Mechanism of bronchodilator effect in chronic airflow limitation

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Objective: To examine the mechanisms through which two bronchodilators (theophylline and salbutamol) influence dyspnea during daily activities.

Methods: Twenty-four patients with chronic airflow limitation participated in a multiple crossover, randomized, placebo-controlled trial. The effect of theophylline and salbutamol, alone or combined, on pulmonary function and dyspnea during daily activities was examined. Correlations of changes in forced expiratory volume in 1 second (FEV_1) and maximum expiratory pressures (MIPs) (independent variables) and changes in dyspnea score during daily activities (dependent variable) were also examined.

Results: The two drugs proved to be beneficial: the effects in general were additive rather than synergistic. The drugs improved the FEV_1; theophylline significantly improved the MIPs. The correlation between the changes in FEV_1 and those in dyspnea score, after adjustment for the changes in MIPs, was 0.55 ($p < 0.001$). The correlation between the changes in MIPs and those in dyspnea score, after adjustment for the changes in FEV_1, was 0.39 ($p < 0.001$).

Conclusions: Changes in airway calibre and in respiratory muscle strength play an independent and important role in dyspnea during daily activities in patients with chronic airflow limitation. Changes in airway calibre may be of greater importance.

Objectif : Déterminer comment deux bronchodilatateurs (la théophylline et le salbutamol) agissent sur la dyspnée au cours des activités quotidiennes.

Méthodes : Vingt-quatre sujets souffrant de limitation chronique de l'écoulement d'air ont participé à un essai multiple croisé, aléatoire et contrôlé par placebo. On a étudié l'effet de la théophylline et du salbutamol, seuls ou combinés, sur la fonction pulmonaire et la dyspnée au cours des activités quotidiennes. On a aussi étudié les corrélations entre les changements du volume expiratoire forcé par seconde (VEF_1) et des pressions expiratoires maximales (PEMs) (variables indépendantes), et les changements des résultats relatifs à la dyspnée au cours des activités quotidiennes (variable dépendante).

Résultats : Les deux médicaments se sont révélés bénéfiques : les effets étaient en général additifs plutôt que synergiques. Les médicaments ont amélioré le VEF_1, et la théophylline a amélioré considérablement les PEMs. La corrélation entre les changements du VEF_1 et ceux des résultats de dyspnée, corrigée des changements des PEMs, était de 0,55 ($p < 0,001$). La corrélation entre les changements des PEMs et ceux des résultats de la dyspnée, corrigée des changements du VEF_1, était de 0,39 ($p < 0,001$).

Conclusions : Les changements de calibre des voies aériennes et de la force des muscles respiratoires jouent un rôle indépendant et important dans la dyspnée au cours des activités quotidiennes chez les sujets qui souffrent de limitation chronique de l'écoulement d'air. Les changements du calibre des voies aériennes peuvent avoir plus d'importance.

Bronchodilators, including inhaled β-agonists and orally administered theophylline, have been shown to lessen exertional dyspnea and improve mood in patients with chronic airflow limitation.[1-4] Although bronchodilation and improved respiratory muscle strength have been observed[4,5] there is still considerable controversy about the role of respiratory muscle strength in chronic

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airflow limitation and about the improvement in strength with theophylline therapy. The effects of theophylline on respiratory muscle function have not been consistently reproduced.[6] Murciano and associates,[5] in their study demonstrating increased diaphragmatic strength in patients with chronic airflow limitation, hypothesized that the observed alleviation of dyspnea was due in part, and perhaps primarily, to augmented respiratory muscle function. However, this was an unblinded, before–after study, and the authors did not try to quantify the relative contributions of bronchodilation and increasing muscle strength to the relief of dyspnea. More recently Murciano and collaborators,[4] in a double-blind, controlled study, hypothesized that although the increase in respiratory muscle strength was accompanied by bronchodilation the former effect was the main mechanism of drug action.

Our group recently performed a crossover trial of salbutamol and theophylline therapy for chronic airflow limitation.[7] Twenty-four patients whose acute response to inhaled salbutamol was less than 25% of their baseline forced expiratory volume in 1 second (FEV_1) underwent treatment for four 2-week periods. The drug combinations were randomly assigned: placebo–placebo, placebo–theophylline, placebo–salbutamol and salbutamol–theophylline. The study showed improvement in airway calibre and respiratory muscle strength as well as alleviation of dyspnea during daily activities. We analysed the data from that study to determine the extent to which changes in FEV_1 and maximum inspiratory pressures (MIPs) influence dyspnea during daily activities in patients with chronic airflow limitation. If increases in muscle strength help to alleviate dyspnea on exertion in such patients the rationale for theophylline therapy may be supported.

Methods

Study design

Details of the design and recruitment of patients, and the primary results have been published previously.[1,7] In brief, 24 patients with a mean age of 66 (standard deviation [SD] 7.3) years who had a mean FEV_1 of 0.93 (SD 0.34) L and a mean forced vital capacity (FVC) of 2.67 (SD 0.76) L were recruited. Each patient received four 2-week regimens: (a) salbutamol, 200 μg inhaled four times daily, and orally administered theophylline, in a dose previously titrated to produce a therapeutic blood level (mean 12.3 [SD 3.40] μg/mL), (b) active theophylline and placebo in an inhaler identical to the one used for salbutamol, (c) active salbutamol and placebo as pills identical to those of theophylline and (d) placebo in an inhaler and as pills. The order of the four sessions was determined through random allocation, and the patients, the caregivers and the study team were blinded to the allocation.

Outcome measures

Outcome was measured at the end of each treatment period. The FEV_1 and the FVC were measured 20 minutes after inhalation of the drug with the use of a Collins water spirometer with a 420 microprocessor (Dr. Warren E. Collins, Braintree, Mass.); the best of three efforts was recorded. We tested the respiratory muscle strength at functional residual capacity (FRC) (i.e., the end of a normal expiration) by measuring the MIPs with a manometer calibrated in centimetres of water that had a sealed mouthpiece and nose clips. The highest pressure that the subjects could maintain for 0.5 seconds was recorded, and then the best of five efforts was recorded.

Quality of life was measured with the use of part of the Chronic Respiratory Disease Questionnaire,[8] which was carefully developed and rigorously validated.[8,9] The part of the questionnaire we used included five questions on exertional dyspnea during activities that are performed frequently and are important in the patient's daily life. Response options for each question were presented as a seven-point scale, 1 representing the worst state (extreme dyspnea) and 7 the best state (no dyspnea). Thus, the scores could vary from 5 to 35. This questionnaire allowed us to determine day-to-day changes in dyspnea in each patient and thus explore the effectiveness of different treatments.

Statistical analyses

Two analyses were performed. The first was an analysis of variance for a 2×2 crossover design to examine the main effects of salbutamol and theophylline.[10] An interaction term, if statistically significant, would indicate that the effect of the two drugs was synergistic rather than additive or that the effect was less than additive.

The second analysis addressed the mechanism of alleviation of dyspnea during daily activities. The correlations between changes in dyspnea score, spirometry results and MIPs were examined. Changes in each variable were calculated by subtracting the values obtained at one point from those obtained at the previous measurement. Through a hierarchic multiple regression analysis with the dyspnea score as the dependent variable we examined the independent variables FEV_1, MIPs, FVC and subjects. The effects of FEV_1 and MIPs were each examined after the other three variables were forced into the model; FEV_1 was thought to indicate the effect of

bronchodilation and MIPs the effect of respiratory muscle strength on dyspnea in daily living. Because each subject contributed multiple data points to each correlation the assumption of the standard Pearson's correlation coefficient, independence of observations, was potentially violated. We therefore analysed the data in two ways: (a) we assumed independence of observations and used a Pearson's correlation and (b) we used a regression approach in which we forced in the effect of subjects and then determined the correlation between the test measures after removing the systematic effect associated with subjects. This approach is similar to that suggested by Feldman.[11]

Finally, we considered that a decrease in dyspnea due to improved MIPs, established after the effect of the FEV_1 change was accounted for, could be the result of a decrease in the FRC or the residual volume as a result of bronchodilation. If the FRC were substantially reduced through bronchodilation the MIPs would be measured at lower lung volumes; this would result in higher MIPs even if the respiratory muscle strength were unchanged. Because we did not measure the FRC or the residual volume we assumed that a decrease in these variables would be associated with an increase in the FVC (assuming a constant total lung capacity). Consequently we determined the proportion of variance in changes in dyspnea explained by changes in the MIPs after accounting for the effect of not only subject and FEV_1 but also FVC. A second reason for including the FVC in the analysis was the known correlation between the MIPs and the FVC in healthy subjects with normal lung volume.[12]

Ethical issues

The study was approved by a local ethics committee, and informed consent was obtained from each subject.

Results

Effect of salbutamol and theophylline

There was no systematic effect of time (i.e., repeated measurement) on any variable. Each drug proved to have clinically and statistically significant effects on physiologic and functional variables. The mean values during each of the four treatment periods are presented in Table 1. The associated p values for these variables are in Table 2. The interaction terms presented in the last column of Table 2 were not statistically significant for any of the four tests; this suggested that an additive model of the effects of salbutamol and theophylline would be appropriate.

Mechanism of alleviation of dyspnea

The correlation between the changes in FEV_1 and those in MIPs was relatively weak (simple $r = 0.25$, $p < 0.01$; $r = 0.33$ after adjustment for subjects). Therefore, we were able to establish

Table 1: Pulmonary function and dyspnea during daily activities in 24 patients with chronic airflow limitation who underwent four 2-week treatment sessions

	Treatment; mean (and standard deviation)			
Variable*	Placebo	Theophylline	Salbutamol	Theophylline and salbutamol
FEV_1, L	0.81 (0.36)	0.94 (0.40)	0.95 (0.30)	1.07 (0.34)
FVC, L	2.25 (0.64)	2.63 (0.76)	2.70 (0.75)	2.93 (0.65)
MIPs, cm H_2O	38.6 (14.4)	41.8 (12.6)	42.1 (15.1)	45.3 (14.2)
Dyspnea score	14.6 (6.1)	17.5 (6.5)	17.4 (5.3)	19.4 (4.6)

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, MIPs = maximum inspiratory pressures.

Table 2: Results of 2 × 2 crossover analysis of the effects of theophylline and salbutamol on pulmonary function and dyspnea during daily activities

	Drug; p value		
Variable	Theophylline	Salbutamol	Interaction
FEV_1	0.0006	0.005	0.65
FVC	0.00005	0.00035	0.14
MIPs, cm H_2O	0.033	0.063	0.97
Dyspnea score	0.016	0.006	0.37

which effect was responsible for the changes in dyspnea score. The correlation between the changes in FEV_1 and those in dyspnea score was strong ($r = 0.55$, $p < 0.001$); the correlation between the changes in MIPs and those in dyspnea score was weaker ($r = 0.39$, $p = 0.001$). After taking into account the effect of subjects and MIPs we found that the correlation between the changes in FEV_1 and those in dyspnea score remained high ($r = 0.50$, $p < 0.001$). After a similar adjustment for subject and FEV_1 we found that the changes in MIPs were still able to explain a significant portion of the remaining changes in dyspnea score ($r = 0.4$, $p < 0.001$), although this portion was lower than that for FEV_1. The correlation between the changes in MIPs and those in dyspnea score after adjustment for not only the FEV_1 and subjects but also the FVC was 0.41 ($p < 0.001$).

Discussion

The primary findings show an unequivocal beneficial effect of theophylline on airway calibre, MIPs and dyspnea during daily activities. The effects on dyspnea were large enough to be considered clinically important.[13] Salbutamol had positive effects on the FEV_1 and showed a substantial trend in effect on the MIPs. Although our data support the hypothesis that theophylline alleviates dyspnea by increasing the respiratory muscle strength (as measured by MIPs) the small change in MIPs and the greater correlation between FEV_1 rather than MIPs and the changes in dyspnea score suggest that this is not the primary mechanism of action of theophylline.[4]

The initial finding that the FEV_1, the MIPs and the dyspnea scores were all improved does not clarify the respective contribution of changes in airway calibre and respiratory muscle strength to the alleviation of dyspnea. The moderately significant correlations between the changes in dyspnea score and those in both FEV_1 and MIPs suggest that both modes of drug action have an effect. Because the correlations between the changes in dyspnea score and those in FEV_1 were higher than the correlations between the changes in dyspnea score and those in MIPs (before and after adjustment for the other variable) we conclude that enhanced airway calibre is likely more important than increased respiratory muscle strength in improving physical function, even after administration of a relatively small and possibly suboptimal dose of inhaled adrenoreceptor agonist.

Since MIPs are influenced by many factors could mechanisms other than increased respiratory muscle strength have been responsible for the improvement in MIPs? Perhaps bronchodilation led to decreased FRC and thus improved MIPs. Indeed, the fact that the changes in FVC were substantially greater than those in the FEV_1 supports this hypothesis. However, the correlation between the changes in MIPs and those in dyspnea score remained high after adjustment for both FEV_1 and FVC. This suggests that at least some component of the effect of MIPs on dyspnea was due to a mechanism unrelated to bronchodilation and the resulting change in lung volumes. This conclusion is further supported by a finding in another study,[4] in which use of theophylline was not associated with a decrease in the FRC. Given the data we cannot exclude another possibility, that the drugs had a central effect on the subjects' motivation.

Our findings show that changes in MIPs (possibly mediated through improved respiratory muscle function), independent of changes in spirometry results, can influence the extent to which patients feel short of breath when performing their daily activities — a variable of most interest to patients with chronic airflow limitation. Furthermore, the findings provide a possible rationale for the addition of theophylline to inhaled β-agonist therapy in the treatment of chronic airflow limitation. However, in the studies to date that have shown a beneficial effect of theophylline beyond that achieved by inhaled β-agonists the theophylline dose has been no greater than 200 μg four times daily (or the equivalent).[1,3] Recent evidence suggests that appreciable increases in bronchodilation in a substantial proportion of patients with chronic airflow limitation may be achieved with the use of larger doses of inhaled sympathomimetics.[14,15] If we had administered larger doses of inhaled salbutamol the additional benefit of theophylline might not have been observed. Whether theophylline would still alleviate dyspnea after the use of larger doses of β-agonist remains unknown.

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Conferences

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Feb. 26-Mar. 2, 1991: 7th International Hypoxia Symposium — High Altitude Physiology and Medicine (sponsored by McMaster University and the Arctic Institute of North America in conjunction with the International Society for Mountain Medicine)
Chateau Lake Louise, Lake Louise, Alta.
Ingrid Ellis, conference coordinator, Rm. 1M10, McMaster University, 1200 Main St. W, Hamilton, ON L8N 3Z5; (416) 525-9140, ext. 2182

Mar. 6-9, 1991: 2nd International Congress on the Immune Consequences of Trauma, Shock and Sepsis: Mechanisms and Therapeutic Approaches
Munich
Official language: English
Dr. Eugen Faist, local organizing secretary, Ludwig-Maximilians-universität Munich, Department of Surgery, Klinikum Großhadern, Postfach 70 12 60, 8000 Munich 70, Germany; telephone 011-49-89-70-95-34-41, FAX 011-49-89-70-95-7-00-44-18

Mar. 8-9, 1991: 1st European Congress on Ambulatory Surgery
Brussels Congress Centre
Official language: English (simultaneous interpretation into French and Dutch)
Administrative Secretariat, European Congress Consultants and Organizers, rue Vilain XIIII, 17a, B-1050, Brussels, Belgium; telephone 011-32-2-647-87-80, FAX 011-32-2-640-66-97

Mar. 18-21, 1991: Cardiovascular Conference (sponsored by the American College of Cardiology, the Alberta Cardiovascular Society and the University of Alberta)
Chateau Lake Louise, Lake Louise, Alta.
Registration secretary, Extramural Programs, American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814; (301) 897-5400, ext. 226

Apr. 9-12, 1991: Joint Scientific Meeting of the Society of Nuclear Medicine in Canada and the Prairie provinces chapter of the SNM (includes the Annual General Meeting of the Canadian Association of Nuclear Medicine)
Banff Springs Hotel, Banff, Alta.
Ingrid Koslowsky, Nuclear Medicine, Foothills Provincial General Hospital, 1403-29 St. NW, Calgary, AB T2N 2T9; (403) 270-1160

Apr. 16-17, 1991: Basic Cardiac Arrhythmia Interpretation
Halifax Hilton
Conference and Seminar Services, Humber College, 205 Humber College Blvd., Etobicoke, ON M9W 5L7; (416) 675-5077, FAX (416) 675-0135

Apr. 16-20, 1991: Canadian Academy of Sport Medicine Annual General Meeting (held in conjunction with the International Congress and Exposition on Sports Medicine and Human Performance)
Vancouver Trade and Convention Centre
Canadian Academy of Sport Medicine, R. Tait MacKenzie Building, 1600 James Naismith Dr., Gloucester, ON K1B 5N4; (613) 748-5671, FAX (613) 748-5729

Apr. 18-19, 1991: 12 Lead ECG Interpretation
Halifax Hilton
Conference and Seminar Services, Humber College, 205 Humber College Blvd., Etobicoke, ON M9W 5L7; (416) 675-5077, FAX (416) 675-0135

Apr. 21-24, 1991: Canadian Organization for the Advancement of Computers in Health (COACH) 16th Annual Conference
Sheraton Centre, Toronto
Steven A. Huesing, executive director, Canadian Organization for the Advancement of Computers in Health, 1200-10460 Mayfield Rd., Edmonton, AB T5P 4P4; (403) 489-4553, FAX (403) 489-3290

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