83.88±10.9	68.2±21.6	0.031*
Two to six months	82±10.4	69.7±14.5	0.031*
FEF _{25%-75%}			
One month	51.5±16.8	37.5±16	0.109
Two to six months	54.3±13.5	39.5±11.8	0.031*

Pulmonary function test parameters are expressed in mean percentage predicted for age. Values are expressed in mean ± standard deviation. *P<0.05 was considered significant. FEV₁ Forced expiratory volume in 1 s; FEF_{25%-75%} Maximal midexpiratory flow rate

inhaled FP compared with the same time of the previous year when patients were receiving oral steroids and to the two to six month period when patients were receiving high dose inhaled fluticasone.

RESULTS

At the baseline (before starting high dose inhaled FP), the mean dose of oral alternate-day prednisone per patient was 38 mg (range 20 to 50 mg). At one month, after starting inhaled FP, the mean oral steroid dose was decreased to 30 mg (range 16 to 34 mg) and no patients had discontinued oral steroids. At two months, after starting FP, the mean oral steroid dose was decreased to 16 mg (range 4 to 20 mg) and still no patients had discontinued oral steroids. By the end of the third month, the mean alternate-day oral steroid dose was decreased to 2.5 mg, and six (75%) patients were able to discontinue the use of oral steroids. In two remaining patients, oral alternate-day prednisone dose was decreased from 40 to 10 mg/patient (Table 2).

There was a significant improvement in the number of mean hospital admissions for asthma for patients with six months on fluticasone (mean ± standard deviation, 0.5±0.75) compared with oral alternate-day steroids (2.75±2.49, P=0.016). There was also a significant improvement in the number of mean asthma exacerbations

TABLE 5: Comparison of lung function parameters, lower dose inhaled fluticasone propionate versus alternate day oral steroids in children with severe, persistent asthma

Parameters	Fluticasone	Oral steroids	P
FEV ₁	89±11.3	73±12.3	0.008*
FEF _{25%-75%}	58.2±511	39.6±11	0.031*

Pulmonary function test parameters are expressed in mean percentage predicted for age. FEV₁ Forced expiratory volume in 1 s; FEF_{25%-75%} Maximal midexpiratory flow rate

for patients with six months on fluticasone compared with oral alternate-day steroid (2.12±2.58 versus 6±4.07, P=0.016). There was significant improvement in the number of mean emergency room visits for patients with six months on fluticasone compared with oral alternate-day prednisone (0.37±0.74 versus 2.87±2.35, P=0.016). There was also significant improvement in mean lost school days for patients with six months on fluticasone compared with oral alternate-day prednisone (1.75±2.76 versus 12.25±6.27, P=0.004) (Table 3).

When mean PFTs for six months before and after starting fluticasone were compared, there was no deterioration in mean FEV₁ and FEF_{25%-75%} after the addition of high dose, inhaled fluticasone. There was a significant improvement in mean FEV₁ at one month after the addition of fluticasone (83.88±10.9 versus 68.2±21.6, P=0.031). Although there was a trend towards improvement, in mean FEF_{25%-75%} at one month after the addition of fluticasone, the difference was not statistically significant (51.5±16.8 versus 37.5±16, P=0.109) (Table 4). There was a significant improvement in mean FEV₁ during the two to six month period on high dose fluticasone while the use of oral steroids was being tapered (82±10.4 versus 69.7±14.5, P=0.031). There was also a significant improvement noted in mean FEF_{25%-75%} during the two to six month period on high dose, inhaled fluticasone (54.3±13.5 versus 39.5±11.8, P=0.031) while steroids were being tapered (Table 4).

After six months on high dose, inhaled fluticasone, the dose was reduced by 50% to 440 µg/day. Over the next six months, no deterioration in the initial improvement in clinical parameters (number of mean emergency room visits per patient, mean lost school days per patient, mean hospital admissions for asthma per patient and mean asthma exacerbations per patient) was noted while patients were receiving low dose, inhaled fluticasone. Because PFT can be affected by seasonal changes, PFT parameters were compared during the same season of the year (while patients were receiving a low dose of inhaled fluticasone versus while patients were on alternate day oral steroids). There was a significant improvement noted in mean FEV₁ (P=0.008) and FEF_{25%-75%} (P=0.031) during the six-month period while patients were receiving lower dose of inhaled fluticasone compared with the same time of the previous year while patients were receiving oral alternate-day steroids (Table 5).

DISCUSSION

This study was conducted to determine whether 880 µg/day of fluticasone propionate could have a significant oral steroid-sparing effect in the long term management of children with steroid-dependent asthma. Both clinical morbidity and lung function parameters were monitored for two years, one year on oral steroids (retrospective) and one year on inhaled fluticasone while tapering the use of oral steroids (prospective). The results show that fluticasone has a significant oral steroid-sparing effect and may be responsible for better control of asthma as noted by improved clinical parameters and lung function measurements. A significant steroid-sparing effect was noted as early as the second month of therapy and was maximized by the third month of therapy. There was no additional response after three months, but the benefit persisted throughout the year of the study. Improvement in PFTs was noted within the first few months of therapy and persisted throughout the duration of the study. In adults, other groups have noted improvement in PFT parameters with the use of fluticasone, despite the reduction in oral prednisone dose (20). In our study, this improvement in PFTs was persistent; even when patients were receiving low dose, inhaled fluticasone.

In most of the children, daily fluticasone either eliminated or substantially reduced their prednisone use over the course of the study. For some patients, inhaled flutica-

sone therapy was able to decrease their oral steroid dose but was not able to eliminate the need for oral steroids. The minimal oral steroid dose was reached with three months of starting inhaled fluticasone therapy, and no further reduction in the dose of oral steroid was possible for the remainder of the study. Other groups have reported similar findings in adults with steroid-dependent asthma (19).

The morbidity, measured in terms of the number of emergency room visits, asthma exacerbations requiring short courses of oral steroids, hospital admissions for asthma exacerbations and missed school days significantly improved on fluticasone compared with oral steroids. These findings suggest that inhaled fluticasone controls asthma better than oral steroids. However, our study has some limitations including a small sample size, lack of placebo controls and lack of randomization. It is well known that patients improve their compliance (with the resultant improvement in outcome measures) during the prospective period of studies. It is possible that the results of the present study, in part, are simply because of improved medication compliance during the prospective period of the study. Thus, our findings should be interpreted with caution, and further studies are needed in this regard.

In summary, inhaled fluticasone has a significant oral steroid-sparing effect accompanied by a better asthma control in children.

REFERENCES

1. National Asthma Education and Prevention Program, Expert Panel Report 2: Guidelines for the diagnosis and management of asthma [publication no 97-4051A]. Bethesda: National Institute of Health, 1997;29.
2. Guidelines for the diagnosis and management of asthma: National Heart, Lung and Blood Institute, National Asthma Education Program. Expert Panel Report. *J Allergy Clin Immunol* 1991;88:425-534.
3. Kemp JP. Approaches to asthma management. Realities and recommendations. *Arch Intern Med* 1993;153:805-12.
4. Cott GR, Cherniack RM. Steroids and "steroid-sparing" agents in asthma. *N Engl J Med* 1988;318:634-6.
5. Truhan AP, Ahmed AR. Corticosteroids: a review with emphasis on complications of prolonged systemic therapy. *Ann Allergy* 1989;62:375-91.
6. Kwong FK, Sue MA, Klaustermeyer WB. Corticosteroid complications in respiratory disease. *Ann Allergy* 1987;58:326-30.
7. Rochester CL, Einarsson O. New directions in therapy for chronic asthma. *Clin Pulm Med* 1995;2:315-26.
8. Balter MS, Rebuck AS. Treatment of the recalcitrant asthmatic. *Ann Allergy* 1989;63:297-300.
9. Shiner RJ, Nunn AJ, Chung KF, Geddes DM. Randomised, double-blind, placebo-controlled trial of methotrexate in steroid-dependent asthma. *Lancet* 1990;336:137-40.
10. Dyer PD, Vaughan TR, Weber RW. Methotrexate in the treatment of steroid-dependent asthma. *J Allergy Clin Immunol* 1991;88:208-12.
11. Alexander AG, Barnes NC, Kay BA. Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. *Lancet* 1992;339:324-8.
12. Ilanogvan P, Pederson S, Godfrey S, Nikander K, Noviski N, Warner JO. Treatment of severe steroid-dependent preschool asthma with nebulised budesonide suspension. *Arch Dis Child* 1993;68:356-9.
13. Gleeson JG, Price JF. Controlled trial of budesonide given by the Nebuhaler in preschool children with asthma. *BMJ* 1988;297:163-6.
14. Bisgaard H, Munck SL, Nielsen JP, Petersen W, Ohlsson SV. Inhaled budesonide for treatment of recurrent wheezing in early childhood. *Lancet* 1990;336:649-51.
15. Lacronique J, Renon D, Georges D, Henry-Amar M, Marsac J. High-dose beclomethasone: oral steroid-sparing effect in severe asthmatic patients. *Eur Respir J* 1991;4:807-12.
16. Tarlo SM, Broder I, Davies GM, Leznoff A, Minz S, Corey PN. Six-month double-blind controlled trial of high dose, concentrated beclomethasone dipropionate in the treatment of severe chronic asthma. *Chest* 1988;93:998-1002.
17. Laursen LC, Taudorf E, Weeke B. High-dose inhaled budesonide in treatment of severe steroid-dependent asthma. *Eur J Respir Dis* 1986;68:19-28.
18. Salmeron S, Guerin JC, Godard P, et al. High doses of inhaled corticosteroids in unstable chronic asthma. *Am Rev Respir Dis* 1989;140:167-71.
19. Hummel S, Lehtonen L. Comparison of oral steroid-sparing by high-dose and low-dose inhaled steroid in maintenance treatment of severe asthma. *Lancet* 1992;340:1483-7.
20. Noonan M, Chervinsky P, Busse WW, et al. Fluticasone propionate reduces oral prednisone use while it improves asthma control and quality of life. *Am J Respir Crit Care Med* 1995;152:1467-73.
21. Grossman J, Sorkness CA, Joseph JC. The use of inhaled corticosteroids in patients with asthma. *Drug Therapy* 1992;22:37-52.
22. Gaddie J, Petrie GR, Reid W, Sinclair DJM, Skinner C, Palmer KNV. Aerosol beclomethasone dipropionate: a dose-response study in chronic bronchial asthma. *Lancet* 1973;ii:280-1.
23. Standardization of spirometry - 1987 Update. Statement of the American Thoracic Society. *Am Rev Respir Dis* 1987;136:1285-1298.